

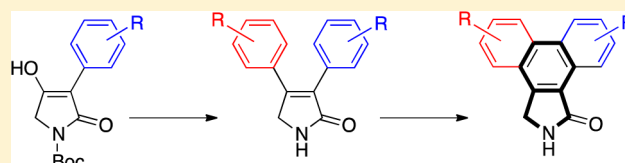
Preparation of Dibenzo[*e,g*]isoindol-1-ones via Scholl-Type Oxidative Cyclization Reactions

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S Supporting Information

ABSTRACT: A flexible synthesis of dibenzo[*e,g*]isoindol-1-ones has been developed. Dibenzo[*e,g*]isoindol-1-ones represent simplified benzenoid analogues of biological indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazol-5-ones (indolocarbazoles), compounds that have demonstrated a wide range of biological activity. The synthesis of the title compounds involved tetramic acid sulfonates. Different aryl groups were introduced at C4 of the heterocyclic ring via Suzuki–Miyaura cross-coupling reactions. Finally, mild Scholl-type oxidative cyclizations mediated by phenyliodine(III) bis(trifluoroacetate) (PIFA) converted some of the latter compounds into the corresponding dibenzo[*e,g*]isoindol-1-ones. A systematic study of the oxidative cyclization revealed the following reactivity trend: 3,4-dimethoxyphenyl > 3-methoxyphenyl > 3,4,5-trimethoxyphenyl > 4-methoxyphenyl ≈ phenyl. Overall, the oxidative cyclization required at least two methoxy groups distributed in the aromatic rings, at least one of which had to be located *para* to the site of the cyclization.



INTRODUCTION

Polycyclic-fused isoindol-1-ones have demonstrated promising utility as heterocyclic scaffolds in the search for enzyme inhibitors (Figure 1). A prominent member of this structural

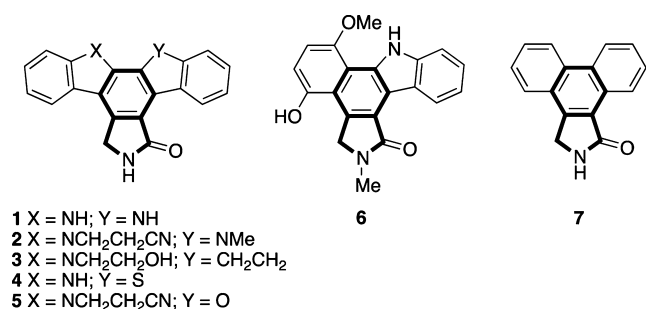


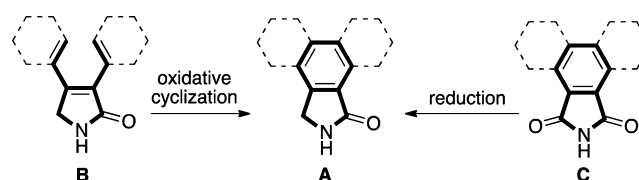
Figure 1. Polycyclic-fused isoindol-1-ones.

class is the natural product staurosporinone (**1**),¹ a submicromolar inhibitor of protein kinase C (PKC) first isolated in 1986.^{2,3} The impressive biological activity inspired several total syntheses of **1**⁴ and the investigation into analogues⁵ that retain the indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazol-5-one (indolocarbazole) backbone of **1**. For example, the indolocarbazole analogue Gö 6976 (**2**) is a selective PKC inhibitor⁶ and HIV-1 antagonist.⁷ Several heterocyclic fused isoindol-1-ones,⁸ ring-modified analogues of **1**, have also been prepared and their biological activity evaluated (e.g., **3**,⁹ **4**,¹⁰ and **5**¹¹). The synthesis of benzo[*a*]pyrrolo[3,4-*c*]carbazol-1-ones (e.g., **6**) was also reported in 2008.¹² Interestingly, only a small number of reports in the literature have described the preparation of the simpler ring system, dibenzo[*e,g*]isoindol-1-

one **7**,¹³ and none of these reports included an example of **7** that is *N*-unsubstituted. Dibenzo[*e,g*]isoindolones, in which both indole rings have been replaced with simple benzene rings, are potentially a new class of indolocarbazole analogues.

Given our interest in the chemistry of 3,4-diaryl-3-pyrrolin-2-ones,¹⁴ along with the diverse biological activity associated with polycyclic-fused isoindol-1-ones, we decided to investigate the conversion of **B** into **A** (Scheme 1) via an intramolecular

Scheme 1. Synthetic Approaches to Fused Isoindol-1-ones

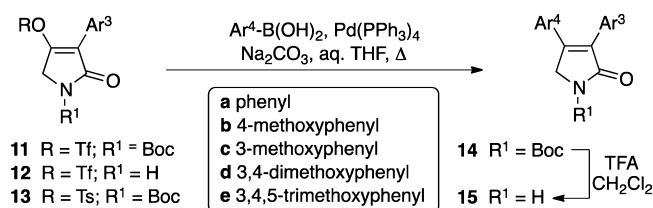


Scholl-type oxidative cyclization.¹⁵ In contrast, most known literature methods to **A** involve reduction of the corresponding maleimides **C**;^{4d,e} this reduction often proves to be unselective in cases of nonsymmetrical substrates.¹⁶ There are several possible methods available for completing oxidative cyclizations to phenanthrenes and fused phenanthrenes; these methods include oxidative photocyclization,¹⁷ transition metal-mediated oxidative cyclization,^{18–21} and oxidative cyclization using nonmetal reagents.^{22–25} We chose to focus our attention on the latter given the mildness of the reagents and ease of use. Kita pioneered an array of different oxidative transformations

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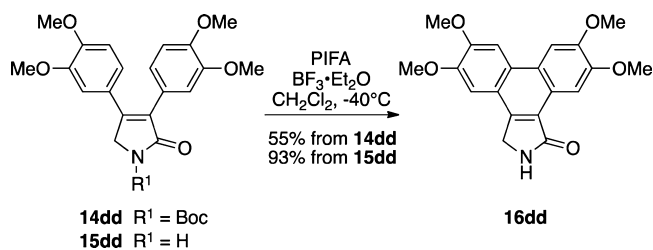
Table 2. Synthesis of 3,4-Diaryl-3-pyrrolin-2-ones



entry	substrate	product ^a	yield ^b (%)
1	11b	14bb	84
2	11c	14cc	45 ^c
3	13c	14cc	25 ^c
4	13c	14dc	72 ^c
5	11d	14dd	96
6	12c	15ac	39
7	12d	15ad	74
8	12b	15bb	55
9	12c	15bc	61 ^c
10	12d	15bd	49
11	12b	15cb	44 ^c
12	12c	15cc ^d	NR ^e
13	12d	15cd	45
14	12b	15db	69
15	12c	15dc	25
16	12d	15dd	80
17	12b	15eb	57
18	12c	15ec	59
19	12d	15ed	49

^aThe product number is comprised first of the letter for Ar⁴ and second of letter for Ar³; 15ac: Ar⁴ = phenyl and Ar³ = 3-methoxyphenyl. ^bYield refers to isolated yields of pure products after column chromatography. ^cReaction conditions: Ar⁴-B(OH)₂, Pd(dppf)Cl₂, Cs₂CO₃, THF. ^d15cc was obtained by treatment of 14cc with TFA. ^eNR = not run.

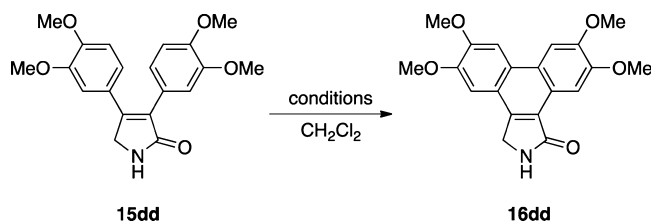
Scheme 3. Preliminary Oxidative Cyclization Results



entry 3). Although the yields in entries 1–3 are effectively the same given the scale of these reactions (0.20–1.00 mmol), we chose the 4 h reaction time to make further comparisons. The use of either DDQ²² (entry 6) or *m*-CPBA²³ (entry 7) as the oxidant and TFA as the acid led to the incomplete conversion of the starting material after 4 h at room temperature. The oxidative cyclization requires an oxidant as reactions run with just BF₃·Et₂O (entry 5) or TFA (entry 8) and no oxidant led to the recovery of only starting material. Interestingly, a reaction run with just PIFA and no BF₃·Et₂O led to the cyclized product in 75% yield (entry 4). Kita and co-workers observed a much more significant difference in yield (91% with PIFA, BF₃·Et₂O vs 25% with PIFA) in a similar comparative set of oxidative cyclization reactions leading to a dibenzo[*a,c*]cycloheptene.^{26b}

We next examined the effect that methoxy-substitution had on the Scholl-type oxidative cyclization by comparing 15

Table 3. Oxidative Cyclization of 15cc



entry	oxidant ^a	additive ^b	temp (°C)	time (h)	16:15 (ratio) ^c	yield ^d (%)
1	PIFA	BF ₃ ·Et ₂ O	−40	0.5	100:0	93
2	PIFA	BF ₃ ·Et ₂ O	−40	4	100:0	96
3	PIFA	BF ₃ ·Et ₂ O	+4	12	100:0	90
4	PIFA	none	−40	4	90:10	75
5	none	BF ₃ ·Et ₂ O	−40	4	0:100	0
6	DDQ	TFA	rt	4	50:50	22
7	<i>m</i> -CPBA	TFA	rt	4	80:20	38
8	none	TFA	rt	4	0:100	0

^aPIFA = phenyliodine(III) bis(trifluoroacetate); *m*-CPBA = *meta*-chloroperbenzoic acid; DDQ = 1,2-dichloro-5,6-dicyanobenzoquinone. ^bTFA = trifluoroacetic acid. ^c16:15 ratio was estimated by ¹H NMR analysis methylene of proton integrations (δ4.67 and δ4.32, respectively). ^dYield refers to isolated yields of pure products after trituration and/or column chromatography; ND = not determined.

different 3,4-diaryl-3-pyrrolin-2-one substrates 15 (Table 4). The substrates in vertical columns differ by the C3-aryl group (4-methoxyphenyl; 3-methoxyphenyl; 3,4-dimethoxyphenyl) and the substrates in horizontal rows differ by the C4-aryl group (phenyl; 4-methoxyphenyl; 3-methoxyphenyl; 3,4-dimethoxyphenyl; 3,4,5-trimethoxyphenyl). All of the oxidative cyclization reactions were run at −40 °C (acetonitrile/CO₂ bath) for 4 h, and then the solvent was removed, and the resulting crude reaction mixtures were analyzed by ¹H NMR. It was convenient to estimate the conversion of starting material 15 to product 16 by examining the relative integrations (rounded to the nearest 10%) of the respective methylene protons (~δ4.3 in 15 vs ~δ4.7 in 16). All substrates containing one 3,4-dimethoxyphenyl group gave conversions between 60 and 90%, whereas the substrate containing two 3,4-dimethoxyphenyl groups (15dd) gave complete conversion. Substrates lacking a 3,4-dimethoxyphenyl group led to conversions under 50% with the exception of the substrate containing two 3-methoxyphenyl groups which gave 70% conversion. Finally, substrates containing just one methoxy group or no methoxy groups located *para* to the site of cyclization gave 0% conversion (16cb also gave 0% conversion). The following relative reactivity trend can be deduced from this data: 3,4-dimethoxyphenyl ≫ 3-methoxyphenyl > 3,4,5-trimethoxyphenyl > 4-methoxyphenyl ≈ phenyl. In addition, we did not observe any regioisomeric cyclization products in cases where more than one regioisomer was possible (although we can definitively rule out their existence).

We attempted to purify the crude reaction mixtures that contained greater than 50% conversion. Pure samples of dibenzo[*e,g*]isoindol-1-ones 16, as demonstrated by ¹H and ¹³C NMR, could be obtained by trituration of the crude reaction mixtures with ethanol. This process worked in the cases where yields are given in Table 4. Although our methodology is limited in scope to electron-rich substrates at this point, we were able to obtain seven analytically pure dibenzo[*e,g*]-

Table 4. Oxidative Cyclizations

 16ab^a 0:100 ^b	 16bb 0:100 ^b	 16cb 0:100 ^b	 16db 80:20 ^b (58% yield) ^c	 16eb 10:90 ^b
 16ac 0:100 ^b	 16bc 10:90 ^b	 16cc 70:30 ^b (45% yield) ^c	 16dc 90:10 ^b (45% yield) ^c	 16ec 40:60 ^b
 16ad 70:30 ^b (58% yield) ^c	 16bd 70:30 ^b (45% yield) ^c	 16cd 80:20 ^b (42% yield) ^c	 16dd 100:0 ^b (96% yield) ^c	 16ed 60:40 ^b

^a3-(4'-Methoxyphenyl)-4-phenyl-1H-pyrrol-2-one (**15ab**) starting material was available from a previous study.^{17d} ^bReported ratios of **16:15** were ascertained by ¹H NMR analysis of methylene proton integrations. ^cYields refer to isolated yields of analytically pure products obtained after trituration with EtOH.

isindol-1-ones from these experiments, which demonstrates its potential for exploring this novel heterocyclic scaffold.

CONCLUSION

We have developed a flexible synthesis of 3,4-diaryl-3-pyrrolin-2-ones from 3-aryltetramic acids, which allowed for the preparation of a small library of methoxyphenyl-substituted analogues (symmetrical and unsymmetrical). This library of compounds was subjected to PIFA-mediated oxidative cyclization reactions leading to the corresponding dibenzo-*[e,g]*isindol-1-ones (phenanthrene-fused 3-pyrrolin-2-ones). The oxidative cyclization reaction worked better with substrates containing 3,4-dimethoxyphenyl groups and 3-methoxyphenyl groups compared to substrates containing 4-methoxyphenyl groups. This work should allow for further exploration into the synthesis of simplified analogues of indolocarbazoles including the further exploration of the biological activity of this class of molecules.

EXPERIMENTAL SECTION

General Methods. All reactions were performed under a positive argon atmosphere with magnetic stirring unless otherwise noted. Tetrahydrofuran (THF) and dichloromethane (CH₂Cl₂) were purified by passage through a column of alumina utilizing a PureSolv 400 solvent purification system. Unless otherwise indicated, all other reagents and solvents were purchased from commercial sources and

were used without further purification. ¹H NMR and ¹³C NMR chemical shifts are reported in parts per million (δ) using the solvent's residual proton or carbon signal (CDCl₃: δH 7.26 ppm, δC 77.3 ppm; DMSO-*d*₆: δH 2.50 ppm, δC 39.5 ppm) as an internal reference. Flash chromatography was performed with silica gel (230–400 mesh), and thin-layer chromatography (TLC) was performed with glass-backed silica gel plates and visualized with UV (254 nm). IR spectra were measured utilizing an infrared spectrometer fitted with an ATR sampler (attenuated total reflectance). High resolution mass spectra (HRMS) were obtained using a double-focusing magnetic sector (DFS) mass spectrometer for electron impact ionization (EI) and a Fourier transfer ion cyclotron resonance (FTICR) mass spectrometer for electrospray ionization (ESI). All yields are for materials obtained after chromatography, trituration, or recrystallization unless otherwise noted.

General Method A for Preparation of Amidoesters 8. A solution of the free amine of ethyl glycinate was generated using a modified procedure.³³ A mixture of ethyl glycinate hydrochloride (6.28 g, 45.0 mmol) in deionized water (100 mL) was treated with potassium carbonate (12.4 g, 90.0 mmol). The mixture was extracted with CH₂Cl₂ (5 × 50 mL). The organic layer was dried over sodium sulfate and used directly in the next reaction. Next, following a modified procedure,³⁴ the previously obtained solution of ethyl glycinate in CH₂Cl₂ was combined with an arylacetic acid (30.0 mmol) and then treated with DMAP (0.367 g, 3.0 mmol) followed by DCC (7.43 g, 36.0 mmol). The reaction mixture was stirred at rt until TLC analysis (EtOAc) showed complete consumption of the starting material. The reaction mixture was filtered, and the solid DCU residue was washed with CH₂Cl₂. Approximately half of the solvent was

removed in vacuo and then cooled and filtered to remove additional DCU. The organic layer was removed in vacuo gave oils or amorphous solids. Trituration (ether) gave the desired products as powders that were used directly without any further purification.

Ethyl 2-((4'-methoxyphenyl)acetamido)acetate (8b).³⁵ White powder (6.08 g, 24.2 mmol, 80% yield): mp 78–79 °C; R_f = 0.35 (1:1 EtOAc/petroleum ether); IR (ATR, neat) 3305, 1742, 1638, 1613 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.20 (d, 2H, J = 8.8 Hz), 6.89 (d, 2H, J = 8.8 Hz), 5.91 (br s, 1H), 4.17 (q, 2H, J = 7.2 Hz), 3.98 (d, 2H, J = 5.2 Hz), 3.80 (s, 3H), 3.56 (s, 2H), 1.25 (t, 3H, J = 7.2 Hz) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 171.8, 170.1, 159.2, 130.9, 126.6, 114.7, 61.8, 55.6, 42.9, 41.7, 14.4 ppm; HRMS (EI-DFS) calcd for $\text{C}_{13}\text{H}_{17}\text{NO}_4$ 251.1158, found 251.1154.

Ethyl 2-((3'-methoxyphenyl)acetamido)acetate (8c).³⁵ White powder (5.03 g, 20.0 mmol, 77% yield): mp 48–50 °C; R_f = 0.33 (1:1 EtOAc/petroleum ether); IR (ATR, neat) 3255, 1741, 1675, 1650 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.26–7.30 (m, 1H), 6.83–6.89 (m, 3H), 5.94 (br s, 1H), 4.18 (q, 2H, J = 7.2 Hz), 3.99 (d, 2H, J = 5.2 Hz), 3.81 (s, 3H), 3.60 (s, 2H), 1.26 (t, 3H, J = 7.2 Hz) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 171.2, 170.0, 160.3, 136.1, 130.4, 122.0, 115.3, 113.4, 61.8, 55.5, 43.9, 41.7, 14.4 ppm; HRMS (EI-DFS) calcd for $\text{C}_{13}\text{H}_{17}\text{NO}_4$ 251.1158, found 251.1153.

Ethyl 2-((3',4'-dimethoxyphenyl)acetamido)acetate (8d).³⁵ White powder (5.36 g, 21.3 mmol, 75% yield): mp 74–76 °C; R_f = 0.32 (2:1 EtOAc/petroleum ether); IR (ATR, neat) 3284, 1747, 1655, 1610 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ (400 MHz, CDCl_3) 6.80–6.84 (m, 3H), 5.98 (br s, 1H), 4.17 (q, 2H, J = 7.4 Hz), 3.99 (d, 2H, J = 5.2 Hz), 3.88 (s, 3H), 3.87 (s, 3H), 3.56 (s, 2H), 1.25 (t, 3H, J = 7.4 Hz) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ (100 MHz, CDCl_3) 171.7, 170.1, 149.5, 148.6, 127.1, 121.9, 112.7, 111.7, 61.8, 56.2 (2), 43.3, 41.7, 14.4 ppm; HRMS (EI-DFS) calcd for $\text{C}_{14}\text{H}_{19}\text{NO}_5$ 281.1263, found 281.1250.

General Method B for Preparation of *N*-Boc Amidoesters 9. Modification of a literature procedure was followed.²⁷ To a rt stirred solution of suitable amidoester 8 (50.0 mmol) and DMAP (0.611 g, 5.00 mmol) in THF (50 mL) was added a solution of Boc_2O (13.1 g, 60.0 mmol) in THF (50 mL) dropwise via addition funnel. The reaction mixture was heated to 40 °C for 2 h and the solvent was removed in vacuo. The resulting oil was taken up in ether (100 mL), and the organic solution was washed with an aqueous solution of HCl (50 mL, 1.0 M) followed by brine (50 mL) and then dried over sodium sulfate. Removal of the solvent in vacuo gave the desired compounds as oils that were used directly without further purification.

Ethyl 2-((*N*-tert-butoxycarbonyl)-2-(4'-methoxyphenyl)acetamido)acetate (9b). Yellow oil (10.6 g, 30.2 mmol, 87% yield): R_f = 0.46 (1:4 EtOAc/petroleum ether); IR (ATR, neat) 1736, 1691, 1612 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.17 (d, 2H, J = 8.8 Hz), 6.85 (d, 2H, J = 8.8 Hz), 4.44 (s, 2H), 4.23 (s, 2H), 4.18 (q, 2H, J = 7.2 Hz), 3.78 (s, 3H), 1.49 (s, 9H), 1.25 (t, 3H, J = 7.2 Hz) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 174.4, 169.2, 158.7, 152.4, 130.9, 127.1, 114.0, 84.2, 61.5, 55.5, 45.8, 43.5, 28.1, 14.4 ppm; HRMS (EI-DFS) calcd for $\text{C}_{18}\text{H}_{25}\text{NO}_6$ 351.1682, found 351.1675.

Ethyl 2-((*N*-tert-butoxycarbonyl)-2-(3'-methoxyphenyl)acetamido)acetate (9c). Colorless oil (1.83 g, 5.21 mmol, 87% yield): R_f = 0.48 (1:4 EtOAc/petroleum ether); IR (ATR, neat) 1736, 1692, 1601 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.22 (t, 1H, J = 7.4 Hz), 6.78–6.85 (m, 3H), 4.45 (s, 2H), 4.28 (s, 2H), 4.19 (q, 2H, J = 7.4 Hz), 3.79 (s, 3H), 1.48 (s, 9H), 1.26 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 173.9, 169.2, 159.8, 152.4, 136.5, 129.5, 122.2, 115.4, 112.8, 84.3, 61.5, 55.5, 45.9, 44.4, 28.1, 14.5 ppm; HRMS (EI-DFS) calcd for $\text{C}_{18}\text{H}_{25}\text{NO}_6$ 351.1682, found 351.1688.

Ethyl 2-((*N*-tert-butoxycarbonyl)-2-(3',4'-dimethoxyphenyl)acetamido)acetate (9d). Yellow oil (5.50 g, 14.4 mmol, 81% yield): R_f = 0.24 (1:4 EtOAc/petroleum ether); IR (ATR, neat) 1736, 1690, 1608 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 6.81 (s, 3H), 4.44 (s, 2H), 4.25 (s, 2H), 4.17 (q, 2H, J = 7.2 Hz), 3.86 (s, 3H), 3.85 (s, 3H), 1.48 (s, 9H), 1.25 (t, 3H, J = 7.2 Hz) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 174.3, 169.2, 152.4, 148.9, 148.2, 127.6, 122.0, 113.1, 111.3, 84.2, 61.5, 56.2, 56.1, 45.9, 43.8, 28.1, 14.5 ppm; HRMS (ESI-DFS) calcd for $\text{C}_{19}\text{H}_{27}\text{NO}_7\text{-Na-Boc}$ 304.1155, found 304.1155.

General Method C for the Dieckmann Cyclization to Tetramic Acids 10. To a 0 °C stirred solution of protected amidoester 9 (20.0 mmol) in THF (50 mL) was added solid potassium *tert*-butoxide (3.37 g, 30.0 mmol). The reaction mixture was heated to 40 °C for 6 h and then cooled back to 0 °C. To the cooled reaction mixture was added an aqueous solution of KHSO_4 (5.45 g, 40.0 mmol in 40 mL H_2O) and stirred an additional 30 min. The bulk of the THF was removed in vacuo, and the aqueous mixture was extracted with ethyl acetate (4 \times 40 mL). The combined organic layers were washed with brine (150 mL) and dried over sodium sulfate. Removal of the solvent in vacuo gave a crude solid. Trituration (ether) of the crude solid provided the desired products as powders, which were used without further purification.

1-(tert-Butoxycarbonyl)-4-hydroxy-3-(4'-methoxyphenyl)-1H-pyrrol-2(5H)-one (10b). White powder (3.49 g, 11.4 mmol, 79% yield): mp 223–225 (dec) °C (lit.³⁶ mp ~250 °C (dec)); R_f = 0.13 (1:10 MeOH/EtOAc); IR (ATR, neat) 3362, 1743, 1677, 1638, 1610 cm^{-1} ; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.83 (d, 2H, J = 9.0 Hz), 6.90 (d, 2H, J = 9.0 Hz), 4.19 (s, 2H), 3.74 (s, 3H), 1.47 (s, 9H) ppm (note: hydroxy proton was not observed); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 168.24, 168.21, 157.4, 149.0, 128.2, 123.6, 113.3, 103.2, 81.0, 55.0, 47.9, 27.8 ppm; HRMS (EI-DFS) calcd for $\text{C}_{16}\text{H}_{19}\text{NO}_5$ 305.1263, found 305.1259.

1-(tert-Butoxycarbonyl)-4-hydroxy-3-(3'-methoxyphenyl)-1H-pyrrol-2(5H)-one (10c). White powder (0.993 g, 3.25 mmol, 60% yield): mp 111–114 °C; R_f = 0.54 (1:10 MeOH/EtOAc); IR (ATR, neat) 1739, 1667, 1642, 1607 cm^{-1} ; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 12.45 (br s, 1H), 7.45–7.50 (m, 2H), 7.26 (t, 1H, J = 8.0 Hz), 6.79 (ddd, 1H, J = 1.2, 2.4, 8.0 Hz), 4.26 (s, 2H), 3.74 (s, 3H), 1.48 (s, 9H) ppm; ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 169.7, 167.9, 158.8, 149.0, 132.4, 128.8, 119.5, 112.6, 111.6, 103.2, 81.1, 54.9, 47.8, 27.8 ppm; HRMS (EI-DFS) calcd for $\text{C}_{16}\text{H}_{19}\text{NO}_5$ 305.1263, found 305.1256.

1-(tert-Butoxycarbonyl)-4-hydroxy-3-(3',4'-dimethoxyphenyl)-1H-pyrrol-2(5H)-one (10d). Pale yellow powder (3.62 g, 10.8 mmol, 65% yield): mp 124–125 °C; R_f = 0.33 (15:85 MeOH/EtOAc); IR (ATR, neat) 1758, 1621, 1602 cm^{-1} ; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 12.27 (br s, 1H), 7.54 (d, 1H, J = 2.0 Hz), 7.45 (dd, 1H, J = 2.0, 8.8 Hz), 6.94 (d, 1H, J = 8.4 Hz), 4.24 (s, 2H), 3.75 (s, 3H), 3.73 (s, 3H), 1.48 (s, 9H) ppm; ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 168.2, 168.1, 149.0, 148.0, 147.2, 123.9, 119.7, 111.4, 110.8, 103.2, 81.0, 55.4, 55.3, 47.8, 27.8 ppm; HRMS (EI-DFS) calcd for $\text{C}_{17}\text{H}_{21}\text{NO}_6$ 335.1369, found 335.1371.

General Method D for the Preparation of Tetramic Acid Triflates 11. To a –15 °C stirred solution of tetramic acid 10 (10.0 mmol) in CH_2Cl_2 (50 mL) was added neat Et_3N (2.1 mL, 15 mmol) followed by neat trifluoromethanesulfonic anhydride (2.0 mL, 12 mmol) dropwise via syringe. The reaction mixture was allowed to slowly warm to room temperature over the course of 2 h. To the reaction mixture was added an aqueous solution of KHSO_4 (2.72 g, 20.0 mmol in 50 mL H_2O) dropwise via additional funnel and stirred an additional 30 min. The reaction mixture was then transferred to a separatory funnel and extracted with CH_2Cl_2 (4 \times 50 mL). The combined organic layers were washed with brine (200 mL) and dried over sodium sulfate. Removal of the solvent in vacuo gave a crude oil or solid. The crude triflates were often taken on directly in the next step (Boc deprotection), or purification by flash chromatography (EtOAc/petroleum ether gradient) gave the title compounds as amorphous solids.

1-(tert-Butoxycarbonyl)-3-(4'-methoxyphenyl)-4-(((trifluoromethyl)sulfonyl)oxy)-1H-pyrrol-2(5H)-one (11b). Tan amorphous solid (1.02 g, 2.33 mmol, 72% yield); trituration (EtOH) gave the analytical sample as a white powder: mp 123–124 °C; R_f = 0.33 (1:8 EtOAc/petroleum ether); IR (ATR, neat) 1774, 1701, 1686, 1610 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.67 (d, 2H, J = 8.8 Hz), 6.96 (d, 2H, J = 8.8 Hz), 4.57 (s, 2H), 3.84 (s, 3H), 1.58 (s, 9H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 165.0, 161.0, 153.5, 149.2, 130.5, 124.0, 118.7, 118.5 (q, J = 319 Hz), 114.4, 84.5, 55.6, 47.7, 28.3 ppm; HRMS (ESI-FTICR) calcd for $\text{C}_{17}\text{H}_{18}\text{F}_3\text{NO}_7\text{-S-Na}$ 460.0648, found 460.0648.

1-(tert-Butoxycarbonyl)-3-(3'-methoxyphenyl)-4-(((trifluoromethyl)sulfonyl)oxy)-1H-pyrrol-2(5H)-one (11c). Yellow amorphous solid (0.424 g, 0.969 mmol, 30% yield): mp 84–86 °C; R_f = 0.50 (1:5 EtOAc/petroleum ether); IR (ATR, neat) 1774, 1703, 1687, 1607 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.35 (t, 1H, J = 8.2 Hz), 7.23–7.25 (m, 2H), 6.97 (ddd, 1H, J = 1.2, 2.4, 8.2 Hz), 4.59 (s, 2H), 3.82 (s, 3H), 1.59 (s, 9H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 164.6, 159.9, 154.9, 149.1, 130.0, 127.3, 124.4, 121.4, 118.3 (q, J = 319 Hz), 116.6, 114.0, 84.7, 55.6, 47.8, 28.3 ppm; HRMS (ESI-FTICR) calcd for $\text{C}_{17}\text{H}_{18}\text{F}_3\text{NO}_5\text{S}\cdot\text{Na}$ 460.0648, found 460.0648.

1-(tert-Butoxycarbonyl)-3-(3',4'-dimethoxyphenyl)-4-(((trifluoromethyl)sulfonyl)oxy)-1H-pyrrol-2(5H)-one (11d). White powder after trituration with EtOH (1.78 g, 3.80 mmol, 64% yield); trituration (EtOH) gave the analytical sample as a white powder: mp 103–105 °C; R_f = 0.20 (1:6 EtOAc/petroleum ether); IR (ATR, neat) 1788, 1706, 1677, 1601 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.35 (dd, 1H, J = 2.0, 8.4 Hz), 7.32 (d, 1H, J = 2.0 Hz), 6.92 (d, 1H, J = 8.4 Hz), 4.56 (s, 2H), 3.91 (s, 3H), 3.89 (s, 3H), 1.58 (s, 9H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 165.0, 153.5, 150.6, 149.11, 149.10, 123.9, 122.4, 118.9, 118.5 (q, J = 319 Hz), 111.7, 111.3, 84.6, 56.16, 56.15, 47.6, 28.3 ppm; HRMS (ESI-FTICR) calcd for $\text{C}_{18}\text{H}_{20}\text{F}_3\text{NO}_5\text{S}\cdot\text{Na}$ 490.0754, found 490.0754.

General Method E for the Conversion of 11 into 12. To a rt stirred solution of triflate **11** (5.00 mmol) in CH_2Cl_2 (10 mL) was added TFA (10 mL). The reaction mixture was stirred until TLC (1:1 EtOAc/petroleum ether) showed consumption of the starting material. The solvent was removed in vacuo, and the crude product was taken up in CH_2Cl_2 (20 mL), and the organic solution was washed with brine (20 mL) and dried over sodium sulfate. Removal of the solvent in vacuo followed by trituration (EtOH) or flash chromatography (EtOAc/petroleum ether gradient) gave the desired products as powders or amorphous solids.

3-(4'-Methoxyphenyl)-4-(((trifluoromethyl)sulfonyl)oxy)-1H-pyrrol-2(5H)-one (12b). Tan amorphous solid (1.48 g, 4.39 mmol, 90% yield): reaction time = 6 h; mp 111–113 °C; R_f = 0.38 (1:1 EtOAc/petroleum ether); IR (ATR, neat) 3202, 1693, 1613 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.72 (br s, 1H), 7.64 (d, 2H, J = 9.2 Hz), 7.05 (d, 2H, J = 9.2 Hz), 4.32 (d, 2H, J = 1.2 Hz), 3.80 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 168.3, 159.9, 154.2, 129.8, 122.7, 119.5, 117.7 (q, J = 319 Hz), 114.0, 55.2, 44.4 ppm; HRMS (EI-DFS) calcd for $\text{C}_{12}\text{H}_{10}\text{F}_3\text{NO}_5\text{S}$ 337.0232, found 337.0222.

3-(3'-Methoxyphenyl)-4-(((trifluoromethyl)sulfonyl)oxy)-1H-pyrrol-2(5H)-one (12c). Yellow powder (1.06 g, 3.14 mmol, 98% yield): reaction time = 1 h; mp 108–110 °C; R_f = 0.39 (1:1 EtOAc/petroleum ether); IR (ATR, neat) 3208, 1686, 1608 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.78 (br s, 1H), 7.41 (t, 1H, J = 8.4 Hz), 7.20–7.23 (m, 2H), 7.03 (ddd, 1H, J = 1.2, 2.4, 8.4 Hz), 4.35 (d, 2H, J = 1.2 Hz), 3.77 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 168.0, 159.0, 155.7, 129.7, 128.4, 123.0, 122.5, 120.6, 117.7 (q, J = 319 Hz), 114.9, 113.9, 55.1, 44.5 ppm; HRMS (EI-DFS) calcd for $\text{C}_{12}\text{H}_{10}\text{F}_3\text{NO}_5\text{S}$ 337.0232, found 337.0237.

3-(3',4'-Dimethoxyphenyl)-4-(((trifluoromethyl)sulfonyl)oxy)-1H-pyrrol-2(5H)-one (12d). Off-white powder (0.662 g, 1.80 mmol, 84% yield): reaction time = 18 h; mp 141–143 °C; R_f = 0.29 (1:1 EtOAc/petroleum ether); IR (ATR, neat) 3202, 1696, 1603 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.76 (br s, 1H), 7.29–7.33 (m, 2H), 7.08 (d, 1H, J = 8.4 Hz), 4.31 (d, 2H, J = 0.8 Hz), 3.80 (s, 3H), 3.75 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 168.3, 154.2, 149.6, 148.3, 122.7, 121.5, 119.6, 117.7 (q, J = 319 Hz), 111.6, 111.5, 55.5, 55.3, 44.3 ppm; HRMS (ESI-FTICR) calcd for $\text{C}_{13}\text{H}_{12}\text{F}_3\text{NO}_5\text{S}\cdot\text{Na}$ 390.0230, found 390.0229.

1-(tert-Butoxycarbonyl)-3-(3'-methoxyphenyl)-4-(tosyloxy)-1H-pyrrol-2(5H)-one (13c). To a rt stirred mixture of **10c** (0.40 g, 1.3 mmol) and toluenesulfonyl chloride (0.27 g, 1.4 mmol) in CH_2Cl_2 (50 mL) was added triethylamine (0.22 mL, 1.6 mmol) dropwise via syringe. The reaction mixture was stirred at rt for 30 min by which time TLC showed consumption of **10c**. The reaction mixture was combined with an aqueous solution of KHSO_4 (1.0 M, 50 mL), and the organic layer was separated. The aqueous layer was further extracted with CH_2Cl_2 (2 \times 50 mL). The combined organic layers

were washed with aqueous solution of NaHCO_3 (1% w/v, 100 mL), brine (100 mL), and dried over sodium sulfate. Removal of the solvent in vacuo gave an oily solid. Purification by flash chromatography (CH_2Cl_2 /petroleum ether gradient) gave the desired product as a white amorphous solid (0.36 g, 0.78 mmol, 60% yield): mp 138–141 °C; R_f = 0.50 (5:95 EtOAc/ CH_2Cl_2); IR (ATR, neat) 1771, 1698, 1678, 1607 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.62 (d, 2H, J = 8.4 Hz), 7.14 (t, 1H, J = 8.0 Hz), 7.13 (d, 2H, J = 8.0 Hz), 6.98–7.01 (m, 1H), 6.91–6.93 (m, 1H), 6.81 (ddd, 1H, J = 1.0, 2.4, 8.0 Hz), 4.59 (s, 2H), 3.73 (s, 3H), 2.37 (s, 3H), 1.58 (s, 9H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 166.0, 159.4, 156.9, 149.3, 146.9, 131.4, 130.2, 129.3, 128.50, 128.45, 122.7, 121.4, 115.4, 113.7, 84.1, 55.4, 48.6, 28.4, 22.0 ppm; HRMS (EI-DFS) calcd for $\text{C}_{23}\text{H}_{25}\text{NO}_7\text{S}$ 459.1352, found 459.1367.

General Method F for the Suzuki–Miyaura Cross-Coupling.

To a rt stirred solution of triflate **11** or **12** (2.00 mmol) in THF (20 mL) was added an arylboronic acid (3.00 mmol), and the solution was stirred until the boronic acid completely dissolved. To this solution was added $\text{Pd}(\text{PPh}_3)_4$ (0.100 mmol) followed by an aqueous solution of sodium carbonate (0.466 g, 4.40 mmol in 2 mL H_2O). The reaction mixture was stirred at rt for 30 min and then heated to reflux until TLC (1:1 EtOAc/petroleum ether) showed complete consumption of the starting material (typically 4–16 h). The reaction mixture was allowed to cool and then was filtered through a short plug of Celite with the aid of ethyl acetate. Removal of the solvent in vacuo gave a crude oil or solid. Flash chromatography (EtOAc/petroleum ether gradient) gave the title compounds as amorphous solids.

General Method G for the Suzuki–Miyaura Cross-Coupling.

The same as Method F with triflate **11** or triflate **12** or tosylate **13c** and $\text{Pd}(\text{dppf})\text{Cl}_2$ (0.100 mmol) as the palladium catalyst and cesium carbonate (4.40 mmol in 2 mL H_2O) as the base.

General Method H for the Conversion of 14 into 15. To a rt stirred solution of 3-pyrrolin-2-ones **14** (1.00 mmol) in CH_2Cl_2 (5 mL) was added TFA (5 mL). The reaction mixture was stirred until TLC (1:1 EtOAc/petroleum ether) showed consumption of the starting material (typically 1–6 h). The solvent was removed in vacuo, and the crude product was taken up in CH_2Cl_2 (20 mL), and the organic solution was washed with brine (20 mL) and dried over sodium sulfate. Removal of the solvent in vacuo followed by trituration (cold EtOH) or flash chromatography (EtOAc/petroleum ether gradient) gave the desired products as powders or amorphous solids.

1-(tert-Butoxycarbonyl)-3,4-bis(4'-methoxyphenyl)-1H-pyrrol-2(5H)-one (14bb). Yellow amorphous solid (Method F: 0.152 g, 0.384 mmol, 84% yield): mp 145–147 °C; R_f = 0.42 (1:2 EtOAc/petroleum ether); IR (ATR, neat) 1771, 1723, 1699, 1639, 1604 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.300 (d, 2H, J = 8.8 Hz), 7.295 (d, 2H, J = 8.8 Hz), 6.89 (d, 2H, J = 8.8 Hz), 6.82 (d, 2H, J = 8.8 Hz), 4.62 (s, 2H), 3.82 (s, 3H), 3.81 (s, 3H), 1.59 (s, 9H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 169.2, 161.1, 159.8, 150.5, 148.4, 131.2, 130.3, 129.6, 125.0, 123.9, 114.4, 114.3, 83.2, 55.6, 55.5, 50.9, 28.5 ppm; HRMS (EI-DFS) calcd for $\text{C}_{23}\text{H}_{25}\text{NO}_5$ 395.1733, found 395.1739.

1-(tert-Butoxycarbonyl)-3,4-bis(3'-methoxyphenyl)-1H-pyrrol-2(5H)-one (14cc). Yellow amorphous solid (from **11c**, Method G: 88 mg, 0.22 mmol, 45% yield; from **13c**, Method G: 0.11 g, 0.28 mmol, 25% yield): mp 70–75 °C; R_f = 0.20 (1:4 EtOAc/petroleum ether); IR (ATR, neat) 1758, 1727, 1637 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.21–7.27 (m, 2H), 6.82–6.93 (m, 6H), 4.66 (s, 2H), 3.73 (s, 3H), 3.61 (s, 3H), 1.60 (s, 9H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 168.6, 159.9, 159.8, 150.2, 149.7, 133.5, 132.59, 132.57, 130.1, 129.8, 122.2, 120.3, 116.4, 114.92, 114.85, 113.3, 83.4, 55.5, 55.4, 51.1, 28.4 ppm; HRMS (EI-DFS) calcd for $\text{C}_{23}\text{H}_{25}\text{NO}_5$ 395.1733, found 395.1737.

1-(tert-Butoxycarbonyl)-3-(3',4'-dimethoxyphenyl)-4-(3"-methoxyphenyl)-1H-pyrrol-2(5H)-one (14dc). Tan amorphous solid (from **13c**, Method G: 0.180 g, 0.423 mmol, 72% yield): mp 147–149 °C; R_f = 0.16 (1:3 EtOAc/petroleum ether); IR (ATR, neat) 1724, 1707, 1630 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.29 (t, 1H, J = 8.4 Hz), 6.99 (dd, 1H, J = 2.0, 8.4 Hz), 6.80–6.93 (m, 5H), 4.68 (s, 2H), 3.89 (s, 3H), 3.76 (s, 3H), 3.51 (s, 3H), 1.60 (s, 9H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 168.8, 160.1, 151.0, 150.5, 149.4, 148.9,

133.3, 130.9, 130.0, 124.7, 122.3, 120.9, 115.0, 114.7, 111.4, 111.1, 83.4, 56.2, 55.7, 55.6, 50.8, 28.5 ppm; HRMS (EI-DFS) calcd for $C_{24}H_{27}NO_6$ 425.1838, found 425.1848.

1-(tert-Butoxycarbonyl)-3,4-bis(3',4'-dimethoxyphenyl)-1H-pyrrol-2(5H)-one (14dd). Yellow amorphous solid (Method F: 0.188 g, 0.412 mmol, 96% yield): mp 165 °C (dec); R_f = 0.32 (1:1 EtOAc/petroleum ether); IR (ATR, neat) 1783, 1727, 1708, 1602 cm^{-1} ; 1H NMR (400 MHz, DMSO- d_6) δ 6.81–6.99 (m, 6H), 4.66 (s, 2H), 3.891 (s, 3H), 3.886 (s, 3H), 3.79 (s, 3H), 3.57 (s, 3H), 1.60 (s, 9H) ppm; ^{13}C NMR (100 MHz, DMSO- d_6) δ 169.1, 150.9, 150.5, 149.3, 149.2, 148.9, 148.7, 130.5, 125.0, 124.2, 122.7, 121.0, 112.3, 111.5, 111.17, 111.15, 83.4, 56.21, 56.20, 56.18, 55.8, 50.8, 28.5 ppm; HRMS (EI-DFS) calcd for $C_{25}H_{29}NO_7$ 455.1944, found 455.1937.

3-(3'-Methoxyphenyl)-4-phenyl-1H-pyrrol-2(5H)-one (15ac). White amorphous solid (Method F: 0.15 g, 0.57 mmol, 39% yield): mp 171–174 °C; R_f = 0.31 (1:1 EtOAc/petroleum ether); IR (ATR, neat) 3161, 1684 cm^{-1} ; 1H NMR (400 MHz, DMSO- d_6) δ 8.52 (br s, 1H), 7.33 (s, 5H), 7.25 (t, 1H, J = 8.0 Hz), 6.87–6.91 (m, 1H), 6.81–6.84 (m, 2H), 4.35 (d, 2H, J = 1.2 Hz), 3.67 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO- d_6) δ 172.2, 158.9, 150.6, 133.6, 133.3, 131.5, 129.2, 129.0, 128.6, 127.5, 121.5, 114.9, 113.1, 54.9, 47.5 ppm; HRMS (EI-DFS) calcd for $C_{17}H_{15}NO_2$ 265.1103, found 265.1101.

3-(3',4'-Dimethoxyphenyl)-4-phenyl-1H-pyrrol-2(5H)-one (15ad). Off-white amorphous solid (Method F: 0.17 g, 0.58 mmol, 74% yield): mp 135–137 °C; R_f = 0.61 (1:9 MeOH/EtOAc); IR (ATR, neat) 3159, 1676 cm^{-1} ; 1H NMR (400 MHz, DMSO- d_6) δ 8.48 (br s, 1H), 7.35 (s, 5H), 6.88–6.94 (m, 2H), 6.84 (d, 1H, J = 1.6 Hz), 4.32 (d, 2H, J = 0.8 Hz), 3.75 (s, 3H), 3.56 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO- d_6) δ 172.5, 149.4, 148.4, 148.1, 133.7, 131.2, 128.8, 128.6, 127.6, 124.4, 121.9, 112.9, 111.5, 55.4, 55.2, 47.5 ppm; HRMS (EI-DFS) calcd for $C_{18}H_{17}NO_3$ 295.1208, found 295.1219.

3,4-Bis(4'-methoxyphenyl)-1H-pyrrol-2(5H)-one (15bb).³⁷ White amorphous solid (Method F: 0.240 g, 0.813 mmol, 55% yield): mp 223–227 °C (lit.^{14d} mp 213–216 °C); R_f = 0.55 (1:9 MeOH/EtOAc); IR (ATR, neat) 3174, 1672, 1626, 1602 cm^{-1} ; 1H NMR (400 MHz, DMSO- d_6) δ 8.36 (br s, 1H), 7.28 (d, 2H, J = 9.2 Hz), 7.22 (d, 2H, J = 9.2 Hz), 6.92 (d, 2H, J = 9.2 Hz), 6.89 (d, 2H, J = 9.2 Hz), 4.29 (s, 2H), 3.76 (s, 3H), 3.74 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO- d_6) δ 172.9, 159.7, 158.7, 148.9, 130.5, 129.6, 128.9, 125.8, 124.7, 1140.0, 113.7, 55.2, 55.0, 47.3 ppm; HRMS (EI-DFS) calcd for $C_{18}H_{17}NO_3$ 295.1208, found 295.1200.

3-(3'-Methoxyphenyl)-4-(4'-methoxyphenyl)-1H-pyrrol-2(5H)-one (15bc). Yellow amorphous powder (Method G: 0.268 g, 0.907 mmol, 61% yield): mp 150–154 °C; R_f = 0.47 (EtOAc); IR (ATR, neat) 3168, 1682, 1607 cm^{-1} ; 1H NMR (400 MHz, DMSO- d_6) δ 8.41 (br s, 1H), 7.27 (d, 2H, J = 9.0 Hz), 7.24–7.28 (m, 1H), 6.89 (d, 2H, J = 9.0 Hz), 6.81–6.92 (m, 3H), 4.32 (d, 2H, J = 0.8 Hz), 3.74 (s, 3H), 3.69 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO- d_6) δ 172.6, 159.8, 159.0, 150.1, 134.1, 130.0, 129.3, 129.0, 125.4, 121.6, 115.0, 114.0, 113.0, 55.2, 54.9, 47.3 ppm; HRMS (ESI-FTICR) calcd for $C_{18}H_{17}NO_3 \cdot Na$ 318.1101, found 318.1100.

3-(3',4'-Dimethoxyphenyl)-4-(4'-methoxyphenyl)-1H-pyrrol-2(5H)-one (15bd). Off-white amorphous solid (Method F: 0.340 g, 1.05 mmol, 49% yield); recrystallization (CH_2Cl_2 /petroleum ether) gave the analytical sample as white crystals: mp 169–170 °C; R_f = 0.56 (1:10 MeOH/EtOAc solvent); IR (ATR, neat) 3179, 1677, 1608 cm^{-1} ; 1H NMR (400 MHz, DMSO- d_6) δ 8.37 (br s, 1H), 7.30 (d, 2H, J = 8.8 Hz), 6.85–6.95 (m, 5H), 4.29 (d, 2H, J = 0.8 Hz), 3.76 (s, 3H), 3.74 (s, 3H), 3.60 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO- d_6) δ 172.9, 159.7, 149.0, 148.3, 148.2, 130.0, 128.9, 125.7, 124.9, 121.9, 114.0, 112.9, 111.5, 55.4, 55.3, 55.2, 47.3 ppm; HRMS (EI-DFS) calcd for $C_{19}H_{19}NO_4$ 325.1314, found 325.1316.

3-(4'-Methoxyphenyl)-4-(3'-methoxyphenyl)-1H-pyrrol-2(5H)-one (15cb). Off-white amorphous solid (Method G: 59 mg, 0.20 mmol, 44% yield): mp 180–185 °C; R_f = 0.38 (EtOAc); IR (ATR, neat) 3232, 1672, 1629, 1600 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, 2H, J = 8.8 Hz), 7.22 (t, 1H, J = 8.0 Hz), 7.07 (br s, 1H), 6.90 (d, 2H, J = 8.8 Hz), 6.83–6.92 (m, 3H), 4.33 (d, 2H, J = 1.2 Hz), 3.81 (s, 3H), 3.65 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 159.9, 159.8, 149.4, 135.0, 132.3, 131.1, 130.0, 124.2, 120.2,

115.2, 114.3, 113.3, 55.5, 55.4, 48.3 ppm; HRMS (ESI-FTICR) calcd for $C_{18}H_{17}NO_3 \cdot Na$ 318.1101, found 318.1101.

3,4-Bis(3'-methoxyphenyl)-1H-pyrrol-2(5H)-one (15cc). Trituration (EtOH) gave the title product as a yellow powder (Method H: 48 mg, 0.16 mmol, 95% yield): mp 118–121 °C; R_f = 0.13 (1:1 EtOAc/petroleum ether); IR (ATR, neat) 3212, 1671 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 8.31 (br s, 1H), 7.22–7.31 (m, 2H), 6.82–6.94 (m, 6H), 4.48 (s, 2H), 3.75 (s, 3H), 3.63 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 160.0, 159.9, 152.5, 133.6, 132.2, 131.9, 130.2, 130.0, 122.1, 120.3, 116.1, 115.0, 114.8, 113.4, 55.5, 55.4, 49.7 ppm; HRMS (EI-DFS) calcd for $C_{18}H_{17}NO_3$ 295.1208, found 295.1220.

3-(3',4'-Dimethoxyphenyl)-4-(3'-methoxyphenyl)-1H-pyrrol-2(5H)-one (15cd). Light orange amorphous solid (Method F: 0.122 g, 0.375 mmol, 45% yield): mp 173–175 °C; R_f = 0.59 (1:10 MeOH/EtOAc solvent); IR (ATR, neat) 3178, 1685, 1604 cm^{-1} ; 1H NMR (400 MHz, DMSO- d_6) δ 8.48 (br s, 1H), 7.23–7.27 (m, 1H), 6.86–6.95 (m, 6H), 4.31 (d, 2H, J = 1.2 Hz), 3.75 (s, 3H), 3.65 (s, 3H), 3.58 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO- d_6) δ 172.5, 159.2, 149.2, 148.5, 148.2, 134.9, 131.4, 129.7, 124.5, 121.9, 119.9, 114.3, 113.1, 113.0, 111.5, 55.4, 55.3, 54.9, 47.5 ppm; HRMS (EI-DFS) calcd for $C_{19}H_{19}NO_4$ 325.1314, found 325.1310.

4-(3',4'-Dimethoxyphenyl)-3-(4'-methoxyphenyl)-1H-pyrrol-2(5H)-one (15db). Off-white amorphous solid (Method F: 0.270 g, 0.830 mmol, 69% yield); recrystallization (CH_2Cl_2 /petroleum ether) gave the analytical sample as white crystals: mp 160–162 °C; R_f = 0.48 (1:10 MeOH/EtOAc); IR (ATR, neat) 3173, 1671, 1607 cm^{-1} ; 1H NMR (400 MHz, DMSO- d_6) δ 8.38 (br s, 1H), 7.23 (d, 2H, J = 8.4 Hz), 6.87–6.95 (m, 5H), 4.32 (s, 2H), 3.76 (s, 3H), 3.74 (s, 3H), 3.50 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO- d_6) δ 172.9, 158.7, 149.4, 149.2, 148.3, 130.7, 129.9, 125.8, 124.8, 120.3, 113.7, 111.6, 110.0, 55.5, 55.10, 55.07, 47.3 ppm; HRMS (EI-DFS) calcd for $C_{19}H_{19}NO_4$ 325.1314, found 325.1318.

4-(3',4'-Dimethoxyphenyl)-3-(3'-methoxyphenyl)-1H-pyrrol-2(5H)-one (15dc). Tan amorphous solid (Method F: 22 mg, 0.068 mmol, 25% yield): mp 160–164 °C; R_f = 0.40 (EtOAc); IR (ATR, neat) 3163, 1676 cm^{-1} ; 1H NMR (400 MHz, DMSO- d_6) δ 8.41 (br s, 1H), 7.29 (t, 1H, J = 8.0 Hz), 6.82–6.95 (m, 6H), 4.35 (d, 2H, J = 0.8 Hz), 3.74 (s, 3H), 3.70 (s, 3H), 3.48 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO- d_6) δ 172.6, 159.1, 150.3, 149.6, 148.2, 134.2, 130.2, 129.3, 125.4, 121.7, 120.4, 115.1, 113.0, 111.5, 111.0, 55.5, 55.0 (2), 47.3 ppm; HRMS (EI-DFS) calcd for $C_{19}H_{19}NO_4$ 325.1314, found 325.1319.

3,4-Bis(3',4'-dimethoxyphenyl)-1H-pyrrol-2(5H)-one (15dd). Yellow amorphous solid (Method F: 0.400 g, 1.13 mmol, 80% yield); recrystallization (CH_2Cl_2 /petroleum ether) gave the analytical sample as yellow crystals: mp 149–150 °C (lit.³⁸ mp 170–172 °C); R_f = 0.46 (1:10 MeOH/EtOAc); IR (ATR, neat) 3165, 1680, 1600 cm^{-1} ; 1H NMR (400 MHz, DMSO- d_6) δ 8.39 (br s, 1H), 6.87–6.97 (m, 6H), 4.32 (s, 2H), 3.76 (s, 3H), 3.74 (s, 3H), 3.62 (s, 3H), 3.52 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO- d_6) δ 172.8, 149.4, 149.2, 148.4, 148.31, 148.25, 130.0, 125.8, 125.1, 122.0, 120.4, 113.0, 111.63, 111.55, 111.1, 55.50, 55.48, 55.4, 55.1, 47.3 ppm; HRMS (ESI-FTICR) calcd for $C_{20}H_{21}NO_5 \cdot Na$ 378.1312, found 378.1311.

3-(4'-Methoxyphenyl)-4-(3',4',5'-trimethoxyphenyl)-1H-pyrrol-2(5H)-one (15eb). Tan amorphous solid (Method F: 0.375 g, 1.06 mmol, 57% yield): mp 160–165 °C; R_f = 0.23 (2:1 EtOAc/petroleum ether); IR (ATR, neat) 3180, 1678, 1628, 1605 cm^{-1} ; 1H NMR (400 MHz, DMSO- d_6) δ 8.43 (br s, 1H), 7.26 (d, 2H, J = 8.8 Hz), 6.95 (d, 2H, J = 8.8 Hz), 6.63 (s, 2H), 4.35 (s, 2H), 3.76 (s, 3H), 3.65 (s, 3H), 3.57 (s, 6H) ppm; ^{13}C NMR (100 MHz, DMSO- d_6) δ 172.7, 158.8, 152.7, 149.2, 138.0, 131.0, 130.7, 128.7, 124.5, 113.6, 105.2, 60.0, 55.6, 55.1, 47.3 ppm; HRMS (EI-DFS) calcd for $C_{20}H_{21}NO_5$ 355.1420, found 355.1419.

3-(3'-Methoxyphenyl)-4-(3',4',5'-trimethoxyphenyl)-1H-pyrrol-2(5H)-one (15ec). Tan amorphous solid (Method F: 0.301 g, 0.847 mmol, 59% yield): mp 135–137 °C; R_f = 0.22 (2:1 EtOAc/petroleum ether); IR (ATR, neat) 3187, 1683, 1605 cm^{-1} ; 1H NMR (400 MHz, DMSO- d_6) δ 8.46 (br s, 1H), 7.30 (t, 1H, J = 8.0 Hz), 6.84–6.92 (m, 3H), 6.62 (s, 2H), 4.38 (d, 2H, J = 0.8 Hz), 3.70 (s, 3H), 3.65 (s, 3H), 3.56 (s, 6H) ppm; ^{13}C NMR (100 MHz, DMSO-

δ 172.3, 159.1, 152.6, 150.3, 138.2, 134.0, 131.5, 129.3, 128.3, 121.7, 115.0, 113.1, 105.3, 60.1, 55.6, 55.0, 47.4 ppm; HRMS (EI-DFS) calcd for $C_{20}H_{21}NO_5$ 355.1420, found 355.1407.

3-(3',4'-Dimethoxyphenyl)-4-(3'',4'',5''-trimethoxyphenyl)-1H-pyrrol-2(5H)-one (15ed). Bright orange powder (Method F: 0.180 g, 0.467 mmol, 49% yield): mp 165–167 °C; R_f = 0.16 (2:1 EtOAc/petroleum ether); IR (ATR, neat) 3178, 1677, 1624 cm^{-1} ; 1H NMR (400 MHz, DMSO- d_6) δ 8.44 (br s, 1H), 6.87–6.97 (m, 3H), 6.65 (s, 2H), 4.34 (s, 2H), 3.75 (s, 3H), 3.65 (s, 3H), 3.62 (s, 3H), 3.59 (s, 6H) ppm; ^{13}C NMR (100 MHz, DMSO- d_6) δ 172.6, 152.7, 149.3, 148.5, 148.3, 138.0, 131.1, 128.7, 124.8, 122.0, 113.1, 111.7, 105.3, 60.0, 55.7, 55.5, 55.4, 47.4 ppm; HRMS (EI-DFS) calcd for $C_{21}H_{23}NO_6$ 385.1525, found 385.1523.

General Method I for the Oxidative Cyclization to Dibenzo[e,g]isoindole-1-ones 16. To a -40 °C stirred solution of **15** (1.00 mmol) and PIFA (0.473 g, 1.10 mmol) in CH_2Cl_2 (10 mL) was added $BF_3 \cdot Et_2O$ (0.15 mL, 1.2 mmol). The reaction mixture was stirred at -40 °C for 4 h. The solvent was then removed in vacuo giving a crude solid. The solid was transferred to a centrifuge tube and triturated with warm EtOH (10 mL). The mixture was centrifuged, and the solvent was removed in vacuo, which gave the title compounds as analytically pure powders.

2,3-Dihydro-9,10-dimethoxy-1H-dibenzo[e,g]isoindole-1-one (16ad). Brown powder (29 mg, 0.099 mmol, 58% yield): mp 295–297 °C (dec); R_f = 0.49 (EtOAc solvent); IR (ATR, neat) 3201, 1672 cm^{-1} ; 1H NMR (400 MHz, DMSO- d_6) δ 8.88 (d, 1H, J = 8.4 Hz), 8.74 (s, 2H), 4.74 (s, 2H), 4.04 (s, 3H), 3.93 (s, 3H), 8.23 (s, 2H), 8.04 (d, 1H, J = 8.0 Hz), 7.78 (t, 1H, J = 8.0 Hz), 7.67 (t, 1H, J = 8.0 Hz) ppm; ^{13}C NMR (100 MHz, DMSO- d_6) δ 172.1, 149.6, 149.2, 142.1, 130.8, 128.2, 126.3, 125.9, 124.8, 124.3, 123.8, 123.7, 122.3, 104.4, 103.7, 55.7, 55.4, 43.7 ppm; HRMS (EI-DFS) calcd for $C_{18}H_{15}NO_3$ 293.1052, found 293.1058.

2,3-Dihydro-6,9,10-trimethoxy-1H-dibenzo[e,g]isoindole-1-one (16bd). Brown powder (18 mg, 0.056 mmol, 45% yield): mp 255–259 °C (dec); R_f = 0.42 (EtOAc solvent); IR (ATR, neat) 3183, 1693, 1621, 1603 cm^{-1} ; 1H NMR (400 MHz, DMSO- d_6) δ 8.72 (s, 1H), 8.58 (br s, 1H), 8.16–8.18 (m, 2H), 7.98 (d, 1H, J = 8.8 Hz), 7.33 (dd, 1H, J = 2.0, 8.8 Hz), 4.70 (s, 2H), 4.05 (s, 3H), 4.04 (s, 3H), 3.93 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO- d_6) δ 172.3, 159.5, 149.7, 148.8, 142.3, 132.6, 126.1, 124.1, 122.8, 121.4, 120.5, 116.4, 105.2, 104.8, 103.6, 55.9, 55.7, 55.4, 43.7 ppm; HRMS (EI-DFS) calcd for $C_{19}H_{17}NO_4$ 323.1158, found 323.1154.

2,3-Dihydro-5,10-dimethoxy-1H-dibenzo[e,g]isoindole-1-one (16cc). Brown powder (14 mg, 0.048 mmol, 45% yield): mp 275–280 °C; R_f = 0.50 (EtOAc solvent); IR (ATR, neat) 3201, 1682, 1615 cm^{-1} ; 1H NMR (400 MHz, DMSO- d_6) δ 8.70–8.75 (m, 4H), 7.39–7.44 (m, 2H), 7.33 (dd, 1H, J = 2.4, 8.8 Hz), 4.74 (s, 2H), 3.95 (s, 3H), 3.91 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO- d_6) δ 171.9, 157.74, 157.69, 144.5, 127.7, 126.8, 125.7, 125.0, 124.5, 124.3, 124.2, 119.0, 117.0, 104.9, 104.1, 55.5, 55.2, 44.0 ppm; HRMS (EI-DFS) calcd for $C_{18}H_{15}NO_3$ 293.1052, found 293.1065.

2,3-Dihydro-5,9,10-trimethoxy-1H-dibenzo[e,g]isoindole-1-one (16cd). Brown powder (21 mg, 0.065 mmol, 42% yield): mp 209–211 °C (dec); R_f = 0.40 (EtOAc solvent); IR (ATR, neat) 3218, 1654, 1622 cm^{-1} ; 1H NMR (400 MHz, DMSO- d_6) δ 8.80 (d, 1H, J = 9.2 Hz), 8.73 (br s, 1H), 8.80 (s, 1H), 8.15 (s, 1H), 7.37–7.42 (m, 2H), 4.71 (s, 2H), 4.02 (s, 3H), 3.95 (s, 3H), 3.91 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO- d_6) δ 172.1, 157.6, 149.3, 148.9, 141.5, 127.2, 125.6, 125.2, 125.1, 124.2, 121.1, 118.5, 104.5, 103.9, 103.6, 55.7, 55.5, 55.3, 43.9 ppm; HRMS (EI-DFS) calcd for $C_{19}H_{17}NO_4$ 323.1158, found 323.1166.

2,3-Dihydro-5,6,9-trimethoxy-1H-dibenzo[e,g]isoindole-1-one (16db). Brown powder (29 mg, 0.090 mmol, 58% yield): mp 236–239 °C (dec); R_f = 0.30 (EtOAc solvent); IR (ATR, neat) 3365, 1681, 1607 cm^{-1} ; 1H NMR (400 MHz, DMSO- d_6) δ 9.12 (d, 1H, J = 8.8 Hz), 8.56 (s, 1H), 8.16 (d, 1H, J = 3.6 Hz), 7.41 (s, 1H), 7.33 (dd, 1H, J = 2.4, 9.2 Hz), 4.69 (s, 2H), 4.07 (s, 3H), 4.01 (s, 3H), 3.97 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO- d_6) δ 172.1, 157.9, 150.4, 149.7, 141.2, 131.0, 125.7, 124.9, 122.4, 121.9, 121.2, 116.1, 105.1,

105.0, 104.5, 56.0, 55.7, 55.5, 43.9 ppm; HRMS (EI-DFS) calcd for $C_{19}H_{17}NO_4$ 323.1158, found 323.1157.

2,3-Dihydro-5,6,10-trimethoxy-1H-dibenzo[e,g]isoindole-1-one (16dc). Brown powder (16 mg, 0.049 mmol, 45% yield): mp 276–280 °C; R_f = 0.41 (EtOAc); IR (ATR, neat) 3176, 1673, 1620, 1605 cm^{-1} ; 1H NMR (400 MHz, DMSO- d_6) δ 8.77 (d, 1H, J = 9.6 Hz), 8.70 (d, 1H, J = 2.8 Hz), 8.62 (br s, 1H), 8.15 (s, 1H), 7.40 (s, 1H), 7.30 (dd, 1H, J = 2.8, 9.2 Hz), 4.72 (s, 2H), 4.04 (s, 3H), 3.95 (s, 3H), 3.91 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO- d_6) δ 172.2, 157.7, 150.9, 148.9, 144.4, 128.1, 126.8, 125.0, 123.7, 121.8, 120.2, 116.6, 104.5, 104.1, 103.7, 55.9, 55.7, 55.2, 44.0 ppm; HRMS (EI-DFS) calcd for $C_{19}H_{17}NO_4$ 323.1158, found 323.1149.

2,3-Dihydro-5,6,9,10-tetramethoxy-1H-dibenzo[e,g]isoindole-1-one (16dd). Off-white powder (48.0 mg, 0.136 mmol, 96% yield): mp 257–260 °C (dec); R_f = 0.67 (1:10 MeOH/EtOAc solvent); IR (ATR, neat) 3369, 1642, 1621 cm^{-1} ; 1H NMR (400 MHz, DMSO- d_6) δ 8.69 (s, 1H), 8.59 (s, 1H), 8.07 (s, 2H), 7.36 (s, 1H), 4.67 (s, 2H), 4.07 (s, 3H), 4.05 (s, 3H), 3.95 (s, 3H), 3.91 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO- d_6) δ 172.3, 150.5, 148.98, 148.97, 148.9, 141.5, 125.9, 124.2, 121.8, 121.7, 120.7, 104.45, 104.37, 104.3, 103.5, 56.0, 55.8, 55.6, 55.3, 43.8 ppm; HRMS (EI-DFS) calcd for $C_{20}H_{19}NO_5$ 353.1263, found 353.1264.

■ ASSOCIATED CONTENT

Supporting Information

Copies of 1H NMR spectra and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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