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# BIOMIMETIC SYNTHESIS OF IHEYAMINE A FROM SPIROCYCLIC OXINDOLES

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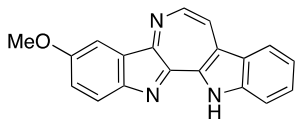
**Abstract** – The biomimetic synthesis of azepinobisindole alkaloid iheyamine A from a spirocyclic oxindole via an oxidative rearrangement has been accomplished for the first time. Furthermore, an unprecedented method for constructing 2,1'-spirocyclic oxindoles from azepinobisindoles through an alternative oxidative rearrangement has been explored.

## INTRODUCTION

Azepinobisindole alkaloid iheyamine A (**1**) was isolated by Higa and co-workers from a colonial ascidian *Polycitorella* sp. collected off the coast of iheya island in Japan (Figure 1).[1] Sperry and co-workers reported the first total synthesis of **1** based on an acid-mediated cross-Mannich reaction.[2] Recently, our group reported the total synthesis of iheyamine A (**1**) by an indium-catalyzed dehydrative Mannich-type reaction to construct the bisindole bond.[3] Despite the significant advances, establishing more straightforward methods as well as developing a biomimetically reaction for the construction of azepinobisindole core are highly desirable.[4]



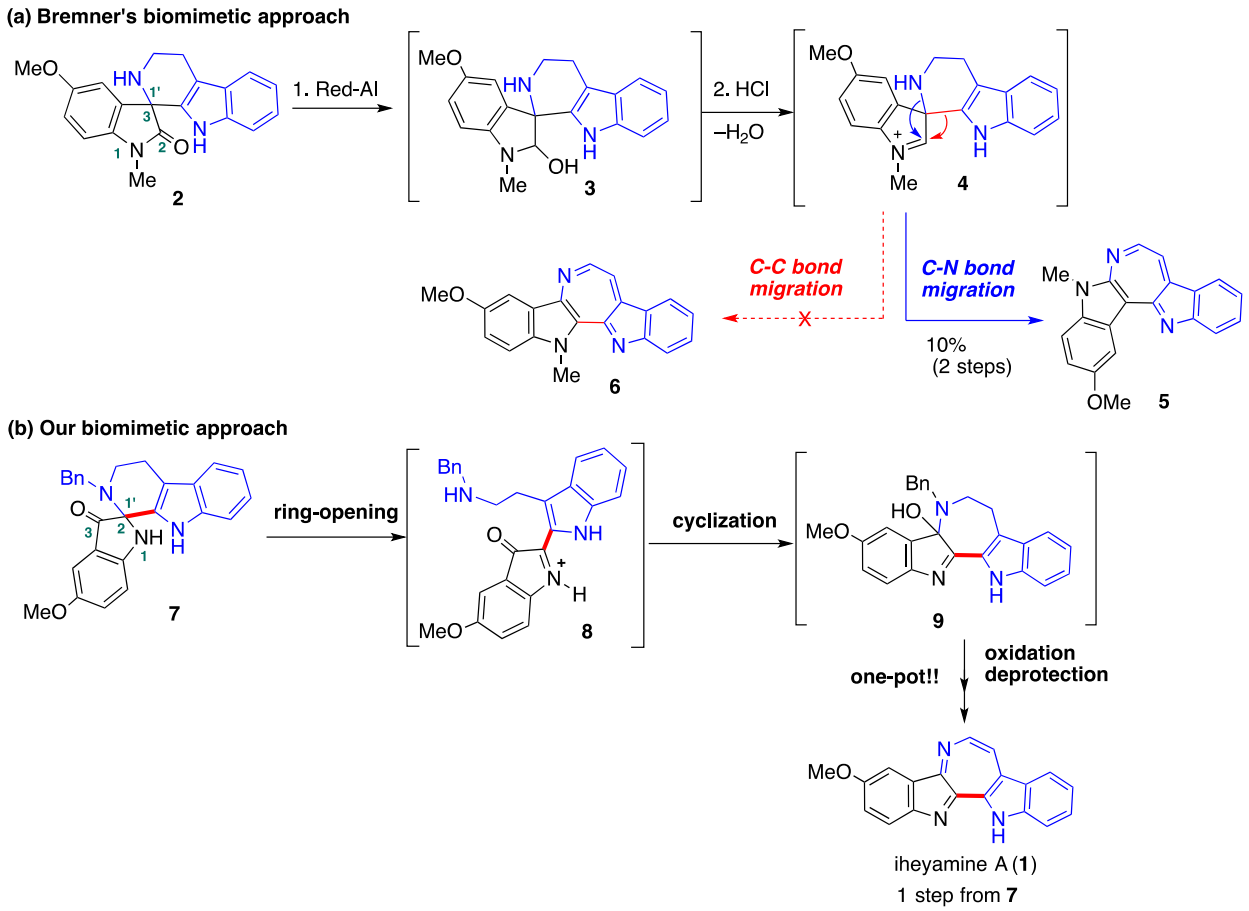

iheyamine A (**1**)

Figure 1. Structure of iheyamine A

Biosynthetically, the azepinobisindole core is postulated to be formed by the oxidative rearrangement of a spirocyclic oxindole. In 2008, Bremner and co-workers reported the oxidative rearrangement of 3,1'-spirocyclic oxindole **2** through intermediate **3** and indolenium **4** to form the azepinobisindoles (Scheme 1a).[5] The undesired formation of isomeric iheyamine **5** via C-N bond migration was preferred

instead of the desired formation of N-Me iheyamine **6** via C-C bond migration. While this affords isomeric iheyamine A derivatives, the biomimetic synthesis of iheyamine A remains unexplored.[4–6]

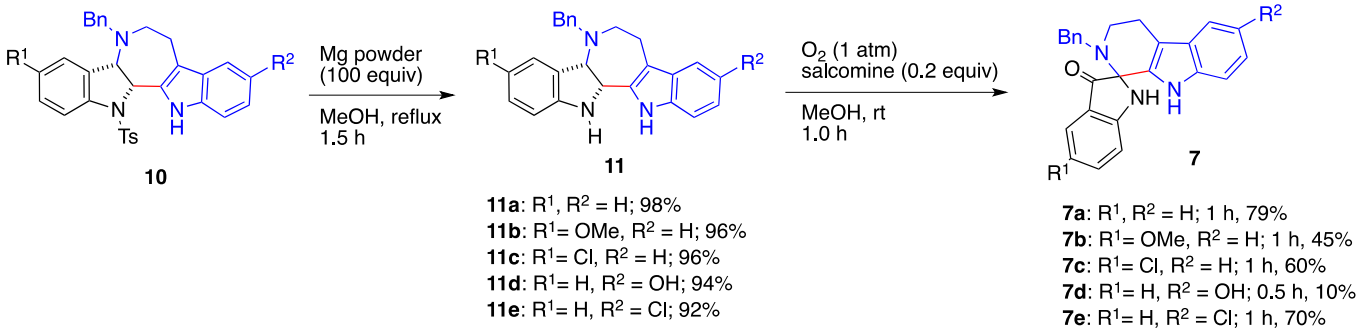
As the continuous study of our group on the synthesis of indole alkaloids,[7] we envisioned that a 2,2-spirocyclic oxindole **7**, which is readily available from a previous synthetic intermediate,[3] would allow ring-opening and cyclization, to afford an indolenium intermediate **9** (Scheme 1b). We also hypothesized that deprotection and oxidation of **9** would lead to compound **1** via a one-pot operation.




Scheme 1. (a) Bremer's biomimetic approach, and (b) our biomimetic approach to iheyamine A (**1**)

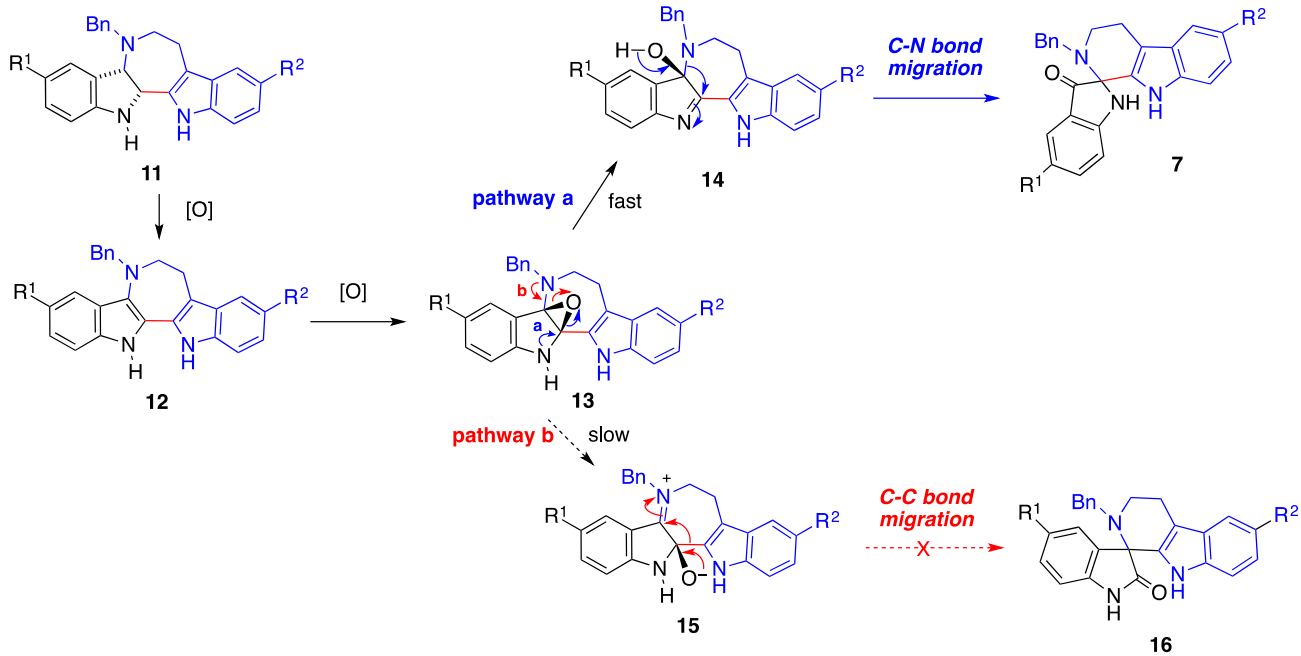
## RESULTS AND DISCUSSION

Initially, the starting materials **10** were prepared by our reported method[3] in 2 steps from an indole-2,3-epoxide equivalent.[8] Deprotection of **10** gave **11** in high yields (92–98%).[9] Subsequent oxidative rearrangement of **11** in the presence of salcomine under $O_2$ atmosphere was carried out to form 2,1'-spirocyclic oxindole **7** (Scheme 2).[10] In the case of the unprotected **11d**, the oxidative rearrangement resulted in low yield due to the instability of **7d**. To the best of our knowledge, there have been no reports on the synthesis of 2,1'-spirocyclic oxindoles from azepinobisindoles.[4]




Scheme 2. Synthesis of spirocyclic oxindoles **7**

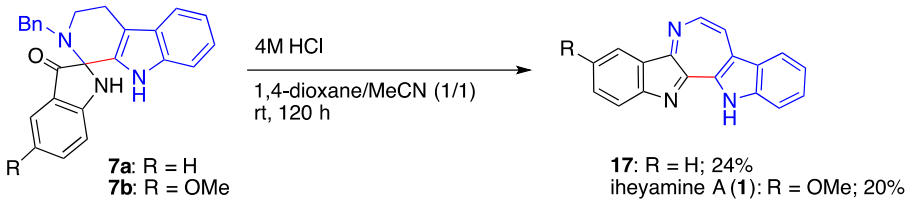
A plausible mechanism underlying the oxidative rearrangement of **11** is proposed on the basis of previous reports (Scheme 3).[5] Initially, indoline **11** is oxidized by $O_2$ to generate indole **12**. Subsequent epoxidation of the indole double bond furnishes epoxide **13**, which can undergo a ring-opening via pathway (a) or (b) to give the corresponding intermediate **14** or **15** depending on the stabilization of the carbocation. Because of the free N-H bond, the intermediate **13** follows pathway (a), with subsequent C-N bond migration to give 2,1'-spirocyclic oxindole **7**. In another reaction pathway (b), the ring-opening of **13** affords the intermediate **15** via C-C bond migration, i.e., known as the retro-Ciamician–Plancher rearrangement,[11] to generate 3,1'-spirocyclic oxindole **16**.




Scheme 3. Proposed mechanism for the formation of **7** *via* C-N bond migration

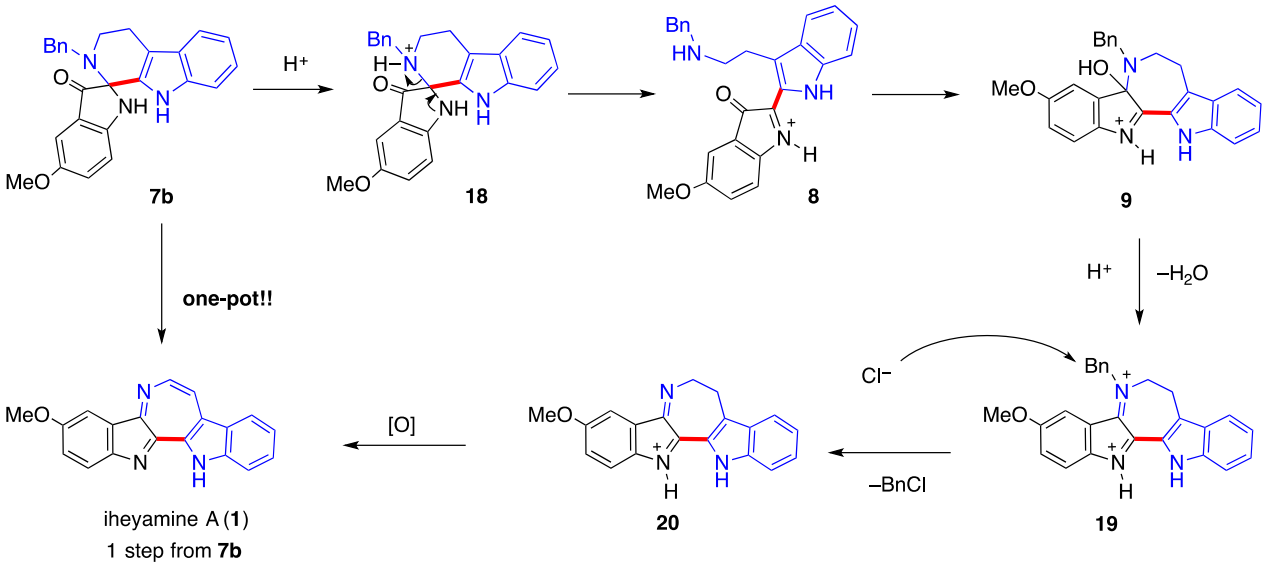
An electronic factor is thought to facilitate the C-N bond migration. In the C-N bond migration, the carbocation generates at the indole C2 position, which is stabilized by the adjacent nitrogen and favored. On the other hands, in the C-C bond migration, the carbocation generates at the electron rich indole C3

position; this is disfavored beacuse of the absence of resonance stabilization from the adjacent benzyl nitrogen, which would be protonated under the reaction conditions. In other words, preferential bond migration is expected depending on the stabilization of the carbocations. In our system, C-N bond migration occurs via the stabilized carbocation in our system.




Scheme 4. Synthesis of iheyamine A (**1**)

With the 2,1'-spirocyclic oxindole **7** in hand, we next evaluated the oxidative rearrangement of **7** (Scheme 4). Treatment of **7a** with 4M HCl under air at room temperature promoted the rearrangement to the azepinobisindole **17** (24% yield). When the substrate **7a** was changed to **7b**, iheyamine A (**1**) was obtained in 20% yield.




Scheme 5. Proposed mechanism for the formation of **1**

A possible mechanism for the formation of **1** from **7b** is postulated in Scheme 5. Initially, the protonation of **7b** affords the ammonium ion **18**, which then undergoes the ring-opening to afford intermediate **8**. Nucleophilic addition of benzylamine to the ketone moiety in **8** generates **9**.[12] Dehydration of **9** and subsequent cleavage of the benzyl substituent by $Cl^-$ furnishes **20**, with release of benzyl chloride.[13] Finally, the oxidation by air furnishes the desired compound **1**. All these reaction sequences occur in one-pot.

In conclusion, we have developed a new methodology for the biomimetic synthesis of iheyamine A from a spirocyclic oxindole through the oxidative rearrangement. Furthermore, an unprecedented method for constructing 2,1'-spirocyclic oxindoles from azepinobisindoles has been explored. Thus, the 2,1'-spirocyclic oxindoles and azepinobisindoles were interchangeable with each other.

## EXPERIMETAL

Melting points were recorded with a Yanaco MP3 and are uncorrected. High-resolution MS spectra were recorded with a JEOL JMS-T100LP mass spectrometers. IR spectra were measured with a Shimadzu IRAffinity-1 spectrometer. The NMR experiments were performed with a JEOL JNM-ECA500 (500 MHz) spectrometer, and chemical shifts are expressed in ppm (δ) using residual undeuterated solvent as an internal reference ($CDCl_3$ $^1$H-NMR δ 7.25, $^{13}$C-NMR δ 77.1; DMSO $^1$H-NMR δ 2.47, $^{13}$C-NMR δ 40.0). The following abbreviations were used to explain NMR peak multiplicities: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad.

Flash column chromatography was performed on silica gel (Silica Gel 60N, Kanto Chemical Co., Ltd.).

### General Procedure for the Reductive Detosylation of 10a-e[9]

A suspension of Mg powder 300 mg (12.5 mmol) in anhydrous MeOH (7.5 mL) was stirred at room temperature until bubbles occur violently. A solution of **10** (0.25 mmol) in THF (7.5 mL) was added to the suspension and the mixture was heated under reflux with stirring for 2 h. After addition of saturated $NH_4Cl$ (7.5 mL), the whole was extracted with AcOEt (3 x 10 mL), washed with brine (10 mL). The organic layer was dried over $Na_2SO_4$ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (AcOEt/hexane = 1/5–1/1) to give **11a-e**.

### *cis*-5-Benzyl-4b,6,7,12,12b,13-hexahydroazepino[3,2-*b*:4,5-*b*']bisindole (11a)

89.4 mg, 98% yield. colorless powder; mp 165–166 °C (MeOH); IR ($CHCl_3$): 3462, 1605, 1462 $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$): δ 7.92 (br s, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.39 (d, *J* = 7.5 Hz, 1H), 7.32–7.36 (m, 3H), 7.29 (t, *J* = 8.0 Hz, 2H), 7.24–7.20 (m, 2H), 7.15 (t, *J* = 8.0 Hz, 1H), 7.13 (t, *J* = 8.0 Hz, 1H), 6.90 (t, *J* = 7.5 Hz, 1H), 6.69 (d, *J* = 7.5 Hz, 1H), 4.99 (d, *J* = 8.6 Hz, 1H), 4.81 (d, *J* = 8.6 Hz, 1H), 4.08 (br s, 1H), 3.94 (d, *J* = 13.7 Hz, 1H), 3.85 (d, *J* = 14.3 Hz, 1H), 3.29–3.23 (m, 1H), 3.07–3.00 (m, 2H), 2.88–2.82 (m, 1H); $^{13}$C-NMR (125 MHz, $CDCl_3$): δ 149.6, 140.3, 135.8, 132.1, 130.7, 129.2, 129.1, 128.5, 128.3, 126.9, 126.3, 122.3, 120.2, 119.5, 118.9, 112.2, 111.0, 110.6, 67.6, 60.3, 55.0, 45.2, 23.5; HRMS (ESI): calcd for $C_{25}H_{24}N_3$ $[M+H]^+$ 366.1970, found 366.1975.

### *cis*-5-Benzyl-3-methoxy-4b,6,7,12,12b,13-hexahydroazepino[3,2-*b*:4,5-*b*']bisindole (11b)

94.8 mg, 96% yield. colorless powder; mp 151–153 °C (MeOH); IR ($CHCl_3$): 3464, 1491 $cm^{-1}$; $^1$H-NMR (500 MHz, DMSO-$d_6$): δ 10.69 (br s, 1H), 7.35 (d, $J$ = 8.0 Hz, 1H), 7.29–7.24 (m, 5H), 7.18 (t, $J$ = 6.8 Hz, 1H), 7.04 (t, $J$ = 7.5 Hz, 1H), 6.93 (t, $J$ = 7.5 Hz, 1H), 6.84 (d, $J$ = 2.9 Hz, 1H), 6.64 (dd, $J$ = 2.9, 8.6 Hz, 1H), 6.51 (d, $J$ = 8.6 Hz, 1H), 5.58 (d, $J$ = 3.5 Hz, 1H), 4.93 (dd, $J$ = 3.5, 8.6 Hz, 1H), 4.68 (d, $J$ = 8.6 Hz, 1H), 3.75 (s, 2H), 3.66 (s, 3H), 3.16 (ddd, $J$ = 5.1, 8.6, 14.3 Hz, 1H), 2.93 (dt, $J$ = 14.9, 5.7 Hz, 1H), 2.84 (ddd, $J$ = 5.1, 8.6, 16.7 Hz, 1H), 2.73 (dt, $J$ = 17.1, 5.1 Hz, 1H); $^{13}$C-NMR (125 MHz, DMSO-$d_6$): δ 153.1, 145.3, 140.8, 136.0, 134.1, 131.1, 128.9, 128.7, 128.7, 127.2, 121.5, 118.7, 118.6, 114.5, 112.2, 111.1, 110.4, 110.1, 67.8, 60.7, 56.1, 53.9, 46.0, 23.5; HRMS (ESI): calcd for $C_{26}H_{26}N_3O$ $[M+H]^+$ 396.2076, found 369.2120.

***cis*-5-Benzyl-3-chloro-4b,6,7,12,12b,13-hexahydroazepino[3,2-*b*:4,5-*b*']bisindole (11c)**

96.0 mg, 96% yield. colorless powder; mp 185–187 °C (MeOH); IR ($CHCl_3$): 3462, 1605, 1477 $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$): δ 7.86 (br s, 1H), 7.50 (d, $J$ = 7.5 Hz, 1H), 7.35–7.29 (m, 6H), 7.25–7.20 (m, 2H), 7.13 (t, $J$ = 8.0 Hz, 1H), 7.09 (dd, $J$ = 2.3, 8.6 Hz, 1H), 6.57 (d, $J$ = 8.6 Hz, 1H), 5.00 (d, $J$ = 8.6 Hz, 1H), 4.76 (d, $J$ = 9.1 Hz, 1H), 4.06 (br s, 1H), 3.96 (d, $J$ = 13.7 Hz, 1H), 3.86 (d, $J$ = 14.3 Hz, 1H), 3.29–3.21 (m, 1H), 3.10–3.02 (m, 2H), 2.84–2.79 (m, 1H); $^{13}$C-NMR (125 MHz, $CDCl_3$): δ 148.0, 139.9, 135.8, 132.5, 131.7, 129.2, 128.9, 128.6, 128.4, 127.1, 126.2, 124.6, 122.5, 119.6, 118.9, 112.3, 111.7, 110.6, 67.2, 60.6, 55.5, 45.1, 23.4; HRMS (ESI): calcd for $C_{25}H_{23}ClN_3$ $[M+H]^+$ 400.1581 and 402.1551, found 400.1602 and 402.1551.

***cis*-5-Benzyl-9-hydroxy-4b,6,7,12,12b,13-hexahydroazepino[3,2-*b*:4,5-*b*']bisindole (11d)**

88.9 mg, 93% yield. colorless powder; mp 158–160 °C (MeOH); IR ($CHCl_3$): 3607, 3462, 1605, 1483 $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$): δ 7.81 (br s, 1H), 7.38 (d, $J$ = 7.5 Hz, 1H), 7.34 (d, $J$ = 7.5 Hz, 2H), 7.29 (t, $J$ = 7.5 Hz, 2H), 7.22 (t, $J$ = 6.9 Hz, 1H), 7.19 (d, $J$ = 9.1 Hz, 1H), 7.15 (t, $J$ = 8.0 Hz, 1H), 6.90–6.87 (m, 2H), 6.77 (dd, $J$ = 2.3, 8.6 Hz, 1H), 6.69 (d, $J$ = 8.1 Hz, 1H), 4.97 (d, $J$ = 8.6 Hz, 1H), 4.80 (d, $J$ = 8.6 Hz, 1H), 4.53 (br s, 1H), 4.08 (br s, 1H), 3.93 (d, $J$ = 13.7 Hz, 1H), 3.84 (d, $J$ = 14.3 Hz, 1H), 3.27–3.21 (m, 1H), 3.02 (dt, $J$ = 14.3, 5.1 Hz, 1H), 2.94 (ddd, $J$ = 5.7, 10.3, 16.1 Hz, 1H), 2.76 (dt, $J$ = 17.1, 4.6 Hz, 1H); $^{13}$C-NMR (125 MHz, $CDCl_3$): δ 149.6, 149.5, 140.3, 133.4, 131.1, 130.6, 130.0, 129.1, 128.5, 128.3, 126.9, 126.2, 120.1, 111.9, 111.6, 111.3, 111.0, 103.5, 67.6, 60.4, 55.2, 45.2, 23.6; HRMS (ESI): calcd for $C_{25}H_{24}N_3O$ $[M+H]^+$ 382.1919, found 382.1919.

***cis*-5-Benzyl-9-chloro-4b,6,7,12,12b,13-hexahydroazepino[3,2-*b*:4,5-*b*']bisindole (11e)**

93.3 mg, 92% yield. colorless powder; mp 172–174 °C (MeOH); IR ($CHCl_3$): 3462, 1605, 1481, 1468 $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$): δ 7.99 (br s, 1H), 7.45 (d, $J$ = 2.3 Hz, 1H), 7.38 (d, $J$ = 7.5 Hz, 1H),

7.33–7.21 (m, 6H), 7.17–7.13 (m, 2H), 6.90 (t, *J* = 7.5 Hz, 1H), 6.70 (t, *J* = 8.0 Hz, 1H), 4.99 (d, *J* = 8.6 Hz, 1H), 4.82 (d, *J* = 8.0 Hz, 1H), 4.10 (br s, 1H), 3.93 (d, *J* = 13.7 Hz, 1H), 3.82 (d, *J* = 14.3 Hz, 1H), 3.25 (ddd, *J* = 4.6, 9.8, 14.3 Hz, 1H), 3.05–2.93 (m, 2H), 2.78 (dt, *J* = 16.6, 4.6 Hz, 1H); $^{13}$C-NMR (125 MHz, $CDCl_3$): δ 149.5, 140.2, 134.1, 133.8, 130.4, 130.4, 129.1, 128.5, 128.3, 127.0, 126.2, 125.2, 122.5, 120.3, 118.4, 111.9, 111.6, 111.1, 67.6, 60.1, 55.3, 45.1, 23.5; HRMS (ESI): calcd for $C_{25}H_{23}ClN_3$ $[M+H]^+$ 400.1581 and 402.1551, found 400.1579 and 402.1551.

**General Procedure for the Oxidative Spiro Formation of 11a-e**[10]

A suspension of **11** (0.10 mmol) and salcomine [*N*,*N*'-bis(salicylidene)ethylenediiminocobalt(II)] (6.6 mg, 0.02 mmol) in MeOH (5 mL) was vigorously stirred at room temperature under oxygen atmosphere for 0.5–1 h. After addition of AcOEt/hexane (1/1, 5 mL), the mixture was passed through silica gel short-column chromatography (AcOEt/hexane = 1/1). The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (AcOEt/hexane = 1/5–1/1) to give **7a-e**.

**2'-Benzyl-2',3',4',9'-tetrahydrospiro[indoline-2,1'-pyrido[3,4-*b*]indol]-3-one (7a)**

30.0 mg, 79% yield. yellow prisms; mp 167–169 °C (MeOH); IR ($CHCl_3$): 3458, 1713, 1616 $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$): δ 7.67 (d, *J* = 7.5 Hz, 1H), 7.56–7.52 (m, 2H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.40 (d, *J* = 7.5 Hz, 2H), 7.30 (t, *J* = 7.5 Hz, 2H), 7.24 (t, *J* = 7.4 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.14 (t, *J* = 8.0 Hz, 1H), 7.09 (t, *J* = 8.0 Hz, 1H), 6.92–6.89 (m, 2H), 5.00 (br s, 1H), 3.82 (d, *J* = 13.8 Hz, 1H), 3.54 (d, *J* = 14.3 Hz, 1H), 3.50 (ddd, *J* = 4.6, 6.3, 11.5 Hz, 1H), 2.95–2.84 (m, 2H), 2.77 (ddd, *J* = 5.2, 6.3, 15.5 Hz, 1H); $^{13}$C-NMR (125 MHz, $CDCl_3$): δ 200.7, 160.1, 139.3, 138.5, 136.4, 130.1, 128.6, 128.4, 127.2, 126.7, 125.3, 122.9, 120.3, 119.8, 119.8, 118.8, 113.5, 112.5, 111.1, 80.0, 53.7, 44.8, 21.4; HRMS (ESI): calcd for $C_{25}H_{22}N_3O$ $[M+H]^+$ 380.1763, found 380.1780.

**2'-Benzyl-5-methoxy-2',3',4',9'-tetrahydrospiro[indoline-2,1'-pyrido[3,4-*b*]indol]-3-one (7b)**

18.4 mg, 45% yield. yellow powder; mp 116–119 °C; IR ($CHCl_3$): 3456, 1703, 1493 $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$): δ 7.56 (br s, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.41 (d, *J* = 6.9 Hz, 2H), 7.30 (t, *J* = 7.5 Hz, 2H), 7.25–7.21 (m, 2H), 7.17 (d, *J* = 8.0 Hz, 1H), 7.15–7.11 (m, 2H), 7.24 (t, *J* = 7.5 Hz, 1H), 6.88 (d, *J* = 8.6 Hz, 1H), 4.77 (br s, 1H), 3.80 (s, 3H), 3.79 (d, *J* = 13.8 Hz, 1H), 3.55 (d, *J* = 13.8 Hz, 1H), 3.47–3.42 (m, 1H), 2.94–2.84 (m, 2H), 2.78–2.74 (m, 1H); $^{13}$C-NMR (125 MHz, $CDCl_3$): δ 200.9, 155.9, 154.0, 139.3, 136.3, 130.4, 128.9, 128.7, 128.4, 127.2, 126.7, 122.9, 120.7, 119.9, 118.8, 114.4, 113.4, 111.1, 105.2, 81.1, 55.9, 53.8, 44.8, 21.5; HRMS (ESI): calcd for $C_{26}H_{24}N_3O_2$ $[M+H]^+$ 410.1869, found 410.1835.

**2'-Benzyl-5-chloro-2',3',4',9'-tetrahydrospiro[indoline-2,1'-pyrido[3,4-*b*]indol]-3-one (7c)**

24.7 mg, 60% yield. yellow prisms; mp 180–183 °C (MeOH); IR ($CHCl_3$): 3458, 1717, 1612, 1472 $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$): δ 7.63 (d, *J* = 2.3 Hz, 1H), 7.52 (br s, 1H), 7.50–7.47 (m, 2H), 7.38 (d, *J* = 7.5 Hz, 2H), 7.31 (t, *J* = 7.5 Hz, 2H), 7.26–7.23 (m, 1H), 7.21 (d, *J* = 8.0 Hz, 1H), 7.15 (t, *J* = 7.5 Hz, 1H), 7.09 (t, *J* = 7.5 Hz, 1H), 6.86 (d, *J* = 8.6 Hz, 1H), 5.02 (br s, 1H), 3.81 (d, *J* = 13.8 Hz, 1H), 3.51 (d, *J* = 13.8 Hz, 1H), 3.51–3.47 (m, 1H), 2.95–2.90 (m, 1H), 2.88–2.82 (m, 1H), 2.77 (ddd, *J* = 5.2, 6.9, 15.5 Hz, 1H); $^{13}$C-NMR (125 MHz, $CDCl_3$): δ 199.7, 158.3, 139.1, 138.3, 136.4, 129.5, 128.5, 128.4, 127.3, 126.6, 125.1, 124.6, 123.1, 121.2, 120.0, 118.9, 113.7, 113.6, 111.2, 80.8, 53.7, 44.8, 21.4; HRMS (ESI): calcd for $C_{25}H_{21}Cl\ N_3O$ $[M+H]^+$ 414.1373 and 416.1344, found 414.1372 and 416.1352.

**2'-Benzyl-6'-hydroxy-2',3',4',9'-tetrahydrospiro[indoline-2,1'-pyrido[3,4-*b*]indol]-3-one (7d)**

4.0 mg, 10% yield. yellow prisms; decomp. 150–153 °C (MeOH); IR ($CHCl_3$): 3601, 3458, 1713, 1616, 1468 $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$): δ 7.67 (d, *J* = 8.1 Hz, 1H), 7.54(t, *J* = 7.5 Hz, 1H), 7.40–7.38 (m, 3H), 7.30 (t, *J* = 7.5 Hz, 2H), 7.25–7.22 (m, 1H), 7.04 (d, *J* = 8.1 Hz, 1H), 6.92–6.90 (m, 3H), 6.70 (dd, *J* = 2.3, 8.6 Hz, 1H), 4.99 (br s, 1H), 4.47 (br s, 1H), 3.81 (d, *J* = 14.3 Hz, 1H), 3.53 (d, *J* = 14.3 Hz, 1H), 3.49–3.45 (m, 1H), 2.93–2.88 (m, 1H), 2.82–2.76 (m, 1H), 2.72–2.68 (m, 1H); $^{13}$C-NMR (125 MHz, $CDCl_3$): δ 200.7, 160.1, 149.7, 139.3, 138.5, 131.6, 131.3, 128.6, 128.4, 127.5, 127.2, 125.3, 120.3, 119.9, 113.0, 112.5, 112.5, 111.8, 103.6, 80.0, 53.7, 44.7, 21.4; HRMS (ESI): calcd for $C_{25}H_{22}N_3O_2$ $[M+H]^+$ 396.1712, found 396.1706.

**2'-Benzyl-6'-chloro-2',3',4',9'-tetrahydrospiro[indoline-2,1'-pyrido[3,4-*b*]indol]-3-one (7e)**

29.1 mg, 70% yield. yellow prisms; mp 195–198 °C (MeOH); IR ($CHCl_3$): 3456, 1715, 1616, 1483, 1468 $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$): δ 7.67 (d, *J* = 7.5 Hz, 1H), 7.59 (br s, 1H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.45 (d, *J* = 1.7 Hz, 1H), 7.38 (d, *J* = 7.5 Hz, 2H), 7.30 (t, *J* = 8.0 Hz, 2H), 7.25–7.22 (m, 1H), 7.12–7.08 (m, 2H), 6.92 (t, *J* = 8.0 Hz, 1H), 6.90 (d, *J* = 8.1 Hz, 1H), 5.00 (br s, 1H), 3.82 (d, *J* = 14.3 Hz, 1H), 3.54–3.48 (m, 2H), 2.94–2.90 (m, 1H), 2.84–2.78 (m, 1H), 2.75–2.70 (m, 1H); $^{13}$C-NMR (125 MHz, $CDCl_3$): δ 200.5, 160.1, 139.1, 138.6, 134.7, 131.7, 128.6, 128.4, 127.8, 127.2, 125.6, 125.3, 123.1, 120.0, 118.4, 113.2, 112.4, 112.1, 79.7, 53.6, 44.6, 21.3; HRMS (ESI): calcd for $C_{25}H_{21}ClN_3O$ $[M+H]^+$ 414.1373 and 416.1344, found 414.1376 and 416.1356.

**12*H*-Azepino[3,2-*b*:4,5-*b*']bisindole (17)**

Migration of **7a** with HCl: To a solution of **7a** (30.0 mg, 0.08 mmol) in MeCN (3 mL) was added a solution of HCl (4M in 1,4-dioxane, 3 mL, 12 mmol) and the mixture was stirred for 120 h at room temperature. The reaction mixture was made alkaline with 5M NaOH under ice cooling and stirred for an

additional 2 h. After addition of $H_2O$, the whole was extracted with AcOEt (3 x 5 mL), washed with brine (5 mL). The organic layer was dried over $Na_2SO_4$ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography ($CHCl_3$ only to 1% MeOH/$CHCl_3$) to give **17** (5.1 mg, 24%). 5.1 mg, 24% yield. purple powder; decomp. 270–280 °C ($CHCl_3$); IR (KBr): 3429, 1618, 1501, 1393 $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$): δ 9.11 (d, *J* = 6.3 Hz, 1H), 8.61–8.59 (m, 2H), 8.42 (d, *J* = 8.0 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.52–7.50 (m, 2H), 7.45 (d, *J* = 8.0 Hz, 1H); $^{13}$C-NMR (125 MHz, $CDCl_3$): δ 151.1, 146.7, 146.2, 145.5, 140.7, 136.9, 135.2, 130.8, 130.1, 127.4, 126.7, 122.8, 122.7, 122.0, 122.0, 121.3, 117.4, 115.1; HRMS (ESI): calcd for $C_{18}H_{12}N_3$ $[M + H]^+$ 270.1031, found 270.1012.

**Iheyamine A (1)**[1–3]

To a solution of **7b** (18.4 mg, 0.05 mmol) in MeCN (2 mL) was added a solution of HCl (4M in 1,4-dioxane, 2 mL, 8 mmol) and the mixture was stirred for 120 h at room temperature. The reaction mixture was made alkaline with 5M NaOH under ice cooling and stirred for an additional 2 h. After addition of $H_2O$, the whole was extracted with AcOEt (3 x 5 mL), washed with brine (5 mL). The organic layer was dried over $Na_2SO_4$ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography ($CHCl_3$ only to 1% MeOH/$CHCl_3$) to give **1** (2.7 mg, 20%).

The spectral data of **1** was identified with previously reported data.[1–3]

2.7 mg, 20% yield. purple powder; $^1$H-NMR (500 MHz, $CDCl_3$): δ 9.42 (d, *J* = 6.3 Hz, 1H), 8.89 (d, *J* = 6.9 Hz, 1H), 8.44 (d, *J* = 8.1 Hz, 1H), 8.08 (d, *J* = 8.6 Hz, 1H), 8.00 (d, *J* = 3.5 Hz, 1H), 8.00 (d, *J* = 8.1 Hz, 1H), 7.51 (t, *J* = 8.1 Hz, 1H), 7.64 (t, *J* = 8.1 Hz, 1H), 7.55 (d, *J* = 9.2, 2.3 Hz, 1H), 4.03 (s, 3H); $^{13}$C-NMR (125 MHz, $CDCl_3$): 157.7, 149.2, 144.0, 143.4, 138.2, 136.0, 133.2, 128.4, 126.2, 124.7, 124.7, 124.4, 124.0, 121.6, 115.8, 115.2, 102.9, 56.1.

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**REFERENCES AND NOTES**

1. T. Sasaki, I. I. Ohtani, J. Tanaka, and T. Higa, *Tetrahedron Lett.*, 1999, **40**, 303.
2. A. C. Lindsay, I. K. H. Leung, and J. Sperry, *Org. Lett.*, 2016, **18**, 5404.
3. T. Abe and K. Yamada, *Org. Lett.*, 2018, **20**, 1469.
4. A. C. Lindsay, S. H. Kim, and J. Sperry, *Nat. Prod. Rep.*, 2018, **35**, 1347.
5. J. Bremner, W. Sengpracha, and B. W. Skelton, *Synth. Commun.*, 2008, **38**, 1931.

6. A. C. Lindsay and J. Sperry, *Tetrahedron*, 2017, **73**, 4355.
7. (a) T. Abe, *Heterocycles*, 2018, **96**, 490; (b) T. Abe and M. Terasaki, *Helv. Chim. Acta*, 2018, **101**, e1700284; (c) T. Abe, T. Haruyama, and K. Yamada, *Synthesis*, 2017, **49**, 4141; (d) T. Abe and K. Yamada, *J. Nat. Prod*., 2017, **80**, 241; (e) T. Abe and K. Yamada, *Org. Lett.*, 2016, **18**, 6504; (f) T. Itoh, T. Abe, T. Choshi, T. Nishiyama, R. Yanada, and M. Ishikura, *Eur. J. Org. Chem*., 2016, 2290; (g) T. Itoh, T. Abe, T. Choshi, T. Nishiyama, and M. Ishikura, *Heterocycles*, 2016, **92**, 1132; (h) T. Abe and M. Ishikura, *Heterocycles*, 2015, **90**, 673; (i) T. Itoh, T. Abe, S. Nakamura, and M. Ishikura, *Heterocycles*, 2015, **91**, 1423; (j) T. Abe, T. Itoh, S. Hibino, T. Choshi, and M. Ishikura, *Tetrahedron Lett*., 2014, **55**, 5268; (k) T. Abe, T. Ikeda, T. Itoh, N. Hatae, E. Toyota, and M. Ishikura, *Heterocycles*, 2014, **88**, 187; (l) T. Abe, S. Nakamura, R. Yanada, T. Choshi, S. Hibino, and M. Ishikura, *Org. Lett*., 2013, **15**, 3622; (m) T. Abe, T. Ikeda, T. Choshi, S. Hibino, N. Hatae, E. Toyota, and M. Ishikura, *Eur. J. Org. Chem*., 2012, 5018; (n) T. Abe, H. Komatsu, T. Ikeda, N. Hatae, E. Toyota, and M. Ishikura, *Heterocycles*, 2012, **86**, 505; (o) T. Abe, T. Ikeda, R. Yanada, and M. Ishikura, *Org. Lett*., 2011, **13**, 3356.
8. (a) T. Abe, T. Suzuki, M. Anada, S. Matsunaga, and K. Yamada, *Org. Lett*., 2017, **19**, 4275; (b) T. Abe, H. Shimizu, S. Takada, T. Tanaka, M. Yoshikawa, and K. Yamada, *Org. Lett.*, 2018, **20**, 1589.
9. B. Nyasse, L. Grehn, and U. Regnarson, *Chem. Commun.*, 1997, 1017.
10. A. Inada, Y. Nakamura, and Y. Morita, *Chem. Lett.*, 1980, 1287.
11. For selected examples of the Ciamician–Plancher rearrangement, see: (a) G. Ciamician and G. Plancher, *Ber. Dtsch. Chem. Ges.*, 1896, **29**, 2475; (b) S. A. Eisenbeis, J. R. Phillips, D. Rescek, and Y. Oyola-Cintron, *Tetrahedron Lett.*, 2010, **51**, 4303; (c) K. G. Liu, A. J. Robichaud, J. R. Lo, J. F. Mattes, and Y. Cai, *Org. Lett*., 2006, **8**, 5769; (d) C. C. J. Loh, G. Raabe, and D. Enders, *Chem. Eur. J*., 2012, **18**, 13250.
12. (a) S. Han and M. Movassaghi, *J. Am. Chem. Soc*., 2011, **133**, 10768; (b) X. Qi, H. Bao, and U. K. Tambar, *J. Am. Chem. Soc*., 2011, **133**, 10050; (c) S. Han, K. C. Morrison, P. J. Hergenrother, and M. Movassaghi, *J. Org. Chem.*, 2014, **79**, 473.
13. H. Ji, Q. Jing, J. Huang, and R. B. Silverman, *Tetrahedron*, 2012, **68**, 1359.