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Tetrahedron 61 (2005) 12330–12338
Tetrahedron

The optimization for cyclization reaction of 2-(2-carbomethoxyethynyl)aniline derivatives and formal synthesis of pyrroloquinoline quinone and its analogue utilizing a sequential coupling-cyclization reaction

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Received 26 August 2005; revised 20 September 2005; accepted 21 September 2005

Available online 10 October 2005

Abstract—The reaction conditions for the Pd-catalyzed cyclization reaction of 2-(2-carbomethoxyethynyl)aniline derivatives were investigated. The amounts of $Pd(PPh_3)_4$, methyl propiolate, and $ZnBr_2$ could be significantly reduced compared with those reported in our preliminary publication by careful tuning of the solvent and the reaction temperature. In addition to the above results, formal syntheses of pyrroloquinoline quinone (PQQ) and its analogue from 2-amino-5-nitrophenol using a Pd-complex-catalyzed sequential coupling-cyclization reaction between methyl propiolate and 2-iodoaniline derivatives are described.

1. Introduction

1.1. Cyclization reaction of 2-(2-carbomethoxylethynyl)-aniline derivatives

In our continuing efforts to develop new methods of synthesis for heterocyclic compounds, we have previously discovered both Cu(II)-catalyzed synthesis of indoles from 2-ethynylaniline derivatives[1] and Pd-complex-catalyzed sequential coupling-cyclization reactions between methyl propiolate and 2-iodoaniline derivatives, and the latter's application to duocarmycin SA synthesis.[2,3] Although the true catalytic species in the Pd-complex-catalyzed reactions has not yet been identified, these reactions are an effective method for the synthesis of indole-2-carboxylate derivatives, which are commonly found in biologically active compounds.

Unfortunately, the substrates for the Pd-complex-catalyzed sequential reaction are limited to compounds having at least one electron-withdrawing group on the aromatic ring (Scheme 1, **1a**→**3a**; 69% vs **1b**→**3b**; 10%).[2] However, the cyclization reactions for the compound **2b** can be realized in almost perfect yield when both $Pd(PPh_3)_4$ and methyl propiolate are present in the reaction medium (Scheme 1, **2b**→**3b**; 94%).[2] These results suggest that the coupling reaction rate for the electron-rich substrate is slower than that for the electron-poor compound in the sequential processes, and it seems likely that the catalyst was deactivated during the long reaction time.

In our previous communication, we reported that methyl propiolate is essential for the Pd-catalyzed cyclization reactions of **2b**.[2] However, we did not optimize the reaction conditions, including the amount of each reagent and the solvent, reaction temperature, and ligand for Pd. In the first half of this article, we describe the results of the optimization for the Pd-catalyzed cyclization reaction conditions (**2b**→**3b**).

1.2. Pyrroloquinoline quinone (PQQ) and its analogues

The characterization of pyrroloquinoline quinone (PQQ) (**4**) from *Pseudomonas* TP1[4] was first reported in 1979 by Salisbury. Initially, the role of PQQ in bacteria seemed to be limited to that of a redox cofactor, but later it was found that

Keywords: Palladium; 2-Ethynylaniline; Methyl propiolate; Indole; Cyclization reaction; Pyrroloquinoline quinone.
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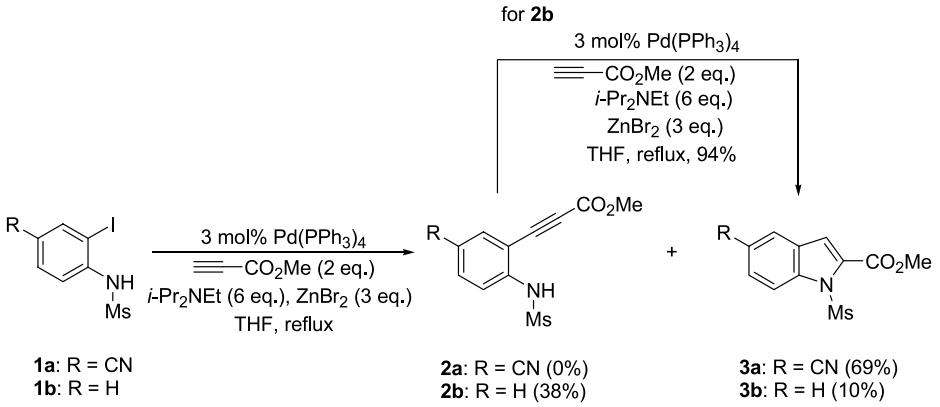
0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.09.084



Scheme 1. Sequential coupling-cyclization reactions for **1a** and **1b** and cyclization reaction for **2b**.

PQQ also acts as a growth factor and tissue-protective agent.[5] Quite recently, another important role for PQQ as the 14th vitamin in mammals was established by Kasahara and Kato.[6,7]

The first total synthesis of PQQ was reported by Corey in 1981, in 11 steps starting from commercially available 2-methoxy-5-nitroaniline.[8a] After this communication, seven articles on the total synthesis of PQQ were published in the 1980s,[8b–h] and three papers reported the preparation of PQQ and/or its trimethyl ester in the 1990s.[8i–k] Interest in PQQ has recently shifted toward understanding the mechanisms of its biological activity[9] and biosynthetic pathway.[10] Thus, the synthetic targets have been not only PQQ itself, but also PQQ analogues, in order to understand the structure–activity relationships of PQQ. Hence, many kinds of PQQ analogues have been synthesized, including mono- and dicarboxylic acid derivatives,[11] 6-deaza derivatives,[12] benzo-,[13a] furo- (FQQ),[13b] thieno- (TQQ),[13b] and imidazole[13c] analogues in place of the pyrrole ring, and azaisomers involving both the pyrrole and pyridine rings.[14,15]

Our synthetic strategies for PQQ (**4**) and its analogue **5** are shown in Figure 1. Briefly, the conversions from **9** via **7** and **6** to PQQ (**4**) and from **8** to PQQ analogue **5** had been reported by Rees's[8g] and Hudson's[14b] research groups, respectively. Thus, compound **8** can be synthesized from **10** by same pyridine ring formation reactions as for **9**. Since both **11** and **12** have the nitro group on the aromatic ring, we planned to use our sequential coupling-cyclization reaction[2], followed by reduction of nitro group to form the indoles **9** and **10**, respectively. Iodides **11** and **12** may be

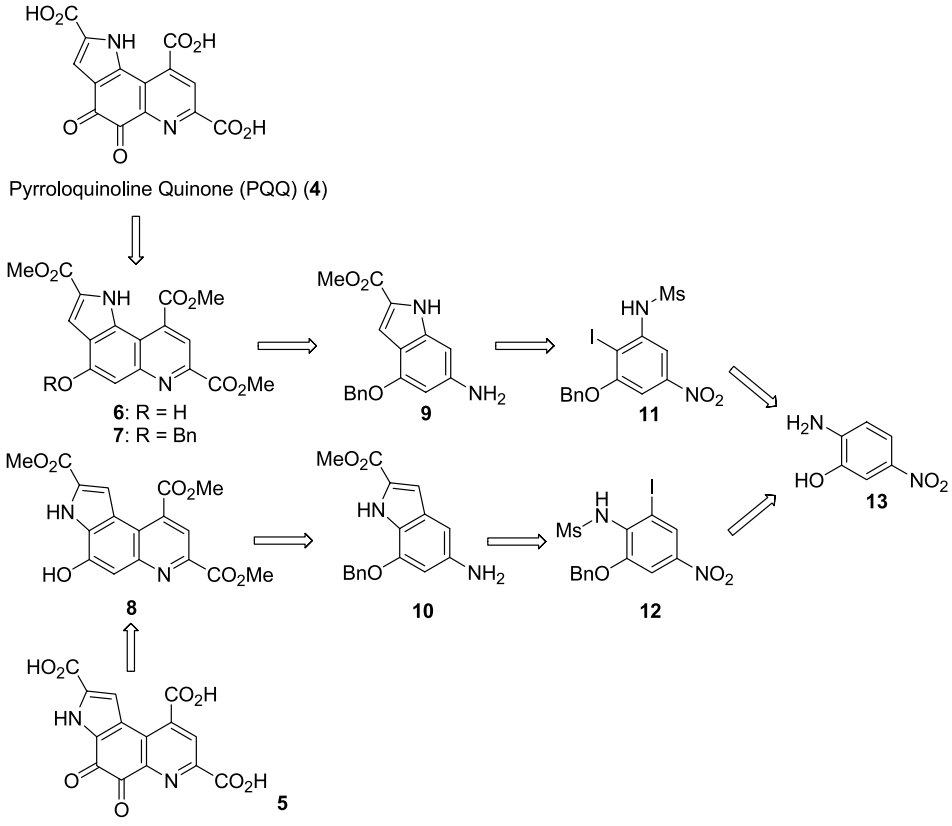


Figure 1. Retrosynthetic analysis for PQQ (**4**) and its analogue **5**.

synthesized from 2-amino-5-nitrophenol (**13**) as the common starting material by regioselective functional group installations.

In the second half of this article, we describe a relatively short synthesis of **7**[8g] and **8**,[14] which are intermediates for the synthesis of PQQ (**4**) and its analogue **5** by Pd-complex-catalyzed sequential coupling-cyclization reactions as the key steps.

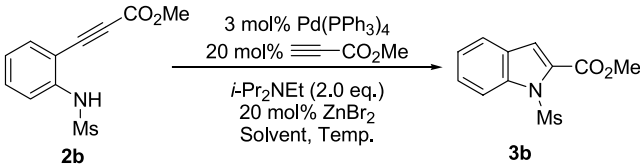
2. Results and discussion

2.1. Optimization of the reaction conditions

Since we have already established that both $Pd(PPh_3)_4$ and methyl propiolate are essential for the cyclization reactions,[2] we first experimented with reducing the amounts of the reagents. The results are summarized in Table 1. When the amount of *i*-Pr_2NEt was reduced from 2.0 to 1.0 equiv, the yield of **3b** was markedly reduced compared to that from the original conditions (Table 1, entry 1 [94%] vs entry 2 [28%]). In contrast, the amount of methyl propiolate could be reduced from 600 to 20 mol%, but not to 10 mol% (Table 1, entries 2–6). Since higher reaction temperature was required for the reactions with less than 100 mol% of methyl propiolate, the reactions were carried out in a sealed tube (Table 1, entry 4 vs entries 5–8). In the presence of 20 mol% of methyl propiolate, the amount of $ZnBr_2$ could also be reduced from 300 to 20 mol% without any loss of yield (Table 1, entry 5 [87%] vs entry 7 [88%]). However, in the absence of $ZnBr_2$, the yield of **3b** decreased from 88 to 35% (Table 1, entries 7 and 8). Presumably, the role of $ZnBr_2$ might be acceleration of the formation of the catalyst, or its activation, or both.

Next, we examined the influence of the solvent and the reaction temperature using optimized amounts of $ZnBr_2$, methyl propiolate, and *i*-Pr_2NEt (Table 2). The reaction barely proceeded in the tested solvents at ambient temperature (ca. 20 °C, Table 2, entries 1–3). At 50 °C, the yield of **3b** was quite low under the original conditions[2] (in THF, Table 2, entry 4) and reasonable yields were observed in both DMF and trifluorotoluene at 50 °C (Table 2, entries 5 and 6). The fastest reaction was observed in CH_2Cl_2 at 50 °C (Table 2, entry 7) and these reaction conditions were included in the further optimizations (Tables 3 and 4).

Table 2. Optimization of the solvent and the reaction temperature



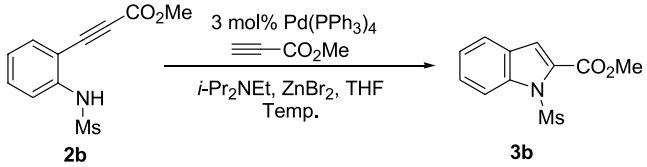
Entry	Solvent	Time (h)	Temperature (°C)	Yield (%)
1	THF	17	Ambient	0
2	DMF	65	Ambient	0
3	CH_2Cl_2	76	Ambient	5
4[a]	THF	12	50	4
5[a]	DMF	12	50	74
6[a]	Trifluorotoluene	12	50	88
7[a]	CH_2Cl_2	6	50	85

[a] Reactions were carried out in a sealed tube.

Because of the volatile nature of methyl propiolate, we were worried that it might evaporate from the reaction mixture. However, contrary to our speculation, the propiolates possessing bulkier ester moieties tended to reduce the reaction rate. When benzyl propiolate was used, there is advantage that the reaction can be carried out without using a sealed tube. However, since no difference in yield between the methyl and benzyl esters was observed and the reaction rate with methyl propiolate is much faster than that with benzyl propiolate (Table 3, entry 1 vs 2), we chose commercially available methyl propiolate in subsequent experiments. The other acetylenes, which do not have an electron withdrawing group, did not show any catalytic activities, even when reacted for 30 h (Table 3, entries 3 and 4).

Finally, the effects of the ligand, using $Pd_2(dba)_3$ as the palladium source, were investigated (Table 4). $Pd_2(dba)_3$ without any ligand did not have effective catalytic activity (Table 4, entry 1). Surprisingly, the yield of **3b** in the reaction with PPh_3 was much lower than that with $Pd(PPh_3)_4$ (Table 4, entry 2 [35%] vs Table 2, entry 7 [85%]). The

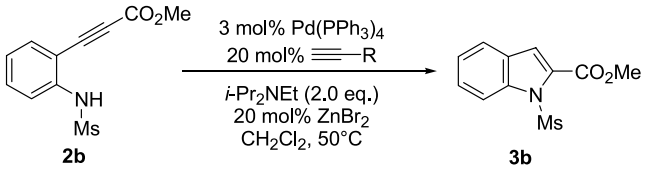
Table 1. The optimized amounts of the reagents for the cyclization reaction



Entry	$ZnBr_2$ (mol%)	Methyl propiolate (mol%)	*i*-Pr_2NEt (equiv)	Temperature (°C)	Time (h)	Yield (%)
1	300	600	2.0	65–67 (Reflux)	17	94
2	300	600	1.0	65–67 (Reflux)	17	28
3	300	100	2.0	65–67 (Reflux)	17	100
4	300	50	2.0	65–67 (Reflux)	22	56 (27)[a]
5[b]	300	20	2.0	100	17	87
6[b]	300	10	2.0	100	17	54
7[b]	20	20	2.0	100	4	88
8[b]	—	20	2.0	100	17	35

[a] The numbers in the parenthesis are the yields of the recovered **2b**.
[b] Reactions were carried out in a sealed tube.

Table 3. The effect of the substituent of the acetylenes



Entry	R	Time (h)	Yield (%)
1[a]	CO_2Me	6	85
2	CO_2Bn	17.5	86
3[a]	Ph	30	15 (85)[b]
4[a]	Bu	30	16 (83)[b]

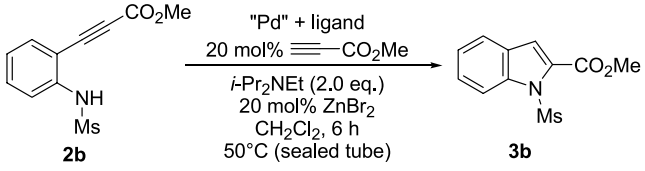
[a] Reactions were carried out in a sealed tube.
[b] The numbers in the parenthesis are the yields of the recovered **2b**.

ligands that have larger cone angles [P(*o*-tol)$_3$ or PBn$_3$] or smaller one (PBu$_3$) or more π-acid character [P(OPh)$_3$] than PPh$_3$ also gave disappointing results (Table 4, entries 3–6). The catalyst with bidentate ligands (BINAP or dppf) also did not show any catalytic activity (Table 4, entries 6 and 7). At this stage, we gave up investigating the reactions with the other ligands and focused on reducing the catalyst [Pd(PPh$_3$)$_4$] loading. The yield was essentially the same between 3 and 1 mol% Pd(PPh$_3$)$_4$ (Table 4, entries 9 and 10). Consequently, the amount of the catalyst could be reduced to 0.5 mol%, although the yield was decreased slightly (Table 4, entry 11). From the above results, we could establish the optimized conditions.

2.2. Synthesis of PQQ and its analogues

Following the retro synthetic scheme (Fig. 1), we began with the synthesis of PQQ. Both the amino and phenol groups of commercially available 2-amino-5-nitrophenol (**13**) were protected as cyclic carbamates by treatment with 1,1′-carbonyldiimidazole in THF in 96% yield. Regioselective nitration was performed by standard reaction conditions to yield dinitro compound **15** as the major product (78%). The cyclic carbamate was essential as the protecting group in achieving the regioselective nitration.

Table 4. Palladium species and ligand effect



Entry	Pd source (mol%)	Ligand (mol%)	Yield (%)
1	Pd$_2$(dba)$_3$ (3)	—	8 (50)[a]
2	Pd$_2$(dba)$_3$ (3)	PPh$_3$ (24)	34 (50)[a]
3	Pd$_2$(dba)$_3$ (3)	P(*o*-tol)$_3$ (24)	Trace
4	Pd$_2$(dba)$_3$ (3)	PBn$_3$ (24)	12 (68)[a]
5	Pd$_2$(dba)$_3$ (3)	PBu$_3$ (24)	14 (51)[a]
6	Pd$_2$(dba)$_3$ (3)	P(OPh)$_3$ (24)	Trace
7	Pd$_2$(dba)$_3$ (3)	BINAP (6)	0
8	Pd$_2$(dba)$_3$ (3)	dppf (12)	Trace
9	Pd(PPh$_3$)$_4$ (3)	—	85
10	Pd(PPh$_3$)$_4$ (1)	—	87
11	Pd(PPh$_3$)$_4$ (0.5)	—	76

[a] The numbers in the parentheses are the yields of recovered **2b**.

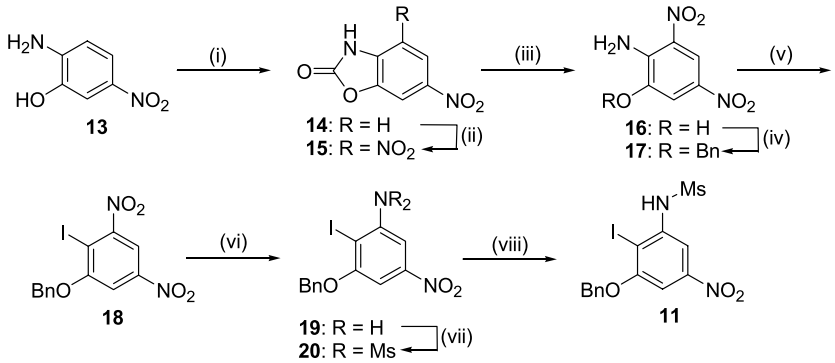
Alkaline hydrolysis of the carbamate moiety of **15** followed by benzylation of the resulting phenol group afforded the amine **17** in good overall yield (91% for two steps). The amino group of **17** was converted to an iodine atom under Sandmeyer conditions to provide 2-benzyloxy-1-iodo-4,6-dinitrobenzene (**18**). It was difficult to reduce only the C6-nitro group of **18**; we tested several reaction conditions (e.g., H_2, Pd/C; H_2, PtO_2; $H_2NNH_2 \cdot H_2O$, etc.). However, the reaction of **18** in the presence of metallic iron in a mixture of AcOH–EtOH (1/1) at 100 °C[16] gave **19** as the major product. Next, the amino group of **19** was converted to the corresponding mesylamide **11** via bis-mesylate **20**, followed by methanolysis, with 89% yield from **19** (Scheme 2).

Having established the synthesis of the desired 2-iodoaniline derivative **11** in large quantities, we applied the sequential coupling-cyclization reaction to **11** (Scheme 3). The coupling reaction of **11** in the presence of methyl propiolate, Pd(PPh$_3$)$_4$, ZnBr$_2$, and *i*-Pr$_2$NEt in THF as previously reported,[2] followed by cyclization, proceeded smoothly to afford the indole **21** in 65% yield.[17] Only the cyclized compound **21** was isolated, and the 2-ethynylaniline derivative produced in the first reaction was not detected. Methanolysis of the mesylamide group on **21** followed by reduction of the nitro group was carried out to produce the aniline **9**[8g] in reasonable yield (73%). The pyridine ring was constructed using the procedure reported by MacKenzie et al.[8g] [dimethyl (*E*)-2-oxoglutaconate, CH_2Cl_2, room temperature 12 h, then cat. HCl in Et_2O, room temperature 12 h] to permit synthesis of the three-ring system of PQQ in 71% yield. The spectral data (IR, ^{1}H NMR, and MS) of **7** were identified with the reported data.[8g] This compound was converted to PQQ (**4**) via ortho-quinone **23**[8a–c,g,i] by four steps. Thus, we furnished formal synthesis of PQQ (**4**) (Scheme 3).

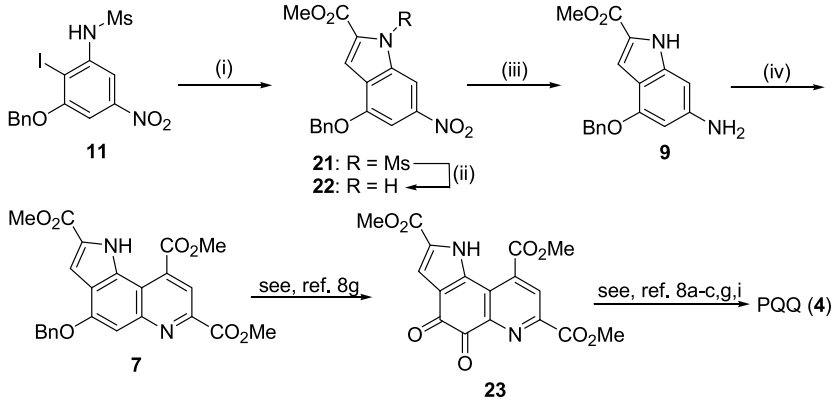
Synthesis of the PQQ analogue was started from the indole derivative **24**, which was synthesized from **13** via **12** in our synthesis of duocarmycin SA.[2] The selective removal of the methanesulfonyl group under methanolysis conditions was followed by reduction of the nitro group on **25** by hydrogenation to provide **10**. The third ring was constructed using the same procedure as in the synthesis of PQQ, to afford **26** (45% yield for two steps). Finally, the benzyl ether of **26** was cleaved under hydrogenolysis conditions to give **8**, which yielded spectral data that matched those previously reported[14b] (Scheme 4).

3. Conclusion

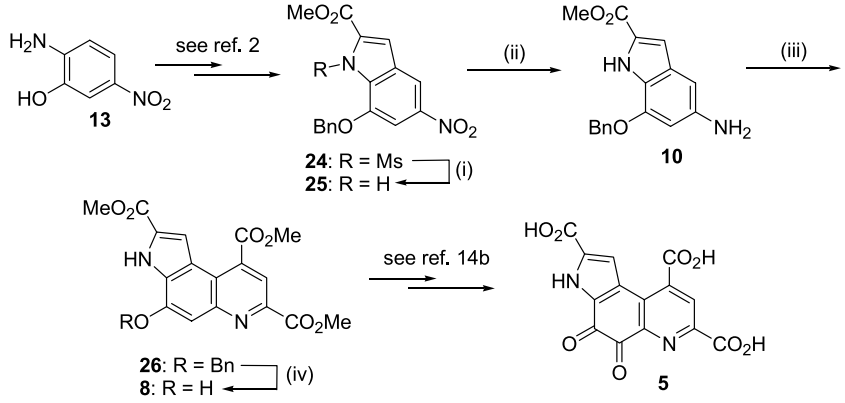
In summary, we optimized the Pd-catalyzed cyclization reaction of 2-(2-carbomethoxyethynyl)aniline derivatives. Namely, the amounts of Pd(PPh$_3$)$_4$, methyl propiolate, and ZnBr$_2$ could be significantly reduced compared with those reported in our previous communication. We also successfully applied a Pd-complex-catalyzed sequential coupling-cyclization reaction between methyl propiolate and 2-iodoaniline derivatives to the synthesis of PQQ and its analogues. The further application is currently underway in our laboratory.



Scheme 2. Reagents and conditions: (i) $(Imid)_2CO$, THF, rt, 2 h (96%); (ii) f. HNO_3, concd H_2SO_4, 0 °C, 5 min (78%); (iii) NaOH, 50 °C, 22 h; (iv) BnBr, K_2CO_3, acetone, reflux, 2 h (91% from **15**); (v) $NaNO_2$, H_2SO_4, AcOH, 5 °C, 5 min, then KI, rt, 2 h (54%); (vi) Fe, AcOH–EtOH (1/1), 100 °C, 1 h (55%); (vii) MsCl, Et_3N, CH_2Cl_2, rt, 5 min; (viii) K_2CO_3, MeOH, rt, 15 min (89% from **19**).



Scheme 3. Reagents and conditions: (i) methyl propiolate, $Pd(PPh_3)_4$, $ZnBr_2$, *i*-Pr_2NEt, THF, 100 °C in a sealed tube, 11 h (65%); (ii) K_2CO_3, MeOH–THF (1/1), rt, 15 min (78%); (iii) H_2, PtO_2, AcOEt–THF (1/1), rt, 2 h (73%); (iv) dimethyl (*E*)-2-oxoglutaconate, CH_2Cl_2, rt, 12 h, then cat. HCl in Et_2O, rt, 12 h (71%).



Scheme 4. Reagents and conditions: (i) K_2CO_3, MeOH–THF (1/1), rt, 20 min (89%); (ii) H_2, PtO_2, AcOEt, rt, 2 h; (iii) dimethyl (*E*)-2-oxoglutaconate, CH_2Cl_2, rt, 12 h, then cat. HCl in MeOH, rt, 10 h (45% from **25**); (iv) H_2, Pd/C, $CHCl_3$–MeOH (1/3), rt, 1.5 h, (97%).

4. Experimental

4.1. General

All melting points were determined with a Yazawa Micro Melting Point BY-2 and are uncorrected. ^1H NMR spectra (400 and 600 MHz) were recorded on JEOL JMN AL-400 and JEOL ECA-600 spectrometers, respectively. ^{13}C NMR spectra (100, 125, 150 MHz) were recorded on JEOL JMN AL-400, JEOL ECP-500, and JEOL ECA-600 spectrometers, respectively. For ^1H NMR spectra, chemical shifts (δ) are given from TMS (0 ppm) in $CDCl_3$ and from residual non-deuterated solvent peak in the other solvents (acetone-d_6:2.04 ppm, DMSO-d_6:2.49 ppm, methanol-d_4:3.30 ppm, and THF-d_8:3.58 ppm) as internal standards. For ^{13}C NMR spectra, chemical shifts (δ) are given from $^{13}CDCl_3$ (77.0 ppm), $(^{13}CD_3)_2CO$ (29.8 ppm), $(^{13}CD_3)_2SO$ (39.7 ppm), and $(^{13}CD_2\text{-}CD_2)_2O$ (25.2 ppm) as internal standards. Standard and high-resolution mass spectra were measured on JEOL JMS-DX303 and MS-AX500 instruments, respectively. IR spectra were recorded on a Shimadzu FTIR-8400.

4.1.1. Methyl 1-methylsulfonyl-2-indolecarboxylate (3b) (Table 4, entry 11). *i*-Pr_2NEt (69 μl, 0.4 mmol), **2b** (50.0 mg, 0.2 mmol), methyl propiolate (4 μl, 0.04 mmol), and $Pd(PPh_3)_4$ (1.4 mg, 0.001 mmol) were successively added to a solution $ZnBr_2$ (8.8 mg, 0.04 mmol) in CH_2Cl_2 (2.0 ml) and the mixture was stirred at 50 °C for 6 h in a sealed tube. Saturated aqueous NH_4Cl solution was added to the mixture and the aqueous phase was extracted with $CHCl_3$. The combined organic solution was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography [AcOEt–hexane (1/3)] to afford **3b** (38.2 mg, 76%) as a colorless solid. The spectral data of **3b** were identified with those of the authentic sample.[1a]

4.1.2. 6-Nitro-3*H*-benzooxazol-2-one (14). 1,1′-Carbonyldiimidazole (5.77 g, 35.6 mmol) was added to a solution of **13** (5.0 g, 32.4 mmol) in anhydrous THF (100 ml) at room temperature and stirred for 2 h at the same temperature. Diluted aqueous HCl solution (50 ml) was added to the mixture and the aqueous phase was extracted with Et_2O. The organic solution was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and concentrated. The resulting solid **14** (5.58 g, 96%) was essentially pure and could be used to the following reaction. Analytical sample was recrystallized from AcOEt–hexane to provide colorless needles. Mp 254–255 °C; IR (film, cm^{-1}) 1794, 1508, 1342; ^1H NMR (400 MHz, methanol-d_4) δ 7.22 (1H, d, $J=8.7$ Hz), 8.11 (1H, d, $J=2.1$ Hz), 8.17 (1H, dd, $J=8.7$, 2.1 Hz); ^{13}C NMR (100 MHz, acetone-d_6) δ 105.3, 109.2, 120.5, 136.4, 142.8, 143.3, 153.6; MS *m/z* 180 (M^+, 100), 134 (19.0), 106 (21.1); HRMS Calcd $C_7H_4N_2O_4$: 180.0171. Found: 180.0154.

4.1.3. 4,6-Dinitro-3*H*-benzooxazol-2-one (15). Concd H_2SO_4 (0.83 ml) was slowly added to 1.52 M f. HNO_3 solution (5.6 ml, 8.51 mmol) at 0 °C. After being stirred for 5 min at the same temperature, **14** (1.4 g, 7.77 mmol) was added to the mixture. After the addition was completed, the solution was poured into a mixture of ice and water. The aqueous phase was extracted with AcOEt and the combined organic solution was successively washed with saturated aqueous $NaHCO_3$ solution and saturated aqueous NaCl solution. The organic solution was dried over anhydrous $MgSO_4$ and concentrated at the reduced pressure. The residue was purified by silica gel column chromatography [AcOEt–hexane (2/3)] to afford **15** (1.09 g, 78%) as a colorless powder. Colorless powder from AcOEt–hexane; mp 200–202 °C; IR (film, cm^{-1}) 3099, 1790, 1634, 1541, 1344; ^1H NMR (400 MHz, acetone-d_6) δ 8.47 (1H, d, $J=2.0$ Hz), 8.80 (1H, d, $J=2.0$ Hz); ^{13}C NMR (100 MHz, acetone-d_6) δ 109.7, 115.1, 130.1, 132.9, 141.5, 145.2, 152.9; MS *m/z* 225 (M^+, 100), 209 (3.0), 179 (3.3); HRMS Calcd $C_7H_3N_3O_6$: 225.0022. Found: 225.0000. Anal. Calcd for $C_7H_3N_3O_6$: C, 37.35; H, 1.34; N, 18.67. Found: C, 37.15; H, 1.63; N, 18.66.

4.1.4. 2-Benzyloxy-4,6-dinitroaniline (17). A suspension of **15** (570 mg, 2.53 mmol) in 0.2 N NaOH (50 ml) was stirred for 22 h at 50 °C. The solution was neutralized with 3 N HCl (3.1 ml) at 0 °C and the aqueous phase was extracted with AcOEt. The organic solution was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and the solvent was evaporated to afford the crude **16**, which was used to the next reaction without further purification.

K_2CO_3 (455 mg, 3.29 mmol) and benzyl bromide (454 mg, 2.65 mmol) were added successively to a solution of the crude **16** in acetone (25 ml) and the mixture was refluxed for 2 h. After being cooled to room temperature, the inorganic precipitate was filtered through a Celite™ pad and the filtrate was concentrated at the reduced pressure. The resulting solid was recrystallized from AcOEt to afford **17** (557 mg) as yellow needles and the mother liquid was chromatographed on silica gel [AcOEt–hexane (1/2)] to afford **17** (110 mg) as a yellow solid (total yield of **17**: 667 mg, 91%). Yellow needles from AcOEt; mp 187–189 °C; IR (film, cm^{-1}) 3489, 3369, 1624, 1541, 1328; ^1H NMR (400 MHz, $CDCl_3$) δ 5.23 (2H, s), 7.41–7.44 (5H, m), 7.81 (1H, d, $J=2.4$ Hz), 8.81 (1H, d, $J=2.4$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 72.1, 108.1, 108.3, 115.6, 115.8, 128.1, 129.0, 129.1, 134.2, 141.2, 146.4; MS *m/z* 289 (M^+, 4.1), 91 (100); HRMS Calcd $C_{13}H_{11}N_3O_5$: 289.0699. Found: 289.0683. Anal. Calcd for $C_{13}H_{11}N_3O_5$: C, 53.98; H, 3.83; N, 14.53. Found: C, 53.90; H, 3.87; N, 14.47.

4.1.5. 2-Benzyloxy-1-iodo-4,6-dinitrobenzene (18). $NaNO_2$ (65.4 mg, 0.948 mmol) was slowly added to concd H_2SO_4 (1 ml) at 0 °C and the mixture was dropped to a solution of **17** (203 mg, 0.702 mmol) in AcOH (10 ml) at 5 °C. After being stirred for 5 min, a solution of KI (157 mg, 0.946 mmol) in ice and H_2O (10 ml) was added to the reaction mixture and the mixture was stirred for another 2 h at room temperature. The mixture was extracted with AcOEt and the combined organic solution was washed with saturated aqueous $NaHCO_3$ solution and saturated aqueous NaCl solution. The organic solution was dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography [AcOEt–hexane (1/9)] to afford **18** (157 mg, 54%) as a light yellow solid. Light yellow plates from AcOEt–hexane; mp 152–154 °C; IR (film, cm^{-1}) 1527; ^1H NMR (400 MHz, $CDCl_3$) δ 5.34 (2H, s), 7.40–7.51 (5H, m), 7.83 (1H, d, $J=2.2$ Hz), 8.14 (1H, d, $J=2.2$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 72.7, 89.6, 108.3, 111.7, 127.3, 128.9, 129.0, 134.1, 148.8, 155.4, 159.7; MS *m/z* 400 (M^+, 2.1), 91 (100); HRMS Calcd $C_{13}H_9IN_2O_5$: 399.9556. Found: 399.9556. Anal. Calcd for $C_{13}H_9IN_2O_5$: C, 39.02; H, 2.27; N, 7.00. Found: C, 39.22; H, 2.45; N, 6.88.

4.1.6. 3-Benzyloxy-2-iodo-5-nitroaniline (19). Fe (75 mg, 1.34 mmol) was added to a solution of **18** (135 mg, 0.337 mmol) in AcOH (3.4 ml) and EtOH (3.4 ml) and the mixture was stirred for 1 h at 100 °C. H_2O was added and the mixture was filtered through a Celite™ pad and the filtrate was extracted with AcOEt. The combined organic solution was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography [AcOEt–hexane (1/9)] to afford **19** (68.4 mg, 55%) as a yellow solid. Yellow needles from AcOEt–hexane; mp 147–148 °C; IR (film, cm^{-1}) 3464, 3369, 1622, 1501, 1435, 1346; ^1H NMR (400 MHz, $CDCl_3$) δ 4.58 (2H, s), 5.19 (2H, s), 7.07 (1H, d, $J=1.6$ Hz), 7.25–7.51 (6H, m); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 71.3, 83.5, 96.0, 101.8, 127.0, 128.1, 128.6, 135.5, 148.5, 149.5, 158.1; MS *m/z* 370 (M^+, 29.8), 264 (7.7), 243 (14.3), 91 (100); HRMS Calcd $C_{13}H_{11}IN_2O_5$: 369.9814. Found: 369.9799. Anal. Calcd for $C_{13}H_{11}IN_2O_5$: C, 42.18; H, 3.00; N, 7.57. Found: C, 42.27; H, 3.18; N, 7.32.

4.1.7. *N*-methanesulfonyl-3-benzyloxy-2-iodo-5-nitroaniline (11). MsCl (0.23 ml, 2.97 mmol) was added to a solution of **19** (432 mg, 1.17 mmol) and Et_3N (0.49 ml, 3.52 mmol) in anhydrous CH_2Cl_2 (1.0 ml) at 0 °C and stirred for 5 min at the same temperature. H_2O was added to the mixture and the aqueous phase was extracted with $CHCl_3$. The combined organic solution was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and the solvent was evaporated to afford **20**, which was used to the next reaction without further purification.

K_2CO_3 was added to a solution of the crude **20** in a mixture of MeOH–THF (1/1, 10 ml) and stirred for 15 min at room temperature. Saturated aqueous NH_4Cl solution was added to the mixture and the aqueous phase was extracted with AcOEt. The organic solution was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and concentrated. The resulting solid was recrystallized from AcOEt–hexane to afford **11** (400 mg) as colorless needles and mother liquor was chromatographed on silica gel [AcOEt–hexane (1/2)] to afford **11** (68.9 mg) as colorless solid (total yield of **11**:468.9 mg, 89% from **19**). Colorless needles from AcOEt–hexane; mp 182–184 °C; IR (film, cm^{-1}) 3273, 1609, 1518, 1327, 1151; ^1H NMR (400 MHz, $CDCl_3$) δ 3.11 (3H, s), 5.27 (2H, s), 7.11 (1H, s), 7.37–7.50 (5H, m), 7.53 (1H, d, J=3.2 Hz), 8.14 (1H, d, J=3.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.9, 72.0, 91.5, 102.4, 107.1, 127.2, 128.6, 128.8, 134.6, 140.0, 149.8, 158.3; MS *m/z* 448 (M^+, 5.5), 321 (2.6), 91 (100); HRMS Calcd $C_{14}H_{13}IN_2O_5S$: 447.9590. Found: 447.9592.

4.1.8. Methyl 4-benzyloxy-1-methanesulfonyl-6-nitroindole-2-carboxylate (21). *i*-Pr_2NEt (11 µl, 0.0631 mmol), **11** (14.5 mg, 0.0324 mmol), methyl propiolate (17 µl, 0.19 mmol), and $Pd(PPh_3)_4$ (5.6 mg, 4.8 µmol) were successively added to a solution of $ZnBr_2$ (22 mg, 0.098 mmol) in THF (1 ml) at room temperature and the mixture was heated at 100 °C in a sealed tube for 11 h. Saturated aqueous NH_4Cl solution was added to the mixture and the aqueous solution was extracted with AcOEt. The combined organic solution was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and the solvent was evaporated at reduced pressure. The residue was chromatographed on silica gel [AcOEt–hexane (1/4)] to provide **21** (8.5 mg, 65%) as a colorless solid. Colorless needles from AcOEt–MeOH; mp 173–175 °C; IR (film, cm^{-1}) 1732, 1522, 1371, 1335; ^1H NMR (600 MHz, $CDCl_3$) δ 3.80 (3H, s), 3.97 (3H, s), 5.28 (2H, s), 7.39–7.49 (6H, m), 7.66 (1H, s), 8.63 (1H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 43.9, 53.0, 71.0, 99.9, 105.1, 113.5, 123.0, 127.7, 128.6, 128.8, 133.0, 135.3, 137.8, 147.9, 153.0, 160.7; MS *m/z* 404 (M^+, 11.2), 326 (3.9), 91 (100); HRMS Calcd $C_{18}H_{16}N_2O_7S$: 404.0678. Found: 404.0692.

4.1.9. Methyl 4-benzyloxy-6-nitroindole-2-carboxylate (22). K_2CO_3 was added to a solution of **21** (73.5 mg, 0.182 mmol) in a mixture of MeOH–THF (1/1, 2.0 ml) and stirred for 15 min at room temperature. Saturated aqueous NH_4Cl solution was added to the mixture and the aqueous solution was extracted with AcOEt. The organic solution was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and the solvent was evaporated at reduced pressure. The residue was purified by silica gel column chromatography [AcOEt–hexane (1/4)] to afford **22** (46.4 mg, 78%) as a yellow powder. Yellow powder from AcOEt–hexane; mp 262–263 °C; IR (film, cm^{-1}) 3296, 1693, 1524; ^1H NMR (400 MHz, THF-d_8) δ 3.89 (3H, s), 5.32 (2H, s), 7.29 (1H, s), 7.31 (1H, t, J=7.2 Hz), 7.38 (2H, t, J=7.2 Hz), 7.49 (1H, s), 7.54 (2H, d, J=7.2 Hz), 7.98 (1H, s), 11.8 (1H, s); ^{13}C NMR (100 MHz, THF-d_8) δ 51.8, 70.8, 96.0, 102.9, 105.9, 123.5, 127.9, 128.3, 128.8, 131.6, 136.9, 137.1, 146.9, 153.8, 161.3; MS *m/z* 326 (M^+, 23.0), 91 100); HRMS Calcd $C_{17}H_{14}N_2O_5$: 326.0903. Found: 326.0894.

4.1.10. Methyl 6-amino-4-benzyloxyindole-2-carboxylate (9). PtO_2 (3 mg, 0.0132 mmol) was added to a solution of **22** (45 mg, 0.138 mmol) in a mixture of AcOEt–THF (1/1, 2.0 ml) and the mixture was vigorously stirred under hydrogen atmosphere for 2 h. PtO_2 was filtered off and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography [AcOEt–hexane (1/1)] to provide **9** (30 mg, 73%) as a tan solid. IR (film, cm^{-1}) 3352, 2924, 1682, 1634, 1520, 1279; ^1H NMR (400 MHz, $CDCl_3$) δ 3.83 (2H, br s), 3.91 (3H, s), 5.18 (2H, s), 6.06 (1H, d, J=1.8 Hz), 6.28 (1H, s), 7.30 (1H, d, J=1.8 Hz), 7.36–7.51 (5H, m), 8.54 (1H, s); ^{13}C NMR (100 MHz, THF-d_8) δ 50.7, 69.7, 88.0, 93.6, 107.0, 112.5, 123.8, 127.5, 127.8, 128.6, 138.3, 141.4, 148.6, 154.4, 162.2; MS *m/z* 296 (M^+, 100), 264 (26.3), 205 (54.8), 173 (34.8); HRMS Calcd $C_{17}H_{16}N_2O_3$: 296.1161. Found: 296.1154.

4.1.11. Trimethyl 4-benzyloxy-1*H*-pyrrolo[2,3-*f*]quinoline-2,7,9-tricarboxylate (7). Dimethyl (*E*)-2-oxoglutaconate (22.8 mg, 0.132 mmol) was added to a solution of **9** (26.2 mg, 0.0884 mmol) in anhydrous CH_2Cl_2 (0.5 ml) at room temperature. After being stirred for 12 h at the same temperature, one drop of hydrogen chloride in diethyl ether was added to the mixture and stirred for another 12 h. Saturated aqueous $NaHCO_3$ solution was added to the mixture and the aqueous phase was extracted with AcOEt. The combined organic solution was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and concentrated. The residual solid was triturated with methanol and dried to give **7** (28.3 mg, 71%) as a bright yellow solid. Mp 211–213 °C (lit.[8g] 215–217 °C); IR (film, cm^{-1}) 3299, 2954, 1717, 1436, 1259; ^1H NMR (400 MHz, $CDCl_3$) δ 4.00 (3H, s), 4.10 (3H, s), 4.16 (3H, s), 5.35 (2H, s), 7.37–7.55 (7H, m), 8.75 (1H, s), 12.56 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.2, 53.3, 53.9, 70.2, 102.0, 106.8, 113.1, 121.2, 122.0, 126.9, 127.3, 128.1, 128.5, 129.4, 131.4, 136.0, 144.7, 151.7, 155.6, 161.3, 165.3, 168.5; MS *m/z* 448 (M^+, 100), 416 (14.4), 388 (23.3); HRMS Calcd $C_{24}H_{20}N_2O_7$: 448.1271. Found: 448.1254.

4.1.12. Methyl 7-benzyloxy-5-nitroindole-2-carboxylate (25). K_2CO_3 (247 mg, 1.79 mmol) was added to a solution of **24**[2] (725 mg, 1.79 mmol) in a mixture of MeOH–THF (1/1, 20 ml) and stirred for 20 min at room temperature.

Saturated aqueous NH_4Cl solution was added to the mixture and the aqueous solution was extracted with AcOEt. The organic solution was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and concentrated. The residue was triturated with diethyl ether to afford **25** (520 mg, 89%) as a light yellow solid. Light yellow needles from AcOEt–hexane; mp 165–167 °C; IR (film, cm^{-1}) 3294, 1705, 1524; ^1H NMR (400 MHz, $CDCl_3$) δ 3.94 (3H, s), 5.26 (2H, s), 7.31 (1H, s), 7.42 (5H, m), 7.68 (1H, s), 8.31 (1H, s), 9.42 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.4, 71.0, 100.3, 110.8, 113.1, 126.6, 128.1, 128.68, 128.73, 129.5, 130.7, 135.1, 143.0, 145.0, 161.2; MS *m/z* 326 (M^+, 14.6), 91 (100); HRMS Calcd $C_{17}H_{14}N_2O_5$: 326.0903. Found: 326.0891. Anal. Calcd $C_{17}H_{14}N_2O_5$: C, 62.57; H, 4.32; N, 8.59. Found: C, 62.71; H, 4.52; N, 8.46.

4.1.13. Trimethyl 4-benzyloxy-3*H*-pyrrolo[3,2-*f*]quinoline-2,7,9-tricarboxylate (26). PtO_2 (3.2 mg, 0.014 mmol) was added to a solution of **25** (22.8 mg, 0.0699 mmol) in AcOEt (2.3 ml) and the mixture was stirred under hydrogen atmosphere for 2 h. PtO_2 was filtered off and the filtrate was concentrated in vacuo to afford the crude **10**, which was used to the next reaction without further purification.

Dimethyl (*E*)-2-oxoglutaconate (14.4 mg, 0.0837 mmol) was added to a solution of **10** in anhydrous CH_2Cl_2 (1 ml) at room temperature. After being for 12 h at the same temperature, anhydrous MeOH (6.2 μl) and AcCl (10 μl) was added to the mixture and stirred for another 10 h. Saturated aqueous $NaHCO_3$ solution was added to the mixture and the aqueous solution was extracted with $CHCl_3$. The combined organic solution was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by preparative TLC [CH_2Cl_2–MeOH (95/5)] to afford **26** (14 mg, 45% from **25**) as a light yellow solid. Semi-opaque powder from Et_2O–hexane; mp 164 °C; IR (film, cm^{-1}) 3287, 2951, 1717, 1252; ^1H NMR (400 MHz, $CDCl_3$) δ 3.96 (3H, s), 4.08 (3H, s), 4.15 (3H, s), 5.35 (2H, s), 7.41–7.63 (7H, m), 8.30 (1H, s), 9.72 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.1, 53.1, 53.2, 70.9, 105.9, 111.7, 118.1, 119.1, 119.8, 126.3, 128.0, 128.6, 128.7, 129.4, 135.2, 136.1, 144.4, 148.8, 149.2, 161.4, 165.4, 168.5; MS *m/z* 448 (M^+, 58.9), 420 (14.3), 389 (18.4), 343 (12.9), 91 (100); HRMS Calcd $C_{24}H_{20}N_2O_7$: 448.1271. Found: 448.1277.

4.1.14. Trimethyl 4-hydroxy-3*H*-pyrrolo[3,2-*f*]quinoline-2,7,9-tricarboxylate (8). Ten percentage Pd/C (3 mg) was added to a solution of **26** (99.7 mg, 0.222 mmol) in a mixture of $CHCl_3$–MeOH (1/3, 4.0 ml) and the mixture was stirred under hydrogen atmosphere for 1.5 h. Pd/C was filtered off eluting with $CHCl_3$ and the filtrate was concentrated in vacuo to afford **8** (77.5 mg, 97%) as a light yellow solid. Light yellow needles from MeOH–$CHCl_3$; mp 294 °C (decomposition) [lit.[14b] 276–278 °C (decomposition)]; IR (film, cm^{-1}) 3292, 2955, 1717, 1254; ^1H NMR (400 MHz, DMSO-d_6) δ 3.88 (3H, s), 3.93 (3H, s), 4.05 (3H, s), 7.24 (1H, s), 7.39 (1H, s), 8.07 (1H, s), 11.17 (1H, s), 12.77 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 51.9, 52.5, 53.3, 106.6, 110.5, 115.5, 116.8, 119.1, 126.8, 129.8, 135.7, 143.8, 148.1, 149.0, 160.7, 164.8, 168.1; MS *m/z* 358 (M^+, 100), 326 (24.9), 300 (61.9), 268 (89.0); HRMS Calcd $C_{17}H_{14}N_2O_7$: 358.0801. Found: 358.0785.

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17. Since the sequential coupling-cyclization reaction was employed for the preparation of indole **21** from 2-iodoaniline derivative **11**, excess methyl propiolate (5.9 equiv) was used and heating is essential for this reaction.