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Total synthesis of PDE-I and -II by copper-mediated double aryl amination

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This paper is dedicated to Professor Teruaki Mukaiyama in celebration of the 40th anniversary of the Mukaiyama aldol reaction

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ABSTRACT

A concise total synthesis of PDE-I and -II featuring copper-mediated double aryl amination with the combination of CuI, CsOAc, and Cs_2CO_3 is described. The highly substituted pyrroloindole skeleton was constructed by a one-pot five-step sequence including double aryl amination, β-elimination, deprotection of a Cbz group, and unexpected formation of an indole via removal of an Ns group followed by rearomatization. The undesired elimination of the protecting group (Ns group) was hampered by using the Boc group as a protecting group in the second-generation synthesis, which excluded the reduction of the indole required in the first-generation synthesis.

1. Introduction

PDE-I (**1**) and PDE-II (**2**), isolated from *Streptomyces* MD769-C6 by Umezawa and co-workers in 1978, are inhibitors of cyclic adenosine-3′,5′-monophosphate phosphodiesterase (Fig. 1).[1] The structures of PDEs were initially identified on the basis of NMR spectroscopy and later confirmed by X-ray crystallography[2] and total synthesis.[3] Since potent sequence-selective DNA alkylating agents, such as CC-1065[4] and yatakemycin,[5] consist of PDEs as a partial structure, construction of the highly functionalized 1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole has attracted considerable attention from the synthetic community.[6] Cava and Rawal reported formal synthesis of PDEs based on a photocyclization of a symmetrical bispyrrole derivative to construct the pyrroloindole.[7] Boger and Coleman achieved total synthesis of PDEs by development of an intramolecular Diels–Alder reaction of alkyne and 1,2-diazines.[8] Martin also accomplished formal synthesis of PDEs using a hetero Cope rearrangement of in situ generated *O*-vinyl-*N*-phenylhydroxamic derivative.[9] In spite of the significant effort toward the synthesis of this class of compounds, an efficient synthetic route is still needed for medicinal and biochemistry.

Recently we developed a method for synthesis of PDE analogs as an application of a mild copper-mediated aryl amination reaction[10] using a combination of CuI and CsOAc,[11] which led to the synthesis of duocarmycins[12] and yatakemycin.[5d,5d] In 2010 we also reported a total synthesis of PDE-II (**2**) utilizing the copper-mediated double aryl amination to construct a tricyclic pyrroloindole in one-pot.[13] In this paper, we describe the full details of the first-generation synthesis of PDE-I and -II based on a one-pot construction of a pyrroloindole skeleton and the second-generation improved synthesis established after careful investigation on the effect of the protecting group on nitrogen in the copper-mediated aryl amination reaction.

2. Results and discussion

To develop a synthetic route to PDE-I (**1**) and -II (**2**) having a carbamoyl or an acetyl group on the nitrogen atom, we envisaged unprotected dihydropyrroloindole **3** as a key synthetic intermediate (Scheme 1). We planned to construct two aryl-nitrogen bonds of **3** via the copper-mediated one-pot double amination of **4** that would be generated from its synthetic equivalent **5** via β-elimination of the amine functionality. We chose a 2-nitrobenzenesulfonyl (Ns) amide[14] as a superior leaving group for the β-elimination due to the

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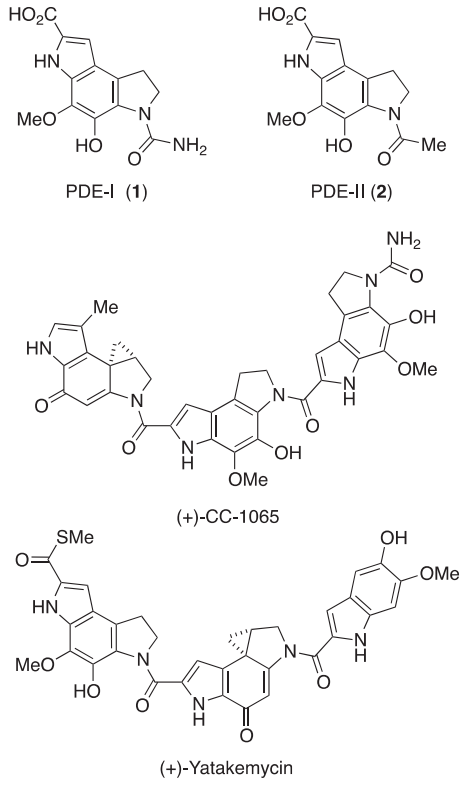
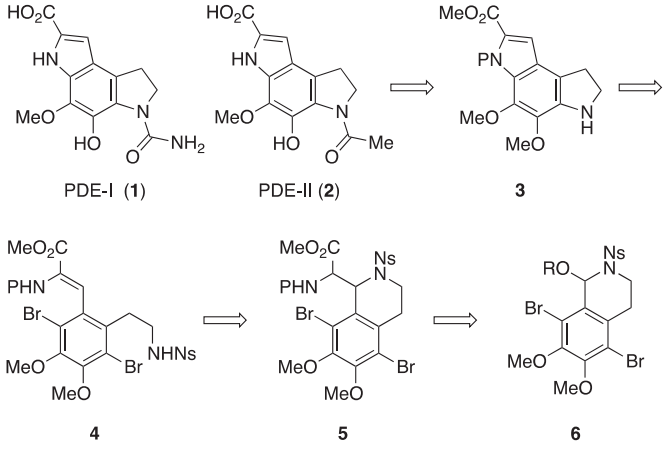


Fig. 1. Natural products having dihydropyrroloindole skeleton.

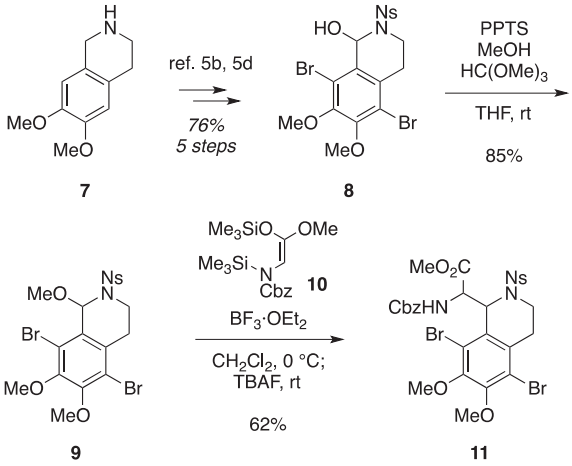


Scheme 1. Retrosynthetic analysis of PDE-I and -II.

strong electron-withdrawing nature of the Ns group. Tetrahydroisoquinoline **5** would be prepared by Mannich-type addition of a glycine unit to hemiaminal **6**.

The synthesis commenced with dibromination and benzylic oxidation of commercially available tetrahydroisoquinoline **7** to provide hemiaminal **8** in five steps according to our synthesis of yatakemycin[5b,5d] (Scheme 2). Treatment of the hemiaminal **8** with trimethyl orthoformate and PPTS smoothly gave **9**, which was subjected to Mannich reaction with ketene silyl acetal **10** derived from glycine in the presence of $BF_3 \cdot OEt_2$ to furnish **11** as a mixture of diastereomers.[15] Treatment with TBAF was necessary for complete removal of a TMS group on nitrogen.

The Mannich adduct **11** was subjected to the standard amination conditions with a combination of CuI and CsOAc to test the one-pot double amination (Table 1, entry 1). Gratifyingly, the desired dihydropyrroloindole **12** was isolated in 12% yield associated with



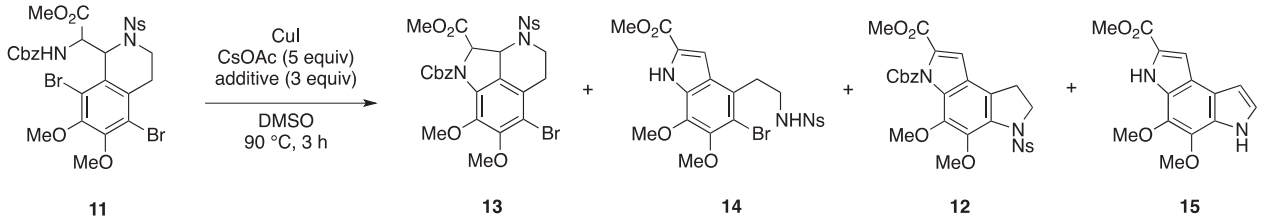
Scheme 2. Preparation of the substrate for the key double amination.

tricyclic compound **13**,[16] indole **14**, and pyrroloindole **15**. These results indicated that the reaction was initiated by amination of the Cbz carbamate to provide tricyclic compound **13**, which would undergo β-elimination to give **16** (Scheme 3). Then, the second amination or removal of the Cbz group furnished **12** or **14**, respectively. Finally, conversion to **17** and subsequent removal of the Ns group followed by aromatization resulted in a formal oxidation providing pyrroloindole **15**. Next, screening of an additional base was carried out to promote the β-elimination of **13** and the second amination of **14**. To this end, even in the presence of various bases, compounds **13** and **14** still remained. On the other hand, the yields of pyrroloindole **15** were substantially improved (entries 2–4). With these results, we turned our attention to improvement of the yield of pyrroloindole **15** since this compound is also a synthetic intermediate of PDEs.[6c] We then examined the amounts of CuI and K_3PO_4/Cs_2CO_3 and found that the use of 1.5 equiv of CuI and 3.0 equiv of Cs_2CO_3 was effective in improving the yield of **15** to 57% (entries 5 and 6).

With the tricyclic pyrroloindole **15** in hand, we then embarked on the total synthesis of PDE-II (**2**) (Scheme 4). Selective reduction of the electron-rich indole of pyrroloindole **15** was carried out according to the reported procedure[6a] to generate dihydropyrroloindole **18**, which was acetylated in one-pot to provide compound **19** in 98% yield. We then attempted a regioselective removal of the methyl group adjacent to acetyl group according to the Coe's report.[17] Thus, the reaction was carried out using BCl_3 and TBAI to provide the desired product **20**, but the reaction was irreproducible (Table 2, entry 1). Since separation of TBAI was difficult, we then increased the amount of trichloroboron; however, the demethylation was not complete with concomitant generation of PDE-II (**2**) (entry 2). Interestingly, additional optimization indicated that high dilution conditions promoted consumption of the starting material **19**. When the reaction was conducted under 0.01 M concentration of **19**, the desired product **20** was obtained in 60% yield with recovery of **19** in 16% (entry 3). Furthermore, we found that 1 mM concentration of **19** was the best reaction conditions and isolated the corresponding demethylated compound **20** in 73% (entry 4). Finally, saponification of the methyl ester was carried out according to Boger's conditions using $Na_2S_2O_4$ as a mild reductant[18] to afford PDE-II (**2**), whose physical properties were identical in all aspects to those reported for the natural product.[1]

End game sequence for the total synthesis of PDE-II (**2**) was also applicable to the synthesis of PDE-I (**1**) and we have established divergent total synthesis of PDE-I (**1**) and -II (**2**) from compound **15** as a common intermediate (Scheme 5). Treatment of the unprotected indoline **18** with trimethylsilyl isocyanate provided urea **21** in one-pot. A carbamoyl group-directed regioselective demethylation was

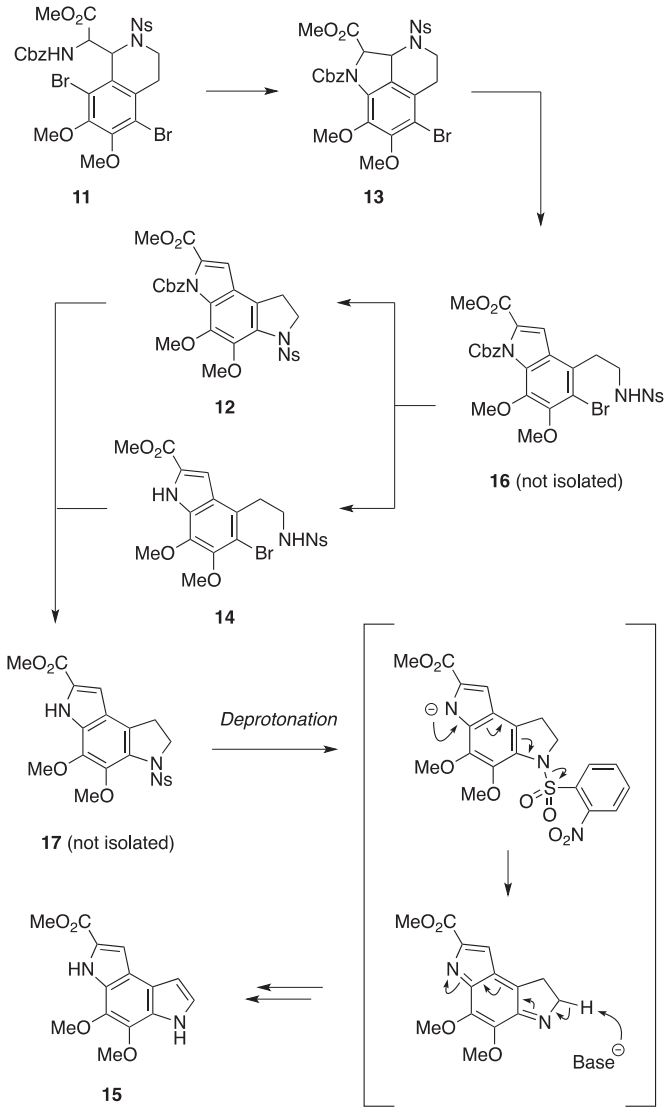
Table 1
Effect of bases on the double amination cascade



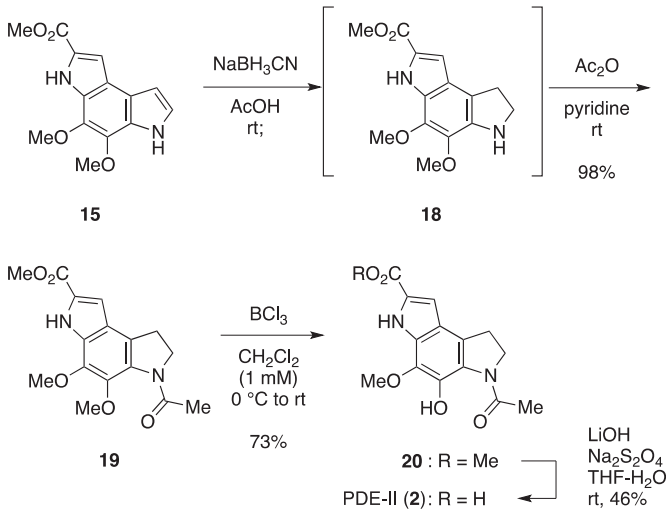
11 13 14 12 15

Entry	CuI (equiv)	Additive	**13** (%)[a]	**14** (%)[a]	**12** (%)[a]	**15** (%)[a]
1	1.0	None	14	22	12	11
2	1.0	KO*t*-Bu	9	15	5	41
3	1.0	K_3PO_4	5	13	9	50
4	1.0	Cs_2CO_3	6	26	3	38
5[b]	1.5	K_3PO_4	13	—	—	18
6	1.5	Cs_2CO_3	—	—	—	57

[a] Isolated yield.
[b] Reaction time: 5 h.



Scheme 3. Outline of the one-pot formation of pyrroloindole.



Scheme 4. Total synthesis of PDE-II (**2**).

Table 2
Regioselective demethylation using trichloroboron

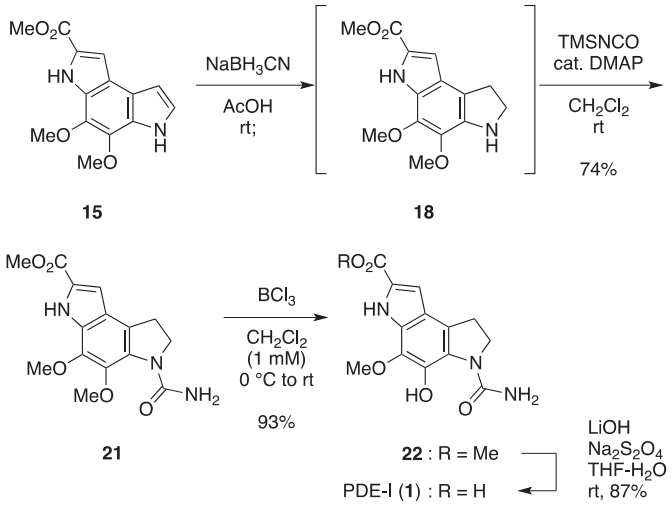
Entry	BCl_3 (equiv)	Additive (4 equiv)	Concentration of **19** (M)	**20** (%)[a]
1[b]	3.0	TBAI	0.05	50–97
2[b]	10	None	0.05	—[c]
3	8.0	None	0.01	60[d]
4	8.0	None	0.001	73

[a] Isolated yield.
[b] Reaction temperature: −78 to 0 °C.
[c] Crude material contained **19**:**20**:PDE-II (**2**)=1:0.7:0.06 by ^{1}H NMR.
[d] Starting material **19** was recovered (16%).

also carried out under the high dilution conditions (**21**: 1 mM) to provide PDE-I methyl ester (**22**). Subsequent hydrolysis of the ester gave PDE-I (**1**), whose physical properties were identical in all aspects to those reported for the natural product.[1]

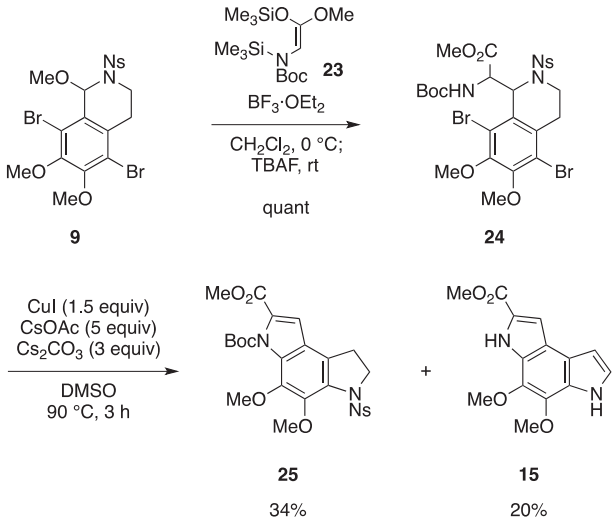
Although the first-generation approach allowed us to synthesize PDE-I (**1**) and -II (**2**), there was a considerable drawback with regard to the unnecessary reduction of the indole, which was caused by the unexpected removal of the Ns group. We decided to improve the highly efficient one-pot double amination strategy to realize redox-economical synthesis of PDE-I and -II. The outline of the formation of pyrroloindole **15** in Scheme 3 indicated that the undesired deprotection of the Ns group occurred after removal of the Cbz group on the indole nitrogen. Thus, we switched the Cbz group to the Boc group, which is more robust under basic conditions.

Gratifyingly, $BF_3\cdot OEt_2$-mediated addition of the Boc-protected ketene silyl acetal **23** also provided the corresponding adduct **24**



Scheme 5. Total synthesis of PDE-I (**1**).

in quantitative yield (Scheme 6). Subjection of **24** to the established amination conditions (Table 1, entry 6) gave the desired dihydropyrroloindole **25** as we expected, with concomitant generation of pyrroloindole **15**.



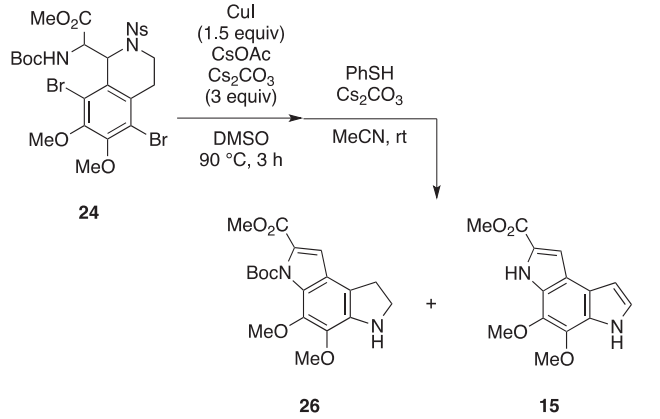
Scheme 6. Effect of the Boc group in the amination reaction.

Due to the difficulty in separation of compounds **25** and **15**, we examined the effect of stoichiometric amount of CsOAc by evaluating yields after deprotection of the nosyl group (Table 3). The amination reaction with 3 equiv of CsOAc followed by removal of nosyl group provided dihydropyrroloindole **26** (36%) and pyrroloindole **15** (13%) (entry 1). In the case of 2 equiv of CsOAc, generation of **15** was not observed, but the yield of **26** was slightly decreased to 33% (entry 2).

Finally, we successfully developed an efficient synthetic route from Mannich adduct **24** to dihydropyrroloindole **27** (Scheme 7). After the double amination, subsequent one-pot switching of the Ns group to the acetyl group via **26** was executed to provide compound **27** in 46% yield from **24**.

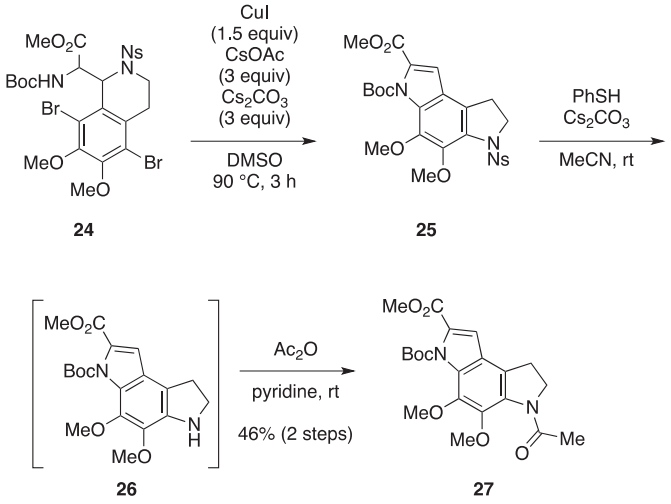
We then attempted an acid-mediated deprotection of the Boc and methyl groups (Scheme 8). Thus, treatment of compound **27** with trichloroboron resulted in generation of unidentified byproducts. On the other hand, thermal deprotection of the Boc group[19] provided unprotected indole **19** that is the intermediate in the first-generation synthesis. Compared to the first-generation

Table 3
Effect of amount of CsOAc in the double amination cascade

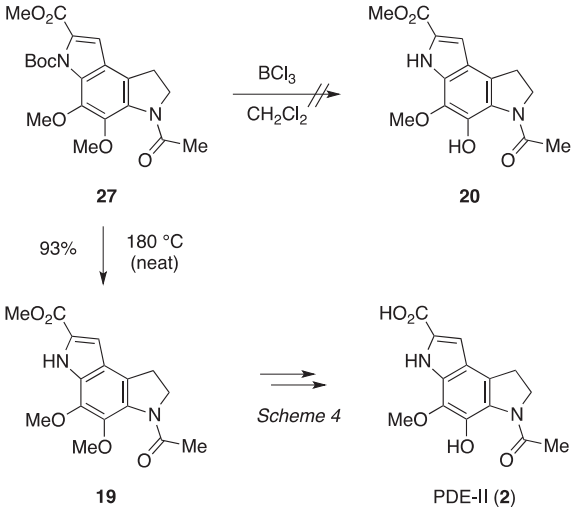


Entry	CsOAc (equiv)	**26** (%)[a]	**15** (%)[a]
1	3.0	36	13
2	2.0	33	—[b]

[a] Isolated yield.
[b] Not observed.



Scheme 7. Synthesis of dihydropyrroloindole **27**.



Scheme 8. Second-generation synthesis of PDE-II (**2**).

synthesis (**9** to **19**, 34%, three steps), the second synthesis excluded the extra reduction step and provided compound **19** in better overall yield (**9** to **19**, 43%, four steps), thus establishing a redox-economical second-generation synthesis.

3. Conclusion

In summary, we have achieved a highly efficient total synthesis of PDE-I (**1**) and -II (**2**) utilizing a one-pot copper-mediated intramolecular double amination. The methodology enabled us to construct the tricyclic pyrroloindole skeleton in one-pot. We then successfully improved our highly efficient double amination strategy to apply for the redox-economical divergent synthesis of PDE-I and -II, in which we found that the Boc group on the indole nitrogen was essential for the suppression of removal of the Ns group, thus eliminating the unnecessary reduction.

4. Experimental section

4.1. General remarks

All reactions were performed in oven-dried glassware, sealed with a rubber septum under a slight positive pressure of argon unless otherwise noted. Anhydrous THF and dichloromethane were purchased from Kanto Chemical Co., Inc. Diisopropylamine and TMSCl were distilled from CaH_2. Unless otherwise mentioned, materials were obtained from commercial suppliers and were used without further purification. Chromatography was carried out using Kanto silica gel 60 (230–400 mesh). Gel permeation chromatography was carried out using a Japan Analytical Industry Co., Ltd LC-9201. Preparative TLC was performed with precoated silica gel 60 F_{254} plates (Merck). IR spectra were measured on a JASCO IR Report-100 spectrometer or a Shimazu FTIR-8300 spectrometer. NMR spectra were measured on a Varian Gemini 2000, a JEOL AL 400, a JEOL ECP 500, or a JEOL ECA 600 spectrometer. For ^{1}H NMR spectra, chemical shifts are expressed in parts per million downfield from internal tetramethylsilane (δ 0) or relative internal $CHCl_3$ (δ 7.26), CHD_2OD (δ 3.30), DMSO-d_5 (δ 2.49), or acetone-d_5 (δ 2.04). For ^{13}C NMR spectra, chemical shifts are expressed in ppm downfield from relative internal $CDCl_3$ (δ 77.0), CD_3OD (δ 49.0), DMSO-d_6 (δ 39.7), or acetone-d_6 (δ 29.8 and 206.5). Coupling constants are in hertz. Mass spectra were recorded on a JEOL JMS-DX-303 (EI), a JMS-700 (FAB), or a BRUKER micrOTOF-II spectrometer (ESI). Elemental analyses were performed by a Yanaco CHN CORDER MT-6 spectrometer.

4.2. 5,8-Dibromo-2-(2-nitrophenylsulfonyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methoxyisoquinoline (9)[13]

A 300-mL round-bottomed flask equipped with a magnetic stirring bar was charged with **8**[5b] (1.00 g, 1.92 mmol), PPTS (528.3 mg, 2.10 mmol), dry THF (4.1 mL), trimethyl orthoformate (1.0 mL), and MeOH (12.3 mL). The resulting mixture was stirred vigorously at room temperature for 21.5 h, after which time TLC (hexanes–ethyl acetate=1:1) indicated complete consumption of the starting material. The reaction mixture was concentrated under reduced pressure. The residue was treated with saturated aqueous ammonium chloride followed by saturated aqueous sodium bicarbonate. The mixture was filtered, and the solid was washed with ethyl acetate and water to afford product **9** (20.7 mg, 36.6 μmol, 1.9%) as a colorless powder. The filtrate was separated, and the aqueous layer was extracted twice with ethyl acetate. The combined organic extracts were washed with 1:1 mixture of saturated aqueous ammonium chloride and saturated aqueous sodium bicarbonate, brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give crude hemiaminal **9**. Trituration with hexanes–ethyl acetate=1:1 and the resulting solid was filtered to afford analytically pure **9** (905.7 mg, 1.60 mmol, 83%, 85% combined yield) as a colorless powder. R_f=0.30 (hexanes–ethyl acetate=1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10–8.04 (m, 1H), 7.73–7.61 (m, 3H), 6.00 (s, 1H), 3.99 (dd, 1H, J=14.6, 7.0 Hz), 3.90 (s, 3H), 3.87 (s, 3H), 3.69 (ddd, 1H, J=14.6, 13.6, 4.4 Hz), 3.50 (s, 3H), 2.79 (dd, 1H, J=17.6, 4.4 Hz), 2.46 (ddd, 1H, J=17.6, 13.6, 7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.3, 150.0, 147.7, 134.0, 133.6, 131.9, 131.1, 130.72, 130.65, 124.6, 119.6, 119.3, 84.6, 60.9, 60.7, 56.2, 37.7, 28.8. IR (neat, cm^{-1}): 2939, 1541, 1458, 1404, 1396, 1339, 1313, 1302, 1173, 1080, 1026, 968, 760. HRMS-EI calcd for $C_{18}H_{18}Br_2N_2O_7S$ (M^+) 563.9201; found 563.9209.

4.3. Benzyl 2-methoxy-2-(trimethylsilyloxy)vinyl(trimethylsilyl)carbamate (10)[13]

A 300-mL three-necked round-bottomed flask equipped with a magnetic stirring bar and fitted with two dropping funnels was charged with glycine (10.0 g, 133 mmol) and 2 M aqueous sodium hydroxide (67.5 mL). The flask was then cooled to 0 °C. To the vigorously stirred solution were added CbzCl (22.8 mL, 160 mmol, 1.2 equiv) and 4 M sodium hydroxide (33.8 mL) simultaneously over a period of 10 min via each dropping funnel. The reaction mixture was stirred for an additional 40 min at 0 °C, after which time TLC (H_2O–AcOEt–n-BuOH–MeOH=1:1:1:1) indicated complete consumption of glycine. The aqueous solution was washed three times with diethyl ether and acidified with 6 M hydrochloric acid to pH 1. The resulting mixture was cooled at 0 °C to give a precipitate, which was collected by filtration, washed with small portions of cold water, and dried under reduced pressure to afford analytically pure *N*-Cbz-glycine (26.4 g, 126 mmol, 95%) as colorless crystals. R_f=0.66 (H_2O–AcOEt–n-BuOH–MeOH=1:1:1:1). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.58 (br s, 1H), 7.62–7.48 (br s, 1H), 7.44–7.25 (m, 5H), 5.05 (s, 2H), 3.70 (d, 2H, J=5.6 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.7, 156.6, 137.1, 128.4, 127.9, 127.8, 65.6, 42.2. IR (neat, cm^{-1}): 3335, 1695, 1541, 1408, 1290, 1252, 1055. HRMS-EI calcd for $C_{10}H_{11}NO_4$ (M^+), 209.0688; found 209.0682.

A 300-mL three-necked round-bottomed flask equipped with a magnetic stirring bar and fitted with a dropping funnel was charged with *N*-Cbz-glycine (2.50 g, 12.0 mmol) and methanol (60 mL). The flask was cooled to 0 °C, and thionyl chloride (1.20 mL, 16.5 mmol, 1.4 equiv) was added to the vigorously stirred solution over a period of 10 min. The mixture was stirred for additional 2 h, after which time TLC (ethyl acetate) indicated complete consumption of the starting *N*-Cbz-glycine. The reaction mixture was concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (ethyl acetate) to afford *N*-Cbz-glycine methyl ester (2.66 g, 11.9 mmol, 99%) as a colorless oil. R_f=0.55 (ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32–7.18 (m, 5H), 5.58 (br s, 1H), 5.02 (s, 2H), 3.84 (d, 2H, J=5.6 Hz), 3.62 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 156.2, 136.1, 128.2, 127.9, 127.8, 66.7, 51.9, 42.3. IR (neat, cm^{-1}): 3337, 2953, 1701, 1508, 1443, 1364, 1207, 1051, 1004. HRMS-EI calcd for $C_{11}H_{13}NO_4$ (M^+) 223.0845; found 223.0833.

A flame-dried 200-mL three-necked round-bottomed flask equipped with a magnetic stirring bar and fitted with dropping funnel was charged with freshly distilled diisopropylamine (2.8 mL, 20 mmol, 2.0 equiv) and dry THF (22.4 mL). The resulting solution was cooled to 0 °C. To the reaction mixture was added *n*-BuLi (1.51 M in *n*-hexane, 13.3 mL, 20 mmol, 2.0 equiv) dropwise over the period of 5 min at 0 °C. The reaction mixture was stirred at 0 °C for 20 min then cooled to −78 °C. To the reaction mixture was added dry THF (6.3 mL) solution of *N*-Cbz-glycine methyl ester (2.25 g, 10.1 mmol) and trimethylsilyl chloride (5.1 mL, 40 mmol, 4.0 equiv) slowly over the period of 15 min via a dropping funnel.

After stirred for 20 min at −78 °C, the reaction mixture was then warmed to room temperature and stirred for another 2 h. The reaction mixture was concentrated under reduced pressure. The residue was diluted with dry hexanes (50 mL) and passed through Celite®, and the filter cake was washed with hexanes (50 mL). The filtrate was concentrated under reduced pressure to afford the crude ketene silyl acetal **10** (3.99 g) as a pale yellow oil, which was used to the next reaction without further purification.

4.4. Methyl 2-(benzyloxycarbonylamino)-2-(5,8-dibromo-6,7-dimethoxy-2-(2-nitrophenylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)ethanoate (11)[13]

An oven-dried 200-mL round-bottomed flask equipped with a magnetic stirring bar was charged with hemiaminal **9** (1.14 g, 201 mmol), ketene silyl acetal **10** (3.99 g, theoretically 5.0 equiv), and dry dichloromethane (20.0 mL). The resulting mixture was cooled to 0 °C. To the reaction mixture was added $BF_3 \cdot OEt_2$ (745 μL, 6.04 mmol, 3.0 equiv) slowly at 0 °C over the period of 12 min. The reaction mixture was stirred at 0 °C for 2 h, after which time TLC (dichloromethane–methanol=50:1) indicated complete consumption of the starting hemiaminal **9** (R_f=0.72). Tetrabutylammonium fluoride (1.0 M in THF, 20 mL, 20 mmol, 10 equiv) was added dropwise to the solution over the period of 3 min. After stirred for 15 min at 0 °C, the reaction mixture was warmed to room temperature and stirred for another 1 h, after which time TLC (dichloromethane–methanol=50:1) indicated complete removal of the TMS group on nitrogen (R_f=0.42). The reaction was quenched with saturated aqueous ammonium chloride. The mixture was concentrated under reduced pressure to remove organic solvents. The residue was extracted three times with ethyl acetate. The combined organic extracts were washed with aqueous ammonium chloride and brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography followed by GPC to provide **11** (952 mg, 1.23 mmol, 62%) as a white amorphous as a mixture of diastereomers. R_f=0.56 (dichloromethane–methanol=50:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00–7.90 (m, 1H), 7.69–7.46 (m, 3H), 7.40–7.15 (m, 5H), 5.78–5.54 (m, 2H), 5.08–4.85 (m, 3H), 4.15–3.54 (m, 11H), 3.10–2.80 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3, 155.7, 151.0, 149.4, 148.0, 136.0, 133.8, 132.2, 131.7, 131.5, 130.9, 126.4, 128.5, 128.2, 127.8, 124.2, 119.6, 118.7, 96.1, 67.2, 60.8, 58.1, 57.2, 53.0, 40.6, 27.3 (observed peaks). IR (neat, cm^{-1}): 1730, 1717, 1541, 1506, 1458, 1373, 1217, 1169, 1028, 772. Elemental analysis; calcd (%) for $C_{28}H_{27}Br_2N_3O_{10}S$: C 44.40, H 3.59, N 5.55; found: C 44.62, H 3.66, N 5.47.

4.5. Methyl 3,6-dihydro-4,5-dimethoxy-benzo[1,2-*b*:4,3-*b*′]dipyrrole-2-carboxylate (15)[13]

A 20-mL flame-dried round-bottomed flask was equipped with a magnetic stirring bar was charged with **11** (312.6 mg, 413 μmol) and copper iodide (118.0 mg, 620 μmol, 1.5 equiv). Cesium acetate (393.9 mg, 2.05 mmol, 5.0 equiv) and cesium carbonate (408.1 mg, 1.25 mmol, 3.0 equiv) were weighed and added to the flask in a glove box. The flask was then evacuated then backfilled with argon three times. To the mixture was added dry DMSO (4.1 mL). The resulting pale yellow solution was stirred at 90 °C for 3 h and was cooled to room temperature. The reaction mixture was treated with 5% aqueous sodium chloride in 10% aqueous ammonium hydroxide. The aqueous layer was extracted three times with ethyl acetate. The combined organic extracts were washed with 5% aqueous sodium chloride in 10% aqueous ammonium hydroxide, brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography and preparative TLC to afford pyrroloindole **15** (64.0 mg, 233 μmol, 57%) as a white solid. R_f=0.48 (hexanes–ethyl acetate=1:1). ^{1}H NMR (500 MHz, acetone-d_6): δ 10.59 (br s, 1H), 10.36 (br s, 1H), 7.35 (d, 1H, J=1.5 Hz), 7.25 (dd, 1H, J=2.4, 2.0 Hz), 6.71 (dd, 1H, J=2.4, 1.6 Hz), 4.03 (s, 3H), 3.98 (s, 3H), 3.85 (s, 3H). ^{13}C NMR (125 MHz, acetone-d_6): δ 162.5, 138.8, 134.7, 129.3, 126.4, 126.1, 123.5, 118.4, 117.9, 108.3, 101.9, 62.0, 61.3, 51.6. IR (neat, cm^{-1}): 3335, 2939, 1693, 1518, 1443, 1379, 1288, 1265, 1202, 1169, 1148, 1053, 760. HRMS-EI calcd for $C_{14}H_{14}N_2O_4$ (M^+) 274.0954; found 274.0942.

4.6. Methyl 6-benzyloxycarbonyl-4,5-dimethoxy-3-(2-nitrophenylsulfonyl)-1,2-dihydro-pyrrolo[3,2-*e*]indole-7-carboxylate (12)[13]

R_f=0.33 (hexanes–ethyl acetate=1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14–8.10 (m, 1H), 7.71–7.60 (m, 3H), 7.50–7.42 (m, 2H), 7.41–7.30 (m, 3H), 7.06 (s, 1H), 5.43 (s, 2H), 4.43 (t, 2H, J=7.5 Hz), 3.83 (s, 3H), 3.70 (s, 3H), 3.38 (s, 3H), 3.14 (t, 2H, J=7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.8, 152.6, 147.5, 142.9, 138.2, 134.9, 134.2, 133.0, 131.8, 131.4, 130.6, 130.3, 128.9, 128.74, 128.71, 128.5, 124.0, 123.3, 119.9, 109.9, 71.0, 61.1, 59.8, 54.2, 52.2, 28.9. IR (neat, cm^{-1}): 1771, 1717, 1541, 1491, 1369, 1350, 1252, 1163, 754. HRMS-FAB calcd for $C_{28}H_{25}N_3O_{10}S$ (M^+) 595.1261; found 595.1265.

4.7. 1-Benzyloxycarbonyl-6-bromo-7,8-dimethoxy-3-(2-nitrophenylsulfonyl)-2-methoxycarbonyl-1,2,2a,3,4,5-hexahydro-1,3-diazaacenaphthylene (13)[13]

R_f=0.42 (hexanes–ethyl acetate=1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.05–8.01 (m, 1H), 7.75–7.68 (m, 2H), 7.63–7.59 (m, 1H), 7.43–7.32 (m, 5H), 5.30–5.17 (m, 3H), 4.83–4.80 (m, 1H), 4.24–4.18 (m, 1H), 3.85 (s, 3H), 3.78 (s, 3H), 3.60 (s, 3H), 3.11–3.04 (m, 1H), 2.93–2.88 (m, 1H), 2.44–2.31 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 153.0, 152.3, 148.3, 141.8, 135.1, 134.3, 131.9, 131.8, 131.6, 131.4, 130.1, 128.7, 128.5, 124.2, 122.3, 112.8, 71.8, 68.7, 60.9, 60.7, 59.0, 52.5, 45.7, 28.2 (one signal of an aromatic carbon is missing due to overlapping). IR (neat, cm^{-1}): 1695, 1539, 1435, 1416, 1337, 1259, 1207, 1161, 1080, 756. HRMS-FAB calcd for $C_{28}H_{26}BrN_3O_{10}S$ (M^+) 675.0522; found 675.0529.

4.8. Methyl 5-bromo-6,7-dimethoxy-4-(2-(2-nitrophenyl-sulfonamido)ethyl)-1*H*-indole-2-carboxylate (14)[13]

R_f=0.31 (hexanes–ethyl acetate=1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.01 (br s, 1H), 8.12–8.07 (m, 1H), 7.87–7.76 (m, 1H), 7.70–7.65 (m, 2H), 7.13 (d, 1H, J=2.5 Hz), 5.44 (t, 1H, J=6.3 Hz), 4.03 (s, 3H), 3.96 (s, 3H), 3.88 (s, 3H), 3.50–3.42 (m, 2H), 3.26 (t, 2H, J=7.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.8, 147.7, 145.9, 138.0, 133.7, 133.4, 132.7, 130.9, 130.2, 127.7, 126.1, 125.5, 125.3, 114.0, 107.3, 61.2, 61.0, 52.2, 42.9, 33.5. IR (neat, cm^{-1}): 1747, 1545, 1468, 1435, 1362, 1296, 1271, 1169, 1016, 968, 754. HRMS-FAB calcd for $C_{20}H_{20}BrN_3O_8S$ (M^+) 541.0154; found 541.0154.

4.9. Methyl 6-acetyl-3,6,7,8-tetrahydro-4,5-dimethoxy-benzo[1,2-*b*:4,3-*b*′]dipyrrole-2-carboxylate (19)[13]

A 50-mL round-bottomed flask equipped with a magnetic stirring bar was charged with pyrroloindole **15** (206.3 mg, 752 μmol) and acetic acid (2.1 mL, 0.36 M). $NaBH_3CN$ (ca. 1 g, excess) was added to the flask, and the resulting reaction mixture was stirred at room temperature for 1 h, after which time TLC (hexanes–ethyl acetate=1:1) indicated complete consumption of the starting pyrroloindole **15** (R_f=0.48). The resulting mixture was cooled to 0 °C. To the reaction mixture was added pyridine (2.1 mL, 0.36 M) and

acetic anhydride (284.4 μL, 3.01 mmol, 4.0 equiv). The resulting solution was stirred at room temperature for 1.5 h, after which time TLC (hexanes–ethyl acetate=1:1) indicated complete consumption of the dihydropyrroloindole. The reaction mixture was diluted with ethyl acetate and basified with saturated aqueous sodium bicarbonate (20 mL) and 1 M NaOH (1 mL). After separation of organic layer, the aqueous layer was extracted twice with ethyl acetate. The combined organic extracts were washed with saturated aqueous sodium bicarbonate, 1 M HCl and brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane–methanol=50:1) to provide crude **19**, which was purified by GPC to afford pure **19** (235.3 mg, 739 μmol, 98%) as a yellow amorphous. R_f=0.40 (dichloromethane–methanol=20:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.04 (br s, 1H), 7.07 (d, 1H, J=2.0 Hz), 4.34 (t, 2H, J=7.6 Hz), 4.05 (s, 3H), 3.95 (s, 3H), 3.84 (s, 3H), 3.10 (t, 2H, J=7.6 Hz), 2.27 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 161.9, 141.3, 137.7, 131.2, 129.8, 128.2, 123.1, 121.1, 107.0, 61.3, 60.5, 52.04, 51.99, 28.3, 22.9. IR (neat, cm^{-1}): 3306, 3001, 2947, 2839, 1715, 1634, 1537, 1504, 1030, 995, 756. HRMS-EI calcd for $C_{16}H_{18}N_2O_5$ (M^+) 318.1216; found 318.1219.

4.10. Methyl 6-acetyl-3,6,7,8-tetrahydro-5-hydroxy-4-methoxy-benzo[1,2-*b*:4,3-*b*′]dipyrrole-2-carboxylate (20, PDE-II methyl ester)[13]

A 2-L oven-dried three-necked round-bottomed flask was equipped with a magnetic stirring bar was charged with dry dichloromethane (670 mL, 1.03 mM) and dry dichloromethane (30 mL) solution of **19** (219.3 mg, 689 μmol). The resulting mixture was cooled to 0 °C. To the solution was added BCl_3 (1.0 M in dichloromethane, 5.51 mL, 5.51 mmol, 8.0 equiv) dropwise at 0 °C over the period of 8 min. After stirred for 1 h at 0 °C, the reaction mixture was warmed to room temperature and stirred for additional 19 h, after which time TLC (dichloromethane–methanol=20:1) indicated complete consumption of the starting material. The reaction mixture was treated with saturated aqueous sodium bicarbonate (50 mL). The organic solvents were removed under reduced pressure. The residue was extracted with ethyl acetate three times. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by recrystallization (dichloromethane) to give pure **20** (131.3 mg, 431 μmol, 63%) as light brown crystals. The residue was purified by preparative TLC (dichloromethane–methanol=50:1) to afford **20** (21.6 mg, 71.0 μmol, 10%) as a white solid. R_f=0.46 (dichloromethane–methanol=20:1). Mp: 248.9–252.1 °C (dichloromethane). ^{1}H NMR (600 MHz, $CDCl_3$): δ 12.03 (s, 1H), 8.85 (br s, 1H), 7.02 (d, 1H, J=2.4 Hz), 4.18 (t, 2H, J=7.8 Hz), 4.02 (s, 3H), 3.93 (s, 3H), 3.28 (t, 2H, J=7.8 Hz), 2.34 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 168.8, 161.9, 139.1, 133.0, 131.3, 127.7, 127.0, 120.4, 117.3, 107.4, 60.6, 51.9, 51.3, 27.0, 23.9. IR (neat, cm^{-1}): 3323, 1688, 1452, 1437, 1298, 1261, 1097. HRMS-EI calcd for $C_{15}H_{16}N_2O_5$ (M^+) 304.1059; found 304.1053.

4.11. 6-Acetyl-3,6,7,8-tetrahydro-5-hydroxy-4-methoxy-benzo[1,2-*b*:4,3-*b*′]dipyrrole-2-carboxylic acid (2, PDE-II)[13]

A 10-mL test tube equipped with a magnetic stirring bar was charged with PDE-II methyl ester (**20**) (15.4 mg, 50.6 μmol) and dry THF (617 μL). To the solution were added $Na_2S_2O_4$ (26.2 mg, 152 μmol, 3.0 equiv) and 1 M LiOH (506 μL, 10 equiv), and the resulting mixture was stirred at room temperature for 5.5 h, after which time TLC (dichloromethane–methanol=10:1) indicated complete consumption of the starting material. The organic solvents were removed under reduced pressure, and the residue was diluted with water and washed with dichloromethane. The aqueous layer was acidified by 1 M hydrochloric acid (541 μL, 10.7 equiv) to give PDE-II as a white precipitate. The precipitate was washed twice with 20 mM hydrochloric acid (2 mL). Benzene (2 mL) was added to the precipitate and the resulting mixture was completely dried under reduced pressure to afford analytically pure PDE-II (**2**) (6.8 mg, 23 μmol, 46%) as a white solid. The physical properties of the synthetic PDE-II (**2**) were identical in all aspects to those reported for the natural product.[6] R_f=0.11 (dichloromethane–methanol=10:1). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.18 (s, 1H), 11.40 (br s, 1H), 6.94 (br s, 1H), 4.22 (t, 2H, J=8.2 Hz), 3.78 (s, 3H), 3.20 (t, 2H, J=8.2 Hz), 2.29 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 169.3, 162.4, 138.1, 132.6, 131.3, 128.8, 126.5, 120.7, 117.2, 106.9, 60.0, 50.8, 26.4, 23.6. IR (KBr, cm^{-1}): 3288, 2922, 2853, 1672, 1574, 1466, 1259, 1097, 1026, 799. HRMS-EI calcd for $C_{14}H_{14}N_2O_5$ (M^+) 209.0903; found 209.0890.

4.12. Methyl 6-(aminocarbonyl)-3,6,7,8-tetrahydro-4,5-dimethoxy-benzo[1,2-*b*:4,3-*b*′]dipyrrole-2-carboxylate (21)

A 50-mL round-bottomed flask equipped with a magnetic stirring bar was charged with pyrroloindole **15** (309 mg, 1.13 mmol) and acetic acid (3.0 mL). $NaBH_3CN$ (835 mg, 13.5 mmol, 12 equiv) was added to the flask, and the resulting reaction mixture was stirred at room temperature for 1 h, after which time TLC (hexanes–ethyl acetate=1:1) indicated complete consumption of the starting pyrroloindole **15** (R_f=0.48). To the reaction mixture was added dry dichloromethane (15 mL), trimethylsilyl isocyanate (152 μL, 1.13 mmol, 1.0 equiv), and DMAP (41.5 mg, 340 μmol, 0.30 equiv). The resulting solution was stirred at room temperature for 5 h, after which time TLC (hexanes–ethyl acetate=1:1) indicated complete consumption of dihydropyrroloindole **18**. The reaction was quenched with saturated aqueous sodium bicarbonate (20 mL). After separation of organic layer, the aqueous layer was extracted twice with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexanes–ethyl acetate=1:3) to afford the desired urea **21** (266 mg, 833 μmol, 74%) as a pale yellow solid. R_f=0.28 (dichloromethane–methanol=20:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.00 (br s, 1H), 7.05 (d, 1H, J=2.0 Hz), 5.80 (br s, 2H), 4.41 (t, 2H, J=7.8 Hz), 4.06 (s, 3H), 3.95 (s, 3H), 3.89 (s, 3H), 3.11 (t, 2H, J=7.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.9, 158.3, 139.3, 137.7, 131.2, 129.1, 128.6, 123.2, 122.0, 107.0, 61.7, 61.2, 52.1, 51.1, 27.7. IR (neat, cm^{-1}): 3423, 3339, 1691, 1651, 1582, 1402, 1300, 1215, 1150, 1099, 745. HRMS-EI calcd for $C_{15}H_{17}N_3O_5$ (M^+) 319.1168; found 319.1163.

4.13. Methyl 6-(aminocarbonyl)-3,6,7,8-tetrahydro-5-hydroxy-4-methoxy-benzo[1,2-*b*:4,3-*b*′]dipyrrole-2-carboxylate (22, PDE-I methyl ester)

A 500-mL oven-dried three-necked round-bottomed flask was equipped with a magnetic stirring bar was charged with **21** (54.4 mg, 170 μmol) and dry dichloromethane (170 mL, 1.00 mM). The resulting mixture was cooled to 0 °C. To the solution was added BCl_3 (1.0 M in dichloromethane, 1.70 mL, 1.70 mmol, 10 equiv) dropwise at 0 °C over a period of 30 s. After stirred for 3 h at 0 °C, the reaction mixture was warmed to room temperature and stirred for another 19 h. The reaction mixture was treated with saturated aqueous sodium bicarbonate (17 mL). The organic solvents were removed under reduced pressure. The residue was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by MPLC (acetone, flow rate: 2.5 mL/min, ULTRA PACK: DIOL-A) to afford pure **22** (39.4 mg, 129 μmol, 76%) as light brown crystals and

starting material (15.3 mg). The starting material was subjected to the above conditions to afford phenol **22** (9.1 mg, 30 μmol, 18%, 93% as a combined yield). R_f=0.67 (acetone). Mp: 213 °C (decomposition). ^{1}H NMR (400 MHz, acetone-d_6): δ 12.75 (s, 1H), 10.36 (br s, 1H), 6.97 (d, 1H, J=2.0 Hz), 6.22 (br s, 2H), 4.17 (t, 2H, J=8.8 Hz), 3.88 (s, 3H), 3.83 (s, 3H), 3.30 (t, 2H, J=8.8 Hz). ^{13}C NMR (150 MHz, acetone-d_6): δ162.3, 158.5, 139.8, 133.8, 131.7, 128.8, 127.7, 119.2, 118.1, 107.6, 60.3, 51.7, 50.3, 27.5. IR (KBr, cm^{-1}): 3427, 3339, 3219, 1684, 1638, 1472, 1439, 1333, 1298, 1261, 1225, 1198, 1096, 772, 748. HRMS-EI calcd for $C_{14}H_{15}N_3O_5$ (M^+) 305.1012; found 305.1026.

4.14. 6-Aminocarbonyl-3,6,7,8-tetrahydro-5-hydroxy-4-methoxy-benzo[1,2-*b*:4,3-*b*′]dipyrrole-2-carboxylic acid (1, PDE-I)

A 20-mL round-bottomed flask equipped with a magnetic stirring bar was charged with PDE-I methyl ester (**22**) (36.8 mg, 121 μmol), $Na_2S_2O_4$ (63.0 mg, 362 μmol, 3.0 equiv) and THF (1.5 mL). To the reaction mixture was added 1 M aqueous lithium hydroxide (1.21 mL, 10 equiv). The reaction mixture was stirred at room temperature for 9 h, after which time TLC (ethyl acetate) indicated complete consumption of the starting material. THF was removed under reduced pressure, and the residue was diluted with water and then the aqueous layer was washed with dichloromethane. The aqueous layer was acidified by 1 M aqueous hydrochloric acid (1.29 mL, 10.7 equiv) to give PDE-I as a white precipitate. The precipitate was washed twice with 20 mM aqueous hydrochloric acid (3 mL). Benzene (2 mL) was added to the precipitate and the resulting mixture was completely dried under reduced pressure to afford crude PDE-I (**1**). Trituration with ethyl acetate and the resulting solid to afford PDE-I (**1**) (30.5 mg, 105 μmol, 46%) as a white solid. The physical properties of the synthetic PDE-I (**1**) were identical with those reported for the natural product.[1,6d,8b] R_f=0.12 (ethyl acetate). Mp: 236 °C (decomposition). [lit. 235 °C (decomposition)]; ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.81 (s, 1H), 11.22 (s, 1H), 6.87 (d, 1H, J=2.0 Hz), 6.84 (br s, 2H), 3.99 (t, 2H, J=9.0 Hz), 3.76 (s, 3H), 3.18 (t, 2H, J=9.0 Hz) (two proton signals were missing owing to broadening). ^{13}C NMR (125 MHz, DMSO-d_6): δ 162.5, 157.5, 137.8, 132.5, 130.2, 128.1, 127.2, 118.1, 117.0, 106.5, 59.9, 49.3, 26.4. IR (KBr, cm^{-1}): 3495, 3458, 3352, 3219, 1663, 1641, 1578, 1489, 1439, 1329, 1290, 1258, 1161, 1132, 1090, 955, 883, 768, 746. HRMS-FAB calcd for $C_{13}H_{13}N_3O_5$ (M^+) 291.0855; found 291.0856.

4.15. *tert*-Butyl 2-methoxy-2-(trimethylsilyloxy)vinyl(-trimethylsilyl)carbamate (23)

A flame-dried 50-mL two-necked round-bottomed flask equipped with a magnetic stirring bar was charged with diisopropylamine (774 μL, 5.52 mmol, 2.0 equiv) and dry THF (6.1 mL). The resulting mixture was cooled to 0 °C. To the reaction mixture was added *n*-BuLi (1.47 M in *n*-hexane, 3.75 mL, 5.52 mmol, 2.0 equiv) dropwise at 0 °C over a period of 1 min. The reaction mixture was stirred at 0 °C for 20 min then cooled to −78 °C. To the reaction mixture was added dry THF (1.7 mL) solution of *N*-Boc-glycine methyl ester (522 mg, 2.76 mmol) and trimethylsilyl chloride (1.4 mL, 11 mmol, 4.0 equiv) slowly over a period of 3 min via cannula. After being stirred for 25 min at −78 °C, the reaction mixture was then warmed to room temperature and stirred for another 1 h. After removal of stirring bar, the reaction mixture was concentrated under reduced pressure. The residue was diluted with hexanes and passed through Celite®, and the filter cake was washed with hexanes. The filtrate was concentrated under reduced pressure to afford a crude ketene silyl acetal **23** (943 mg) as a yellow oil, which was used to the next reaction without further purification.

4.16. Methyl 2-(*tert*-butyloxycarbonylamino)-2-(5,8-dibromo-6,7-dimethoxy-2-(2-nitrophenylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)ethanoate (24)

An oven-dried 50-mL round-bottomed flask equipped with a magnetic stirring bar was charged with hemiaminal **9** (521 mg, 920 μmol), ketene silyl acetal **23** (943 mg, theoretically 3.0 equiv), and dry dichloromethane (9.2 mL). The resulting mixture was cooled to 0 °C. To the reaction mixture was added $BF_3\cdot OEt_2$ (340 μL, 2.76 mmol, 3.0 equiv) slowly at 0 °C over a period of 2 min. The reaction mixture was stirred at 0 °C for 2 h, after which time TLC (hexanes–ethyl acetate=3:1) indicated complete consumption of the starting hemiaminal **9**. The reaction was quenched with saturated aqueous ammonium chloride. The mixture was concentrated under reduced pressure to remove organic solvents. The residue was extracted with ethyl acetate. The combined organic extracts were washed with saturated aqueous ammonium chloride and brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexanes–ethyl acetate=1:1) to afford the desired Mannich adduct **24** (663 mg, 917 μmol, quant) as a colorless amorphous as a mixture of diastereomers. R_f=0.46 (hexanes–ethyl acetate=1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00–7.85 (m, 1H), 7.66–7.46 (m, 3H), 5.75–5.52 (m, 1H), 5.45–5.27 (m, 1H), 4.98–4.75 (m, 1H), 3.85 (s, 9H), 3.75–3.72 (m, 2H), 3.06–2.85 (m, 2H), 1.36–1.20 (m, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.5, 154.6, 150.8, 149.3, 147.9, 133.8, 132.1, 131.6, 131.5, 131.4, 130.8, 129.2, 124.1, 124.0, 119.4, 118.7, 80.1, 80.0, 60.8, 60.72, 60.67, 58.2, 58.1, 56.5, 55.4, 52.8, 52.6, 52.1, 40.5, 39.3, 28.2, 28.0, 27.5, 27.0 (observed peaks). IR (neat, cm^{-1}): 3381, 2982, 1744, 1715, 1547, 1504, 1462, 1406, 1367, 1348, 1302, 1165, 1028, 970, 912, 853, 733. HRMS-ESI calcd for $C_{25}H_{29}{}^{79}Br^{81}BrN_3O_{10}SNa$ ($M+Na^+$) 745.9819; found 745.9837.

4.17. 3-*tert*-Butyl 2-methyl-7,8-dihydro-4,5-dimethyl-6-[(2-nitrophenyl)sulfonyl]-benzo[1,2-*b*:4,3-*b*']dipyrrole-2,3(6*H*)-dicarboxylate (25)

A flame-dried 10-mL two-necked round-bottomed flask equipped with a magnetic stirring bar was charged with **24** (146.6 mg, 203 μmol), copper iodide (58.6 mg, 308 μmol, 1.5 equiv). Cesium acetate (195.6 mg, 1.02 mmol, 5.0 equiv) and cesium carbonate (197.9 mg, 607 μmol, 3.0 equiv) were weighed and added to the flask in a glove box. The flask was then evacuated then backfilled with argon. To the mixture was added dry DMSO (2.0 mL). The resulting solution was stirred at 90 °C for 3 h. The reaction mixture was cooled to room temperature. Then treated with 5% aqueous sodium chloride in 10% aqueous ammonium hydroxide, and the mixture was extracted with ethyl acetate. The combined organic extracts were washed with 5% aqueous sodium chloride in 10% aqueous ammonium hydroxide, brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to afford crude dihydropyrroloindole **25** (106 mg) as a brown oil, which was purified by column chromatography (hexanes–ethyl acetate=2:1 to 1:3, gradient) to provide dihydropyrroloindole **25** (38.4 mg, 68.3 μmol, 34%) and pyrroloindole **15** (11.0 mg, 40.1 μmol, 20%). Physical data for **25**; R_f=0.47 (hexanes–ethyl acetate=1:1). ^{1}H NMR (500 MHz, acetone-d_6): δ8.07–8.01 (m, 1H), 7.90–7.77 (m, 3H), 7.10 (s, 1H), 4.36 (t, 2H, J=7.5 Hz), 3.85 (s, 3H), 3.80 (s, 3H), 3.46 (s, 3H), 3.11 (t, 2H, J=7.5 Hz), 1.59 (s, 9H). ^{13}C NMR (125 MHz, acetone-d_6): δ 161.4, 151.0, 148.7, 144.0, 139.1, 134.9, 134.7, 132.7, 132.4, 131.2, 130.9, 129.3, 125.1, 124.8, 120.5, 109.9, 85.8, 61.4, 60.2, 54.8, 52.4, 30.5, 27.5. IR (neat, cm^{-1}): 1771, 1717, 1541, 1489, 1350, 1254, 1229, 1146, 1030, 849, 754. HRMS-FAB calcd for $C_{25}H_{27}N_3O_{10}S$ (M^+) 561.1417; found 561.1422.

4.18. Methyl 1-(*tert*-butyloxycarbonyl)-3,6,7,8-tetrahydro-4,5-dimethoxy-benzo[1,2-*b*:4,3-*b*′]dipyrrole-2-carboxylate (26)

Crude dihydropyrroloindole **25**, which was obtained by the amination using **24** (102.2 mg, 141 μmol), CsOAc (81.3 mg, 424 μmol, 3.0 equiv), Cs_2CO_3 (138.0 mg, 424 μmol, 3.0 equiv), was treated with cesium carbonate (230.0 mg, 705 μmol, 5.0 equiv), and dry MeCN (284 μL). To the resulting mixture was added PhSH (14.0 μL, 141 μmol, 1.0 equiv) and the mixture was stirred at room temperature for 4 h, after which time TLC (hexanes–ethyl acetate=1:1) indicated complete consumption of the starting nosyl amide **25**. The mixture was diluted with EtOAc and filtered through Celite plug and the filtrate was concentrated under reduced pressure. The crude material was purified by preparative TLC (hexanes–ethyl acetate=1:1, developed twice) to provide unprotected dihydropyrroloindole **26** (19.0 mg, 50.4 μmol, 36% over two steps) as a colorless amorphous and pyrroloindole **15** (5.0 mg, 18.2 μmol, 13% over two steps). Physical data for **26**; R_f=0.26 (hexanes–ethyl acetate=1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.99 (s, 1H), 3.93 (s, 3H), 3.90 (s, 3H), 3.89 (s, 3H), 3.66 (t, 2H, J=8.5 Hz), 3.16 (t, 2H, J=8.5 Hz), 1.66 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 161.2, 151.1, 141.3, 139.2, 138.0, 127.6, 127.0, 120.7, 115.2, 108.9, 84.7, 61.1, 60.2, 51.8, 48.3, 29.3, 27.4. IR (neat, cm^{-1}): 3368, 2939, 1765, 1715, 1493, 1258, 1238, 1148, 1030, 845, 731. HRMS-FAB calcd for $C_{19}H_{24}N_2O_6$ (M^+) 376.1634; found 376.1625.

4.19. Methyl 6-acetyl-1-(*tert*-butyloxycarbonyl)-3,6,7,8-tetrahydro-4,5-dimethoxy-benzo[1,2-*b*:4,3-*b*′]dipyrrole-2-carboxylate (27)

A flame-dried 20-mL two-necked round-bottomed flask equipped with a magnetic stirring bar was charged with the crude **25** (74.5 mg), cesium carbonate (231.0 mg, 710 μmol, 5.0 equiv), and dry MeCN (284 μL). To the resulting mixture was added PhSH (14.6 μL, 142 μmol, 1.0 equiv) and the mixture was stirred at room temperature for 4 h, after which time TLC (hexanes–ethyl acetate=1:1) indicated complete consumption of the starting nosyl amide **25**. To the mixture were added Ac_2O (67.1 μL, 710 μmol, 5.0 equiv) and pyridine (568 μL). The mixture was stirred at room temperature for 1 h, after which time TLC (hexanes–ethyl acetate=1:1) indicated complete consumption of the unprotected dihydropyrroloindole **26**. The mixture was filtered through Celite plug and the filtrate was concentrated under reduced pressure. The resulting mixture was partitioned between ethyl acetate and saturated aqueous ammonium chloride. The aqueous layer was extracted twice with ethyl acetate. The combined organic extracts were dried over sodium sulfate and filtered. The organic solvents were removed under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexanes–ethyl acetate=1:1) to provide dihydropyrroloindole **27** (27.3 mg, 65.2 μmol, 46% over two steps) as a colorless amorphous. R_f=0.19 (hexanes–ethyl acetate=1:1). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.07 (s, 1H), 4.33 (t, 2H, J=7.8 Hz), 3.96 (s, 3H), 3.91 (s, 3H), 3.84 (s, 3H), 3.08 (t, 2H, J=7.8 Hz), 2.26 (s, 3H), 1.67 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 172.3, 160.8, 150.5, 142.6, 138.7, 131.9, 129.7, 128.6, 123.3, 120.2, 109.1, 85.3, 61.3, 60.4, 52.1, 51.9, 28.1, 27.4, 22.9. IR (neat, cm^{-1}): 2982, 2942, 1767, 1720, 1659, 1410, 1372, 1336, 1257, 1220, 1152, 1028, 733. HRMS-FAB calcd for $C_{21}H_{26}N_2O_7$ (M^+) 418.1740; found 418.1725.

4.20. Methyl 6-acetyl-3,6,7,8-tetrahydro-4,5-dimethoxy-benzo[1,2-*b*:4,3-*b*′]dipyrrole-2-carboxylate (19)

A 10-mL test tube was charged with **27** (10.2 mg, 24.4 μmol), evacuated, and backfilled with argon. The test tube was heated at 180 °C for 30 min, after which time TLC (ethyl acetate) indicated complete consumption of the starting Boc carbamate **27**. Purification was performed by silica gel column chromatography (ethyl acetate) to provide unprotected indole **19** (7.2 mg, 23 μmol, 93%), whose spectral data were identical with those reported in the first-generation synthesis of PDE-II.[13]

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