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A facile approach to polysubstituted 2-pyridones. Application to the synthesis of 3,4-disubstituted isoquinolinone and total synthesis of oxyisoterihanine

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Abstract—A facile approach to polysubstituted 2-pyridones from 1-benzyl-5,6-dialkyl-3-(4-toluenesulfonyl)pyridin-2-one was described. A new approach to 3,4-disubstituted isoquinolinone and total synthesis of oxyisoterihanine will also be reported.

1. Introduction

The 2-pyridone core is an important framework that can be found in numerous biologically active compounds.[1] It is a common template utilized for the synthesis of a wide variety of nitrogen heterocycles such as pyridine, piperidine, quinolizidine, and indolizidine alkaloids.[2] Although a great number of methods have been reported for the synthesis of 2-pyridones,[3] the development of new and flexible approach to polysubstituted 2-pyridones is still required. During the course of our study of regioselective introduction of substituent at C-6 carbonyl in 3-sulfonyl glutarimides **1**,[4] the resulting *exo* or *endo* enlactams **2** have been successfully converted to L-733,060 **3**, CP-99,994 **4**, and cassine **5**[5] (Fig. 1). We envisioned that this result can be further applied to the synthesis of polysubstituted 2-pyridones.

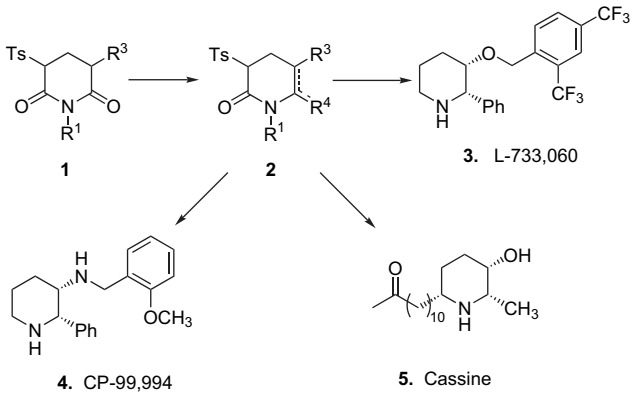


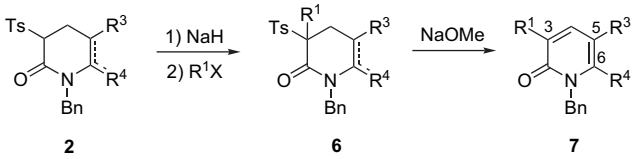
Figure 1. The application of *exo* or *endo* enlactams to L-733,060 **3**, CP-99,994 **4** and cassine **5**.

2. Results and discussion

2.1. Synthesis of polysubstituted 2-pyridones

We first examined the synthesis of 3,6-disubstituted and 3,5,6-trisubstituted 2-pyridones. Alkylation of enlactam **2** at C-3 position followed by dehydrosulfonation with sodium methoxide furnished the desired 2-pyridones **7**. Some representative examples are listed in Table 1.

Table 1. Synthesis of 3,6-disubstituted and 3,5,6-trisubstituted 2-pyridones **7** from **2**



Entry	R^1	R^3	R^4	Yield (%)
7a	Me	H	Et	86
7b	Bn	H	Et	80
7c	Me	Me	Me	85
7d	Me	Me	Et	81

All yields are based on compound **2**.

Keywords: 2-Pyridones; Isoquinolinone; Benzo[*c*]phenanthridine; Oxyisoterihanine.
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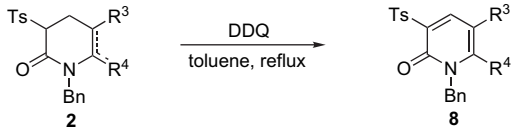
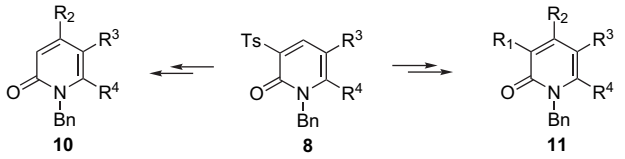
We next investigated the synthesis of 4,5,6-trisubstituted **10** and tetrasubstituted 2-pyridone **11**. We envisioned that 3-sulfonyl-2-pyridone **8** might be a reasonable precursor for the synthesis of these compounds. 2-Pyridones **8** was easily accomplished by oxidation of enlactam **2** with DDQ (Table 2).

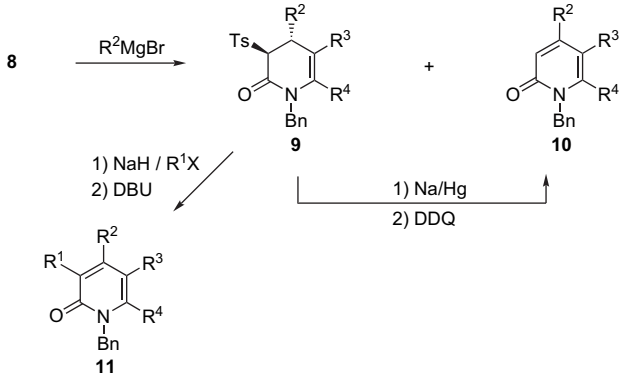
Table 2. Synthesis of 5,6-disubstituted 2-pyridone **8** from **2**



Entry	R^3	R^4	Yield (%)
8a	Me	Me	85
8b	Me	Et	90
8c	Me	Ph	81
8d	Bn	Me	88



With desired 2-pyridone **8** in hand, we investigated the introduction of substituent at C-4 position. Treatment of **8** with 3 equiv of Grignard reagents furnished 1,4-addition product **9**[6b] in all substrates except **8c** (Scheme 1 and Table 3).



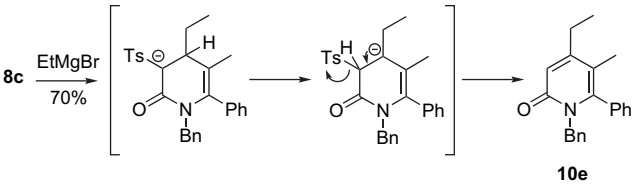
Scheme 1. Synthesis of 4,5,6-trisubstituted 2-pyridones **10** and tetrasubstituted 2-pyridones **11** from **8**.

We were slightly surprised to obtain **10e** as the major product during the reaction. It indicated that proton exchange occurred after 1,4-addition. The presence of phenyl group at C-6 position might promote the proton migration and elimination (Scheme 2). The synthesis of 4,5,6-trisubstituted 2-pyridone was demonstrated by the conversion of **9a** to **10a**. Removing the tosyl group on **9a** with sodium amalgam followed by oxidation of the resulting enlactam with DDQ yielded **10a** in 80%. Alkylation of **9** followed by dehydrosulfonation with DBU provided the corresponding tetrasubstituted 2-pyridones **11**.[7] Some examples are listed in Table 4. It is noteworthy that 2-pyridones **11c** contained four different substituents.

Table 3. Ratio of compounds **9** and **10**

Entry	R^2	R^3	R^4	Reaction time (h)	Yield (%)	**9**:**10**
a	Me	Me	Me	24	70	70:0
b	Me	Me	Et	24	75	75:0
c	Ph	Me	Et	24	70	70:0
d	Vinyl	Me	Et	24	73	73:0
e	Et	Me	Ph	24	81	30:70

All yields are based on compound **8**.



Scheme 2. Proposed mechanism for the formation of **8c** to **10e**.

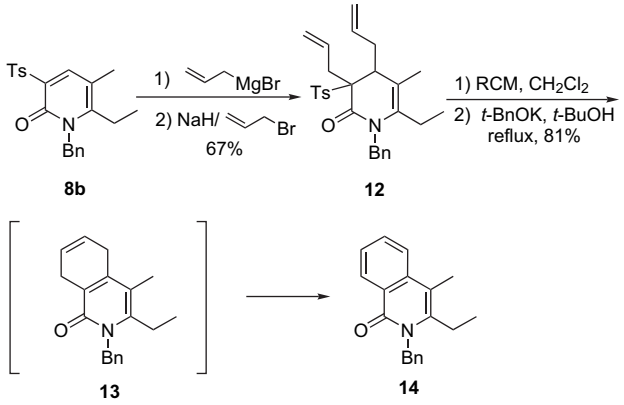
Table 4. Synthesis of tetrasubstituted 2-pyridones **11** from **9**

Entry	R^1	R^2	R^3	R^4	Yield (%)
11a	Me	Me	Me	Me	95
11b	Me	Me	Me	Et	93
11c	Allyl	Ph	Me	Et	90
11d	Me	Et	Bn	Me	92

All yields are based on compound **9**.

2.2. A new approach to isoquinolinone skeleton 14

To demonstrate the synthetic potential of these results, a new approach to isoquinolinone skeleton was tested. As shown in Scheme 3, 1,4-addition of an allylmagnesium bromide to **8b** followed by allylation furnished diallyl enlactam **12**. Performing ring-closing metathesis reaction on **12** with first generation Grubbs catalyst followed by dehydrosulfonation produced isoquinolinone **14**. Presumably, after dehydrosulfonation of **12**, the resulting **13** oxidized spontaneously to form isoquinolinone **14**.



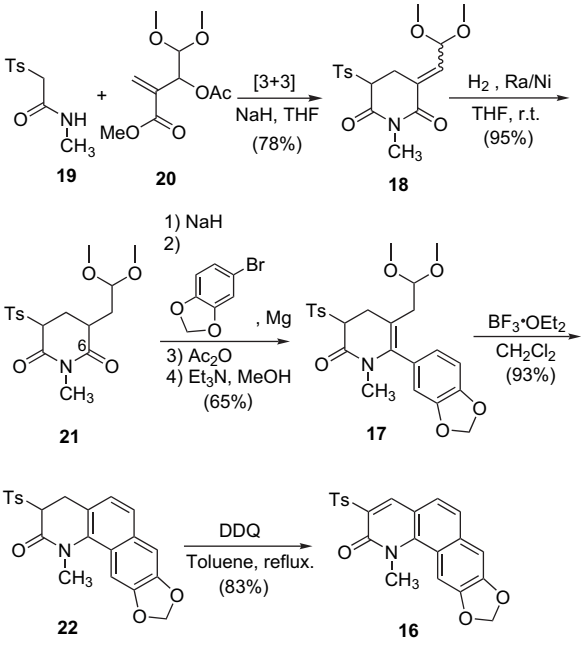
Scheme 3. Synthesis of isoquinolinone **14**.

2.3. Synthesis of benzo[*c*]phenanthridine nucleus

Encouraged by the successful construction of isoquinolinone skeleton, we further investigated the possibility of building

up the core structure of benzo[*c*]phenanthridine alkaloids distributed in Papaveraceous and Rutaceous plants.[8] The alkaloids have attracted considerable attention from synthetic organic chemists and biochemists over the last two decades due to their unique structure and biological activity.[9] Oxyterihanine **15a**, a phenolic benzo[*c*]phenanthridine, was isolated from Xanthoxylum nitidum (Roxb.) D. C. (Fagara nitida Roxb.) in 1984.[9c] The structures of **15a** and **15b** were further confirmed by Ishii et al. (Fig. 2).[10b] Our strategy for the synthesis of **15** was shown in Scheme 4. The core structure of **15b** was envisaged to arise from tricyclic pyridone derivative **16** via the procedures developed above. Pyridone **16** was predicted to derive from enlactam **17** through Friedel–Crafts reaction. Enlactam **17** was anticipated to arise from [3+3] cycloaddition adduct **18**.

To test the strategy toward **15b**, we first set out to synthesize tricyclic pyridone derivative **16** (Scheme 5). Following the method developed in our laboratory,[4] reaction of α-sulfonyl acetamide **19** with Baylis–Hillman adduct **20** furnished [3+3] annulation product glutarimide **18** in 78% yield. Hydrogenation of **18** in the presence of Ra/Ni gave **21** in 95% yield. Regioselective addition of aryl group at C-6 position in **21** followed by dehydration of the resulting hydroxylactam produced enlactam **17**.[5] Exposure of **17** to boron trifluoride yielded Friedel–Crafts reaction and aromatization product **22**. Oxidation of **22** with DDQ furnished the desired tricyclic pyridone **16**.



Scheme 5. Synthesis of tricyclic pyridone **16**.

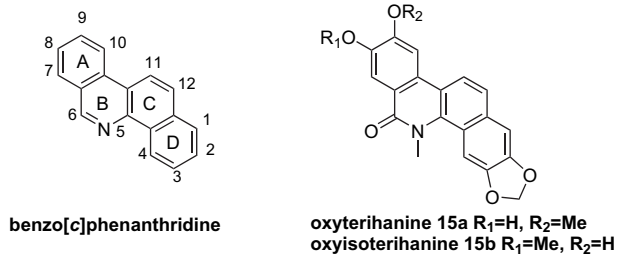
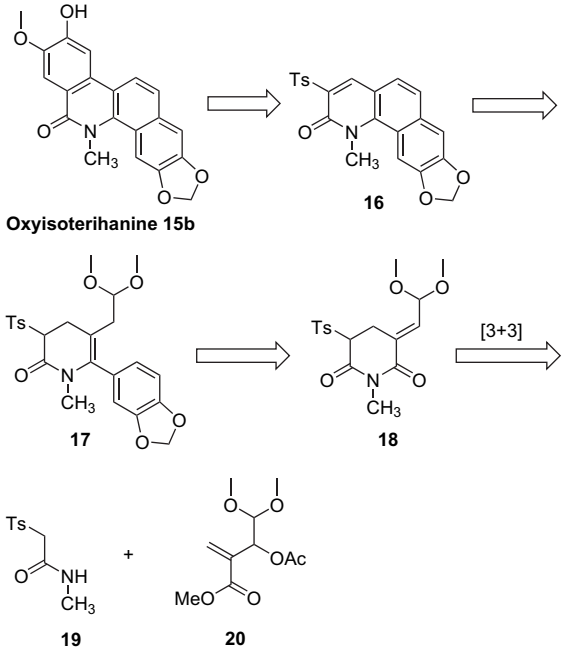


Figure 2. The core structure of benzo[*c*]phenanthridine alkaloids.

With required **16** in hand, the next task was to build the fourth ring on **16**. Following the procedures described in Scheme 6, tetracyclic enlactam **25**[6a] was prepared in 84% from **16**. To accomplish the synthesis of the core skeleton of benzo[*c*]phenanthridine, enlactam **25** was dehydrosulfonated with DBU, and the resulting **26** was oxidized with DDQ, which afforded the desired **27** in 92% yield for two steps sequence.

2.4. Total synthesis of oxyisoterihanine 15b

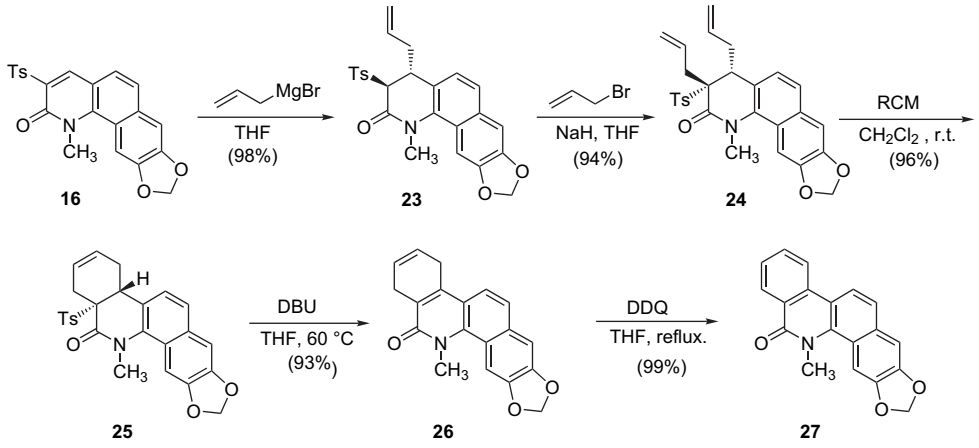
The synthesis of oxyisoterihanine **15b** was carried out as depicted in Scheme 7. Oxidation of **25** with *m*-CPBA furnished epoxide **28**[6c] in 94% yield. Exposure of **28** in methanol and dichloromethane in the presence of boron trifluoride afforded **29** in 85% yield. The structure of **29** was unequivocally established by single-crystal X-ray analysis (Diagram 1).[6a] Finally, Swern oxidation of **29** furnished ketone **30**, which was further dehydrosulfonated with DBU to afford **15b** in 65% yield. The spectral data of **15b** were in agreement with those reported in the literature.[10]



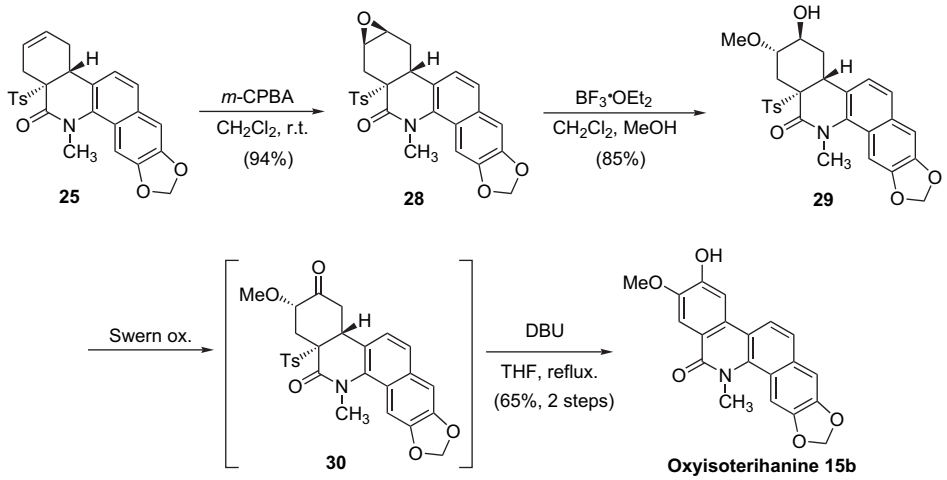
Scheme 4. Retrosynthesis of oxyisoterihanine **15b**.

3. Conclusion

In conclusion, we have disclosed an efficient and regiocontrolled synthesis of polysubstituted 2-pyridones. Starting from readily available glutarimides, the substituents can be introduced to glutarimides or the corresponding 2-pyridones in different stages at desired positions to form substituted 2-pyridones. Synthesis of isoquinolinone **14** was accomplished, which provided a potential new approach to isoquinolinone derivatives with different substituents at C-3 and C-4 positions. New approach to the core skeleton of



Scheme 6. Synthesis of benzo[*c*]phenanthridine **27**.



Scheme 7. Completion of the total synthesis of oxyisoterihanine **15b**.

benzo[*c*]phenanthridine was developed. Total synthesis of oxyisoterihanine **15b** was accomplished. Further application of these results to the synthesis of polysubstituted pyridines, tri and tetracyclicquinoline and isoquinoline alkaloids are underway in our laboratory.

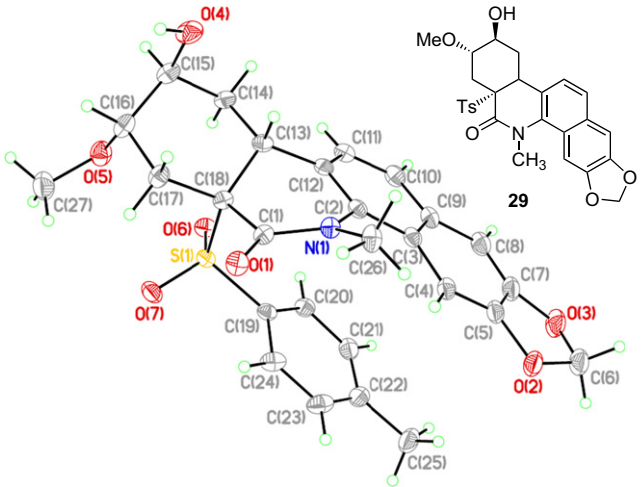


Diagram 1. X-ray crystallography of **29**.

4. Experimental

4.1. General

Melting points were determined with melting point apparatus and were uncorrected. ^{1}H NMR and ^{13}C NMR were recorded on Varian VRX 500 spectrometer. NMR spectra were recorded in $CDCl_3$ (^{1}H NMR at 500 MHz and ^{13}C NMR at 125 MHz), and chemical shifts are expressed in parts per million (δ) relative to internal Me_4Si.

Tetrahydrofuran was distilled prior to use. All other reagents and solvents were obtained from commercial sources and were used without any further purification. Reactions were routinely carried out under an atmosphere of dry nitrogen with magnetic stirring. Solutions of products in organic solvents were dried with anhydrous magnesium sulfate before concentration under vacuum.

4.2. Synthesis of polysubstituted 2-pyridones

4.2.1. General procedure for the preparation of 5,6-disubstituted-D-enlactams (2). A solution of glutarimide **1** (387 mg, 1 mmol) in dry THF (5 mL) was added to a rapidly stirred suspension of sodium hydride (60 mg, 1.5 mmol,

60%) in tetrahydrofuran (20 mL). The reaction mixture was stirred at room temperature for 15 min, methylmagnesium bromide (1.3 mmol) was added in one portion and further stirred at room temperature for 30 min, then quenched with acetic anhydride (122.4 mg, 1.2 mmol) and the reaction mixture was stirred for an additional 30 min. After the reaction was completed, the reaction mixture was quenched with a saturated ammonium chloride solution (1 mL), filtered through Celite. The organic layer was extracted with ethyl acetate (3×20 mL), dried, filtered, and concentrated. The crude product was purified by silica gel chromatography (*n*-hexane/ethyl acetate=4:1 to 2:1) to afford **2**.

4.2.2. General procedure for the preparation of 3,6-disubstituted pyridin-2-one and 3,5,6-trisubstituted pyridin-2-one (7). A solution of enlactam **2** (1 mmol) in dry THF (5 mL) was added to a rapidly stirred suspension of sodium hydride (1.5 mmol, 60%) in tetrahydrofuran (20 mL). After the reaction mixture was stirred at room temperature for 15 min, alkyl halide (1.1 mmol) was added. The reaction was completed, the reaction mixture was quenched with a saturated ammonium chloride solution (1 mL) and filtered through Celite. The organic layer was extracted with ethyl acetate (3×20 mL), dried, filtered, and concentrated. The crude product was purified by silica gel chromatography (*n*-hexane/ethyl acetate=4:1 to 2:1) to afford **6**. Sodium methoxide (1.1 mmol) was added to a rapidly stirred solution of **6** in THF (20 mL) at room temperature. After the reaction was accomplished (monitored by TLC), the reaction mixture was quenched with water (2 mL) and filtered through Celite. The organic layer was extracted with ethyl acetate (3×20 mL), dried, filtered, and concentrated. The crude product was purified by silica gel chromatography (*n*-hexane/ethyl acetate=4:1 to 2:1) to afford **7**.

4.2.2.1. 1-Benzyl-6-ethyl-3-methylpyridin-2-one (7a). Yield 77%; yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) 7.31–7.20 (m, 6H), 7.11 (d, *J*=8.0 Hz, 2H), 5.99 (d, *J*=7.0 Hz, 1H), 5.39 (br s, 2H), 2.55 (q, *J*=8.0 Hz, 2H), 2.17 (s, 3H), 1.17 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 164.1, 148.5, 137.0, 136.5, 128.7 (2C), 127.1, 126.4, 126.3 (2C), 104.0, 46.6, 25.7, 17.3, 12.5; HRMS (ESI, M^++1) calcd for $C_{15}H_{18}NO$ 228.1388, found 228.1390.

4.2.2.2. 1,3-Dibenzyl-6-ethylpyridin-2-one (7b). Yield 68%; yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.20 (m, 8H), 7.10 (d, *J*=7.0 Hz, 2H), 6.99 (d, *J*=8.0 Hz, 1H), 5.98 (d, *J*=7.0 Hz, 1H), 5.39 (br s, 2H), 3.89 (s, 2H), 2.55 (q, *J*=7.5 Hz, 2H), 1.15 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.5, 149.0, 140.0, 136.9, 136.4, 129.9, 128.4 (2C), 128.7 (2C), 128.4 (2C), 127.1, 126.2 (2C), 126.1, 104.0, 46.7, 36.7, 25.7, 12.4; HRMS (ESI, M^++1) calcd for $C_{21}H_{22}NO$ 304.1701, found 304.1699.

4.2.2.3. 1-Benzyl-3,5,6-trimethylpyridin-2-one (7c). Yield 87%; yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.10 (m, 6H), 5.41 (br s, 2H), 2.18 (s, 2H), 2.17 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.5, 140.5, 139.7, 137.0, 128.7 (2C), 128.5, 127.1, 126.4 (2C), 112.4, 47.7, 18.0, 17.2, 16.4; FAB $C_{15}H_{17}NO$, *m/z* (%)=91 (100.0), 228 (M^++1, 15.3).

4.2.2.4. 1-Benzyl-6-ethyl-3,5-dimethylpyridin-2-one (7d). Yield 89%; yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29–7.22 (m, 5H), 7.10 (s, 1H), 7.09 (d, *J*=6.0 Hz, 2H), 5.41 (br s, 2H), 2.56 (q, *J*=7.5 Hz, 2H), 2.16 (s, 3H), 2.07 (s, 3H), 1.09 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.4, 144.8, 140.8, 137.5, 128.6 (2C), 127.0, 126.2 (2C), 126.1, 112.0, 76.8, 47.1, 23.0, 17.2, 12.6; HRMS (ESI, M^++1) calcd for $C_{16}H_{20}NO$ 242.1545, found 242.1546.

4.2.3. General procedure for the preparation of 5,6-disubstituted pyridin-2-one (8). DDQ (1.2 mmol) was added to a solution of 5,6-disubstituted-D-enlactams **2** (1 mmol) in toluene (20 mL). After the reaction mixture was stirred at refluxing temperature for 10 h, 10% NaOH (1 mL) was added to destroy the remaining DDQ and filtered through Celite. The organic layer was extracted with dichloromethane (3×20 mL), dried, filtered, and concentrated. The crude product was purified by silica gel chromatography (dichloromethane/methanol=100:1) to afford **8**.

4.2.3.1. 1-Benzyl-5,6-dimethyl-3-(4-toluenesulfonyl)-pyridin-2-one (8a). Yield 85%; yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (s, 1H), 8.00 (d, *J*=7.5 Hz, 2H), 7.3 (d, *J*=8.0 Hz, 2H), 7.27–7.23 (m, 3H), 7.02 (d, *J*=7.5 Hz, 2H), 5.32 (br s, 2H), 2.41 (s, 3H), 2.25 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.7, 151.5, 144.5, 144.0, 137.1, 135.3, 129.2 (2C), 128.9 (4C), 127.6, 126.6, 126.4 (2C), 112.5, 47.8, 21.6, 18.2, 17.6; HRMS (ESI, M^++1) calcd for $C_{21}H_{22}NO_3S$ 368.1320, found 368.1318.

4.2.3.2. 1-Benzyl-6-ethyl-5-methyl-3-(4-toluenesulfonyl)pyridin-2-one (8b). Yield 90%; yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (s, 1H), 8.09 (d, *J*=7.5 Hz, 2H), 7.30 (d, *J*=7.5 Hz, 2H), 7.26–7.20 (m, 3H), 6.98 (d, *J*=6.5 Hz, 2H), 5.32 (br s, 2H), 2.61 (q, *J*=8.0 Hz, 2H), 2.41 (s, 3H), 2.19 (s, 3H), 1.089 (t, *J*=8.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.7, 156.4, 145.0, 144.0, 137.0, 135.8, 129.2 (2C), 129.0 (2C), 128.9 (2C), 127.5, 126.8, 126.2 (2C), 112.0, 47.2, 24.0, 21.6, 17.2, 11.8; HRMS (ESI, M^++1) calcd for $C_{22}H_{24}NO_3S$ 382.1477, found 382.1477.

4.2.3.3. 1-Benzyl-5-methyl-6-phenyl-3-(4-toluenesulfonyl)pyridin-2-one (8c). Yield 81%; yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (s, 1H), 8.07 (d, *J*=8.5 Hz, 2H), 7.42–7.07 (m, 8H), 6.85 (d, *J*=7.0 Hz, 2H), 6.63 (d, *J*=7.0 Hz, 2H), 5.01 (br s, 2H), 2.44 (s, 3H), 1.81 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.2, 153.6, 144.7, 144.2, 136.9, 136.2 (2C), 133.0, 129.6, 129.2 (2C), 129.1 (2C), 128.9 (2C), 128.3 (2C), 128.0 (2C), 127.2, 126.9 (2C), 113.4, 49.2, 21.7, 17.9; HRMS (ESI, M^++1) calcd for $C_{26}H_{24}NO_3S$ 430.1477, found 430.1479.

4.2.3.4. 1,5-Dibenzyl-6-methyl-3-(4-toluenesulfonyl)-pyridin-2-one (8d). Yield 88%; yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (s, 1H), 8.01 (d, *J*=9.0 Hz, 2H), 7.32–7.25 (m, 8H), 7.07 (d, *J*=7.5 Hz, 2H), 7.01 (d, *J*=8.0 Hz, 2H), 5.32 (br s, 2H), 3.87 (s, 2H), 2.42 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.7, 152.6, 144.6, 144.1, 138.5, 136.9, 135.1, 129.2 (2C), 129.0 (2C), 128.9 (2C), 18.9 (2C), 127.9 (2C), 127.6, 127.0, 126.8, 126.3 (2C), 115.7, 47.9, 37.8, 21.6, 17.7; HRMS (ESI, M^++1) calcd for $C_{27}H_{26}NO_3S$ 444.1633, found 444.1635.

4.2.4. General procedure for the preparation of 4,5,6-trisubstituted pyridin-2-one (9). Grignard reagent (1.3 mmol) was added to a solution of compound **8** (1 mmol) in dry THF (5 mL) at room temperature. After the reaction was accomplished (monitored by TLC), the reaction mixture was quenched with water (2 mL) and filtered through Celite. The organic layer was extracted with ethyl acetate (3× 20 mL), dried, filtered, and concentrated. The crude product was purified by silica gel chromatography (*n*-hexane/ethyl acetate=4:1 to 2:1) to afford **9**.

4.2.4.1. 1-Benzyl-4,5,6-trimethyl-3-(4-toluenesulfonyl)-3,4-dihydropyridin-2-one (9a). Yield 70%; yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, J=8.5 Hz, 2H), 7.32–7.22 (m, 7H), 5.13 (d, J=16.0 Hz, 1H), 4.49 (d, J=16.0 Hz, 1H), 3.85–3.84 (m, 1H), 2.96 (dd, J=6.5, 14.0 Hz, 1H), 2.43 (s, 3H), 1.73 (s, 3H), 1.60 (s, 3H), 1.05 (d, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.4, 144.9, 137.7, 136.1, 129.4 (2C), 128.8 (2C), 128.7 (2C), 128.3, 127.2, 126.9 (2C), 115.1, 72.9, 45.8, 33.4, 21.7, 17.6, 17.5, 14.5; HRMS (ESI, M^++1) calcd for $C_{22}H_{26}NO_3S$ 384.1633, found 384.1636.

4.2.4.2. 1-Benzyl-6-ethyl-4,5-dimethyl-3-(4-toluenesulfonyl)-3,4-dihydropyridin-2-one (9b). Yield 75%; yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, J=8.5 Hz, 2H), 7.33–7.23 (m, 7H), 5.20 (d, J=15.5 Hz, 1H), 4.53 (d, J=15.5 Hz, 2H), 3.80 (s, 1H), 2.95 (q, J=7.5 Hz, 1H), 2.42 (s, 3H), 2.32–2.24 (m, 1H), 2.18–2.11 (m, 1H), 1.04–0.98 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.8, 144.9, 137.8, 136.4, 133.4, 129.7 (2C), 128.6 (2C), 128.5 (2C), 127.1, 127.0 (2C), 115.4, 72.4, 45.5, 32.9, 21.7, 21.0, 17.5, 17.3, 12.3; HRMS (ESI, M^++1) calcd for $C_{23}H_{28}NO_3S$ 398.1790, found 398.1792.

4.2.4.3. 1-Benzyl-6-ethyl-5-methyl-4-phenyl-3-(4-toluenesulfonyl)-3,4-dihydropyridin-2-one (9c). Yield 70%; yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, J=8.5 Hz, 2H), 7.34–7.18 (m, 10H), 7.01–7.00 (m, 2H), 5.22 (d, J=15.5 Hz, 1H), 4.58 (d, J=15.5 Hz, 1H), 4.21 (s, 1H), 4.09 (s, 1H), 2.48–2.42 (m, 1H), 2.44 (s, 3H), 2.38–2.33 (m, 1H), 1.82 (s, 3H), 1.11 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.3, 145.1, 137.9, 137.4, 136.0, 129.9 (2C), 129.0 (2C), 128.7 (2C), 128.5, 128.4 (2C), 127.6 (2C), 127.5 (2C), 127.3, 126.5, 112.1, 73.1, 45.7, 43.2, 21.7, 21.3, 17.9, 12.5; HRMS (ESI, M^++1) calcd for $C_{28}H_{30}NO_3S$ 460.1946, found 460.1948.

4.2.4.4. 1-Benzyl-6-ethyl-5-methyl-3-(4-toluenesulfonyl)-4-vinyl-3,4-dihydropyridin-2-one (9d). Yield 73%; yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J=8.0 Hz, 2H), 7.34 (d, J=8.0 Hz, 2H), 7.29–7.20 (m, 5H), 5.61–5.55 (m, 1H), 5.22 (d, J=15.5 Hz, 1H), 5.09–5.02 (m, 2H), 4.50 (d, J=15.5 Hz, 1H), 4.95 (s, 1H), 3.54 (d, J=5.5 Hz, 1H), 2.44 (s, 3H), 2.36–2.28 (m, 1H), 2.24–2.14 (m, 1H), 1.83 (s, 3H), 1.03 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.8, 145.0, 137.6, 136.4, 135.3, 133.5, 129.7 (2C), 128.6 (2C), 128.4 (2C), 127.14, 127.05 (2C), 116.9, 111.7, 70.3, 45.5, 41.6, 21.7, 21.1, 17.4, 12.4; HRMS (ESI, M^++1) calcd for $C_{24}H_{28}NO_3S$ 410.1790, found 410.1788.

4.2.4.5. 1-Benzyl-4-ethyl-5-methyl-6-phenyl-3-(4-toluenesulfonyl)-3,4-dihydropyridin-2-one (9e). Yield 30%; yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, J=8.0 Hz, 2H), 7.38–6.92 (m, 12H), 5.05 (d, J=15.0 Hz, 1H), 3.99 (d, J=15.0 Hz, 1H), 3.95 (s, 1H), 2.89 (t, J=7.5 Hz, 1H), 2.47 (s, 3H), 1.66 (s, 3H), 1.59–1.52 (m, 1H), 1.40–1.34 (m, 1H), 0.93 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.8, 145.0, 137.4, 136.6, 134.4, 134.2, 129.8 (3C), 128.6 (3C), 128.2, 128.1 (3C), 128.0 (3C), 127.1, 117.6, 70.7, 47.1, 40.0, 25.0, 21.7, 19.3, 11.4; HRMS (ESI, M^++1) calcd for $C_{28}H_{30}NO_3S$ 460.1946, found 460.1950.

4.2.5. General procedure for the preparation of 4,5,6-trisubstituted pyridin-2-one (10). Sodium amalgam (Na/Hg, 3.0 g) and sodium phosphate (40 mg) were added to a stirred solution of **9** (1 mmol) in methanol (20 mL) and vigorously stirred for 2 h at room temperature. The residue was filtered and washed with methanol (2×10 mL). The combined organic layers were concentrated to obtain the crude product. After the crude product was purified by silica gel chromatography (*n*-hexane/ethyl acetate=4:1 to 2:1), to afford the desulfonation product, which then dissolved in toluene (10 mL), DDQ (2 equiv) was added and stirred at refluxing temperature for 10 h. After the reaction was accomplished (monitored by TLC), the reaction mixture was quenched with water (2 mL) and filtered through Celite. The organic layer was extracted with ethyl acetate (3×20 mL), dried, filtered, and concentrated. The crude product was purified by silica gel chromatography (*n*-hexane/ethyl acetate=4:1 to 2:1) to afford **10**.

4.2.5.1. 1-Benzyl-4-ethyl-5-methyl-6-phenylpyridin-2-one (10e). Yield 70%; yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.30 (m, 3H), 7.16–7.14 (m, 4H), 6.95 (d, J=7.0 Hz, 2H), 6.82–6.80 (m, 2H), 5.08 (br s, 2H), 2.67 (q, J=7.5 Hz, 2H), 1.75 (s, 3H), 1.27 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.4, 143.3, 138.1, 137.7, 134.5, 133.7, 129.3 (2C), 128.7, 128.5 (2C), 128.1 (2C), 126.9 (2C), 126.7, 113.4, 49.1, 23.8, 17.9, 12.7; HRMS (ESI, M^++1) calcd for $C_{21}H_{21}NO$ 304.1701, found 304.1698.

4.2.6. General procedure for the preparation of 3,4,5,6-tetrasubstituted pyridin-2-one (11). A solution of compound **9** (1 mmol) in dry THF (5 mL) was added to a rapidly stirred suspension of sodium hydride (60 mg, 1.2 mmol, 60%) in THF (20 mL). The resulting mixture was stirred at room temperature for 15 min, iodide methane (1.3 mmol) was added. After the reaction was completed (monitored by TLC), the reaction mixture was quenched with water (2 mL) and filtered through Celite. The organic layer was extracted with ethyl acetate (3×20 mL) and dried with anhydrous $MgSO_4$, filtered and concentrated. After the crude alkylated product was purified by silica gel chromatography (*n*-hexane/ethyl acetate=4:1 to 2:1), *t*-BuOH (15 mL) and *t*-BuOK (1.1 mmol) were added to a solution of alkylated product in THF (20 mL) at room temperature and stirred for 10 h. After the reaction was accomplished (monitored by TLC), the reaction mixture was quenched with water (2 mL) and filtered through Celite. The organic layer was extracted with ethyl acetate (3×20 mL), dried, filtered, and concentrated. The crude product was purified by silica gel chromatography (*n*-hexane/ethyl acetate=4:1 to 2:1) to afford **11**.

4.2.6.1. 1-Benzyl-3,4,5,6-tetramethylpyridin-2-one (11a). Yield 95%; yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.19 (m, 3H), 7.11 (d, J=7.0 Hz, 2H), 5.43 (br s, 2H), 2.22 (s, 3H), 2.20 (s, 3H), 2.16 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.8, 146.3, 138.0, 137.2, 128.6 (2C), 126.9, 126.2 (2C), 123.0, 113.2, 48.0, 17.2, 16.6, 15.1, 13.5; HRMS (ESI, M^++1) calcd for $C_{16}H_{20}NO$ 242.1545, found 242.1547.

4.2.6.2. 1-Benzyl-6-ethyl-3,4,5-trimethylpyridin-2-one (11b). Yield 93%; yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29–7.20 (m, 3H), 7.09 (d, J=7.5 Hz, 2H), 5.43 (br s, 2H), 2.61 (q, J=7.5 Hz, 2H), 2.19 (s, 3H), 2.17 (s, 3H), 2.06 (s, 3H), 1.09 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.8, 146.7, 143.2, 137.7, 128.7 (2C), 126.9, 126.1 (2C), 123.5, 112.8, 47.5, 23.2, 17.1, 14.5, 13.5, 12.9; HRMS (ESI, M^++1) calcd for $C_{17}H_{22}NO$ 256.1701, found 256.1699.

4.2.6.3. 1-Benzyl-6-ethyl-5-methyl-4-phenyl-3-propenylpyridin-2-one (11c). Yield 90%; yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47–7.11 (m, 10H), 7.05–6.98 (m, 1H), 5.87 (d, J=14.0 Hz, 1H), 5.50 (br s, 2H), 2.83 (q, J=7.5 Hz, 2H), 1.74 (s, 3H), 1.66 (d, J=1.5 Hz, 3H), 1.15 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.7, 150.9, 144.9, 139.3, 137.4, 131.1, 128.7 (2C), 128.5 (2C), 128.4 (2C), 127.2, 127.1, 126.2 (2C), 126.0, 122.8, 112.1, 47.4, 23.7, 19.9, 15.6, 12.7; HRMS (ESI, M^++1) calcd for $C_{24}H_{26}NO$ 344.2014, found 344.2017.

4.2.6.4. 1,5-Dibenzyl-4-ethyl-3,6-dimethylpyridin-2-one (11d). Yield 92%; yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.02 (m, 10H), 5.45 (br s, 2H), 3.88 (s, 2H), 2.50 (q, J=7.5 Hz, 2H), 2.23 (s, 3H), 2.16 (s, 3H), 1.06 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.4, 151.9, 140.7, 139.8, 137.1, 128.7 (2C), 128.6 (2C), 127.5 (2C), 127.1, 126.3, 126.2 (2C), 123.3, 114.7, 48.1, 33.9, 23.8, 16.8, 13.3, 13.0; HRMS (ESI, M^++1) calcd for $C_{23}H_{26}NO$ 332.2014, found 332.2012.

4.3. Synthesis of isoquinolinone skeleton 14

4.3.1. 3,4-Diallyl-1-benzyl-6-ethyl-5-methyl-3-(4-toluenesulfonyl)-3,4-dihydropyridin-2-one (12). Allylmagnesium bromide (2.0 mL, 1.3 mmol) was added to a solution of compound **8b** (570 mg, 1.5 mmol) in dry THF (15 mL). After the reaction was accomplished (monitored by TLC), the reaction mixture was quenched with water (5 mL) and filtered through Celite. The organic layer was extracted with ethyl acetate (3×20 mL), dried, filtered, and concentrated. Without purification, the residue in dry THF (5 mL) was added to a suspension of sodium hydride (72 mg, 1.2 mmol, 60%) in THF (10 mL) and stirred at room temperature for 15 min. Allyl bromide (270 mg, 1.5 mmol) was added to the solution. After the reaction was completed (monitored by TLC), the reaction mixture was quenched with water (5 mL) and the organic solvent was evaporated under reduced pressure. The residue was extracted with ethyl acetate (3×20 mL) and dried with anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel chromatography (*n*-hexane/ethyl acetate=4:1 to 2:1) to afford single diallyl compound **12** (450 mg, 67%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, J=8.0 Hz, 2H), 7.34–7.23 (m, 7H), 5.82–5.74 (m, 1H), 5.72–5.63 (m, 1H), 5.12 (d, J=15.0 Hz, 1H), 5.06–4.84 (m, 4H), 4.53 (d, J=15.0 Hz, 1H), 2.97–2.93 (m, 1H), 2.80 (dd, J=5.0, 10.0 Hz, 1H), 2.64–2.42 (m, 3H), 2.44 (s, 3H), 2.32–2.15 (m, 2H), 1.76 (s, 3H), 0.90 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 144.6, 137.7, 136.5, 135.8, 134.3, 131.3 (2C), 131.2 (2C), 129.1 (2C), 128.6 (2C), 127.3 (2C), 124.5, 119.6, 116.7, 115.0, 74.9, 45.1, 37.2, 29.7, 21.6 (2C), 20.9, 12.4; HRMS (ESI, M^++1) calcd for $C_{28}H_{34}NO_3S$ 464.2259, found 464.2256.

4.3.2. 2-Benzyl-3-ethyl-4-methylisoquinolin-1-one (14). Diallyl compound **12** (165 mg, 0.36 mmol) in dry dichloromethane (40 mL) was added to first generation Grubbs catalyst $[(C_6H_{11})_3P]_2Cl_2RuC_2H_3Ph$ (29.6 mg, 0.036 mmol, 10 mol %), and the mixture was allowed to react for 12 h at room temperature. After the reaction was completed (monitored by TLC), the mixture was quenched with water (20 mL) and extracted with dichloromethane (2×30 mL) and dried with anhydrous $MgSO_4$, filtered and concentrated. To the solution of the residue in *t*-BuOH (15 mL) was added *t*-BuOK (44 mg, 1.1 mmol) and then heated to reflux for 24 h. The organic solvent was evaporated under reduced pressure and the residue was extracted with water (15 mL) and ethyl acetate (3×20 mL). The combined organic layer was dried with anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel chromatography (*n*-hexane/ethyl acetate=4:1 to 2:1) to afford isoquinolinone derivative **14** (78 mg, 81%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (d, J=10.0 Hz, 1H), 7.71–7.69 (m, 2H), 7.50–7.46 (m, 1H), 7.31–7.21 (m, 3H), 7.14 (d, J=7.5 Hz, 2H), 5.51 (br s, 2H), 2.73 (q, J=7.5 Hz, 2H), 2.34 (s, 3H), 1.18 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.0, 141.0, 137.8, 137.5, 132.3, 128.7 (2C), 128.5, 127.0, 126.0 (2C), 125.9, 124.6, 122.6, 109.1, 47.1, 23.1, 13.5, 13.3; HRMS (ESI, M^++1) calcd for $C_{19}H_{20}NO$ 278.1545, found 278.1547.

4.4. Synthesis of benzo[*c*]phenanthridine nucleus

4.4.1. 3-(2,2-Dimethoxyethylidene)-1-methyl-5-(4-toluenesulfonyl)piperidine-2,6-dione (18). A solution of α-sulfonyl methylacetamide **19** (3.0 g, 13.2 mmol) in dry THF (30 mL) was added to a rapidly stirred suspension of sodium hydride (1.6 g, 39.6 mmol, 60%) in dry THF (20 mL). After the reaction mixture was stirred at room temperature for 30 min, a solution of α,β-unsaturated ester **20** (3.7 g, 15.8 mmol) in dry THF (70 mL) was added. The resulting mixture was stirred for 15 min, quenched with saturated ammonium chloride solution (25 mL) in an ice bath, and concentrated under reduced pressure. The residue was diluted with water (10 mL) and extracted with ethyl acetate (3×50 mL). The combined organic layers were washed with brine (2×40 mL), dried over anhydrous $MgSO_4$, filtered and evaporated. Purification on silica gel (*n*-hexane/ethyl acetate/triethyl amine=4:1:0.01 to 2:1:0.01) produced glutarimide **18** (3.8 g, 78%) as a white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76–7.72 (m, 2H), 7.39–7.37 (m, 2H), 6.99 (dd, J=2.5, 5.5 Hz, 0.8 H), 5.77 (d, J=7.0 Hz, 0.2H), 5.29 (dd, J=1.0, 5.5 Hz, 0.8 H), 4.17 (m, 1H), 3.78–3.74 (m, 1H), 3.48 (s, 0.6H), 3.44 (s, 0.6H), 3.42 (s, 2.4H), 3.35 (s, 2.4H), 3.21 (s, 2.4H), 3.19 (s, 0.6H), 2.99–2.93 (m, 1H), 2.47 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$)

δ 164.5, 164.4 (0.2C), 164.3 (0.8C), 146.0 (0.8C), 145.9 (0.2C), 142.5 (0.2C), 140.1 (0.8C), 134.6 (0.2C), 134.3 (0.8C), 123.0 (1.6C), 129.9 (0.4C), 129.2 (0.4C), 129.1 (1.6C), 127.0 (0.8C), 124.9 (0.2C), 99.1 (0.8C), 98.9 (0.2C), 66.0 (0.2C), 65.8 (0.8C), 54.7 (0.2C), 53.9 (0.2C), 53.0 (0.8C), 52.2 (0.8C), 28.4 (0.2C), 27.8 (0.8C), 27.4 (0.2C), 22.0 (0.8C), 21.8; HRMS (ESI, M^++1) calcd for $C_{17}H_{21}O_6NSNa$ 390.0987, found 390.0985. Mp: 118.6–119.7 °C.

4.4.2. 3-(2,2-Dimethoxyethyl)-1-methyl-5-(4-toluenesulfonyl)piperidine-2,6-dione (21). To a solution of glutarimide **18** (3.2 g, 8.7 mmol) in dry THF (60 mL) was added 2.1 g of Raney nickel 2800 (H_2O). The reaction slurry was stirred at room temperature for 12 h under 40 psi H_2. The reaction mixture was filtered over Celite and the solution was concentrated under reduced pressure. Purification on silica gel (hexane/ethyl acetate/triethyl amine=4:1:0.01 to 2:1:0.01) produced **21** (3.1 g, 95%) as a white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, *J*=8.0 Hz, 0.4H), 7.76 (d, *J*=8.0 Hz, 1.6H), 7.39–7.37 (m, 2H), 4.65 (t, *J*=5.5 Hz, 0.2H), 4.61 (t, *J*=5.5 Hz, 0.8H), 4.20 (dd, *J*=5.5, 13.0 Hz, 0.2H), 4.14 (dd, *J*=3.0, 6.0 Hz, 0.8H), 3.40–3.32 (m, 7H), 3.17 (s, 2.4H), 3.08 (s, 0.6H), 2.91–2.87 (m, 0.8H), 2.78–2.73 (m, 0.2H), 2.47 (s, 2.4H), 2.46 (s, 0.6H), 2.37–2.32 (m, 1H), 2.19–2.13 (m, 1H), 1.80–1.75 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4 (0.8C), 173.0 (0.2C), 165.2 (0.2C), 164.7 (0.8C), 145.7 (0.8C), 145.4 (0.2C), 135.6 (0.2C), 135.1 (0.8C), 129.9 (1.6C), 129.6 (0.4C), 129.5 (0.4C), 129.0 (1.6C), 103.0 (0.8C), 102.5 (0.2C), 65.8 (0.8C), 65.6 (0.2C), 53.9, 53.5 (0.8C), 53.2 (0.2C), 37.1 (0.2C), 34.9 (0.8C), 34.0 (0.8C), 33.4 (0.2C), 27.5 (0.8C), 27.5 (0.2C), 24.0 (0.8C), 23.7 (0.2C), 21.7 (0.8C), 21.7 (0.2C). Anal. Calcd for $C_{17}H_{23}NO_6S$: C, 55.27; H, 6.28; N, 3.79. Found: C, 55.11; H, 6.43; N, 3.58.

4.4.3. 6-(Benzo[1,3]dioxol-5-yl)-5-(2,2-dimethoxyethyl)-1-methyl-3-(4-toluenesulfonyl)-3,4-dihydro-1*H*-pyridin-2-one (17). A solution of glutarimide **21** (890 mg, 2.4 mmol) in dry THF (40 mL) was added to a rapidly stirred suspension of sodium hydride (140 mg, 3.6 mmol, 60%) in THF (10 mL). After the reaction mixture was stirred at room temperature for 15 min, the Grignard reagent, which was prepared by 4-bromo-1,2-(methylenedioxy)benzene (1.5 mL, 12.0 mmol) with magnesium (410 mg, 16.8 mmol) in dry THF (30 mL) at reflux temperature for 1 h, was added at room temperature in one portion by syringe. The resulting mixture was stirred at room temperature for 60 min. After the reaction was accomplished (monitored by TLC), acetic anhydride (2.3 mL, 24.1 mmol) was added at room temperature for 30 min. After the reaction was accomplished (monitored by TLC), the reaction mixture was quenched with water (3 mL) and filtered through Celite. The organic layer was extracted with ethyl acetate (3×30 mL) and dried with anhydrous $MgSO_4$, filtered, and concentrated. The residue was diluted with methanol (20 mL), and was added triethyl amine (0.5 mL). After the reaction mixture was stirred at room temperature for 36 h, then concentrated under reduced pressure. The residue was diluted with water (10 mL) and extracted with ethyl acetate (3×30 mL). The combined organic layers were washed with brine (2×40 mL), dried over anhydrous $MgSO_4$, filtered and evaporated. The crude product was purified by silica gel chromatography (*n*-hexane/ethyl acetate/triethyl amine=6:1:0.01 to 4:1:0.01) to afford **17** (733 mg, 65%) as a pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J*=8.0 Hz, 2H), 7.34 (d, *J*=8.0 Hz, 1H), 6.84–6.77 (m, 1H), 6.70–6.66 (m, 1H), 6.58–6.55 (m, 1H), 5.98 (dd, *J*=1.5, 3.0 Hz, 2H), 4.40 (t, *J*=5.5 Hz, 1H), 4.00 (dd, *J*=4.0, 7.0 Hz, 1H), 3.30 (s, 3H), 3.26 (s, 3H), 3.15 (dd, *J*=3.5, 17.5 Hz, 1H), 2.95 (dd, *J*=7.0, 17.5 Hz, 1H), 2.75 (s, 3H), 2.44 (s, 3H), 2.37–2.25 (m, 2H); HRMS (ESI, M^++1) calcd for $C_{24}H_{28}NO_7S$ 474.1578, found 474.1585.

4.4.4. 1-Methyl-8,9-methylenedioxy-3-(4-toluenesulfonyl)-3,4-dihydro-1*H*-benzo[*h*]quinoline-2-one (22). To a solution of lactam **17** (1.8 g, 3.3 mmol) and anhydrous $MgSO_4$ (2.0 g) in dichloromethane was added boron trifluoride diethyl ether complex (0.75 mL, 8.1 mmol) at −30 °C. The mixture was stirred for 20 h at that temperature. The reaction mixture was filtered and was added saturated sodium bicarbonate solution to neutralize. The mixture was extracted with dichloromethane (3×50 mL). The combined organic layers were washed with brine (2×40 mL), dried over anhydrous $MgSO_4$, filtered and evaporated. The crude product was purified by silica gel chromatography (*n*-hexane/ethyl acetate=4:1 to 2:1) to afford **22** (1.5 g, 93%) as a white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, *J*=8.0 Hz, 2H), 7.42 (d, *J*=8.5 Hz, 1H), 7.18 (d, *J*=8.5 Hz, 1H), 7.06 (s, 1H), 6.97 (d, *J*=8.0 Hz, 2H), 6.75 (s, 1H), 6.05 (d, *J*=6.0 Hz, 2H), 4.28 (t, *J*=5.5 Hz, 1H), 3.55–3.54 (m, 2H), 3.44 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.3, 147.4, 147.2, 144.5, 136.6, 135.4, 131.9, 129.0 (2C), 128.7 (2C), 124.8, 124.0, 121.8, 121.1, 104.5, 101.4, 99.9, 67.0, 38.4, 28.0, 21.3; HRMS (ESI, M^++1) calcd for $C_{22}H_{20}NO_5S$ 410.1062, found 410.1059. Anal. Calcd for $C_{22}H_{19}NO_5S$: C, 64.53; H, 4.68; N, 3.42. Found C, 64.23; H, 4.39; N, 3.45. Mp: 209.4–211.3 °C.

4.4.5. 1-Methyl-8,9-methylenedioxy-3-(4-toluenesulfonyl)-1*H*-benzo[*h*]quinoline-2-one (16). To a solution of **22** (610 mg, 1.5 mmol) in toluene (35 mL) was added DDQ (1.0 g, 4.5 mmol). The resulting mixture was refluxed for 1 day. After removal of the precipitates by filtration, a large amount of 5% NaOH was added to the filtrate and the mixture was extracted with dichloromethane (3×30 mL). The combined organic layers were washed with 5% NaOH, dried over anhydrous $MgSO_4$, filtered and evaporated. Purification on silica gel (dichloromethane/methanol=200:1 to 100:1) produced **16** (500 mg, 83%) as a white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.78 (s, 1H), 8.06 (d, *J*=8.5 Hz, 2H), 7.70 (s, 1H), 7.53 (d, *J*=8.5 Hz, 1H), 7.50 (d, *J*=8.5 Hz, 1H), 7.33 (d, *J*=8.5 Hz, 2H), 7.21 (s, 1H), 3.95 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3, 149.6, 147.5, 144.5, 142.9, 142.3, 136.6, 135.3, 129.4 (2C), 129.3 (2C), 129.2, 125.1, 124.2, 119.2, 116.1, 105.5, 103.2, 102.1, 40.5, 21.7; HRMS (ESI, M^++1) calcd for $C_{22}H_{18}NO_5S$ 408.0906, found 408.0903. Anal. Calcd for $C_{22}H_{17}NO_5S$: C, 64.85; H, 4.21; N, 3.44. Found C, 64.84; H, 4.10; N, 3.51. Mp: 329.5–331.8 °C.

4.4.6. 4-Allyl-1-methyl-8,9-methylenedioxy-3-(4-toluenesulfonyl)-3,4-dihydro-1*H*-benzo[*h*]quinoline-2-one (23). To a solution of **16** (100 mg, 0.25 mmol) in dry THF (10 mL) was added allylmagnesium bromide (1.0 mmol) in one portion by syringe. The resulting mixture was stirred

at room temperature for 1.5 h. After the reaction was accomplished (monitored by TLC), the reaction mixture was quenched with water (2 mL) and filtered through Celite. The organic layer was extracted with ethyl acetate (3× 20 mL) and dried with anhydrous $MgSO_4$, filtered, and concentrated. The crude product was purified by silica gel chromatography (*n*-hexane/ethyl acetate=4:1 to 2:1) to afford **23** (108 mg, 98%), which was crystallized from *n*-hexane/ethyl acetate as a colorless solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, J=8.5 Hz, 1H), 7.24 (d, J=8.5 Hz, 2H), 7.13 (d, J= 8.5 Hz, 1H), 7.04 (s, 1H), 6.77 (d, J=8.5 Hz, 2H), 6.63 (s, 1H), 6.05–6.04 (m, 2H), 5.77–5.69 (m, 1H), 5.15 (d, J= 10.5 Hz, 1H), 5.07 (d, J=17.0 Hz, 1H), 4.30 (s, 1H), 3.67 (t, J=7.0 Hz, 1H), 3.41 (s, 3H), 2.45–2.40 (m, 1H), 2.28–2.22 (m, 1H), 2.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.3, 147.2, 147.1, 144.3, 136.1, 134.8, 133.0, 131.9, 128.8 (2C), 128.2 (2C), 124.9, 124.4, 123.9, 121.8, 119.4, 104.4, 101.4, 100.2, 72.1, 39.2, 39.1, 38.8, 21.1; HRMS (ESI, M^++1) calcd for $C_{25}H_{24}NO_5S$ 450.1375, found 450.1373. Anal. Calcd for $C_{25}H_{23}NO_5S$: C, 66.80; H, 5.16; N, 3.12. Found C, 66.88; H, 5.24; N, 3.20. Mp: 227.1–228.7 °C.

4.4.7. 3,4-Diallyl-1-methyl-8,9-methylenedioxy-3-(4-toluenesulfonyl)-3,4-dihydro-1*H*-benzo[*h*]quinoline-2-one (24). A solution of **23** (108 mg, 0.24 mmol) in dry THF (10 mL) was added to a rapidly stirred suspension of sodium hydride (13 mg, 0.31 mmol, 60%) in dry THF (2 mL). After the reaction mixture was stirred at room temperature for 30 min, the allyl bromide (0.04 mL, 0.48 mmol) was added. The resulting mixture was stirred for 30 h, quenched with water (3 mL), and concentrated under reduced pressure. The residue was diluted with water (3 mL) and extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine (2×30 mL), dried over anhydrous $MgSO_4$, filtered and evaporated. Purification on silica gel (*n*-hexane/ethyl acetate=4:1 to 2:1) produced **24** (111 mg, 94%) as a white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (d, J=8.0 Hz, 1.2H), 7.45–7.35 (m, 2.8H), 7.12–7.01 (m, 3H), 6.71 (d, J=7.5 Hz, 0.6H), 6.64 (s, 0.4H), 6.07–6.03 (m, 2H), 5.98–5.90 (m, 0.4H), 5.78–5.67 (m, 1H), 5.39 (d, J=17.0 Hz, 0.4H), 5.32–5.26 (m, 1.4H), 5.17 (d, J=10.0 Hz, 0.4H), 4.95 (d, J=10.0 Hz, 0.6H), 4.87 (d, J= 17.0 Hz, 0.6H), 4.73 (d, J=10.0 Hz, 0.6H), 4.10 (d, J=17.0 Hz, 0.6H), 3.73–3.70 (m, 0.4H), 3.61–3.58 (m, 0.6H), 3.49–3.44 (m, 3.4H), 3.24–3.14 (m, 1H), 3.04–2.96 (m, 0.8H), 2.74–2.68 (m, 0.6H), 2.44 (s, 1.8H), 2.29 (dd, J=7.5, 16.0 Hz, 0.6H), 2.16 (dd, J=7.5, 16.0 Hz, 0.6H), 2.06 (s, 1.2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6 (0.6C), 167.2 (0.4C), 147.8 (0.6C), 147.4 (0.6C), 147.1 (0.4C), 146.9 (0.4C), 144.9 (0.6C), 143.6 (0.4C), 137.4 (0.4C), 136.0 (1.2C), 135.3 (0.8C), 134.5 (0.6C), 131.8 (0.4C), 131.7 (0.4C), 131.6 (0.6C), 131.3 (1.2C), 130.3 (0.6C), 129.3 (1.2C), 128.5 (0.8C), 128.3 (0.8C), 125.7 (0.6C), 124.9 (0.4C), 124.7, 124.4 (0.6C), 122.3 (0.4C), 121.7 (0.6C), 121.1 (0.4C), 121.1 (0.4C), 119.9 (0.6C), 117.6 (0.6C), 116.5 (0.4C), 104.8 (0.6C), 104.2 (0.4C), 101.4 (0.6C), 101.3 (0.4C), 100.3 (0.4C), 99.8 (0.6C), 75.0 (0.6C), 74.7 (0.4C), 44.6 (0.6C), 39.7 (0.4C), 39.3 (0.4C), 38.5 (0.6C), 36.5 (0.6C), 36.1 (0.6C), 34.0 (0.4C), 29.5 (0.4C), 21.6 (0.6C), 21.1 (0.4C); HRMS (ESI, M^++1) calcd for $C_{28}H_{28}NO_5S$ 490.1688, found 490.1690. Anal. Calcd for $C_{28}H_{27}NO_5S$: C, 68.69; H, 5.56; N, 2.86. Found C, 68.50; H, 5.40; N, 2.93. Mp: 213.5–214.6 °C.

4.4.8. 5-Methyl-2,3-methylenedioxy-6a-(4-toluenesulfonyl)-6a,7,10,10a-tetrahydrobenzo[*c*]phenanthridin-6(5*H*)-one (25). First generation Grubbs catalyst (22 mg, 0.02 mmol) was added to a solution of **24** (100 mg, 0.2 mmol) in dichloromethane (10 mL) at room temperature for 7.5 h. The mixture was concentrated and purified by flash column chromatography (*n*-hexane/ethyl acetate= 4:1 to 2:1) to yield **25** (91 mg, 96%), which was crystallized from *n*-hexane/ethyl acetate as colorless crystals; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, J=8.5 Hz, 1H), 7.29 (d, J=8.5 Hz, 1H), 7.12 (d, J=8.0 Hz, 2H), 7.07 (s, 1H), 6.78 (d, J=8.0 Hz, 2H), 6.62 (s, 1H), 6.05 (dd, J=1.0, 3.5 Hz, 2H), 6.02–5.97 (m, 1H), 5.86–5.82 (m, 1H), 3.66 (dd, J=6.5, 11.5 Hz, 1H), 3.48–3.43 (m, 1H), 3.41 (s, 3H), 3.31–3.23 (m, 1H), 2.82–2.72 (m, 2H), 2.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 144.6, 144.6, 141.3, 134.05, 133.8, 129.3, 126.0 (2C), 126.0 (2C), 123.1, 122.27, 122.25, 120.5, 118.8, 117.9, 101.8, 98.7, 97.8, 66.7, 36.4, 35.3, 28.3, 23.6, 18.6; HRMS (ESI, M^++1) calcd for $C_{26}H_{23}NO_5S$ 462.1375, found 462.1377. Anal. Calcd for $C_{26}H_{22}NO_5S$: C, 67.66; H, 5.02; N, 3.03. Found C, 66.25; H, 4.63; N, 2.88. Mp: 203.2–205.1 °C.

4.4.9. 7,10-Dihydro-5-methyl-2,3-methylenedioxybenzo[*c*]phenanthridin-6(5*H*)-one (26). To a solution of **25** (70 mg, 0.15 mmol) in dry THF (10 mL) was added DBU (0.05 mL, 0.3 mmol). The resulting mixture was heated to 60 °C for 20 h. After the reaction was accomplished (monitored by TLC), the resulting mixture was concentrated under reduced pressure. The residue was diluted with water (10 mL) and extracted with dichloromethane (3×30 mL). The combined organic layers were washed with brine (2×40 mL), dried over anhydrous $MgSO_4$, filtered and evaporated. Purification on silica gel (*n*-hexane/ethyl acetate=2:1 to 1:1) to yield **26** (45 mg, 93%) as a white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.52 (d, J=8.5 Hz, 1H), 7.49 (d, J=8.5 Hz, 1H), 7.18 (s, 1H), 6.11 (s, 2H), 6.05–6.00 (m, 1H), 6.94–6.90 (m, 1H), 3.98 (s, 3H), 3.58–3.54 (m, 2H), 3.34–3.30 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.3, 147.7, 146.8, 139.3, 137.5, 132.2, 124.5, 124.1, 122.8, 121.8, 119.9, 119.2, 117.8, 104.8, 102.8, 101.5, 40.5, 27.0, 25.5; HRMS (ESI, M^++1) calcd for $C_{19}H_{16}NO_3$ 306.1130, found 306.1129. Anal. Calcd for $C_{19}H_{15}NO_3$: C, 74.74; H, 4.95; N, 4.59. Found C, 74.29; H, 5.24; N, 4.46. Mp: 232.6–233.9 °C.

4.4.10. 5-Methyl-2,3-methylenedioxybenzo[*c*]phenanthridin-6(5*H*)-one (27). To a solution of **26** (36 mg, 0.1 mmol) in dry THF (10 mL) was added DDQ (79 mg, 0.35 mmol), and the resulting mixture was refluxed for 2 h. The mixture was concentrated and purified by column chromatography (dichloromethane/methanol=1:0 to 100:1)) to yield **27** (38 mg, 99%) as a pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (dd, J=1.0, 8.0 Hz, 1H), 8.27 (d, J=8.0 Hz, 1H), 8.12 (d, J=8.5 Hz, 1H), 7.79–7.76 (m, 1H), 7.64 (s, 1H), 7.60–7.57 (m, 2H), 7.19 (s, 1H), 6.11 (s, 2H), 3.99 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.8, 147.7, 147.1, 136.5, 134.0, 132.6, 132.4, 128.5, 127.7, 125.1, 123.4, 121.9, 121.0, 118.6, 116.9, 104.8, 102.7, 101.6, 41.2; HRMS (ESI, M^++1) calcd for $C_{19}H_{13}NO_3$ 304.0974, found 304.0975.

4.5. Total synthesis of oxyisoterihanine 15b

4.5.1. 5-Benzyl-8,9-epoxy-8,9-dihydroxy-2,3-methylenedioxy-6a-(4-toluenesulfonyl)-6a,7,8,9,10,10a-hexahydrobenzo[*c*]phenanthridin-6(5*H*)-one (28). To a solution of **25** (30 mg, 0.065 mmol) in dichloromethane (2.0 mL) was added *m*-CPBA (28 mg, 0.16 mmol) at room temperature for 2 days. After the reaction was accomplished (monitored by TLC), quenched with saturated sodium bicarbonate aqueous solution, and extracted with dichloromethane (3×20 mL). The combined organic layers were washed with brine (2×40 mL), dried over anhydrous $MgSO_4$, filtered and evaporated. Purification on silica gel (*n*-hexane/ethyl acetate=4:1 to 2:1) produced **28** (29 mg, 94%) as a white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, J=8.5 Hz, 1H), 7.25 (d, J=8.5 Hz, 1H), 7.18 (d, J=8.0 Hz, 2H), 7.03 (s, 1H), 6.80 (d, J=8.0 Hz, 2H), 6.72 (s, 1H), 6.06 (d, J=9.5 Hz, 2H), 3.64–3.53 (m, 3H), 3.49–3.45 (m, 1H), 3.39 (s, 3H), 2.98–2.86 (m, 2H), 2.54 (d, J=17.5 Hz, 1H), 2.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.0, 147.2, 147.2, 144.0, 136.2, 135.4, 131.8, 128.8 (2C), 128.5 (2C), 124.9, 124.1, 121.2, 120.2, 104.3, 101.4, 100.3, 67.2, 53.3, 50.5, 39.3, 34.0, 29.6, 25.2, 21.2; HRMS (ESI, M^++1) calcd for $C_{26}H_{24}NO_6S$ 478.1324, found 478.1321. Mp: 202.6 °C (dec).

4.5.2. 9-Hydroxy-8-methoxy-5-methyl-2,3-methylenedioxy-6a-(4-toluenesulfonyl)-6a,7,8,9,10,10a-hexahydrobenzo[*c*]phenanthridin-6(5*H*)-one (29). To a solution of **28** (109 mg, 0.23 mmol) in methanol (9 mL) and dichloromethane (3 mL) was added boron trifluoride diethyl ether complex (0.09 mL, 0.68 mmol) in an ice bath for 1 h and allowed to warm to room temperature for 35 h. After the reaction was accomplished (monitored by TLC), quenched with saturated sodium bicarbonate aqueous solution, and extracted with dichloromethane (3×30 mL). The combined organic layers were washed with brine (2×40 mL), dried over anhydrous $MgSO_4$, filtered and evaporated. Purification on silica gel (dichloromethane/methanol=40:1) produced **29** (98 mg, 85%), which was crystallized from *n*-hexane/ethyl acetate as colorless crystals; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, J=8.0 Hz, 1H), 7.29 (d, J=8.0 Hz, 1H), 7.07 (s, 1H), 6.81 (d, J=7.5 Hz, 2H), 6.55 (d, J=7.5 Hz, 2H), 6.25 (s, 1H), 6.02 (dd, J=1.0, 4.5 Hz, 2H), 4.34–4.32 (m, 1H), 3.80 (dd, J=4.0, 13.0 Hz, 1H), 3.57–3.55 (m, 1H), 3.54 (s, 3H), 3.37 (dd, J=3.5, 16.0 Hz, 1H), 3.34 (s, 3H), 3.21 (dt, J=3.5, 13.5 Hz, 1H), 2.39 (dd, J=3.5, 16.0 Hz, 1H), 2.21 (td, J=3.5, 13.5 Hz, 1H), 2.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 147.0, 146.9, 143.5, 138.6, 136.6, 131.7, 128.4 (2C), 127.9 (2C), 125.0, 124.9, 121.7, 120.3, 104.4, 101.2, 100.1, 78.0, 70.2, 67.8, 57.3, 38.8, 35.0, 27.7, 26.8, 21.0; HRMS (ESI, M^++1) calcd for $C_{27}H_{28}NO_7S$ 510.1586, found 510.1587. Anal. Calcd for $C_{27}H_{27}NO_7S$: C, 63.64; H, 5.34; N, 2.75. Found C, 63.34; H, 5.21; N, 2.75. Mp: 188.6 °C (dec).

4.5.3. 9-Hydroxy-8-methoxy-5-methyl-2,3-methylenedioxybenzo[*c*]phenanthridin-6(5*H*)-one (15b). To a solution of oxalyl chloride (0.02 mL, 0.16 mmol) in dichloromethane (2 mL) was added dimethyl sulfoxide (0.02 mL, 0.27 mmol) at −78 °C for 10 min. Then to added the solution, which have **29** (26.3 mg, 0.05 mmol) in dichloromethane (2 mL) for 1 h, and then to added triethyl amine (0.5 mL) for 30 min. After the reaction was accomplished and allowed to warm to room temperature, then quenched with water (3 mL), and concentrated under reduced pressure. The residue was diluted with water (3 mL) and extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine (2×30 mL), dried over anhydrous $MgSO_4$, filtered and evaporated. The residue was dissolved in THF (5 mL) and added DBU (0.02 mL, 0.13 mmol). The resulting mixture was refluxed for 1 h. After the reaction was accomplished (monitored by TLC), the resulting mixture was concentrated under reduced pressure. The residue was diluted with water (5 mL) and extracted with dichloromethane (5×30 mL). The combined organic layers were washed with brine (2×40 mL), dried over anhydrous $MgSO_4$, filtered and evaporated. Purification on silica gel (dichloromethane/methanol=100:1) to yield **15b** (11.7 mg, 65%) as a white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, J=8.4 Hz, 1H), 7.94 (s, 1H), 7.74 (s, 1H), 7.64 (s, 1H), 7.56 (d, J=8.4 Hz, 1H), 7.19 (s, 1H), 6.18 (s, 1H), 6.10 (s, 2H), 4.08 (s, 3H), 3.98 (s, 3H); HRMS (FAB, M^++1) $C_{20}H_{16}NO_5$ 350.1028, found 350.1037. Mp: 299.8–302.0 °C.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.06.101.

References and notes

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