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Construction of pyrrolophenanthridinone scaffolds mediated by samarium(II) diiodide and access to natural product synthesis

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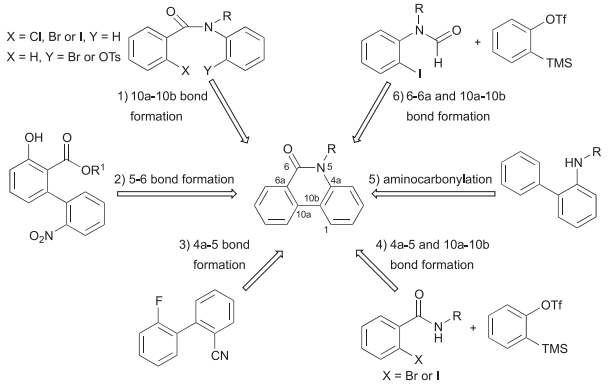
ABSTRACT

Pyrrolophenanthridinone derivatives including the natural products were readily synthesized by samarium(II)-mediated reductive cyclization of aryl radical onto a benzene ring under mild reaction conditions. This methodology was applied to the concise synthesis of anhydrolycorinone, a natural pyrrolophenanthridinone and a precursor of hippadine and anhydrolycorine.

1. Introduction

Phenanthridinone scaffolds possessing a condensed 6-6-6-tricyclic skeleton that includes a δ-lactam structure, are the one of important nuclei found in natural products and biologically active molecules.[1] Reactions for the construction of phenanthridinones are classified into six major types: (1) intramolecular C–C (10a–10b) bond formation by transition-metal-catalyzed annulation[2] or radical cyclization;[3] (2) intramolecular C–N (5–6) bond formation by cyclization of nitrocarbonyl-biphenyls and subsequent reductive lactamization;[4] (3) intramolecular C–N (4a–5) bond formation by transition-metal-catalyzed annulation[5] or microwave-assisted anionic ring closure reaction;[6] (4) intermolecular C–C (10a–10b) and C–N (4a–5) bond formation by transition-metal-catalyzed annulation;[7] (5) C(sp^2)-H aminocarbonylation of *o*-arylanilines;[8] and (6) intermolecular double C–C (6–6a and 10a–10b) bond formation by transition-metal-catalyzed annulation (Scheme 1).[9] However, in some of those, harsh conditions such as a high reaction temperature, use of a strong acid and/or base, and/or a long reaction time, are required. Therefore, the development of novel, practical, and mild procedures is desired.

Pyrrolophenanthridinones, which have a condensed 5-6-6-6-tetracyclic skeleton that includes a dihydroindole structure, are widely found in natural products, particularly *Amaryllidaceae* alkaloids, such as anhydrolycorinone **1a**, hippadine **1c**, oxoassoanine **1e**, and pratosine **1g** (Fig. 1). Because they possess diverse biological activities, including antitumor, antilymphoma, and antiviral activities,[10] the development of efficient synthetic methods has been a fascinating research topic.[11]



Scheme 1. Methods for the construction of phenanthridinones.

Samarium(II) diiodide (SmI_2) is an important reductant for versatile single electron transfer (SET) reactions due to its low toxicity, ease of preparation, tunable reactivity by changing additives, and usefulness under mild reaction conditions.[12,13] Recently, we have reported an intramolecular reductive cyclization of aryl

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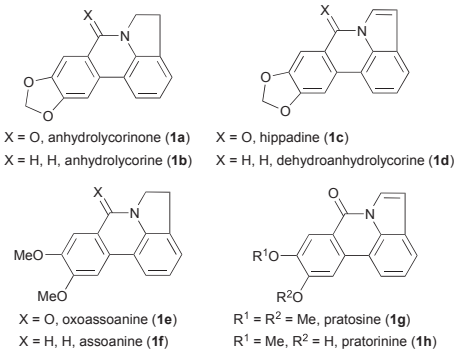
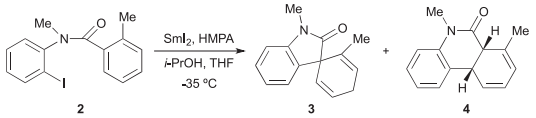


Fig. 1. Pyrrolophenanthridinone-based *Amaryllidaceae* alkaloids.

radicals onto an aromatic ring mediated by SmI_2 for the synthesis of spirocycles **3** as the major product and fused rings **4** as the minor product (Scheme 2).[14] That was the first example of the selective synthesis of spirocycles by aryl radical addition to an aromatic ring. However, product distribution is dependent on the reaction conditions and the substrate. The reaction of benzamide derivatives in the absence of a proton source afforded phenanthridinone derivatives in low yields. From the point of view of the synthesis of phenanthridinone derivatives, our procedure has room for improvement in terms of generality and yield. Therefore, we devised a method for the construction of pyrrolophenanthridinone scaffolds having a more complicated skeleton than phenanthridinone scaffolds. That method was mediated by SmI_2 under mild reaction conditions, and was applied to the synthesis of natural products.



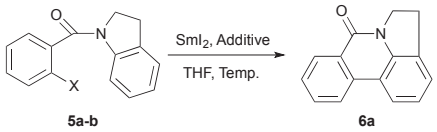
Scheme 2. SmI_2-mediated spirocyclization reaction.

2. Results and discussion

2.1. Cyclization of 1-(2-halobenzoyl)-2,3-dihydroindoles

Because the substrates could be easily prepared by condensation of commercially available substrates, we first examined the aryl radical coupling reaction of 1-(2-halobenzoyl)-2,3-dihydroindole **5**, which has a halogen atom on the benzoyl site.[2j,3a] The reaction of 1-(2-bromobenzoyl)-2,3-dihydroindole **5a** mediated by SmI_2 (5.0 equiv) in THF at −40 °C with HMPA as the additive[14] gave desired product **6a** in low yield (Table 1, entry 1). That reaction, which was attempted at 0 °C, was not efficient and afforded **6a** in 13% yield (entry 2). Next, we examined the cyclization reaction of 1-(2-iodobenzoyl)-2,3-dihydroindole **5b** under the same reaction conditions as those of entry 2, and obtained **6a** in 13% yield (entry 3). In general, the treatment of aryl iodide with SmI_2 produces aryl radical species more easily than that of aryl bromide. However, the halogen species did not affect the yield of this reaction. The addition of *i*-PrOH as the proton source also did not improve the yield (entry 4). Decreasing the amount of SmI_2 to 3.0 equiv slightly improved the yield of **6a**, whereas the reaction with 2.4 equiv of SmI_2 did not proceed at all (entries 5 and 6). When the reaction of **5b** was conducted in the presence of tetramethylethylenediamine (TMEDA) instead of HMPA, the yield of **6a** was increased to 39% (65% based on recovered starting material: b.r.s.m.) (entry 8). However, the yield was not improved in the absence of an additive or when 1,10-phenathroline was used (entries 9 and 10). The cyclization into the pyrrolophenanthridinone scaffold from **5**, which has a halogen atom on the benzoyl site, gave only low yields.

Table 1
Screening for reaction conditions



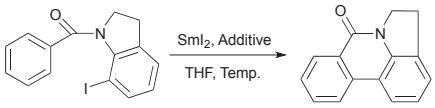
Entry	Starting material	X	SmI_2[a] (equiv)	Additive	Temp (°C)	Yield[b] (%)
1	**5a**:	Br	5.0	HMPA	−40	7
2	**5a**:	Br	5.0	HMPA	0	13
3	**5b**:	I	5.0	HMPA	0	13
4	**5b**:	I	5.0	HMPA, *i*-PrOH	0	12
5	**5b**:	I	3.0	HMPA	0	22
6	**5b**:	I	2.4	HMPA	0	0[c]
7	**5b**:	I	3.0	HMPA	rt	19
8	**5b**:	I	3.0	TMEDA[d]	0	39 (65% b.r.s.m.)
9	**5b**:	I	3.0	1,10-Phenanthroline	0	0[c]
10	**5b**:	I	3.0	None	0	23

[a] SmI_2 (5.0 equiv) was prepared in situ with 6.7 equiv of Sm metal and 5.0 equiv of 1,2-diiodoethane.
[b] Isolated yield.
[c] Starting material was recovered.
[d] TMEDA of 2.2 equiv relative to SmI_2 was used.

2.2. Cyclization of 1-benzoyl-2,3-dihydro-7-iodoindoles

Undaunted by our unsatisfactory results, the cyclization from **7**, which has a halogen atom on the dihydroindole site, was examined. When the reaction was conducted with **7a**[2j] under the optimum conditions (SmI_2 (3.0 equiv)/TMEDA/0 °C) shown in Table 1, **6a** was obtained in only 22% yield along with the deiodinated product, 1-benzoyl-2,3-dihydroindole, in 55% yield (Table 2, entry 1). Then, re-optimization of the reaction conditions for the cyclization of **7a**

Table 2
Optimization of reaction conditions



7a 6a

Entry	SmI_2[a] (equiv)	Additive	Temp (°C)	Yield[b] (%)
1	3.0	TMEDA[c]	0	22[d]
2	3.0	HMPA	0	75
3	3.0	HMPA	−30	60[e]
4	2.5	HMPA	0	70
5	3.5	HMPA	0	84
6	4.0	HMPA	0	62
7	3.5	HMPA, *i*-PrOH	0	22
8	3.5	None	0	30

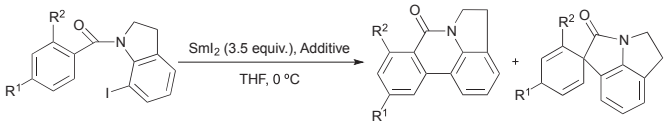
[a] SmI_2 (3.5 equiv) was prepared in situ with 4.8 equiv of Sm metal and 3.5 equiv of 1,2-diiodoethane.
[b] Isolated yield.
[c] TMEDA of 2.2 equiv relative to SmI_2 was used.
[d] Deiodinated product of **7a** was obtained in 55% yield.
[e] Starting material was recovered in 18% yield.

was performed. The use of HMPA as an additive instead of TMEDA dramatically improved the yield of **6a** to 75% (entry 2). It was reported that the SmI_2/amine-mediated reaction without H_2O on the ketone reduction gave a low chemical yield, but the clear reason was not mentioned.[15] In the SmI_2/TMEDA-mediated reaction without a proton source, the similar result was obtained. The reaction at −30 °C was not efficient for the yield improvement of **6a** (entry 3). Screening for the amount of SmI_2 revealed that 3.5 equiv of SmI_2 gave **6a** in the highest yield (84%) (entry 5). The addition of *i*-PrOH as the proton source or the absence of HMPA did not improve the yield (entries 7 and 8). The reactions with other additives such as H_2O and *N*,*N*-dimethylpropyleneurea (DMPU) were examined, however, **6a** was obtained in only low yields.

Next, we investigated the scope and limitations, and summarized the results in Table 3. In *para*-substituted benzamides **7b**–**f**, methyl- and methoxy-substituted benzamides **7b** and **7c** were cyclized into corresponding fused rings **6b** and **6c** in moderate yields by treatment with SmI_2 in the presence of HMPA, respectively (entries 2 and 3). Benzamides **7d**–**f** having an electron-withdrawing group such as chlorine, trifluoromethyl, or methoxycarbonyl group gave **6** in low yields relative to benzamides having an electron-donating group (entries 4–9 vs 2, 3). The reactions of chlorine-substituted analogue **7d** gave dechlorinated cyclized product **6a** in 42% yield together with **6d** in 19% yield (entry 4). In order to block the dechlorination reaction,[16] the reaction of **7d** without HMPA was examined and found to afford **6d** in 57% yield (entry 5). Moreover, treatment of trifluoromethyl derivative **7e** afforded defluorinated cyclized product **6b** in 2% yield together with **6e** in 41% yield (entry 6). Changing the additive to LiBr decreased the yield of **6e** (entry 7). In addition, treatment of **7e** without an additive gave **6e** in 50% yield (entry 8). It was found that the reaction without an additive is efficient for deterring the dehalogenation and improving the yield of the desired product **6e**. Meanwhile, the reaction of *ortho*-methyl-substituted benzamide **7g** gave desired product **6g** in only 15% yield together with spirocycle **8g** in 39% yield (entry 10). This result is in good accordance with our previous report[14] showing that the reaction of *ortho*-methyl-substituted benzamide derivative **2** in the presence of *i*-PrOH gave corresponding spirocycle **3** selectively. The formation of spirocycles **8** indicates that the aryl radical generated by SmI_2 would undergo 5-*exo*-type intramolecular cyclization onto the benzene ring to produce the unstable spirohexadienyl radical intermediate, and that intermediate could be easily rearranged into the fused ring intermediate to give desired cyclized product **6**. Interestingly, treatment of *ortho*-methoxy-substituted benzamide **7h** with SmI_2 and HMPA gave *ipso*-substituted cyclized product **6a** in 45% yield along with spirocycle **8h** in 23% yield (entry 11). Previously, we reported that the ketyl radical *ipso* substitution reaction of an aromatic methoxy group is effectively promoted by SmI_2 without HMPA to afford cyclized products.[17] Thus, we examined the reaction of **7h** with LiBr instead of HMPA or without an additive. Unexpectedly, the yield of the *ipso*-substituted product was decreased or null compared with that when HMPA was used (entries 12 and 13 vs entry 11). We expected that this radical *ipso* substitution could be applied to the regioselective radical cyclization in the cases that undesired regioisomers would be obtained. Therefore, we explored the leaving group at the *ortho*-position of the benzene ring for the *ipso* substitution reaction (entries 11–16), and found that the methoxy group is the most efficient leaving group.

In order to investigate the steric effect of the substituent on the dihydroindole moiety, we next examined the reaction of 1-benzoyl-2,3-dihydro-7-iodo-2-methylindole **9a** and 1-benzoyl-2,3-dihydro-7-iodo-3-methylindole **9b** (Table 4). The reaction of **9a** and **9b** gave corresponding cyclized products **10a** and **10b** in moderate yields, respectively (entries 1 and 2). When the reaction of 1-benzyl-2,3-dihydro-7-iodoindole **9c** containing an alkyl tether instead of a carbonyl group was performed, **10c** was obtained in only 6% yield along with the deiodinated product of **9c** in 48% yield and recovered **9c** in 45% yield (entry 3). This result clearly shows that the amide tether is essential for the samarium(II)-mediated cyclization reaction, probably because it brings the aryl radical close to the benzene ring as a radical acceptor, and/or stabilizes the radical intermediates. Treatment of 1-benzoyl-7-iodoindole **9d** with SmI_2 and HMPA afforded no desired product along with the deiodinated product of **9d** in 25% yield and recovered of **9d** in 9% yield (entry 4). Next, we prepared starting material **9e** that had a tetrahydroquinoline ring instead of a dihydroindole ring. It has been reported that phenanthridinones possessing a condensed 6-6-6-6-tetracyclic skeleton also exhibit biological activities.[18] Therefore, we examined the reaction of 1-benzoyl-1,2,3,4-tetrahydro-8-iodoquinoline **9e** and obtained **10e** in 31% yield along with spirocycle **11e** in 28% yield (entry 5). When we decreased the amount of

Table 3
Scope and limitations[a]

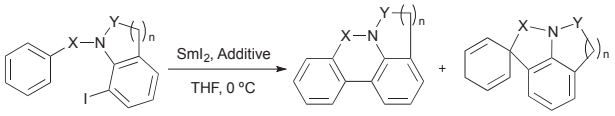


7a-k 6a-k 8a-k

Entry	Starting material			Additive	Product yield[b] (%)		
		R^1	R^2		**6**	**8**	**7**
1	**7a**	H	H	HMPA	**6a**: 84	0	0
2	**7b**	Me	H	HMPA	**6b**: 72	0	**7b**: 17
3	**7c**	OMe	H	HMPA	**6c**: 62	0	0
4	**7d**	Cl	H	HMPA	**6d**: 19, **6a**:42	0	0
5	**7d**	Cl	H	None	**6d**: 57	0	**7d**: 20
6	**7e**	CF_3	H	HMPA	**6e**: 41, **6b**: 2	0	**7e**: 7
7[c]	**7e**	CF_3	H	LiBr	**6e**: 29, **6b**: 10	0	**7e**: 4
8	**7e**	CF_3	H	None	**6e**: 50	0	**7e**: 12
9	**7f**	CO_2Me	H	HMPA	**6f**: 35	0	0
10	**7g**	H	Me	HMPA	**6g**: 15	**8g**: 39	**7g**: 31
11	**7h**	H	OMe	HMPA	**6a**: 45	**8h**: 23	0
12[c]	**7h**	H	OMe	LiBr	**6a**: 24	**8h**: 47	0
13	**7h**	H	OMe	None	0	0	**7h**: 93
14	**7i**	H	OPh	HMPA	**6i**/**6a** 36 (2.4:1)[d]	**8i**: 32	0
15	**7j**	H	CN	HMPA	**6a**: 7	0	0
16	**7k**	H	Cl	HMPA	**6a**: 26	**8k**: 31	0

[a] SmI_2 (3.5 equiv) was prepared in situ with 4.8 equiv of Sm metal and 3.5 equiv of 1,2-diiodoethane.
[b] Isolated yield.
[c] The reaction was performed at room temperature.
[d] The ratio was determined by ^1H NMR measurement.

Table 4
Samarium(II)-mediated cyclization reactions



9a-e 10a-e 11e

Entry	Starting material				SmI_2[a] (equiv)	Additive	Product yield[b] (%)	
		X	Y (C_2–C_3)	*n*			**10**	**11**
1	**9a**	CO	$CH(CH_3)$–CH_2	0	3.5	HMPA	**10a**: 43	0
2	**9b**	CO	CH_2–$CH(CH_3)$	0	3.5	HMPA	**10b**: 58	0
3	**9c**	CH_2	CH_2–CH_2	0	3.5	HMPA	**10c**: 6[c]	0
4	**9d**	CO	CH=CH	0	3.5	HMPA	**10d**: 0[d]	0
5	**9e**	CO	CH_2–CH_2	1	3.5	HMPA	**10e**: 31	**11e**: 28
6	**9e**	CO	CH_2–CH_2	1	3.0	HMPA	**10e**: 50	**11e**: 9
7	**9e**	CO	CH_2–CH_2	1	3.5	LiBr[e]	**10e**: 57	**11e**: 42

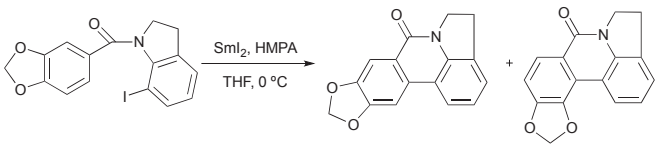
[a] SmI_2 (3.5 equiv) was prepared in situ with 4.8 equiv of Sm metal and 3.5 equiv of 1,2-diiodoethane.
[b] Isolated yield.
[c] Deiodinated product of **9c** was obtained in 48% yield with recovery of **9c** in 45% yield.
[d] Deiodinated product of **9d** was obtained in 25% yield with recovery of **9d** in 9% yield.
[e] The reaction was carried out at room temperature.

SmI_2, the yield of **10e** was increased to 50% and the yield of spirocycle **11e** was decreased to 9% (entry 6). Changing the additive to LiBr dramatically increased the yields of **10e** and **11e** (entry 7).[19] In the case of **9e**, even the reaction of the substrate without the substituent at the *ortho*-position gave spirocycle **11e**. This is probably due to the stability of the spirohexadienyl radical intermediates caused by ring size expansion.

2.3. Application to synthesis of anhydrolycorinone

For the synthesis of natural products, we chose **12** as the substrate. Hayama et al. reported that anhydrolycorinone **1a** was obtained as the minor product in 15% yield along with **13** in 60% yield when **12** was treated with $Pd(OAc)_2$ and P(*o*-tol)$_3$.[2h] We examined the reaction of **12** with 3.5 equiv of SmI_2 in the presence of HMPA as the additive, and obtained **1a** as the major product in 39% yield along with regioisomer **13** in 25% yield (Table 5, entry 1). Decreasing the equivalents of SmI_2 gave **1a** in 48% yield along with regioisomer **13** in 22% yield (entry 2).[20] Synthetic **1a** displayed spectral properties that were in good agreement with those of reported **1a**.[3a] The SmI_2-mediated formation of pyrrolophenanthridinone could be an efficient method for the synthesis of natural products in terms of regioselectivity. Cyclized product **1a** is readily transformed into anhydrolycorine **1b** by reduction with $LiAlH_4$[3f,21] and hippadine **1c** by oxidation with DDQ.[22]

Table 5
Synthesis of anhydrolycorinone



12 anhydrolycorinone **(1a)** 13

Entry	SmI_2[a] (equiv)	Product yield[b] (%)	
		1a	**13**
1	3.5	39	25
2	3.0	48	22

[a] SmI_2 (3.0 equiv) was prepared in situ with 4.1 equiv of Sm metal and 3.0 equiv of 1,2-diiodoethane.
[b] Isolated yield.

3. Conclusion

We have demonstrated a samarium(II)-mediated synthesis of pyrrolophenanthridinone derivatives from 1-benzoyl-2,3-dihydro-7-iodoindole derivatives under mild reaction conditions, which involves a reductive cyclization of aryl radicals onto a benzene ring via a spirohexadienyl radical intermediate. The utility of our synthetic method has been confirmed in the rapid total synthesis of anhydrolycorinone and the formal total synthesis of pyrrolophenanthridinone derivatives, such as anhydrolycorine and hippadine, which are *Amaryllidaceae* alkaloids that have significant value in biochemistry and medicinal chemistry. Studies aimed at extending the scope of the regioselective cyclization reaction and improving product yield are ongoing.

4. Experimental section

4.1. General

All reactions were performed using dried glasswares under an atmosphere of argon. Anhydrous THF was purchased from Kanto Chemicals Inc. and used without further purification. HMPA was distilled from CaH_2 under reduced pressure. All other chemicals were purchased at the highest commercial grade and used without further purification. Melting points were measured with a Yanaco MP micro-melting apparatus and uncorrected. NMR spectra were measured on JEOL JNM-LA-500 (^{1}H: 500 MHz; ^{13}C: 125 MHz), JEOL ECS-400 (^{1}H: 400 MHz; ^{13}C: 100 MHz), JEOL AL-300 (^{1}H: 300 MHz; ^{13}C: 75.5 MHz), and Varian INOVA 400NB (^{1}H: 400 MHz, ^{13}C: 100 MHz) spectrometers with tetramethylsilane as an internal standard. Chemical shifts are reported in parts per million (ppm). IR spectra were taken with Shimadzu FTIR-8400 spectrophotometers, and only noteworthy absorptions are listed. A JEOL JMS-GC mate spectrometer was used for low-resolution and high-resolution electron ionizations MS (LR-EIMS and HR-EIMS). Silica gel 60N (60-230 mesh, Kanto Chemical Co., Inc.) for column chromatography, silica gel 60 F_{254} pre-coated glass plates (0.25 mm-thickness, Merck) for analytical thin-layer chromatography (TLC), and silica gel 60 F_{254} (0.5 mm and 1.0 mm-thickness, Merck) for preparative TLC were used. Compound **12** was prepared according to reported procedures.[2j] Cyclized products **1a**, **6a**, **6b**, **6c**, **10e**, and **13** were known compound.[3a,4a,19a,23]

4.2. General procedure for samarium(II)-mediated cyclization. Synthesis of 4*H*-pyrrolo[3,2,1-*de*]phenanthridin-7(5*H*)-one (6a) (Table 2, entry 5)

The reaction was carried out under positive pressure of argon, and glassware and syringes were dried prior to use. A mixture of samarium (144 mg, 0.960 mmol) and 1,2-diiodoethane (197 mg, 0.700 mmol) in THF (6.7 mL) was stirred for 1.5 h at room temperature. After cooling to 0 °C, HMPA (0.44 mL, 2.52 mmol) was added to the mixture, and stirring was continued for 20 min at this temperature. A solution of **7a** (70.0 mg, 0.200 mmol) in THF (4.9 mL) was added to the mixture, and the mixture was stirred for 30 min. After the mixture was exposed to air, saturated $NaHCO_3$ was added to the mixture, and the whole was extracted with Et_2O. The extract was washed with saturated $NaHCO_3$ and brine. After drying the extract over $MgSO_4$, the filtrate was concentrated under reduced pressure to leave a residue, which was purified by column chromatography over silica gel with *n*-hexane/EtOAc (2:1) to give **6a** (37.3 mg, 84% yield).

Compound ***6a***:[3a] ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.45 (t, J=11.2 Hz, 2H), 4.51 (t, J=11.2 Hz, 2H), 7.23 (t, J=10.0 Hz, 1H), 7.34 (dd, J=10.0, 1.6 Hz, 1H), 7.60 (dt, J=10.0, 1.6 Hz, 1H), 7.77 (dt, J=10.0, 1.6 Hz, 1H), 7.94 (d, J=10.0 Hz, 1H), 8.23 (d, J=10.0 Hz, 1H), 8.57 (dd, J=10.0, 1.6 Hz, 1H); MS (EI) *m*/*z* (%) 221 (M^+, 100.0), 96 (12), 165 (13), 191 (24), 220 (98); HRMS (EI) calcd for $C_{15}H_{11}NO$ (M^+): 221.0841; found: 221.0845.

4.3. General procedure for samarium(II)-mediated cyclization in the presence of LiBr. Synthesis of 5,6,-dihydropyrido[3,2,1-*de*]phenanthridin-8(*4H*)-one (10e) and 5′,6′-dihydrospiro[cyclohexa[2,5]diene-1,1′-pyrrolo[3,2,1-*ij*]quinolin]-2′(4′*H*)-one (11e) (Table 4, entry 7)

The reaction was carried out under positive pressure of argon, and glassware and syringes were dried prior to use. A mixture of samarium (139 mg, 0.926 mmol) and 1,2-diiodoethane (191 mg, 0.676 mmol) in THF (6.4 mL) was stirred for 2 h at room temperature. After cooling to 0 °C, a solution of LiBr (469 mg, 5.40 mmol) in THF (5.1 mL) was added to the mixture, and stirring was continued for 40 min at room temperature. A solution of **9e** (70.0 mg, 0.193 mmol) in THF (2.9 mL) was added to the mixture, and the mixture was stirred for 30 min. After the mixture was exposed to air, saturated $Na_2S_4O_7$ was added to the mixture, and the mixture was extracted with Et_2O. The extract was washed with saturated $NaHCO_3$ and brine. After drying the extract over $MgSO_4$, the filtrate was concentrated under reduced pressure to leave a residue, which was purified by column chromatography over silica gel with *n*-hexane/EtOAc (2:1) to give **10e** (25.8 mg, 57% yield) and **11e** (19.1 mg, 42%).

Compound ***11e***: colorless prisms: mp 148–149 °C (EtOAc); IR (KBr, cm^{-1}): 1713; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.03 (quin, J=6.0 Hz, 2H), 2.80 (t, J=6.0 Hz, 2H), 2.77–3.04 (m, 2H), 3.73 (t, J=6.0 Hz, 2H), 5.42 (dt, J=10.4, 1.6 Hz, 2H), 6.13 (dt, J=10.4, 3.2 Hz, 2H), 6.92–6.99 (m, 2H), 7.01–7.07 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 24.5, 25.7, 39.2, 52.9, 120.1, 122.3 (2C), 123.8 (2C), 127.1, 127.2 (2C), 132.8, 138.8, 176.8; MS (EI) *m*/*z* (%) 237 (M^+, 41.6), 220 (12), 236 (100); HRMS (EI) calcd for $C_{16}H_{15}NO$ (M^+): 237.1154; found: 237.1159.

4.4. 10-Chloro-4*H*-pyrrolo[3,2,1-*de*]phenanthridin-7(5*H*)-one (6d)

Compound **6d** was synthesized with a similar manner to **6a** except without HMPA. Colorless prisms (26.7 mg, 57%): mp 211–212 °C (EtOAc); IR (KBr, cm^{-1}): 1643; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.41 (t, J=8.4 Hz, 2H), 4.44 (t, J=8.4 Hz, 2H), 7.20 (t, J=7.6 Hz, 1H), 7.33 (d, J=7.2 Hz, 1H), 7.49 (dd, J=8.8, 1.2 Hz, 1H), 7.77 (d, J=8.0 Hz, 1H), 8.06 (s, 1H), 8.42 (d, J=8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.2, 46.4, 115.6, 119.8, 121.9, 123.4, 125.2, 125.6, 128.0, 129.9, 130.9, 135.1, 138.6, 140.1, 159.2; MS (EI) *m*/*z* (%) 255 (M^+, 100.0), 191 (15), 219 (23), 254 (80), 256 (42), 257 (33); HRMS (EI) calcd for $C_{15}H_{10}ClNO$ (M^+): 255.0451; found: 255.0446.

4.5. 10-Trifluoromethyl-4*H*-pyrrolo[3,2,1-*de*]phenanthridin-7(5*H*)-one (6e)

Compound **6e** was synthesized with a similar manner to **6a** except without HMPA. Colorless prisms (24.4 mg, 50%): mp 239–240 °C (EtOAc); IR (KBr, cm^{-1}): 1649; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.47 (t, J=8.4 Hz, 2H), 4.51 (t, J=8.4 Hz, 2H), 7.27 (dd, J=8.0, 7.2 Hz, 1H), 7.39 (dd, J=7.2, 0.8 Hz, 1H), 7.80 (dd, J=8.0, 0.8 Hz, 1H), 7.94 (d, J=8.0 Hz, 1H), 8.44 (br s, 1H), 8.66 (d, J=8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.3, 46.6, 115.9, 119.4 (q, J=4.0 Hz), 120.0, 123.80, 123.81 (q, J=271.5 Hz), 123.9 (q, J=3.5 Hz), 125.5, 129.4, 129.6, 131.0, 133.7 (q, J=32.3 Hz), 134.1, 140.1, 159.0; MS (EI) *m*/*z* (%) 289 (M^+, 100.0), 191 (11), 240 (9); HRMS (EI) calcd for $C_{16}H_{10}F_3NO$ (M^+): 289.0715; found: 289.0718.

4.6. Methyl-4*H*-pyrrolo[3,2,1-*de*]phenanthridin-7(5*H*)-one-10-carboxylate (6f)

Compound **6f** was synthesized with a similar manner to **6a**. Colorless prisms (16.6 mg, 35%): mp 188–189 °C (EtOAc); IR (KBr, cm^{-1}): 1719, 1647; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.47 (t, J=8.4 Hz, 2H), 4.02 (s, 3H), 4.52 (t, J=8.4 Hz, 2H), 7.27 (t, J=7.6 Hz, 1H), 7.38 (d, J=7.2 Hz, 1H), 8.03 (d, J=8.0 Hz, 1H), 8.20 (dd, J=8.0, 1.2 Hz, 1H), 8.62 (d, J=8.0 Hz, 1H), 8.91 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.2, 46.5, 52.6, 116.3, 120.1, 123.6, 123.9, 125.0, 127.9, 128.6, 130.2, 130.8, 132.9, 133.7, 139.8, 159.2, 166.4; MS (EI) *m*/*z* (%) 279 (M^+, 100.0), 96 (12), 219 (14), 278 (51); HRMS (EI) calcd for $C_{17}H_{13}NO_3$ (M^+): 279.0895; found: 279.0890.

4.7. 8-Methyl-4*H*-pyrrolo[3,2,1-*de*]phenanthridin-7(5*H*)-one (6g) and 2-methyl-4′,5′-dihydro-2′*H*-spiro[cyclohexa[2,5]diene-1,1′-pyrrolo[3,2,1-*hi*]indol]-2′-one (8g)

Compounds **6g** and **8g** were synthesized with a similar manner to **6a**. Compound **6g**. Colorless prisms (6.7 mg, 15%): mp 176.6–177.1 °C (EtOAc); IR (KBr, cm^{-1}): 1641; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.00 (s, 3H), 3.40 (t, J=8.4 Hz, 2H), 4.45 (t, J=8.4 Hz, 2H), 7.18 (t, J=7.6 Hz, 1H), 7.28–7.32 (m, 1H), 7.32–7.37 (m, 1H), 7.59 (t, J=7.6 Hz, 1H), 7.89 (dd, J=7.6, 0.4 Hz, 1H), 8.10 (d, J=7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.2, 27.1, 46.6, 116.8, 120.1, 120.3, 123.0, 124.4, 125.6, 130.4, 131.2, 131.6, 135.4, 139.8, 142.6, 161.3; MS (EI) *m*/*z* (%) 235 (M^+, 100.0), 83 (12), 191 (12), 204 (10), 219 (11), 234 (95); HRMS (EI) calcd for $C_{16}H_{13}NO$ (M^+): 235.0997; found: 235.0999.

Compound **8g**. Colorless prisms (17.6 mg, 39%): mp 120–121 °C (EtOAc); IR (KBr, cm^{-1}): 1661; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.06 (s, 3H), 3.10–3.27 (m, 3H), 3.87–3.93 (m, 1H), 3.99–4.16 (m, 2H), 5.44 (dd, J=9.3, 3.2 Hz, 1H), 5.89–5.93 (m, 1H), 5.99 (ddd, J=9.3, 5.3, 3.2 Hz, 1H), 6.96 (t, J=7.6 Hz, 1H), 7.05 (d, J=7.6 Hz, 1H), 7.10 (dd, J=7.6, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.0, 27.7, 37.2, 45.4, 45.5, 120.8, 122.1, 123.55, 123.64, 124.86, 124.88, 126.0, 128.9, 133.3, 140.6, 167.3; MS (EI) *m*/*z* (%) 237 (M^+, 80.8), 193 (15), 208 (31), 222 (56), 236 (100); HRMS (EI) calcd for $C_{16}H_{15}NO$ (M^+): 237.1154; found: 237.1147.

4.8. 2-Methoxy-4′,5′-dihydro-2′*H*-spiro[cyclohexa[2,5]diene-1,1′-pyrrolo[3,2,1-*hi*]indol]-2′-one (8h)

Compound **8h** was synthesized with a similar manner to **6a**. Colorless oil (22.1 mg, 47%); IR ($CHCl_3$, cm^{-1}): 1663; ^{1}H NMR

(400 MHz, $CDCl_3$) δ 3.10–3.31 (m, 3H), 3.72 (s, 3H), 3.99–4.16 (m, 3H), 5.17 (d, J=6.0 Hz, 1H), 5.19 (dd, J=9.2, 2.8 Hz, 1H), 6.01 (ddd, J=9.2, 6.0, 2.8 Hz, 1H), 6.97 (t, J=7.6 Hz, 1H), 7.06 (d, J=7.6 Hz, 1H), 7.11 (dd, J=7.6, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.7, 38.4, 45.7, 45.9, 55.2, 93.9, 119.9, 121.7, 123.6, 123.7, 124.9, 125.5, 129.1, 140.5, 155.4, 165.8; MS (EI) m/z (%) 253 (M^+, 100.0), 210 (15), 222 (38), 224 (38), 225 (44), 238 (31); HRMS (EI) calcd for $C_{16}H_{15}NO_2$ (M^+): 235.1103; found: 235.1100.

4.9. 2-Phenoxy-4′,5′-dihydro-2′*H*-spiro[cyclohexa[2,5]diene-1,1′-pyrrolo[3,2,1-*hi*]indol]-2′-one (8i)

Compound **8i** was synthesized with a similar manner to **6a**. Colorless oil (15.9 mg, 32%); IR ($CHCl_3$, cm^{-1}): 1663; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.10–3.30 (m, 2H), 3.50 (d, J=8.5 Hz, 1H), 3.99–4.09 (m, 1H), 4.12–4.22 (m, 2H), 5.11 (d, J=6.0 Hz, 1H), 5.21 (dd, J=9.5, 2.5 Hz, 1H), 5.90 (ddd, J=9.0, 6.0, 3.0 Hz, 1H), 7.00 (t, J=7.5 Hz, 1H), 7.10 (d, J=7.5 Hz, 1H), 7.14 (d, J=7.5 Hz, 1H), 7.16 (t, J=7.8 Hz, 1H), 7.28 (d, J=7.8 Hz, 2H), 7.36 (t, J=7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.7, 38.9, 44.8, 45.7, 100.6, 121.4 (2C), 121.5, 121.6, 123.8, 123.9, 124.6, 125.08, 125.10, 129.3, 129.6 (2C), 140.6, 155.1 (2C), 165.9; MS (EI) m/z (%) 315 (M^+, 100.0), 193 (26), 198 (10), 221 (11), 222 (50), 287 (35), 314 (70); HRMS (EI) calcd for $C_{21}H_{17}NO_2$ (M^+): 315.1259; found: 315.1263.

4.10. 2-Chloro-4′,5′-dihydro-2′*H*-spiro[cyclohexa[2,5]diene-1,1′-pyrrolo[3,2,1-*hi*]indol]-2′-one (8k)

Compound **8k** was synthesized with a similar manner to **6a**. Colorless prisms (14.6 mg, 31%): mp 194.4–195.0 °C (EtOAc); IR (KBr, cm^{-1}): 1657; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.11–3.29 (m, 2H), 3.48 (d, J=8.8 Hz, 1H), 4.00–4.09 (m, 1H), 4.11–4.20 (m, 2H), 5.52 (dd, J=9.2, 2.9 Hz, 1H), 5.97 (ddd, J=9.2, 5.6, 2.9 Hz, 1H), 6.30 (d, J=5.6 Hz, 1H), 6.99 (t, J=7.6 Hz, 1H), 7.06 (d, J=7.6 Hz, 1H), 7.13 (dd, J=7.6, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.7, 38.7, 45.8, 47.8, 120.4, 123.3, 124.0, 124.1, 124.9, 125.0, 127.0, 129.3, 129.5, 140.3, 164.7; MS (EI) m/z (%) 257 (M^+, 88.2), 96 (13), 165 (14), 193 (31), 222 (100), 228 (26), 256 (94), 258 (44), 259 (30); HRMS (EI) calcd for $C_{15}H_{12}ClNO$ (M^+): 257.0607; found: 257.0609.

4.11. 5-Methyl-4*H*-pyrrolo[3,2,1-*de*]phenanthridin-7(5*H*)-one (10a)

Compound **10a** was synthesized with a similar manner to **6a**. Colorless oil (19.3 mg, 43%); IR ($CHCl_3$, cm^{-1}): 1641; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.64 (d, J=6.5 Hz, 3H), 2.99 (dd, J=16.5, 3.5 Hz, 1H), 3.65 (dd, J=16.5, 9.5 Hz, 1H), 5.13 (dqd, J=9.5, 6.5, 3.5 Hz, 1H), 7.24 (t, J=7.5 Hz, 1H), 7.32 (d, J=7.5 Hz, 1H), 7.56 (t, J=7.5 Hz, 1H), 7.76 (t, J=7.5 Hz, 1H), 7.94 (d, J=7.5 Hz, 1H), 8.22 (d, J=7.5 Hz, 1H), 8.56 (d, J=7.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.6, 36.3, 56.0, 116.8, 119.9, 122.0, 123.4, 124.7, 127.8 (2C), 128.4, 129.5, 132.0, 133.9, 139.2, 160.0; MS (EI) m/z (%) 235 (M^+, 57.9), 191 (12), 220 (100), 221 (17); HRMS (EI) calcd for $C_{16}H_{13}NO$ (M^+): 235.0997; found: 235.0994.

4.12. 4-Methyl-4*H*-pyrrolo[3,2,1-*de*]phenanthridin-7(5*H*)-one (10b)

Compound **10b** was synthesized with a similar manner to **6a**. Colorless prisms (26.1 mg, 58%): mp 140–141 °C (EtOAc); IR (KBr, cm^{-1}): 1641; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.48 (d, J=7.0 Hz, 3H), 3.78 (sext, J=7.0 Hz, 1H), 4.03 (dd, J=12.5, 5.5 Hz, 1H), 4.66 (dd, J=12.5, 9.5 Hz, 1H), 7.25 (t, J=7.5 Hz, 1H), 7.32 (d, J=7.5 Hz, 1H), 7.59 (t, J=7.5 Hz, 1H), 7.75 (t, J=7.5 Hz, 1H), 7.93 (d, J=7.5 Hz, 1H), 8.21 (d, J=7.5 Hz, 1H), 8.56 (d, J=7.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.7, 34.7, 54.4, 116.7, 120.1, 122.1, 123.47, 123.53, 127.4, 127.8, 128.4, 132.0, 133.9, 136.0, 139.2, 160.1; MS (EI) m/z (%) 235 (M^+, 69.1), 191 (14), 220 (100), 221 (17); HRMS (EI) calcd for $C_{16}H_{13}NO$ (M^+): 235.0997; found: 235.0994.

4.13. 5,7-Dihydro-4*H*-pyrrolo[3,2,1-*de*]phenanthridine (10c)

Compound **10c** was synthesized with a similar manner to **6a**. Colorless prisms (2.4 mg, 6%): mp 73–75 °C (EtOAc); IR (KBr, cm^{-1}): 1601; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.02 (t, J=8.0 Hz, 2H), 3.34 (t, J=8.0 Hz, 2H), 4.15 (s, 2H), 6.77 (t, J=7.6 Hz, 1H), 7.04 (d, J=7.6 Hz, 1H), 7.13 (d, J=7.6 Hz, 1H), 7.19 (t, J=7.6 Hz, 1H), 7.29 (t, J=7.6 Hz, 1H), 7.42 (d, J=7.6 Hz, 1H), 7.67 (d, J=7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.9, 53.4, 55.5, 118.8, 119.6, 120.1, 121.9, 124.1, 127.07, 127.13, 127.7, 128.8, 131.4, 132.1, 150.3; MS (EI) m/z (%) 207 (M^+, 47.7), 102 (11), 103 (14), 204 (19), 206 (100); HRMS (EI) calcd for $C_{15}H_{13}N$ (M^+): 207.1048; found: 207.1042.

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Supplementary data

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