An Alternative to Pictet–Gams Reaction Triggered by Hendrickson Reagent: Isoquinolines and β-Carbolines from Amides

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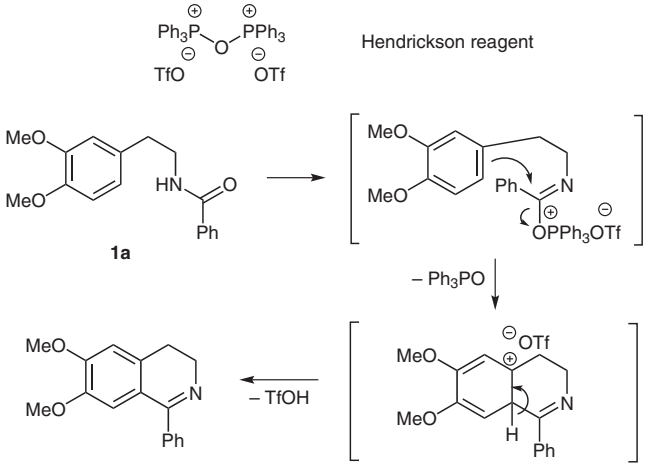
Abstract: The Hendrickson reagent derived from triflic anhydride and triphenylphosphine oxide exhibited high oxophilicity and induced the intramolecular cyclization of β-arylethylamides perfectly. Thus, a one-pot protocol to access isoquinoline and β-carboline was developed involving cyclization followed by oxidative aromatization.

Key words: Hendrickson reagent, isoquinoline, β-carboline, β-arylethylamide, manganese(IV) oxide

Isoquinoline and β-carboline are important scaffolds existing in various naturally occurring alkaloids and synthetic pharmaceuticals with extensive bioactivities.[1,2] In past decades, considerable efforts have been devoted to the assembly of isoquinoline and β-carboline, and some strategies developed became name reactions.[3] Among them, Pictet–Gams isoquinoline synthesis concerns cascade cyclization and dehydration of β-hydroxy-β-arylethylamides promoted by $POCl_3$ or P_2O_5. Different from the Pictet–Gams process, an approach was herein explored to rapidly construct isoquinoline and β-carboline motifs starting from β-arylethylamides without a hydroxy group. It involves intramolecular cyclization triggered by Hendrickson reagent.

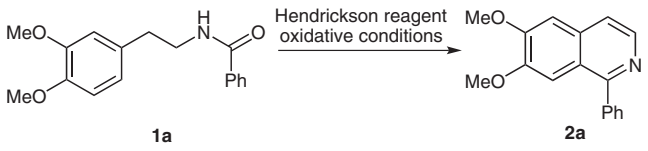
Pioneered by the discovery that bis(triphenyl)oxodiphosphonium trifluoromethanesulfonate (named as Hendrickson reagent) derived from triphenylphosphine oxide and triflic anhydride is possessed of high dehydrative ability,[4] Kelly revealed the structure by X-ray diffraction and explored its application. By utilizing the O-bridged bisphosphonium salt, dipeptides can be converted into thiazolines, oxazolines, and imidazolidines without loss of stereochemical integrity.[5] Recently, Yao employed the [4+2] aza-Diels–Alder strategy promoted by Hendrickson reagent as a key step to carry out the total synthesis of camptothecin-family alkaloids.[6]

During the course of our ongoing program on heterocycle synthesis, we found that under the action of Hendrickson reagent generated in situ from 1.5 equivalents of triflic anhydride and 3.0 equivalents of triphenylphosphine oxide in CH_2Cl_2, amide **1a** was converted into 1-phenyl-3,4-dihydroisoquinoline in 95% yield within 30 minutes at room temperature. The proposed mechanism is depicted in Scheme 1. As shown, Hedrickson reagent selectively activated amide to form imidate, then intramolecular nucleophilic attack took place to afford dihydroisoquinoline accompanied by extrusion of Ph_3PO and triflic acid. The high oxophilicity of Hendrickson reagent attracted us. Since the cyclization triggered by Hendrickson reagent occurred perfectly, we envisioned a one-pot protocol for preparation of isoquinoline and β-carboline compounds just by combining another aromatization.



Scheme 1

Initially MnO_2[7] was utilized as oxidant and amide **1a** was chosen as a model compound (Scheme 2, Table 1). After completion of the cyclization promoted by Hendrickson reagent, oxidant was added and the oxidation reaction was performed under room temperature in CH_2Cl_2. To our disappointment, the yield of the desired isoquinoline was lower than 5% (entry 1). We deduced that the low reaction temperature impeded the oxidation. Thus, the solvent was switched to dichloroethane. The cyclization triggered by Hendrickson reagent in dichloroethane proceeded cleanly as that in CH_2Cl_2. When the oxidation was run at 80 °C for



Scheme 2

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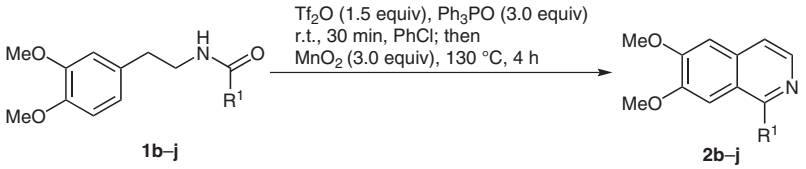


Scheme 3

Table 1 Different Oxidative Conditions Screened

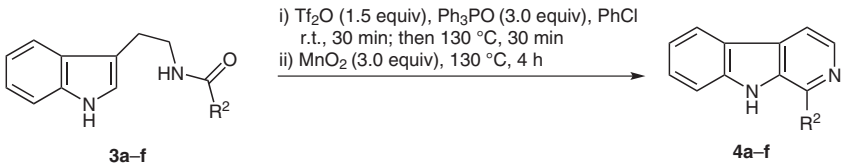
Entry	Oxidative conditions[a]	Yield (%)[b]
1	MnO_2 (3 equiv), CH_2Cl_2, r.t., 8 h	<5
2	MnO_2 (3 equiv), $ClCH_2CH_2Cl$, 80 °C, 8 h	50
3	DDQ (2 equiv), $ClCH_2CH_2Cl$, 80 °C, 12 h	44
4	TPCD (3 equiv), $ClCH_2CH_2Cl$, 80 °C, 8 h	18
5[c]	Pd/C (10%), O_2, $ClCH_2CH_2Cl$, 80 °C, 8 h	<5
6	MnO_2 (3 equiv), PhCl, 130 °C, 4 h	80
7	MnO_2 (3 equiv), PhCl, 130 °C, 8 h	76
8	MnO_2 (6 equiv), PhCl, 130 °C, 4 h	80

[a] Oxidant was added to the reaction mixture after the completion of cyclodehydration promoted by Hendrickson reagent.
[b] Isolated yield by flash chromatography.
[c] Catalytic amount of 10% Pd/C.

8 hours, the yield was improved to 50% (entry 2). Then, several oxidants other than MnO_2 were screened. When DDQ[8] was used, the yield dropped to 44% (entry 3). Metallic oxidant such as TPCD[9] [tetrakispyridine cobalt(II) dichromate] and 10% Pd/C[10] showed inferior dehydrogenative ability (entries 4, 5). Finally, when the oxidation reaction temperature was elevated to 130 °C by changing the solvent from dichloroethane to chlorobenzene, the yield increased to 80% (entry 6). Attempt to either prolong the reaction time or increase the amount of oxidant led to marginal improvements in the yield (entries 7, 8).

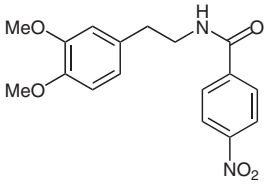
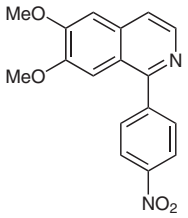
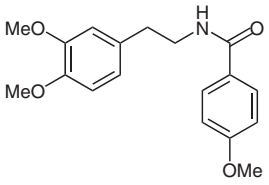
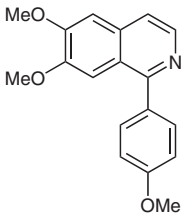
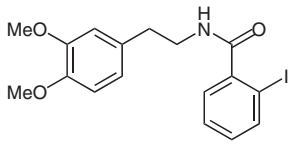
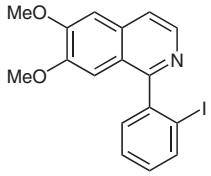
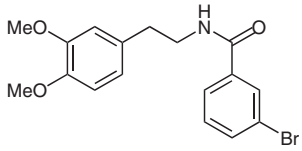
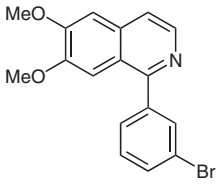
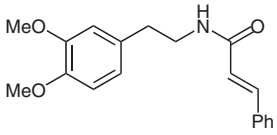
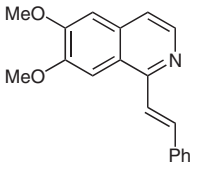
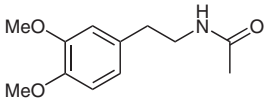
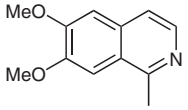
With the optimized condition in hand, the scope of the process was next examined (Scheme 3, Table 2). Different benzamides were screened to investigate the electronic and steric effects by switching substituents on benzoyl moiety, As illustrated, both electron-withdrawing (4-NO_2) and electron-donating (4-OMe) groups are well tolerated, providing expedient access to isoquinoline **2b**,**c** (entries 1, 2). However, the yield of **2b** is higher than **2c** and it seems likely that the presence of electron-withdrawing group is more advantageous. Besides nitro and methoxy groups, halo substituents were compatible with the reaction and good yields of expected isoquinolines **2d**,**e** were obtained (entries 3, 4). The steric effect on benzoyl ring was not perceived, since, when sterically demanding substituent (2-I) was introduced, the yield was almost unaffected. In addition, 2-propenamide **1f** and acetamide **1g** underwent sequential cyclization-oxidative aromatization smoothly as benzamides did. Isoquinolines **2f** and **2g** were prepared, albeit in slightly lower yields (entries 5, 6). Noteworthy is that isoquinoline **2g** is a naturally occurring alkaloid named nigellimine, which was extracted from an herbaceous plant.[11]

After screening different amides derived from 2-(3,4-dimethoxyphenyl)ethylamine, we turned our attention to tryptamine (Scheme 4, Table 3). However, the cyclization step of benzamide **3a** differed from **1a**. Only after performing the reaction at 130 °C for about 30 minutes, could MnO_2 be allowed to add to the reaction system. Otherwise, no β-carboline **4a** could be detected. The experiment result showed that the intermediate generated by the action of Hendrickson reagent with benzamide **3a** is stable enough at room temperature and is easily destroyed by MnO_2. Accordingly, β-carboline **4a** was obtained in 76% yield (entry 1). Benzamides containing bromo and nitro group also transformed into the tricyclic products **4b**,**c** in good yields (entries 2, 3). Furthermore, the process provides an effective access to prepare β-carboline alkaloids. Thus, starting from 2-butenamide **3d**, acetamide **3e**, and propanamide **3f**, different β-carbolines **4d**–**f** were isolated in yields ranging from 71 to 85% (entries 4–6). Among them, the β-carboline natural products **4d** (vulcanine)[12] and **4e** (harman),[13] and 1-ethyl-β-carboline **4f**, which occurs in the wood of *Ailanthus malabarica*,[14] were synthesized.



Scheme 4

Table 2 Isoquinoline Synthesis by Cyclization–Aromatization[a]

Entry	Amide		Isoquinoline		Yield (%)[b]
1	**1b**		**2b**		86
2	**1c**		**2c**		61
3	**1d**		**2d**		85
4	**1e**		**2e**		87
5	**1f**		**2f**		77
6	**1g**		**2g**		75

[a] All reactions were performed at a concentration of 0.05 M.
[b] Isolated yield by flash chromatography.

Table 3 β-Carboline Synthesis by Cyclization-Aromatization[a]

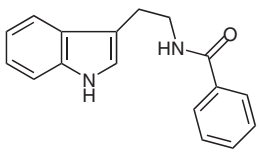
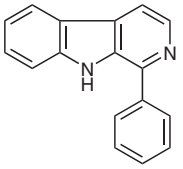
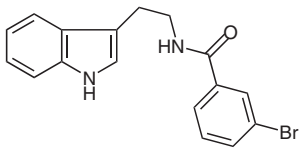
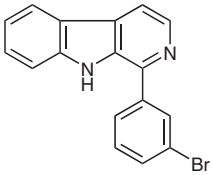
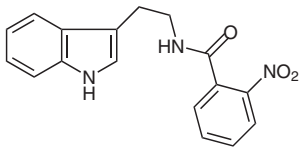
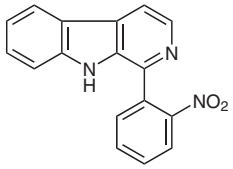
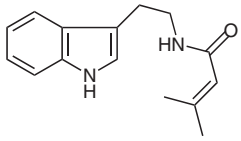
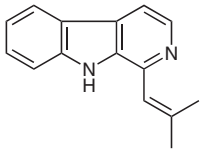
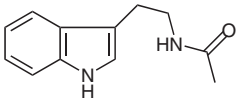
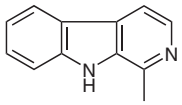
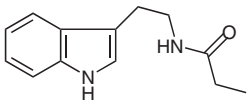
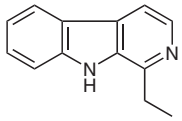
Entry	Amide		β-Carboline		Yield (%)
1	**3a**		**4a**		76
2	**3b**		**4b**		88

Table 3 β-Carboline Synthesis by Cyclization-Aromatization[a] (continued)

Entry	Amide		β-Carboline		Yield (%)
3	**3c**		**4c**		65
4	**3d**		**4d**		71
5	**3e**		**4e**		82
6	**3f**		**4f**		85

[a] All reactions were performed in 0.05 M concentration.
[b] Isolated yield by flash chromatography.

In conclusion, an alternate process for the synthesis of isoquinolines/β-carbolines was developed by utilizing the oxophilicity of Hendrickson reagent. The process also was extended successfully to alkaloid synthesis. Further application of Hendrickson reagent in organic synthesis will be explored in future.

All melting points were determined on a Yanaco apparatus and are uncorrected. IR spectra were recorded on a Shimider IDP440 spectrometer as KBr pellets, ^{1}H NMR spectra on a Bruker ACF-300 spectrometer with TMS or residual solvent as internal reference, and MS spectra on a VG-ZAB-HS mass spectrometer at 70 eV. Elemental analyses were performed on a PerkinElmer 240C instrument. Petroleum ether (PE) refers to the fraction boiling in the range 60–90 °C.

Isoquinolines 2a–g; General Procedure

Triflic anhydride (0.05 mL, 0.3 mmol) was added dropwise by syringe to a stirred solution of Ph_3PO (0.166 g, 0.6 mmol) in anhyd chlorobenzene (4.0 mL) at 0 °C. After 10 min, the appropriate amide **1** (0.2 mmol) was added in one portion. Then the reaction mixture was stirred at r.t. for 30 min. MnO_2 (52.0 mg, 0.6 mmol) was added and the reaction was heated at 130 °C for 4 h. After cooling, the mixture was diluted with $CHCl_3$ (20 mL) and filtered through Celite to remove insoluble precipitates. The filtrate was washed successively with aq 10% $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by chromatography with EtOAc–PE (1:2) as eluent to afford the pure product (Table 2).

6,7-Dimethoxy-1-phenylisoquinoline (2a)[15]

Colorless solid; mp 119–122 °C (EtOH–PE).

IR (KBr): 2993, 1624, 1560, 1507, 1475, 1236, 764 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.47 (d, *J* = 5.4 Hz, 1 H), 7.71 (d, *J* = 7.8 Hz, 2 H), 7.55–7.48 (m, 4 H), 7.37 (s, 1 H), 7.11 (s, 1 H), 4.02 (s, 3 H), 3.85 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.0, 152.5, 149.8, 141.1, 139.8, 133.6, 129.4, 128.32, 128.30, 122.3, 118.6, 105.4, 104.8, 55.9, 55.7.

MS: *m*/*z* (%) = 266 (M + 1, 2), 265 (M$^+$, 100), 264 (M – 1, 90), 250 (66), 235 (35), 234 (13).

Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 77.08; H, 5.78; N, 5.38.

6,7-Dimethoxy-1-(4-nitrophenyl)isoquinoline (2b)[16]

Yellow needles; mp 243–244 °C (EtOH).

IR (KBr): 3008, 1560, 1515, 1508, 1483, 1267, 1238, 853 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.51 (d, *J* = 5.7 Hz, 1 H), 8.40 (d, *J* = 8.7 Hz, 2 H), 7.91 (d, *J* = 8.7 Hz, 2 H), 7.59 (d, *J* = 5.7 Hz, 1 H), 7.22 (s, 1 H), 7.18 (s, 1 H), 4.07 (s, 3 H), 3.89 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.4, 152.9, 150.6, 147.7, 146.3, 141.2, 133.9, 130.6, 123.6, 122.2, 119.8, 105.1, 104.2, 56.1, 55.9.

MS: *m*/*z* (%) = 311 (M + 1, 3), 310 (M$^+$, 100), 309 (M – 1, 17), 295 (28), 280 (24), 279 (28), 249 (30).

Anal. Calcd for $C_{17}H_{14}N_2O_4$: C, 65.80; H, 4.55; N, 9.03. Found: C, 65.89; H, 4.47; N, 9.07.

6,7-Dimethoxy-1-(4-methoxyphenyl)isoquinoline (2c)[17]

Colorless solid; mp 114–116 °C (EtOAc–PE).

IR (KBr): 2967, 1513, 1482, 1250, 860, 826 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.46 (d, *J* = 5.7 Hz, 1 H), 7.69–7.66 (m, 2 H), 7.46 (d, *J* = 5.7 Hz, 1 H), 7.41 (s, 1 H), 7.11 (s, 1 H), 7.08–7.05 (m, 2 H), 4.04 (s, 3 H), 3.89 (s, 3 H), 3.88 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.7, 157.9, 152.5, 149.8, 141.3, 133.7, 132.5, 130.8, 122.4, 118.3, 113.8, 105.6, 104.9, 56.0, 55.8, 55.3.

MS: *m*/*z* (%) = 296 (M + 1, 3), 295 (M$^+$, 100), 294 (M – 1, 41), 280 (77), 265 (29), 264 (29).

Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.11; H, 5.81; N, 4.95.

6,7-Dimethoxy-1-(2-iodophenyl)isoquinoline (2d)
Colorless solid; mp 74–78 °C (EtOH–PE).

IR (KBr): 2958, 2933, 1621, 1563, 1504, 1477, 1234, 859, 760 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.49 (d, *J* = 5.4 Hz, 1 H), 8.01 (d, *J* = 8.1 Hz, 1 H), 7.59 (d, *J* = 5.4 Hz, 1 H), 7.54–7.43 (m, 2 H), 7.21–7.16 (m, 2 H), 6.80 (s, 1 H), 4.05 (s, 3 H), 3.81 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.6, 152.9, 150.1, 144.1, 140.8, 139.2, 133.3, 130.3, 129.8, 128.2, 122.5, 119.4, 105.2, 104.9, 97.8, 56.1, 55.9.

MS: *m*/*z* (%) = 392 (M + 1, 14), 391 (M^+, 100), 264 (65), 220 (13).

Anal. Calcd for $C_{17}H_{14}INO_2$: C, 52.19; H, 3.61; N, 3.58. Found: C, 52.27; H, 3.68; N, 3.74.

6,7-Dimethoxy-1-(3-bromophenyl)isoquinoline (2e)
Colorless solid; mp 125–127 °C (EtOH–PE).

IR (KBr): 2928, 1623, 1504, 1475, 1421, 1233, 1221, 854 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.47 (d, *J* = 5.4 Hz, 1 H), 7.89 (t, *J* = 1.8 Hz, 1 H), 7.66–7.60 (m, 2 H), 7.52 (dd, *J* = 6.0, 0.6 Hz, 1 H), 7.40 (dt, *J* = 7.8, 0.6 Hz, 1 H), 7.30 (s, 1 H), 7.13 (s, 1 H), 4.05 (s, 3 H), 3.88 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.4, 152.7, 150.2, 141.9, 141.2, 133.7, 132.6, 131.4, 129.8, 128.1, 122.6, 122.3, 119.1, 104.96, 104.87, 55.0, 55.9.

MS: *m*/*z* (%) = 345 (M + 2, 53), 344 (M + 1, 23), 343 (M^+, 100), 342 (M – 1, 21), 330 (30), 328 (46), 220 (19).

Anal. Calcd for $C_{17}H_{14}BrNO_2$: C, 59.32; H, 4.10; N, 4.07. Found: C, 59.34; H, 4.21; N, 4.13.

6,7-Dimethoxy-1-(2-phenylethenyl)isoquinoline (2f)[18]
Yellow solid; mp 172–175 °C (acetone–PE).

IR (KBr): 2963, 1626, 1509, 1479, 1418, 1241, 853 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.42 (d, *J* = 5.4 Hz, 1 H), 7.95 (d, *J* = 15.6 Hz, 1 H), 7.81 (d, *J* = 15.6 Hz, 1 H), 7.70–7.67 (m, 2 H), 7.48 (s, 1 H), 7.44–7.38 (m, 3 H), 7.35–7.30 (m, 1 H), 7.03 (s, 1 H), 4.06 (s, 3 H), 4.01 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.5, 152.0, 150.0, 141.3, 137.0, 135.1, 133.6, 128.6, 128.3, 127.3, 123.1, 122.5, 118.8, 105.1, 102.6, 55.93, 55.90.

MS: *m*/*z* (%) = 292 (M + 1, 0.4), 291 (M^+, 23), 290 (M – 1, 100), 276 (18), 274 (15).

Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.29; H, 6.03; N, 4.90.

6,7-Dimethoxy-1-methylisoquinoline (2g)[11]
Colorless solid; mp 142–145 °C (acetone–PE).

IR (KBr): 2968, 1620, 1569, 1508, 1479, 1422, 1234, 1205, 1160, 861, 839 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.28 (d, *J* = 5.7 Hz, 1 H), 7.38 (d, *J* = 5.7 Hz, 1 H), 7.27 (s, 1 H), 7.06 (s, 1 H), 4.04 (s, 3 H), 4.03 (s, 3 H), 2.89 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.8, 152.4, 149.8, 140.8, 132.6, 123.1, 118.1, 105.2, 103.7, 55.94, 55.90, 22.4.

MS: *m*/*z* (%) = 204 (M + 1, 2), 203 (M^+, 100), 202 (M – 1, 1), 188 (15), 160 (65), 145 (8), 117 (15).

Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.87; H, 6.37; N, 6.89.

β-Carbolines 4a–f; General Procedure
Triflic anhydride (0.05 mL, 0.3 mmol) was added dropwise by syringe to a stirred solution of Ph_3PO (0.166 g, 0.6 mmol) in anhyd chlorobenzene (4.0 mL) at 0 °C. After 10 min, the appropriate amide **3** (0.2 mmol) was added in one portion. The reaction mixture was stirred at r.t. for 30 min and then heated at 130 °C for another 30 min. MnO_2 (52.0 mg, 0.6 mmol) was added and the reaction was maintained at the same temperature for 4 h. After cooling, the mixture was diluted with $CHCl_3$ (20 mL) and filtered through Celite to remove insoluble precipitates. The filtrate was washed with aq 10% $NaHCO_3$ (10 mL) and brine (10 mL) successively. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by chromatography with EtOAc–PE (1:1) as eluent to afford pure β-carboline (Table 3).

1-Phenyl-9*H*-pyrido[3,4-*b*]indole (4a)[19]
Yellow solid; mp 248–250 °C (EtOH).

IR (KBr): 3044, 1624, 1561, 1416, 1235, 737 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 11.55 (s, 1 H), 8.47 (d, *J* = 5.4 Hz, 1 H), 8.26 (d, *J* = 7.8 Hz, 1 H), 8.12 (d, *J* = 5.1 Hz, 1 H), 8.05 (d, *J* = 7.2 Hz, 2 H), 7.68–7.50 (m, 5 H), 7.27 (t, *J* = 7.2 Hz, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 142.1, 141.1, 138.31, 138.27, 133.0, 129.2, 128.7, 128.5, 128.4, 128.2, 121.6, 120.8, 119.5, 113.9, 112.4.

MS: *m*/*z* (%) = 245 (M + 1, 1), 244 (M^+, 89), 243 (M – 1, 100).

Anal. Calcd for $C_{17}H_{12}N_2$: C, 83.58; H, 4.95; N, 11.47. Found: C, 83.67; H, 5.01; N, 11.64.

1-(3-Bromophenyl)-9*H*-pyrido[3,4-*b*]indole (4b)
Colorless needles; mp 150–151 °C (EtOH–PE).

IR (KBr): 3055, 1625, 1561, 1499, 1456, 1233, 740 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 9.19 (s, 1 H), 8.52 (d, *J* = 5.1 Hz, 1 H), 8.13 (d, *J* = 7.8 Hz, 1 H), 8.01 (t, *J* = 1.8 Hz, 1 H), 7.93 (d, *J* = 5.1 Hz, 1 H), 7.77 (td, *J* = 8.1, 1.2 Hz, 1 H), 7.53–7.44 (m, 3 H), 7.32–7.24 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.1, 140.6, 140.3, 139.2, 133.5, 131.6, 131.0, 130.4, 130.2, 128.6, 126.6, 123.1, 121.7, 121.6, 120.3, 114.3, 111.7.

MS: *m*/*z* (%) = 324 (M + 2, 79), 323 (M + 1, 13), 322 (M^+, 100), 243 (60), 242 (32).

Anal. Calcd for $C_{17}H_{11}BrN_2$: C, 63.18; H, 3.43; N, 8.67. Found: C, 63.11; H, 3.57; N, 8.59.

1-(2-Nitrophenyl)-9*H*-pyrido[3,4-*b*]indole (4c)[20]
Yellow needles; mp 208–209 °C (acetone–PE).

IR (KBr): 3068, 1626, 1524, 1351, 1235, 738 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 11.61 (s, 1 H), 8.36 (d, *J* = 5.4 Hz, 1 H), 8.29 (d, *J* = 7.8 Hz, 1 H), 8.16 (d, *J* = 5.7 Hz, 2 H), 7.95–7.88 (m, 2 H), 7.81–7.75 (m, 1 H), 7.58–7.57 (m, 2 H), 7.31–7.26 (m, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 149.1, 141.0, 139.3, 138.0, 133.5, 133.1, 132.5, 131.5, 129.7, 128.9, 128.4, 124.6, 121.7, 120.7, 119.6, 114.5, 112.1.

MS: *m*/*z* (%) = 290 (M + 1, 2), 289 (M^+, 100), 272 (18), 257 (57), 256 (16), 243 (79), 242 (64).

Anal. Calcd for $C_{17}H_{11}N_3O_2$: C, 70.58; H, 3.83; N, 14.53. Found: C, 70.51; H, 4.01; N, 14.55.

1-(2-Methylprop-1-en-1-yl)-9*H*-pyrido[3,4-*b*]indole (4d)[12]
Pale yellow solid; mp 162–165 °C (acetone–PE).

IR (KBr): 3060, 1660, 1624, 1563, 1505, 1424, 1252, 1241, 746 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 11.56 (s, 1 H), 8.32 (d, *J* = 5.4 Hz, 1 H), 8.18 (d, *J* = 7.8 Hz, 1 H), 7.90 (d, *J* = 5.1 Hz, 1 H), 7.60 (d, *J* = 8.4 Hz, 1 H), 7.52 (td, *J* = 6.9, 0.6 Hz, 1 H), 7.22 (t, *J* = 6.9 Hz, 1 H), 6.82 (s, 1 H), 2.25 (s, 3 H), 2.05 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 141.5, 140.9, 140.2, 137.5, 134.0, 127.8, 127.5, 121.5, 121.0, 119.6, 119.2, 112.4, 111.9, 27.4, 20.2.

MS: *m*/*z* (%) = 223 (M + 1, 0.3), 222 (M^+, 72), 221 (M – 1, 4), 207 (100), 206 (42).

Anal. Calcd for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35; N, 12.60. Found: C, 81.01; H, 6.36; N, 12.61.

1-Methyl-9*H*-pyrido[3,4-*b*]indole (4e)[13]
Yellow solid; mp 230–232 °C (EtOH–PE).

IR (KBr): 3060, 1624, 1567, 1503, 1321, 1235, 751 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 11.57 (s, 1 H), 8.21–8.17 (m, 2 H), 7.92 (d, *J* = 5.1 Hz, 1 H), 7.60 (d, *J* = 8.1 Hz, 1 H), 7.53 (dt, *J* = 8.1, 1.2 Hz, 1 H), 7.22 (dt, *J* = 8.1, 1.2 Hz, 1 H), 2.77 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 142.1, 140.3, 137.5, 134.4, 127.8, 126.8, 121.7, 121.1, 119.2, 112.6, 111.9, 20.4.

MS: *m*/*z* (%) = 183 (M + 1, 1), 182 (M^+, 100), 181 (M – 1, 11).

Anal. Calcd for $C_{12}H_{10}N_2$: C, 79.10; H, 5.53; N, 15.37. Found: C, 78.93; H, 5.47; N, 15.21.

1-Ethyl-9*H*-pyrido[3,4-*b*]indole (4f)[14]
Brown solid; mp 192–195 °C (acetone–PE).

IR (KBr): 3066, 2966, 1624, 1505, 1324, 1243, 1023, 742 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 9.57 (s, 1 H), 8.42 (d, *J* = 5.4 Hz, 1 H), 8.12 (d, *J* = 7.8 Hz, 1 H), 7.85 (d, *J* = 5.4 Hz, 1 H), 7.55–7.47 (m, 2 H), 7.30–7.25 (m, 1 H), 3.18 (q, *J* = 7.5 Hz, 2 H), 1.44 (t, *J* = 7.8 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.9, 140.4, 138.3, 134.1, 128.7, 128.2, 121.9, 121.7, 119.9, 112.9, 111.6, 27.3, 12.8.

MS: *m*/*z* (%) = 197 (M + 1, 0.3), 196 (M^+, 759), 195 (M – 1, 100), 168 (12).

Anal. Calcd for $C_{13}H_{12}N_2$: C, 79.56; H, 6.16; N, 14.27. Found: C, 79.59; H, 6.17; N, 14.31.

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References

(1) For isoquinoline alkaloids: (a) Bentley, K. W. *Nat. Prod. Rep.* **1992**, *9*, 365. (b) Bentley, K. W. *Nat. Prod. Rep.* **2000**, *17*, 247. (c) Bentley, K. W. *Nat. Prod. Rep.* **2001**, *18*, 148. (d) Bentley, K. W. *Nat. Prod. Rep.* **2002**, *19*, 332. (e) Bentley, K. W. *Nat. Prod. Rep.* **2003**, *20*, 342. (f) Bentley, K. W. *Nat. Prod. Rep.* **2004**, *21*, 395.

(2) For β-carboline alkaloids: (a) Love, B. E. *Org. Prep. Proced. Int.* **1996**, *28*, 1. (b) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797.

(3) For name reactions: (a) Bischler, A.; Napieralski, B. *Ber. Dtsch. Chem. Ges.* **1893**, *26*, 1903. (b) Wolfe, J. P. *Bischler–Napieralski Reaction,* In *Name Reactions in Heterocyclic Chemistry*; Li, J. J.; Corey, E. J., Eds.; Wiley: Hoboken, NJ, **2005**, 376–385. (c) Pictet, A.; Spengler, T. *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 2030. (d) Tinsley, J. M. *Pictet–Gams Isoquinoline Synthesis,* In *Name Reactions in Heterocyclic Chemistry*; Li, J. J.; Corey, E. J., Eds.; Wiley: Hoboken, NJ, **2005**, 469–479. (e) Pictet, A.; Gams, A. *Ber. Dtsch. Chem. Ges.* **1909**, *42*, 1973. (f) Holsworth, D. D. *Pictet–Gams Isoquinoline Synthesis,* In *Name Reactions in Heterocyclic Chemistry*; Li, J. J.; Corey, E. J., Eds.; Wiley: Hoboken, NJ, **2005**, 457–465. (g) Pomeranz, C. *Monatsh. Chem.* **1893**, *14*, 116. (h) Hudson, A. *Pomeranz–Fritsch Reaction,* In *Name Reactions in Heterocyclic Chemistry*; Li, J. J.; Corey, E. J., Eds.; Wiley: Hoboken NJ, **2005**, 480–486.

(4) (a) Hendrickson, J. B.; Schwartzman, S. M. *Tetrahedron Lett.* **1975**, *16*, 277. (b) Hendrickson, J. B.; Hussoin, M. S. *J. Org. Chem.* **1987**, *52*, 4137. (c) Hendrickson, J. B.; Hussoin, M. S. *J. Org. Chem.* **1989**, *54*, 1144. (d) Hendrickson, J. B.; Hussoin, M. S. *Synthesis* **1989**, 217. (e) Hendrickson, J. B.; Hussoin, M. S. *Synlett* **1990**, 423. (f) Hendrickson, J. B.; Walker, M. A.; Varvak, A.; Hussoin, M. S. *Synlett* **1996**, 661.

(5) (a) You, S.-L.; Razavi, H.; Kelly, J. W. *Angew. Chem. Int. Ed.* **2003**, *42*, 83. (b) You, S.-L.; Kelly, J. W. *J. Org. Chem.* **2003**, *68*, 9506. (c) You, S.-L.; Kelly, J. W. *Org. Lett.* **2004**, *6*, 1681.

(6) (a) Zhou, H.-B.; Liu, G.-S.; Yao, Z.-J. *J. Org. Chem.* **2007**, *72*, 6270. (b) Zhou, H.-B.; Liu, G.-S.; Yao, Z.-J. *Org. Lett.* **2007**, *9*, 2003.

(7) (a) Janin, Y. L.; Roulland, E.; Beurdeley-Thomas, A.; Decaudin, D.; Monneret, C.; Poupon, M.-F. *J. Chem. Soc., Perkin Trans. 1* **2002**, 529. (b) Dehmlow, H.; Aebi, J. D.; Jolidon, S.; Ji, Y.; von de Mark, E. M.; Himber, J.; Morand, O. H. *J. Med. Chem.* **2003**, *46*, 3354.

(8) (a) Somei, M.; Sato, H.; Komura, N.; Kaneko, C. *Heterocycles* **1985**, *23*, 1101. (b) Winkler, J. D.; Londregan, A. T.; Hammann, M. T. *Org. Lett.* **2006**, *8*, 2591.

(9) (a) Wei, X.; Hu, Y.; Li, T.; Hu, H. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2487. (b) Wang, B.; Zhang, X.; Li, J.; Jiang, X.; Hu, Y.; Hu, H. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1571.

(10) Nakamichi, N.; Kawashita, Y.; Hayashi, M. *Org. Lett.* **2002**, *4*, 3955.

(11) Rahman, A.; Malik, S.; Zaman, K. *J. Nat. Prod.* **1992**, *55*, 676.

(12) Gozler, T.; Gozler, B.; Linden, A.; Hesse, M. *Phytochemistry* **1996**, *43*, 1425.

(13) Blackman, A. J.; Matthews, D. J.; Narkowicz, C. K. *J. Nat. Prod.* **1987**, *50*, 494.

(14) Aono, H.; Koike, K.; Kaneko, J.; Ohmoto, T. *Phytochemistry* **1994**, *37*, 579.

(15) Movassaghi, M.; Hill, M. D. *Org. Lett.* **2008**, *10*, 3485.

(16) Walker, K. A.; Boots, M. R.; Stubbins, J. F.; Rogers, M. E.; David, C. W. *J. Med. Chem.* **1983**, *26*, 174.

(17) Batra, S.; Sabnis, Y. A.; Rosenthal, P. J.; Avery, M. A. *Bioorg. Med. Chem.* **2003**, *11*, 2293.

(18) Balogh, G.; Doman, I.; Blasko, G.; Simig, G.; Kovacs, N. K. E.; Gyertyan, I.; Egyed, A.; Gacsalyi, I.; Bilkei-Gorzo, A.; Pallagi, K.; Szemeredi, K.; Kazo, N. D. K. European Patent EP 680953, **1995**; *Chem. Abstr.* **1996**, *124*, 175859.

(19) Kusurkar, R. S.; Goswami, S. K. *Tetrahedron* **2004**, *60*, 5315.

(20) Saha, B.; Kumar, R.; Maulik, P. R.; Kundu, B. *Tetrahedron Lett.* **2006**, *47*, 2765.