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Total Synthesis of Calothrixin A and B via C−H Activation

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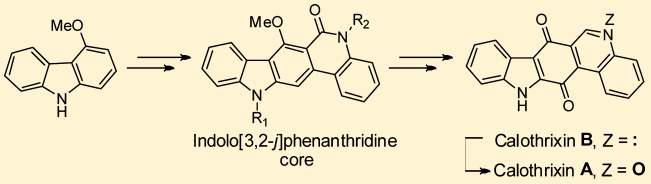
Supporting Information

ABSTRACT: Bioactive indolo[3,2-*j*]phenanthridine alkaloids Calothrixin A and B have been synthesized by exploiting Pd-catalyzed cross-coupling reaction via C−H activation as a key step starting from 4-methoxycarbazole.



The novel indolo[3,2-*j*]phenanthridine alkaloids, Calothrixin A (**1**) and B (**2**) (Figure 1) were originally isolated

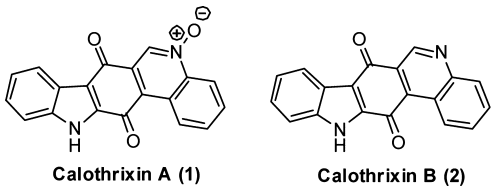
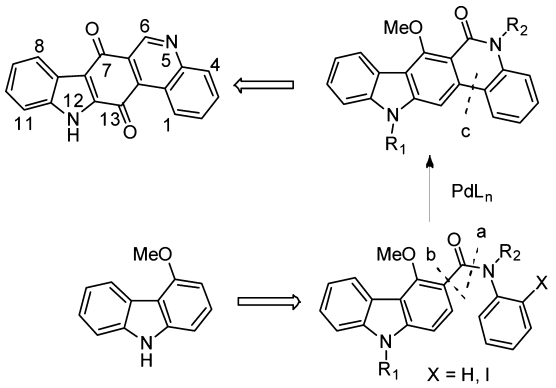


Figure 1. Calothrixin A (**1**) and B (**2**).

from *Calothrix* cyanobacteria and extensively studied by Rickards's group in 1999.[1] These unique pentacyclic alkaloids show potent antimalarial activity, inhibition of RNA polymerase, as well as DNA topoisomerase I poisoning activity and antiproliferative properties against human HeLa cancer cells.[2] Owing to their novel structural scaffolds and potential biological activities, calothrixins are remarkable synthetic targets for total synthesis.[4] In 2000, the first total synthesis of calothrixins was reported by Kelly,[3] employing *ortho*-lithiation strategies, and several synthetic methods[4] have been reported later including two biosynthetic routes.[5] In this context, we outlined a route to the synthesis of **1** and **2**, in which the quinoline ring would be constructed from an appropriately substituted carbazole in the last synthetic steps by Pd-catalyzed intramolecular cross-coupling reaction via C−H activation. In this manner, a C−C bond is formed by activating the C_2 position of the carbazole skeleton (C_{13a}−C_{13b}bond formed) to make the indolo[3,2-*j*]phenanthridine core system, which could be considered as a prominent step (scheme 1).

Transition-metal-catalyzed cross-coupling reactions[6] are the powerful tools for C−C bond formation in organic synthesis for building molecular architectures and abound in the spectacular synthesis of various naturally occurring alkaloids.[7] Among alkaloid total syntheses, methods utilizing Pd-catalyzed cross-coupling reactions offer fascinate routes,[8] and the combination of palladium with other metals such as Cu and Ag proved to be an alternative strategy to facilitate C−H activation of substrates.[9]

Scheme 1. Retrosynthetic Analysis to Calothrixin B (2)



The retrosynthetic analysis of **2** shown in Scheme 1. We envisaged that amides **6** (C_6−C_5, bond a) and **16** (C_{6a}−C_6, bond b) could be synthesized from 4-methoxycarbazole **3** in two different methods. By Pd-catalyzed reaction **7**, **8**, and **16** were converted into indolophenanthridinones **9**, **13**, and **17** through intramolecular C−H/C-I and C−H/C-H (C_{13a}-C_{13b}, bond c) cross coupling via C−H activation. Subsequently, compounds **9**, **13**, and **17** would be easily transformed into calothrixin B **2** through phenols **11** and **15**.

Our investigation began with the synthesis of precursors **7** and **8**, a model precursor bearing the required benzene moiety connected to the third position of carbazole as functionalized amide group. This compound was easily accessible from **3** as depicted in Scheme 2. Vilsmeier−Haack formylation of **3** with NMF/$POCl_3$ in 1,2-dichlorobenzene at 70 °C for 3 h yielded only 3-formylated product **4**. Oxidation of **4** with 30% H_2O_2, $NaClO_2$, and KH_2PO_4 in THF/H_2O (2:1) readily gave 4-methoxycarbazole-3-carboxylic acid **5**. Acid **5** was transformed into amide **6** upon treatment with $SOCl_2$ in dry $CHCl_3$ at reflux condition, followed by the addition of 2 equiv of K_2CO_3, 2-iodoaniline in dry THF. Amide **6** was subsequently converted into bis-*N*-protected compound **7** and amide *N*-protected

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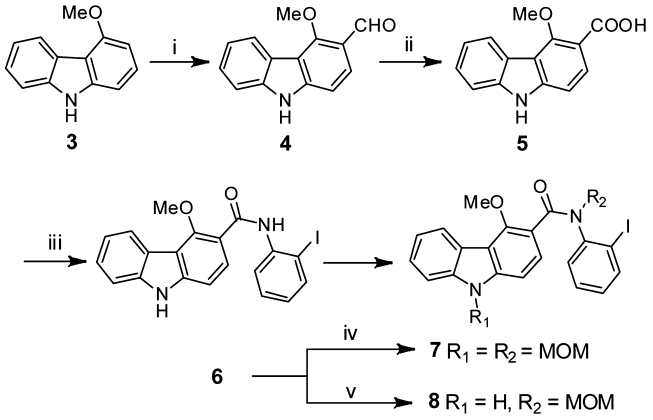
Scheme 2. Synthesis of Precursors 7 and 8[a]

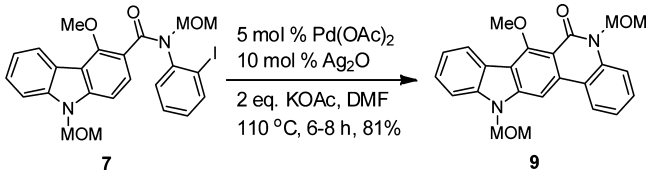


[a]Reagents and conditions: (i) *N*-methylformanilide, $POCl_3$, *o*-DCB, 70 °C, 3 h, 82%; (ii) 30% H_2O_2, $NaClO_2$, KH_2PO_4, THF/H_2O (2:1), rt, 8 h, 97%; (iii) (a) $SOCl_2$, $CHCl_3$, reflux, 6 h, 95%; (b) 2-iodoaniline, 2 equiv K_2CO_3, dry THF, rt, overnight, 96%; (iv) NaH, MOMCl, dry THF, N_2, 50 °C, 20 h, 92%. (v) P_2O_5, dimethoxymethane, dry $CHCl_3$, rt, 8 h, 89%.

compound **8** by treatment with NaH, MOMCl in dry THF at 50 °C for 20 h and P_2O_5, dimethoxymethane in dry $CHCl_3$ at room temperature for 8 h, respectively.

Our ultimate goal is to carry out Pd-catalyzed cross-coupling of bis-*N*-protected compound **7** to construct the indolo[3,2-*j*]pheanthridine skeleton (Scheme 3) and subsequent conversion to calothrixin B **2**. This was achieved, when the reaction of **7** in conjunction with 2 equiv of KOAc, 5 mol % $Pd(OAc)_2$, 10 mol % Ag_2O in DMF at 110 °C for 6 h afforded **9** with good yield of 81%. Catalyst evaluation revealed that the presence of Ag_2O was important and proved to be a good promoter of cross-coupling reaction between aryl iodide and sp^2-carbon (2-position) of the carbazole skeleton.

Scheme 3. Key Pd-Catalyzed Cross-Coupling Reaction

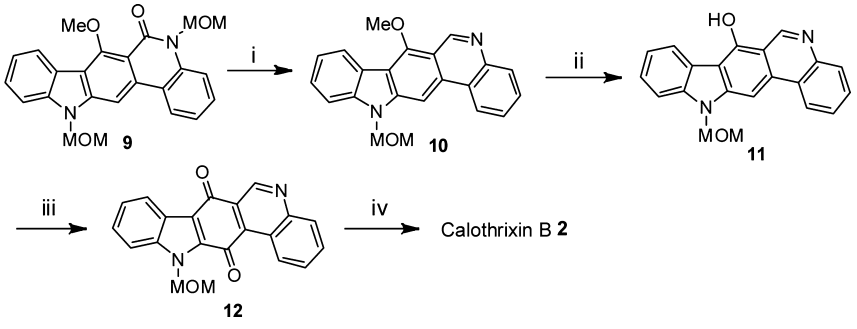


With pentacycle **9** in hand, the subsequent conversion into **12** was achieved in a three-step sequence (Scheme 4). Reduction of indolo[3,2-*j*]phenanthridinone **9** with excess of $LiAlH_4$ in dry Et_2O readily gave **10**. Demethylation of **10** with iodotrimethylsilane[10] and catalytic amount of pyridine in sulfolane at 70 °C for 20 h provided indolo[3,2-*j*]-phenanthridinol **11**. *N*-MOM calothrixin **12**, a known intermediate precursor of calothrixin B was prepared by oxidation with molecular oxygen under basic condition.[11] Removal of MOM group in the next step afforded **2** with almost quantitative yield. Thus, we completed the synthesis of calothrixin B with good overall yield of 30% over 10 steps.

To our knowledge, methods previously reported for the synthesis of calothrixin B have shown that the indole nitrogen atom was always initially protected and cleaved in the final step. So we attempted a route to avoid the protection of the free indole nitrogen of calothrixin B, which was attained from the precursor **8** (scheme 5). The precursor **8** was subjected to our Pd-catalyzed cross-coupling condition gave **13**, which was then treated with LAH followed by cleavage of methyl group with TMSI to provide **15**. Phenol **15**, another known intermediate precursor of calothrixin B, was converted into **2** by oxidation with $FeCl_3$.[12] Finally, we achieved the synthesis of calothrixin B without any substitution at indole nitrogen in a total of 9 steps, in 27% overall yield from 4-methoxycarbazole. In addition, selective oxidation of the pyridine nitrogen[13] of the synthetic **2** with PhCN and TBHP/NaOH in acetone afforded calothrixin A **1**.

Though we have synthesized calothrixins by utilizing simple methods with good yields, the methods comprise a greater number of steps. Next, we attempted to reduce the number of steps so that the overall yield will increase considerably and become more concise. A short synthetic route to calothrixins is outlined in Scheme 6. The precursor **16** was synthesized in one pot by Friedel–Crafts acylation of **3** with oxalyl chloride in the presence of $AlCl_3$ in dry DCM followed by amidation with aniline. Then we conducted the Pd-catalyzed intramolecular oxidative coupling of **16**. When amide **16** was heated at 120 °C for 24 h in the presence of 5 mol % $Pd(TFA)_2$ under an oxygen atmosphere in melted benzoic acid, indolophenanthridinone **17** was obtained in 83%. After that **17** was subjected to chemoselective reduction[14] with Tf_2O/Et_3SiH to provide **14**. Indolophenanthridine **14** was then easily transformed into **2** in a couple of steps that were shown in Scheme 5. Finally, we accomplished the synthesis of **2** in a total of 5 steps over 35% overall yield.

Scheme 4. Preparation of *N*-MOM Calothrixin B 12[a]



[a]Reagents and conditions: (i) $LiAlH_4$, dry Et_2O, rt, 3 h then 6 N HCl, 87%; (ii) TMSI, pyridine, sulfolane, 70 °C, 20 h then dry MeOH, 76%; (iii) NaOH, O_2, acetone, rt, 20 h, 88%; (iv) conc HCl, THF, 60 °C, 20 h, 98%.

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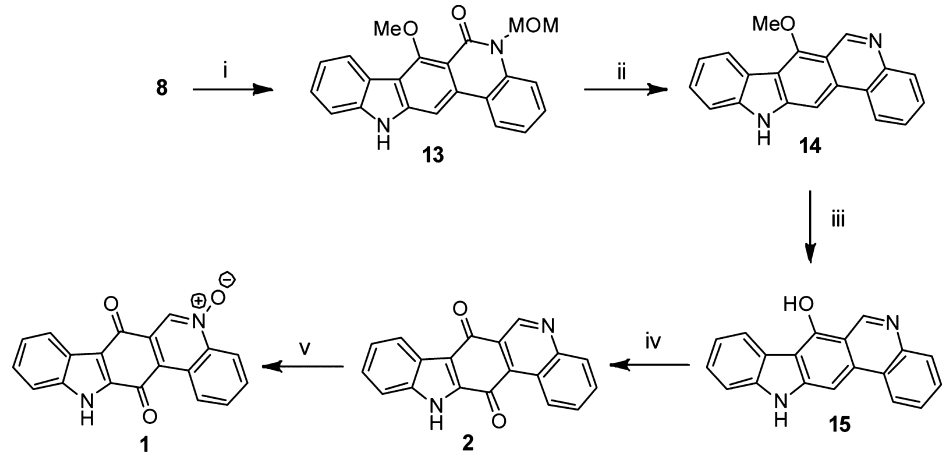
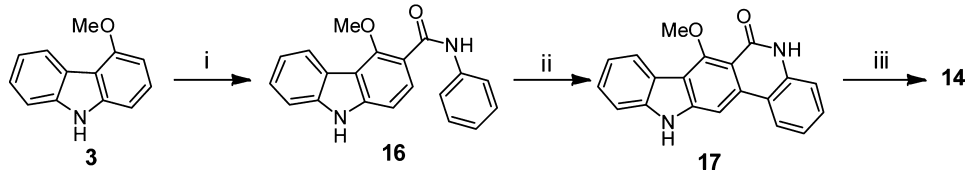
Scheme 5. Synthesis of Calothrixin B (2) and A (1)[a]



[a]Reagents and conditions: (i) 3 equiv KOAc, 5 mol % $Pd(OAc)_2$, 10 mol % Ag_2O, DMF, 110 °C, 8 h, 74%; (ii) $LiAlH_4$, dry Et_2O, rt, 3 h then 6 N HCl, 92−96%; (iii) TMSI, pyridine, sulfolane, 70 °C, 20 h then dry MeOH, 81−86%; (iv) $FeCl_3$, cat. 2,6-dicarboxypyridine 1-oxide, 70% aq TBHP, *tert*-amyl alcohol, rt, 8 h, 71%; (v) PhCN, TBHP/NaOH, acetone, rt, 24 h, 70%.

Scheme 6. Short Synthesis to Calothrixins[a]



[a]Reagents and conditions: (i) $AlCl_3$, $(COCl)_2$, dry DCM, N_2, 0 °C to rt, 3 h then aniline, K_2CO_3, dry THF, rt, overnight, 81%; (ii) 5 mol % $Pd(TFA)_2$, PhCOOH, O_2, 120 °C, 24h, 83%; (iii) Tf_2O, pyridine, dry DCM, −40 °C to rt, 2 h then Et_3SiH, rt, 5 h, 87%.

In summary, we herein report the synthesis of calothrixin B utilizing Pd-catalyzed intramolecular C−H/C−I and C−H/C−H cross-coupling reactions that were used to construct the indolophenanthridine system. For the first time, calothrixin-related pentacycles **13**−**15** and **17** were prepared without any substitution at the indole nitrogen. Also of particular note is the fact that recourse to protection of the indole nitrogen atom was unnecessary to achieve the pentacyclic ring of calothrixin B, which was constructed with good overall yield of 27−35% and also included the synthesis of calothrixin A.

EXPERIMENTAL SECTION

General Information and Materials. The NMR experiments were performed with 400 or 500 MHz spectrometer, and chemical shifts are expressed in ppm (δ) with TMS as an internal reference. J values are given in hertz. IR spectra were recorded by using KBr pellets or neat. TOF and quadrupole mass analyzer types were used for the HRMS measurements. Reactions were carried out under an inert atmosphere (nitrogen) or oxygen and monitored by TLC. Column chromatography was performed on silica gel (100−200 mesh) in glass columns to purify the compounds. The solvents acetone, diethyl ether, tetrahydrofuran (THF), methanol, chloroform, and dichloromethane were dried by using standard distillation methods. Commercially available reagents and solvents were used without further purification and were purchased. Melting points were determined using open capillary tubes and are uncorrected.

Preparation of 4-Methoxy-9*H*-carbazole-3-carbaldehyde (4). To a solution of 4-methoxy-9*H*-carbazole **3** (2 g, 10.9 mmol) and NMF (2.0 mL, 16.4 mmol) in 1,2-dicholorobenzene (20 mL) was added $POCl_3$ (3.0 mL, 32.7 mmol) dropwise under ice cooling. Then, the mixture was gradually raised to room temperature and stirred for 3 h at 70 °C. The mixture was then poured into ice and neutralized with 10% aqueous NaOH, and the residue was extracted with ethyl acetate (200 mL). The extract was washed with brine and dried over Na_2SO_4. The solvent was removed, and the residue was purified by column chromatography with hexanes/ethyl acetate (1:5) to give **4** (1.87 g, 82%). Yellow solid; mp 166−169 °C; IR (KBr) 3317, 2843, 2740, 1631 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 10.22 (s, 1H), 9.00 (br, s, 1H), 7.85 (d, J = 7.6 Hz, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.34 (d, J = 7.6 Hz, 1H), 7.22 (t, J = 7.6 Hz, 1H), 7.07 (t, J = 7.2 Hz, 1H), 6.69 (d, J = 8.4 Hz, 1H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.4, 155.4, 140.6, 138.8, 122.7, 122.3, 120.8, 119.5, 117.7, 117.5, 114.8, 109.4, 107.5, 55.6; HRMS (ESI-MS) m/z $[M]^+$ calcd for $C_{14}H_{11}NO_2$ 225.0790, found 225.0757.

Preparation of 4-Methoxy-9*H*-carbazole-3-carboxylic Acid (5). To a solution of **4** (2.0 g, 8.8 mmol) in THF (20 mL) was added 30% aq H_2O_2 (3.0 mL, 88.7 mmol) dropwise under ice cooling. Then, KH_2PO_4 (1.2 g, 8.8 mmol) in water (5 mL) followed by $NaClO_2$ (1.59 g, 17.6 mmol) in water (5 mL) was added in a dropwise manner. The reaction mixture was then raised to room temperature and stirred for 8 h. After completion of the reaction, the mixture was neutralized with 10% aq HCl and filtered. The solid obtained was recrystallized from warm ethanol to yield **5** (2.06 g, 97%). Yellow solid, mp 183−186 °C; IR (KBr) 3327, 2833, 2740, 1664 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 12.47 (s, 1H), 10.86 (br, s, 1H), 8.22 (d, J = 7.6 Hz, 1H), 8.17 (d, J = 8.8 Hz, 1H), 7.60 (t, J = 8.4 Hz, 2H), 7.49 (t, J = 7.2 Hz, 1H), 7.33 (t, J = 7.6 Hz, 1H), 3.94 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.3, 155.4, 140.6, 138.8, 122.7, 122.3, 120.8, 119.5, 117.7, 117.5, 114.8, 109.4, 107.5, 56.1; HRMS (ESI-MS) m/z $[M]^+$ calcd for $C_{14}H_{11}NO_3$ 241.0739, found 241.0716.

Preparation of *N*-(2-Iodophenyl)-4-methoxy-9*H*-carbazole-3-carboxamide (6). A mixture of **5** (1 g, 4.1 mmol) and thionyl chloride (1.5 mL, 20.4 mmol) in 20 mL of chloroform was heated at reflux temperature for 6 h. Then, the residue was concentrated by the aid of rotary evaporation. To a solution of the concentrated crude product in THF (20 mL) K_2CO_3 (1.13 g, 8.2 mmol) and 2-iodoaniline (1.34 g, 6.2 mmol) in THF (5 mL) were added. The mixture was then

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allowed to stir for 12 h at room temperature. After completion of the reaction, the residue was extracted with ethyl acetate (100 mL), washed with 10% aq HCl and brine, and dried over Na_2SO_4. The solvent was removed, and the solid obtained was recrystallized from methanol to afford **6** (1.63 g, 96%). Yellow solid, mp 176−179 °C; IR (KBr) 3320, 2850, 2735, 1673, 1448, 1104, 765 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, J = 7.5 Hz, 1H), 8.30 (d, J = 8.0 Hz, 1H), 7.93 (br, s, 1H), 7.84−7.81 (dd, J_1 = 1.2 Hz, J_2 = 8.0 Hz, 1H), 7.54−7.46 (m, 4H), 7.44−7.40 (m, 1H), 7.32−7.28 (m, 1H), 6.90−6.87 (m, 1H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 152.8, 141.1, 139.6, 138.8, 130.8, 129.3, 127.9, 127.5, 125.8, 125.6, 123.9, 123.2, 123.1, 121.8, 119.6, 108.7, 90.0, 55.8; HRMS (ESI-MS) m/z $[M - H]^+$ calcd for $C_{20}H_{15}IN_2O_2$ 441.0100, found 441.0105.

Preparation of *N*-(2-Iodophenyl)-4-methoxy-*N*,9-bis(methoxymethyl)-9*H*-carbazole-3-carboxamide (7). To a suspension of NaH (60% dispersion in oil, 236 mg, 9.8 mmol) in dry THF (20 mL) under ice cooling was added a solution of **6** (500 mg, 1.1 mmol) in dry THF (10 mL) slowly followed by freshly prepared chloro(methoxy)methane (1.5 mL, 19.3 mmol) under nitrogen atmosphere, and the mixture was stirred for 30 min. The mixture was gradually raised to room temperature and heated to 50 °C for 20 h. The mixture was concentrated on rotary evaporator, the residue was extracted with ethyl acetate (100 mL), and the extract was washed with brine and dried over Na_2SO_4. The solvent was removed, and the residue was recrystallized from methanol to give **7** (0.55 g, 92%). Yellow solid, mp 248−251 °C; IR (KBr) 2891, 2387, 1641, 1221, 1109 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, J = 7.6 Hz, 1H), 8.30 (d, J = 8.0 Hz, 1H), 7.84−7.82 (dd, J_1 = 1.2 Hz, J_2 = 8.0 Hz, 1H), 7.54−7.50 (m, 4H), 7.48−7.40 (m, 1H), 7.32−7.26 (m, 1H), 6.90−6.86 (m, 1H), 5.94 (s, 2H), 5.81 (d, J = 9.2 Hz, 1H), 4.86 (d, J = 6.4 Hz, 1H), 3.84 (s, 3H), 3.75 (s, 3H), 3.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 151.9, 141.1, 139.6, 138.8, 130.8, 129.3, 127.9, 127.5, 125.8, 125.6, 123.9, 123.2, 123.1, 121.8, 119.6, 108.7, 90.0, 76.1, 73.1, 56.7, 56.3, 55.8; HRMS (ESI-MS) m/z $[M]^+$ calcd for $C_{24}H_{23}IN_2O_4$ 530.0703, found 530.0710.

Preparation of *N*-(2-Iodophenyl)-4-methoxy-*N*-(methoxymethyl)-9*H*-carbazole-3-carboxamide (8). To a solution of **6** (500 mg, 1.1 mmol) in dry $CHCl_3$ (20 mL) was added P_2O_5 (0.96 g, 3.3 mmol) under nitrogen atmosphere. Then, dimethoxymethane (1 mL, 11.3 mmol) was added in a dropwise manner. The reaction mixture was allowed warm to room temperature and stirred for 8 h. After completion of the reaction, the solvent was removed, and the residue obtained was quenched with 10% aq Na_2CO_3 (100 mL) and then extracted with ethyl acetate (200 mL). The extract was concentrated and purified by silica gel column chromatography with hexanes/ethyl acetate (7:3) to give **8** (0.48 g, 89%). Yellow solid, mp 231−234 °C; IR (KBr) 3389, 2745, 1651, 1192, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, J = 7.6 Hz, 1H), 8.30 (d, J = 8.0 Hz, 1H), 7.93 (br, s, 1H), 7.84−7.82 (dd, J_1 = 1.2 Hz, J_2 = 8.0 Hz, 1H), 7.54−7.50 (m, 3H), 7.44−7.40 (m, 2H), 7.32−7.26 (m, 1H), 6.90−6.86 (m, 1H), 6.53 (d, J = 6.4 Hz, 1H), 5.81 (d, J = 9.2 Hz, 1H), 3.83 (s, 3H), 3.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 151.9, 141.1, 139.6, 138.8, 130.8, 129.3, 127.9, 127.5, 125.8, 125.6, 123.9, 123.2, 123.1, 121.8, 119.6, 108.7, 90.0, 77.7, 56.7, 55.8; HRMS (ESI-MS) m/z $[M]^+$ calcd for $C_{22}H_{19}IN_2O_3$ 486.0440, found 486.0442.

General Procedure for the Synthesis of Compounds 9 and 13. An oven-dried Ace Pressure tube was charged with $Pd(OAc)_2$ (5 mol %), Ag_2O (10 mol %), appropriate compound **7** or **8** (1 mmol), KOAc (2 mmol) [in case of **8**, 3 mmol of base used], and DMF (5 mL) and then capped with a Teflon screw cap, and the mixture was heated to 110 °C with stirring for appropriate time. After completion of the reaction, the mixture was cooled to room temperature and diluted with water, and the residue was extracted with ethyl acetate. The extract was then washed with 10% aq NH_4Cl and brine and dried over Na_2SO_4. The solvent was removed; the resulting residue was purified by silica gel column chromatography on hexanes/ethyl acetate (7:3) to afford the titled compound.

7-Methoxy-5,12-bis(methoxymethyl)-5*H*-indolo[3,2-*j*]-phenanthridin-6(12*H*)-one (9). Yield 81%; white solid; mp 274−277 °C; IR (KBr) 2874, 2598, 1664, 1452 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, J = 7.6 Hz, 1H), 8.30 (d, J = 8.0 Hz, 1H), 7.84−7.82 (dd, J_1 = 1.2 Hz, J_2 = 8.0 Hz, 1H), 7.54−7.45 (m, 3H), 7.44−7.40 (m, 1H), 7.32−7.28 (dt, J_1 = 1.2 Hz, J_2 = 8.0 Hz, 1H), 6.90−6.86 (dt, J_1 = 1.6 Hz, J_2 = 8.0 Hz, 1H), 5.91 (s, 2H), 5.81 (d, J = 10.4 Hz, 1H), 4.66 (d, J = 10.4 Hz, 1H), 3.88 (s, 3H), 3.77 (s, 3H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 152.4, 141.1, 139.6, 138.8, 134.6, 130.8, 129.3, 127.9, 127.5, 125.8, 125.6, 123.9, 123.2, 123.1, 121.8, 119.6, 117.4, 108.7, 82.4, 72.6, 57.8, 55.6, 53.7; HRMS (ESI-MS) m/z calcd for $C_{24}H_{22}N_2O_4$ 402.1580, found 401.1872 $[M - 1]^+$, 402.1545 $[M]^+$.

7-Methoxy-5-(methoxymethyl)-5*H*-indolo[3,2-*j*]-phenanthridin-6(12*H*)-one (13). Yield 74%; White solid, mp 269−272 °C; IR (KBr) 3361, 1647 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.11 (br, s, 1H), 8.51 (d, J = 7.6 Hz, 1H), 8.30 (d, J = 8.0 Hz, 1H), 7.84−7.82 (dd, J_1 = 1.2 Hz, J_2 = 8.0 Hz, 1H), 7.54−7.50 (m, 1H), 7.48−7.44 (m, 2H), 7.42−7.40 (m, 1H), 7.32−7.26 (dt, J_1 = 1.2 Hz, J_2 = 6.8 Hz, 1H), 6.90−6.86 (dt, J_1 = 1.6 Hz, J_2 = 8.0 Hz, 1H), 5.81 (d, J = 10.4 Hz, 1H), 4.66 (d, J = 10.4 Hz, 1H), 3.88 (s, 3H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 151.6, 141.1, 139.6, 138.8, 134.6, 130.8, 129.3, 127.9, 127.5, 125.8, 125.6, 123.9, 123.2, 123.1, 121.8, 119.6, 117.4, 108.7, 74.2, 61.2, 56.4; HRMS (ESI-MS) m/z $[M]^+$ calcd for $C_{22}H_{18}N_2O_3$ 358.1317, found 358.1316.

General Procedure for the Preparation of Compounds 10 and 14. To a solution of compound **9** or **13** (1 mmol) in dry Et_2O (10 mL) was added LAH (10 mmol) portionwise under ice-cold condition with stirring. The reaction was gradually raised to room temperature and stirred for 3 h. Then, 6 N HCl was added slowly to the mixture under ice cooling, and the mixture was stirred for 30 min. The precipitate formed was filtered, and the filtrate was washed with Et_2O (3 × 10 mL). The extracts were then washed with brine and dried over Na_2SO_4. The solvent was removed on a rotary evaporator, and the residue was recrystallized from methanol to yield the titled compound.

7-Methoxy-12-(methoxymethyl)-12*H*-indolo[3,2-*j*]-phenanthridine (10). Yield 87%; light orange solid, mp 267−269 °C; IR (KBr) 2764, 2334, 1349, 1151 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.30 (d, J = 8.0 Hz, 1H), 7.84−7.82 (dd, J_1 = 1.6 Hz, J_2 = 8.0 Hz, 1H), 7.93 (s, 1H), 7.54−7.50 (m, 3H), 7.48−7.40 (m, 1H), 7.32−7.26 (m, 1H), 6.90−6.86 (dt, $J1$ = 1.2 Hz, J_2 = 8.0 Hz, 1H), 5.85 (s, 2H), 3.81 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 148.3, 141.1, 139.6, 138.8, 130.8, 129.3, 127.9, 127.5, 125.8, 125.6, 123.9, 123.2, 123.1, 121.8, 119.6, 117.4, 108.7, 74.1, 61.1, 55.5; HRMS (ESI-MS) m/z $[M]^+$ calcd for $C_{22}H_{18}N_2O_2$ 342.1368, found 342.1348.

7-Methoxy-12*H*-indolo[3,2-*j*]phenanthridine (14). Yield 94%; light yellow oil; IR (neat) 3421, 3365, 2786, 1320, 1167 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.04 (br, s, 1H), 8.50 (s, 1H), 8.30 (d, J = 8.0 Hz, 1H), 7.84−7.82 (dd, J_1 = 1.2 Hz, J_2 = 8.0 Hz, 2H), 7.54−7.50 (m, 3H), 7.48−7.40 (m, 1H), 7.32−7.26 (dt, J_1 = 1.2 Hz, J_2 = 6.8 Hz, 1H), 6.90−6.86 (dt, J_1 = 1.6 Hz, J_2 = 8.0 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 148.1, 141.1, 139.6, 138.8, 130.8, 129.3, 127.9, 127.5, 125.8, 125.6, 123.9, 123.2, 123.1, 121.8, 119.6, 117.4, 108.7, 57.7; HRMS (ESI-MS) m/z $[M]^+$ calcd for $C_{20}H_{14}N_2O$ 298.1106, found 298.1112.

General Procedure for the Preparation of Compounds 11 and 15. A 25-mL oven-dried, round-bottom flask was charged with 1 mmol of **10** or **14**. The flask was purged with nitrogen and sealed with a rubber septum. With oven-dried syringes, 10 mL of sulfolane, pyridine (0.5 mL, 0.06 mmol), and freshly prepared iodotrimethylsilane (3.5 mL, 24 mmol) were injected into the flask in the order specified. When the iodotrimethylsilane is added, the solution becomes slightly yellow and a precipitate appears. The mixture was heated with stirring at 70° for 20 h, after which the reaction was normally complete. Anhydrous methanol (5 mL) was added, the mixture was cooled to room temperature, and the volatile components were removed on a rotary evaporator. Approximately 20 mL of anhydrous diethyl ether was added, and the resulting suspension was filtered, removing pyridinium hydro iodide. The flask and the filter cake were washed thoroughly with 50 mL of anhydrous ether. The solvent was evaporated, and the residual oil was purified by chromatography on

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silica gel packed with anhydrous ether in a glass column. The column was eluted with anhydrous ether, and 10−15 mL fractions were collected and analyzed by TLC. Fractions containing product were combined and evaporated, affording title compound.

12-(Methoxymethyl)-12*H*-indolo[3,2-*j*]phenanthridin-7-ol (11). Yield 76%; orange oil; IR (neat) 3382, 2576, 2471, 1451, 1194 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 11.46 (s, 1H), 8.43 (s, 1H), 7.82 (d, J = 7.6 Hz, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.52 (s, 1H), 7.22−7.20 (m, 2H), 7.06 (t, J = 8.4 Hz, 1H), 7.02 (t, J = 10.4 Hz, 1H), 6.94−6.90 (m, 1H), 6.85−6.82 (m, 1H), 5.72 (s, 2H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 150.6, 148.5, 140.8, 139.8, 131.1, 128.4, 126.4, 122.8, 122.0, 120.2, 119.6, 119.0, 117.7, 117.1, 113.6, 111.9, 108.5, 107.5, 105.5, 70.4, 53.3; HRMS (ESI-MS) m/z $[M + H]^+$ calcd for $C_{21}H_{16}N_2O_2$ 328.1291, found 329.1314.

12*H*-Indolo[3,2-*j*]phenanthridin-7-ol (15). Yield 86%; thick orange liquid; IR (neat) 3402, 3386, 2845, 1441, 1197 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 11.86 (s, 1H), 10.86 (br, s, 1H), 8.41 (s, 1H), 8.22 (d, J = 7.6 Hz, 1H), 8.15 (d, J = 8.8 Hz, 1H), 7.62−7.57 (m, 2H), 7.50 (t, J = 10.4 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.32 (t, J = 7.6 Hz, 1H), 7.24−7.20 (m, 1H), 6.90−6.86 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 150.8, 148.5, 140.8, 139.8, 133.4, 131.1, 128.4, 126.4, 122.8, 122.0, 120.2, 119.6, 119.0, 117.7, 117.1, 113.6, 111.9, 108.5, 107.5; HRMS (ESI-MS) m/z calcd for $C_{19}H_{12}N_2O$ 284.0950, found 284.1072 $[M]^+$, 285.1082 $[M + 1]^+$.

Preparation of 12-(Methoxymethyl)-7*H*-indolo[3,2-*j*]-phenanthridine-7,13(12*H*)-dione (12). Phenol **11** (20 mg, 0.060 mmol) in a 5:1 mixture of acetone/5% aq NaOH (5 mL) was stirred at room temperature under O_2 for 18 h. The mixture was concentrated, water (5 mL) was added, and the precipitate formed was collected by filtration and recrystallized from ethanol to give **12** (18 mg, 88%). Orange solid; mp 230−232 °C (lit.[5] mp 234−235 °C); IR (KBr) 2921, 2853, 1650 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.79 (s, 1H), 9.62 (d, J = 8.8 Hz, 1H), 8.41 (d, J = 8.2 Hz, 1H), 8.20 (d, J = 8.1 Hz, 1H), 7.86−7.78 (m, 2H), 7.61 (d, J = 8.5 Hz, 1H), 7.56−7.53 (m, 1H), 7.44−7.40 (m, 1H), 5.83 (s, 2H), 3.84 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.4, 179.6, 152.3, 148.1, 135.6, 133.1, 131.7, 131.5, 130.5, 130.3, 128.4, 127.6, 125.5, 124.5, 123.8, 123.1, 119.6, 113.3, 76.1, 56.3; HRMS (ESI-MS) m/z $[M + H]^+$ calcd for $C_{21}H_{14}N_2O_3$ 343.1083, found 343.1080.

Synthesis of 4-Methoxy-*N*-phenyl-9*H*-carbazole-3-carboxamide (16). To a solution of 4-methoxycarbazole **3** (1 g, 5.1 mmol) in dry DCM (20 mL) was added $AlCl_3$ (1.02 g, 7.65 mmol) in a two neck round-bottom flask, which was purged with nitrogen and sealed with a rubber septum. The contents were stirred at room temperature for 30 min. Then, oxalyl chloride (0.95 mL, 10.1 mmol) was added slowly to the mixture at 0 °C and stirred for 30 min. The mixture was then brought back to room temperature for a further 3 h of stirring. The solid residue was filtered off, and the filtrate was directly added to a MeOH solution containing aniline (0.42 mL, 4.63 mmol) and K_2CO_3 (1 g, 7.72 mmol) in a dropwise manner. The whole contents were stirred at room temperature overnight. After the completion of the reaction, the mixture was poured into 10% aq HCl (60 mL) and extracted with ethyl acetate (3 × 40 mL). The solvent was removed; the solid obtained was washed with hot ether (5 × 30 mL) gave **16** (1.4 g, 81%). Yellow solid; mp 209−211 °C; IR (KBr) 3369, 2945, 2426, 1643, 1198, 1046 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6, 400 MHz) δ 11.04 (s, 1H), 10.04 (s, 1H), 7.81−7.76 (m, 2H), 7.58 (d, J = 8.4 Hz, 1H), 7.32−7.30 (m, 2H), 7.13 (d, J = 8.4 Hz, 1H), 6.96 (t, J = 7.6 Hz, 1H), 6.91 (t, J = 8.0 Hz, 1H), 6.82 (t, J = 7.6 Hz, 1H), 6.74 (t, J = 7.6 Hz, 1H), 6.27−6.22 (m, 1H), 3.67 (s, 3H); ^{13}C NMR $CDCl_3$+DMSO-d_6, 100 MHz) δ 192.7, 158.5, 140.2, 137.7, 132.2, 129.0, 124.4, 124.0, 121.49, 121.45, 120.4, 119.9, 119.3, 118.5, 111.6, 110.8, 109.9, 54.6; HRMS (ESI-MS) m/z $[M - H]^+$ calcd for $C_{20}H_{16}N_2O_2$ 315.1133, found 315.1112.

Typical Procedure for Pd-Catalyzed Oxidative Coupling Reaction of 16. To a Schlenk tube were added $Pd(OCOCF_3)_2$ (35 mg, 0.079 mmol), **16** (0.5 g, 1.58 mmol), and benzoic acid (5.0 g). The Schlenk tube was flushed and maintained with O_2, and then the reaction mixture was stirred at 120 °C for 24 h. After cooling to room temperature, the mixture was dissolved in AcOEt and neutralized with aqueous Na_2CO_3 to remove benzoic acid. The aqueous layer was extracted with AcOEt (three times). The combined organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated to give crude, in which benzoic acid was not contained. The residue was purified by column chromatography on silica gel on hexanes/ethyl acetate (7:3) to afford **17** as a light yellow solid (0.41 g, 83%).

7-Methoxy-5*H*-indolo[3,2-*j*]phenanthridin-6(12H)-one (17). Pale yellow solid; mp 246−248 °C; IR (KBr) 3341, 2871, 1609, 1204 cm^{-1}; ^1H NMR ($CDCl_3$+DMSO-d_6, 400 MHz) δ 10.93 (s, 1H), 9.97 (s, 1H), 7.99 (s, 1H), 7.56 (d, J = 9.2 Hz, 1H), 7.49 (d, J = 8.8 Hz, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.16 (t, J = 7.6 Hz, 1H), 7.00 (t, J = 7.2 Hz, 1H), 6.69−6.65 (m, 2H), 6.38 (d, J = 8.8 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR $CDCl_3$+DMSO-d_6, 100 MHz) δ 172.6, 156.7, 140.1, 139.5, 134.0, 130.8, 128.8, 124.6, 124.2, 123.1, 122.4, 122.2, 120.6, 118.8, 116.1, 115.8, 108.0, 107.4, 53.8; HRMS (ESI-MS) m/z $[M - H]^+$ calcd for $C_{20}H_{14}N_2O_2$ 314.1055, found 313.0935.

Calothrixin B (2). Ferric chloride (8 mg, 0.05 mmol) was added by portions to a mixture of **15** (30 mg, 0.1 mmol), 70% aq TBHP (0.1 mL, 1 mmol), and 2,6-dicarboxy pyridine-1-oxide (2 mg, 0.01 mmol) in *tert*-amyl alcohol (2 mL) under ice cooling. Then, the mixture was gradually raised to room temperature and stirred for 8 h. The mixture was diluted with CH_2Cl_2 (50 mL), washed with brine, and dried over Na_2SO_4. The solvent was removed, and the residue obtained was purified by silica gel column chromatography on hexanes/ethyl acetate (5:1) to give **2** (18 mg, 71%). Red solid; mp 296−299 °C (lit.[1] mp ≥300 °C); IR (KBr) 3389, 1651 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 12.84 (br s, 1H), 9.60 (s, 1H), 9.55 (d, J = 8.2 Hz, 1H), 8.18 (d, J = 7.6 Hz, 1H), 8.14 (t, J = 8.4 Hz, 1H), 7.91 (t, J = 7.6 Hz, 1H), 7.83 (t, J = 8.8 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.44 (t, J = 6.6 Hz, 1H), 7.34 (t, J = 7.8 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 181.0, 180.7, 151.7, 148.0, 133.1, 132.1, 130.7, 130.3, 127.7, 127.6, 125.5, 124.8, 123.9, 123.1, 122.8, 116.2, 114.8; HRMS (ESI-MS) m/z calcd for $C_{19}H_{10}N_2O_2$ 298.0821; found 298.1036 $[M]^+$, 299.0872 $[M + H]^+$.

Calothrixin A (1). A mixture of benzonitrile (9 mg, 0.08 mmol), 70% aq TBHP (0.2 mL), and NaOH (5 mg, 0.1 mmol) in acetone (2 mL) was cooled to 0 °C. Charge calothrixin B **2** (10 mg, 0.03 mmol) in acetone (1 mL) was added dropwise. The reaction mixture was stirred at room temperature for 24 h and then poured into saturated aqueous sodium hydrogen carbonate (10 mL). The mixture was extracted with dichloromethane (3 × 15 mL), the combined organic phases were dried over Na_2SO_4, and the solvent was evaporated. The crude material was subjected to column chromatography, eluting with dichloromethane containing triethylamine (1% v/v), to give the title compound **1** (7 mg, 70%). Red solid; mp 286−288 °C (lit.[1] mp ≥280 °C); IR (KBr) 3340, 1671 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 12.89 (br s, 1H), 9.64 (d, J = 6.7 Hz, 1H), 8.85 (s, 1H), 8.58 (d, J = 6.8 Hz, 1H), 8.10 (d, J = 7.0 Hz, 1H), 7.94 (t, J = 8.3 Hz, 1H), 7.91 (t, J = 5.5 Hz, 1H), 7.59 (d, J = 7.2 Hz, 1H), 7.41 (t, J = 6.6 Hz, 1H), 7.35 (t, J = 9.9 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 178.8, 178.3, 143.7, 139.2, 138.8, 132.5, 132.3, 130.5, 128.7, 127.6, 127.4, 125.0, 124.1, 122.6, 122.5, 119.5, 115.7, 114.8; HRMS (ESI-MS) m/z $[M + H]^+$ calcd for $C_{19}H_{10}N_2O_3$ 315.0770, found 315.0774.

■ ASSOCIATED CONTENT

Supporting Information

Complete characterization data (^1H NMR, ^{13}C NMR, and mass spectra) for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

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■ REFERENCES

(1) Rickards, R. W.; Rothschild, J. M.; Willis, A. C.; de Chazal, N. M.; Kirk, J.; Kirk, K.; Saliba, K. J.; Smith, G. D. *Tetrahedron* **1999**, *55*, 13513−13520.

(2) (a) Matsumoto, K.; Choshi, T.; Hourai, M.; Zamami, Y.; Sasaki, K.; Abe, T.; Ishikura, M.; Hatae, N.; Iwamura, N.; Tohyama, S.; Nobuhiro, J.; Hibino, S. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 4762−4764. (b) Bernardo, P. H.; Chai, C. L. L.; Heath, G. A.; Mahon, P. J.; Smith, G. D.; Waring, P.; Wilkes, B. A. *J. Med. Chem.* **2004**, *47*, 4958−4963. (c) Khan, Q. A.; Lu, J.; Hecht, S. M. *J. Nat. Prod.* **2009**, *72*, 438−442.

(3) Kelly, T. R.; Zhao, Y.; Cavero, M.; Torneiro, M. *Org. Lett.* **2000**, *2*, 3735−3737.

(4) (a) Choshi, T.; Hibino, S. *Heterocycles* **2009**, *77*, 85−97. (b) Tohyama, S.; Choshi, T.; Matsumoto, K.; Yamabuki, A.; Hieda, Y.; Nobuhiro, J.; Hibino, S. *Heterocycles* **2010**, *82*, 397−416. (c) Abe, T.; Ikeda, T.; Yanada, R.; Ishikura, M. *Org. Lett.* **2011**, *13*, 3356−3359. (d) Bhosale, S. M.; Gawade, R. L.; Puranik, V. G.; Kusurkar, R. S. *Tetrahedron Lett.* **2012**, *53*, 2894−2896. (e) Bennasar, M. -L.; Roca, T.; Ferrando, F. *Org. Lett.* **2006**, *8*, 561−564. (f) Bernardo, P. H.; Chai, C. L. L. *J. Org. Chem.* **2003**, *68*, 8906−8909. (g) Bernardo, P. H.; Chai, C. L. L.; Elix, J. A. *Tetrahedron Lett.* **2002**, *43*, 2939−2940. (h) Sissouma, D.; Maingot, L.; Collet, S.; Guingant, A. *J. Org. Chem.* **2006**, *71*, 8384−8389. (i) Tohyama, S.; Choshi, T.; Matsumoto, K.; Yamabuki, A.; Ikegata, K.; Nobuhiro, J.; Hibino, S. *Tetrahedron Lett.* **2005**, *46*, 5263−5264.

(5) (a) McErlean, C. S. P.; Sperry, J.; Blake, A. J.; Moody, C. J. *Tetrahedron* **2007**, *63*, 10963−10970. (b) Yamabuki, A.; Fujinawa, H.; Choshi, T.; Tohyama, S.; Matsumoto, K.; Ohnuma, K.; Nobuhiro, J.; Hibino, S. *Tetrahedron Lett.* **2006**, *47*, 5859−5861. (c) Sperry, J.; McErlean, C. S. P.; Slawin, A. M. Z.; Moody, C. J. *Tetrahedron Lett.* **2007**, *48*, 231−234.

(6) (a) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; deMeijere, A.; Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004. (b) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley Interscience: New York, 2002.

(7) (a) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147−1169. (b) Díaz-Requejo, M. M.; Pérez, P. J. *Chem. Rev.* **2008**, *108*, 3379−3394. (c) Schmidt, A. W.; Reddy, K. R.; Knölker, H.-J. *Chem. Rev.* **2012**, *112*, 3193−3328. (d) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731−1770. (e) Díaz-Requejo, M. M.; Pérez, P. J. *Chem. Rev.* **2008**, *108*, 3379−3394. (f) Knölker, H.-J. *Chem. Lett.* **2009**, *38*, 8−13. (g) Knölker, H.-J.; Reddy, K. R. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: Amsterdam, 2008; Vol. *65*, p 1. (h) Bauer, I.; Knölker, H.-J. *Top. Curr. Chem.* **2012**, *309*, 203−253.

(8) (a) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359−1469. (b) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442−4489. (c) Pulido, F. J.; Barbero, A.; García, C. *Tetrahedron* **2009**, *65*, 5535−5540. (d) Bowie, A. L.; Trauner, D. *J. Org. Chem.* **2009**, *74*, 1581−1586. (e) Frye, E. C.; O'Connor, C. J.; Twigg, D. G.; Elbert, B.; Laraia, L.; Hulcoop, D. G.; Venkitaraman, A. R.; Spring, D. R. *Chem.—Eur. J.* **2012**, *18*, 8774−8779.

(9) (a) Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, *111*, 1417−1492. (b) Weibel, J.-M.; Blanc, A.; Pale, P. *Chem. Rev.* **2008**, *108*, 3149−3173. (c) Shi, W.; Liu, C.; Lei, A. *Chem. Soc. Rev.* **2011**, *40*, 2761−2776. (d) Harayama, T.; Akamatsu, H.; Okamura, K.; Miyagoe, T.; Akiyama, T.; Abe, H.; Takeuchi, Y. *J. Chem. Soc., Perkin Trans. 1* **2001**, 523−528.

(10) (a) Olah, G. A; Narang, S. C. *Tetrahedron* **1982**, *38*, 2225−2227. (b) Ho, T.-L.; Olah, G. A. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 774−775. (c) Ho, T.-L.; Olah, G. A. *Synthesis* **1977**, 417−418.

(11) (a) Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217−6254. (b) Möoller, K.; Wienhöofer, G.; Schröoder, K.; Join, B.; Junge, K.; Beller, M. *Chem.—Eur. J.* **2010**, *16*, 10300−10303. (c) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* **2011**, *111*, 1293−1314.

(12) (a) Asche, C.; Frank, W.; Albert, A.; Kucklaender, U. *Bioorg. Med. Chem.* **2005**, *13*, 819−837. (b) Tao, Z.-F.; Sowin, T. J.; Lin, N.-H. *Tetrahedron Lett.* **2005**, *46*, 7615−7618.

(13) (a) Katritzky, A. R.; Lagowski, J. M. *Chemistry of the Heterocyclic N-Oxides*; Academic Press: London, 1971. (b) Rousseau, R. J.; Robins, R. K. *J. Heterocycl. Chem.* **1965**, *2*, 196−201. (c) Katritzky, A. R.; Lam, J. N. *Heterocycles* **1992**, *33*, 1011−1049.

(14) (a) Hanada, S.; Tsutsumi, E.; Motoyama, Y.; H. Nagashima, H. *J. Am. Chem. Soc.* **2009**, *131*, 15032−15040. (b) Das, S.; Addis, D.; Zhou, S.; Junge, K.; Beller, M. *J. Am. Chem. Soc.* **2010**, *132*, 1770−1771. (c) Pelletier, G.; Bechara, W. S.; Charette, A. B. *J. Am. Chem. Soc.* **2010**, *132*, 12817−12819.

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Figure 1 and Schemes 3 and 5 were corrected on March 15, 2013.