

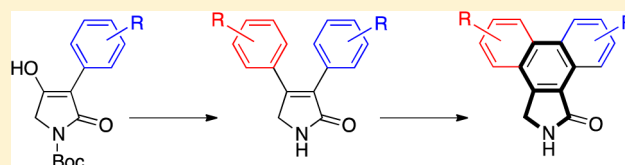
Preparation of Dibenzo[*e,g*]isoindol-1-ones via Scholl-Type Oxidative Cyclization Reactions

Amy A. van Loon, Maeve K. Holton, Catherine R. Downey, Taryn M. White, Carly E. Rolph, Stephen R. Bruening, Guanqun Li, Katherine M. Delaney, Sarah J. Pelkey, and Erin T. Pelkey\*

Department of Chemistry, Hobart and William Smith Colleges, Geneva, New York 14456, United States

## 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  $\gg$  3-methoxyphenyl  $>$  3,4,5-trimethoxyphenyl  $>$  4-methoxyphenyl  $\approx$  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

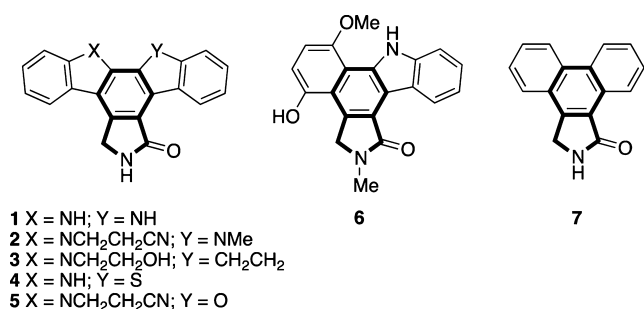


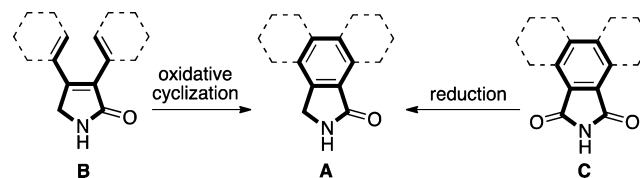
Figure 1. Polycyclic-fused isoindol-1-ones.

class is the natural product staurosporinone (**1**),<sup>1</sup> a submicromolar inhibitor of protein kinase C (PKC) first isolated in 1986.<sup>2,3</sup> The impressive biological activity inspired several total syntheses of **1**<sup>4</sup> and the investigation into analogues<sup>5</sup> 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 inhibitor<sup>6</sup> and HIV-1 antagonist.<sup>7</sup> Several heterocyclic fused isoindol-1-ones,<sup>8</sup> ring-modified analogues of **1**, have also been prepared and their biological activity evaluated (e.g., **3**,<sup>9</sup> **4**,<sup>10</sup> and **5**<sup>11</sup>). The synthesis of benzo[*a*]pyrrolo[3,4-*c*]carbazol-1-ones (e.g., **6**) was also reported in 2008.<sup>12</sup> 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**,<sup>13</sup> 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-pyrroli-2-ones,<sup>14</sup> 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.<sup>15</sup> In contrast, most known literature methods to **A** involve reduction of the corresponding maleimides **C**;<sup>4d,e</sup> this reduction often proves to be unselective in cases of nonsymmetrical substrates.<sup>16</sup> There are several possible methods available for completing oxidative cyclizations to phenanthrenes and fused phenanthrenes; these methods include oxidative photocyclization,<sup>17</sup> transition metal-mediated oxidative cyclization,<sup>18–21</sup> and oxidative cyclization using nonmetal reagents.<sup>22–25</sup> 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

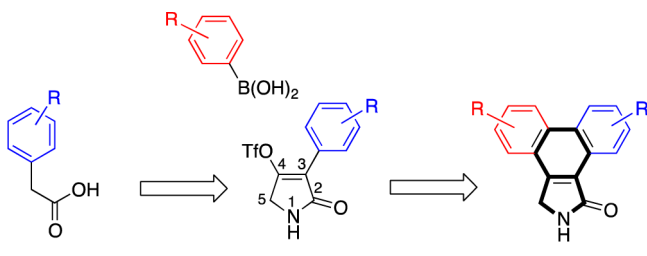
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involving electron-rich arenes that used the hypervalent iodine reagent, phenyliodine(III) bis(trifluoroacetate) (PIFA).<sup>26</sup> PIFA-mediated cyclizations leading to phenanthrenes and fused phenanthrenes were subsequently reported by Domínguez<sup>24</sup> and others.<sup>25</sup> By exploring the PIFA-mediated oxidative cyclization of 3,4-diaryl-3-pyrrolin-2-ones, we set out to synthesize new dibenzo[*e,g*]isoindol-1-one analogues of indolocarbazoles and related biologically active heterocyclic scaffolds including congeners containing either symmetrical or unsymmetrical substitution patterns in the phenanthrene rings or heterocyclic variants.

Our synthetic plan involved extending our synthesis of 3,4-diaryl-3-pyrrolin-2-ones from 3-aryltetramic acid triflates (Scheme 2).<sup>14b,c</sup> Our strategy allows for easy access to 3-

### Scheme 2. Synthetic Plan to Dibenzo[*e,g*]isoindol-1-ones

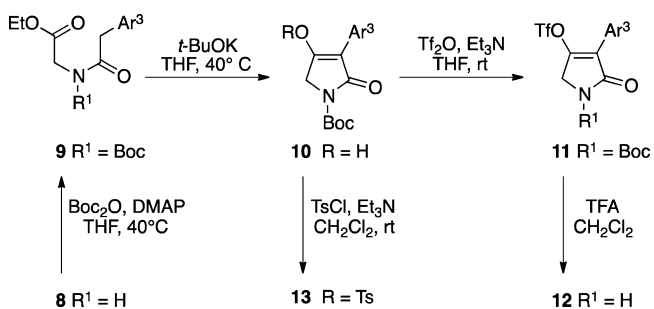


pyrrolin-2-ones with different aryl groups at the 3- and 4-positions. The choice of arylacetic acid starting material leads to different aryl groups at the 3-positions (in blue), while different aryl groups can be introduced at the 4-position (in red) via Suzuki–Miyaura cross-coupling reactions with commercially available arylboronic acids. With a small library of 3,4-diaryl-3-pyrrolin-2-ones in hand, we explored their subsequent intramolecular Scholl-type oxidative cyclizations into dibenzo[*e,g*]isoindol-1-ones.

## RESULTS AND DISCUSSION

We prepared methoxyaryl-substituted tetramic acids by extending our previously reported synthetic strategy to a 3-phenyltetramic acid (Table 1).<sup>14c</sup> Freshly prepared ethyl glycinate free amine was coupled with arylacetic acids in the presence of DCC/DMAP giving amidoesters **8** as white powders after trituration. Next, treatment of **8** with Boc<sub>2</sub>O/DMAP<sup>27</sup> gave the Boc-protected acetamides **9**.<sup>28</sup> We next

Table 1. Synthesis of Tetramic Acid Triflates



Ar <sup>3</sup>	yields (%)					
	8	9	10	11	12	13
b Ar <sup>3</sup> = 4-methoxyphenyl	80	87	79	72	90	–
c Ar <sup>3</sup> = 3-methoxyphenyl	77	87	60	30	98	60
d Ar <sup>3</sup> = 3,4-dimethoxyphenyl	75	81	65	64	84	–

attempted to form the tetramic acids **10** by treatment of **9** with sodium *tert*-butoxide as we had done previously (**9**: Ar<sup>3</sup> = Ph).<sup>14b</sup> Unexpectedly, the attempted cyclocondensations of methoxyaryl-substituted acetamides **9** (b Ar<sup>3</sup> = 4'-methoxyphenyl; c Ar<sup>3</sup> = 3'-methoxyphenyl; d Ar<sup>3</sup> = 3',4'-dimethoxyphenyl) with sodium *tert*-butoxide failed to produce the corresponding tetramic acids **10**. Fortunately, the use of potassium *tert*-butoxide<sup>29</sup> gave methoxyaryl-substituted tetramic acids **10** in moderate yields. Treatment of **10** with triflic anhydride led to the corresponding triflates **11**; in some of the runs, purification of **11** led to the loss of the Boc protecting group and the formation of unprotected lactams **12**.<sup>30</sup> Triflates **12** were also obtained by treatment of purified **11** with TFA in CH<sub>2</sub>Cl<sub>2</sub> (the yields of these reactions leading to **12** are reported in Table 1). We subsequently found substrates **11c/12c** to be capricious in the subsequent cross-coupling reactions, so we prepared the alternate cross-coupling substrate, tosylate **13c**, by treatment of **10c** with tosyl chloride and triethylamine.<sup>31</sup>

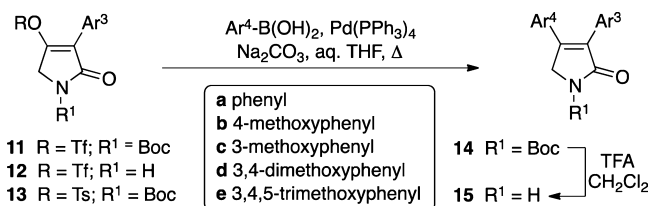
We briefly investigated an alternative synthesis of **12** that avoided the use of the Boc protecting group altogether. Cyclization of unprotected acetamides **8** with potassium *tert*-butoxide gave the corresponding *N*-unsubstituted 3-aryltetramic acids in isolated yields that were very low (<10%); we believe the low yields observed were due to the difficulty in purifying these unprotected tetramic acids and this strategy was not pursued further.<sup>32</sup>

We next examined Suzuki–Miyaura cross-coupling reactions of tetramic acid sulfonates **11–13**. Cross-coupling reactions of all three types of substrates with methoxy-substituted arylboronic acids gave the corresponding 3,4-diaryl-3-pyrrolin-2-ones **14** and **15**, respectively, in good to excellent yields in many cases (Table 2). As expected, we did observe higher yields using protected triflates **11** compared to unprotected triflates **12** (e.g., entry 5 vs entry 16), but we favored the use of unprotected triflates as it saves one synthetic operation per substrate. Inexplicably, cross-coupling reactions of either triflate **11c**, unprotected triflate **12c**, or tosylate **13c** (substrates with a 3-methoxyphenyl group) suffered from low yields or gave intractable mixtures. Nonetheless, this strategy still allowed for the preparation of a small library of methoxy-substituted 3,4-diaryl-3-pyrrolin-2-ones for our oxidative cyclization study.

We chose to start exploring intramolecular Scholl-type oxidative cyclizations of bis(3',4'-dimethoxyphenyl)-3-pyrrolin-2-ones **14dd** and **15dd** (Scheme 3) using PIFA.<sup>24–26</sup> Satisfyingly, on our first attempt, treatment of **14dd** with PIFA and BF<sub>3</sub>·Et<sub>2</sub>O at –40 °C for 30 min led to the formation of dibenzo[*e,g*]isoindol-1-one **16dd** in 55% yield. The reaction proceeded with loss of the Boc protecting group. We next tried the cyclization with *N*-unprotected lactam substrate **15dd** and obtained **16dd** in 93% yield. Since the yield was excellent for the free lactam, we subsequently used *N*-unprotected 3-pyrrolin-2-ones in all of the subsequent oxidative cyclization reactions. Evidence for the cyclization could readily be seen in the <sup>1</sup>H NMR, which showed a significant downfield shift of the arene protons (δ6.8–7.0 in **15dd** to δ7.2–8.7 in **16dd**) and methylene protons (δ4.32 in **15dd** to δ4.67 in **16dd**). We used this type of analysis to diagnose crude reaction mixtures involving the oxidative cyclizations.

A brief exploration of the reaction conditions of the oxidative cyclization with **15dd** was conducted (Table 3). Extending the reaction time (entry 1 vs entry 2) slightly increased the yield (93 to 96%). The yield decreased slightly (96 to 90%) when the reaction was run at +4 °C compared to –40 °C (entry 2 vs

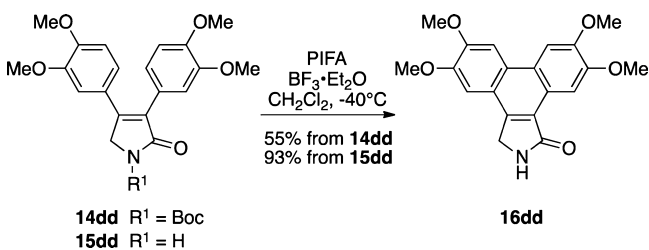
Table 2. Synthesis of 3,4-Diaryl-3-pyrrolin-2-ones



entry	substrate	product <sup>a</sup>	yield <sup>b</sup> (%)
1	11b	14bb	84
2	11c	14cc	45 <sup>c</sup>
3	13c	14cc	25 <sup>c</sup>
4	13c	14dc	72 <sup>c</sup>
5	11d	14dd	96
6	12c	15ac	39
7	12d	15ad	74
8	12b	15bb	55
9	12c	15bc	61 <sup>c</sup>
10	12d	15bd	49
11	12b	15cb	44 <sup>c</sup>
12	12c	15cc <sup>d</sup>	NR <sup>e</sup>
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

<sup>a</sup>The product number is comprised first of the letter for Ar<sup>4</sup> and second of letter for Ar<sup>3</sup>; 15ac: Ar<sup>4</sup> = phenyl and Ar<sup>3</sup> = 3-methoxyphenyl. <sup>b</sup>Yield refers to isolated yields of pure products after column chromatography. <sup>c</sup>Reaction conditions: Ar<sup>4</sup>-B(OH)<sub>2</sub>, Pd(dppf)Cl<sub>2</sub>, Cs<sub>2</sub>CO<sub>3</sub>, THF. <sup>d</sup>15cc was obtained by treatment of 14cc with TFA. <sup>e</sup>NR = not run.

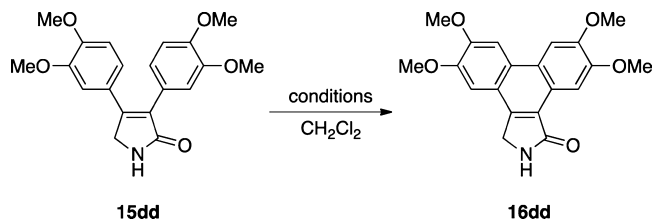
## Scheme 3. Preliminary Oxidative Cyclization Results



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 DDQ<sup>22</sup> (entry 6) or *m*-CPBA<sup>23</sup> (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 BF<sub>3</sub>·Et<sub>2</sub>O (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 BF<sub>3</sub>·Et<sub>2</sub>O 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, BF<sub>3</sub>·Et<sub>2</sub>O vs 25% with PIFA) in a similar comparative set of oxidative cyclization reactions leading to a dibenzo[*a,c*]cycloheptene.<sup>26b</sup>

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

Table 3. Oxidative Cyclization of 15cc



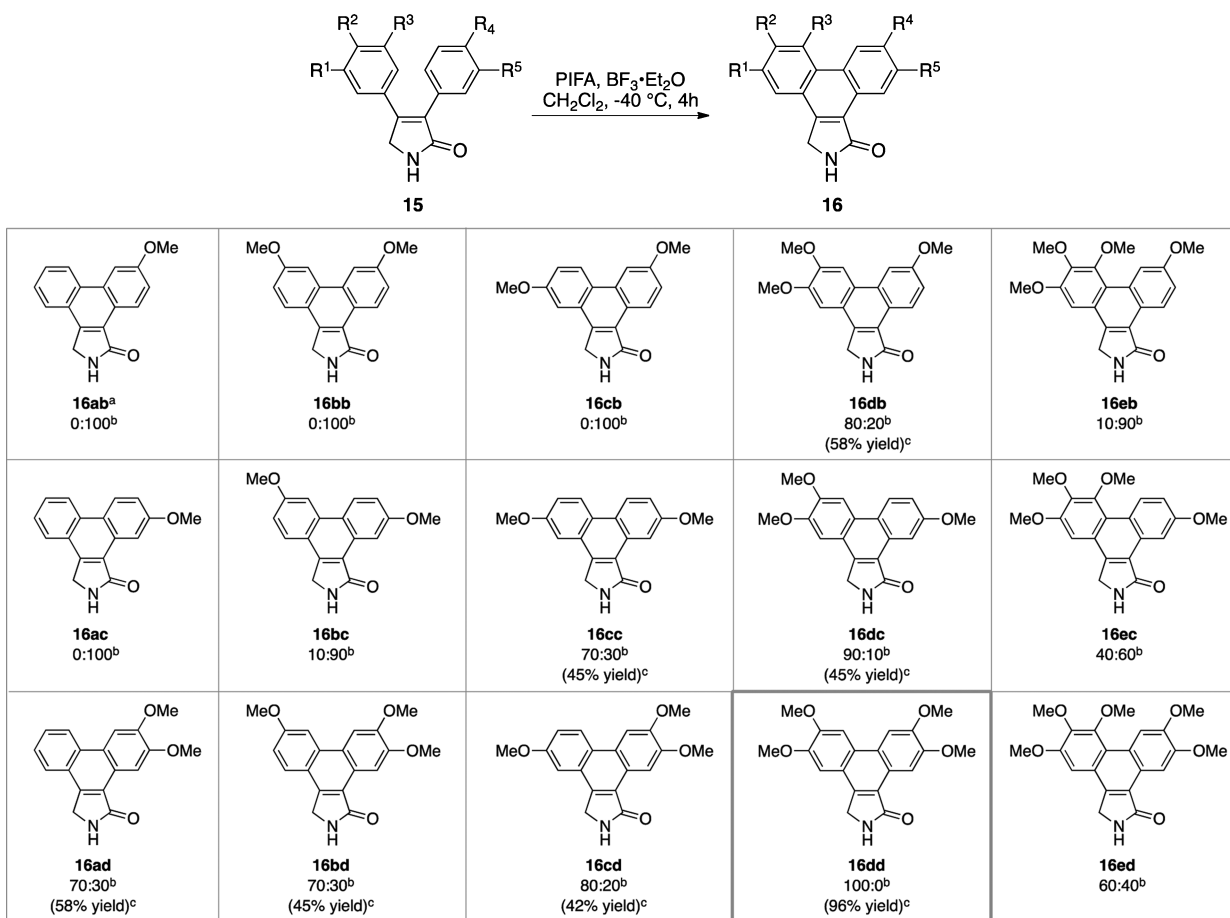
entry	oxidant <sup>a</sup>	additive <sup>b</sup>	temp (°C)	time (h)	16:15 (ratio) <sup>c</sup>	yield <sup>d</sup> (%)
1	PIFA	BF <sub>3</sub> ·Et <sub>2</sub> O	-40	0.5	100:0	93
2	PIFA	BF <sub>3</sub> ·Et <sub>2</sub> O	-40	4	100:0	96
3	PIFA	BF <sub>3</sub> ·Et <sub>2</sub> O	+4	12	100:0	90
4	PIFA	none	-40	4	90:10	75
5	none	BF <sub>3</sub> ·Et <sub>2</sub> 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

<sup>a</sup>PIFA = phenyliodine(III) bis(trifluoroacetate); *m*-CPBA = *meta*-chloroperbenzoic acid; DDQ = 1,2-dichloro-5,6-dicyanobenzoquinone. <sup>b</sup>TFA = trifluoroacetic acid. <sup>c</sup>16:15 ratio was estimated by <sup>1</sup>H NMR analysis methylene of proton integrations (δ4.67 and δ4.32, respectively). <sup>d</sup>Yield 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/CO<sub>2</sub> bath) for 4 h, and then the solvent was removed, and the resulting crude reaction mixtures were analyzed by <sup>1</sup>H 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 <sup>1</sup>H and <sup>13</sup>C 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



<sup>a</sup>3-(4'-Methoxyphenyl)-4-phenyl-1*H*-pyrrol-2(5*H*)-one (**15ab**) starting material was available from a previous study.<sup>17d</sup> <sup>b</sup>Reported ratios of **16:15** were ascertained by <sup>1</sup>H NMR analysis of methylene proton integrations. <sup>c</sup>Yields 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 (CH<sub>2</sub>Cl<sub>2</sub>) 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. <sup>1</sup>H NMR and <sup>13</sup>C NMR chemical shifts are reported in parts per million (δ) using the solvent's residual proton or carbon signal (CDCl<sub>3</sub>: δH 7.26 ppm, δC 77.3 ppm; DMSO-*d*<sub>6</sub>: 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.<sup>33</sup> 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 CH<sub>2</sub>Cl<sub>2</sub> (5 × 50 mL). The organic layer was dried over sodium sulfate and used directly in the next reaction. Next, following a modified procedure,<sup>34</sup> the previously obtained solution of ethyl glycinate in CH<sub>2</sub>Cl<sub>2</sub> 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 CH<sub>2</sub>Cl<sub>2</sub>. 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).**<sup>35</sup> 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  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  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;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  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).**<sup>35</sup> 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  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  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;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  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).**<sup>35</sup> 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  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (400 MHz,  $\text{CDCl}_3$ ) 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;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (100 MHz,  $\text{CDCl}_3$ ) 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.<sup>27</sup> 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  $\text{Boc}_2\text{O}$  (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  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  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;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  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;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  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;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $\text{KHSO}_4$  (5.45 g, 40.0 mmol in 40 mL  $\text{H}_2\text{O}$ ) 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 × 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.<sup>36</sup> mp ~250 °C (dec));  $R_f$  = 0.13 (1:10 MeOH/EtOAc); IR (ATR, neat) 3362, 1743, 1677, 1638, 1610  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  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);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ )  $\delta$  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  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  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;  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ )  $\delta$  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  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  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;  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ )  $\delta$  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  $\text{CH}_2\text{Cl}_2$  (50 mL) was added neat  $\text{Et}_3\text{N}$  (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  $\text{KHSO}_4$  (2.72 g, 20.0 mmol in 50 mL  $\text{H}_2\text{O}$ ) dropwise via additional funnel and stirred an additional 30 min. The reaction mixture was then transferred to a separatory funnel and extracted with  $\text{CH}_2\text{Cl}_2$  (4 × 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  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  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;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  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;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  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;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $\text{C}_{18}\text{H}_{20}\text{F}_3\text{NO}_8\text{S}\cdot\text{Na}$  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  $\text{CH}_2\text{Cl}_2$  (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  $\text{CH}_2\text{Cl}_2$  (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  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  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;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  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;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  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;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $\text{C}_{13}\text{H}_{12}\text{F}_3\text{NO}_6\text{S}\cdot\text{Na}$  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  $\text{CH}_2\text{Cl}_2$  (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  $\text{KHSO}_4$  (1.0 M, 50 mL), and the organic layer was separated. The aqueous layer was further extracted with  $\text{CH}_2\text{Cl}_2$  (2  $\times$  50 mL). The combined organic layers

were washed with aqueous solution of  $\text{NaHCO}_3$  (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 ( $\text{CH}_2\text{Cl}_2$ /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/ $\text{CH}_2\text{Cl}_2$ ); IR (ATR, neat) 1771, 1698, 1678, 1607  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  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;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $\text{H}_2\text{O}$ ). 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  $\text{H}_2\text{O}$ ) 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  $\text{CH}_2\text{Cl}_2$  (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  $\text{CH}_2\text{Cl}_2$  (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  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  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;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  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;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  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;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  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- $d_6$ )  $\delta$  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- $d_6$ )  $\delta$  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- $d_6$ )  $\delta$  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- $d_6$ )  $\delta$  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- $d_6$ )  $\delta$  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- $d_6$ )  $\delta$  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).**<sup>37</sup> White amorphous solid (Method F: 0.240 g, 0.813 mmol, 55% yield): mp 223–227 °C (lit.<sup>14d</sup> 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- $d_6$ )  $\delta$  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- $d_6$ )  $\delta$  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- $d_6$ )  $\delta$  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- $d_6$ )  $\delta$  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- $d_6$ )  $\delta$  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- $d_6$ )  $\delta$  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,  $CDCl_3$ )  $\delta$  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,  $CDCl_3$ )  $\delta$  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,  $CDCl_3$ )  $\delta$  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,  $CDCl_3$ )  $\delta$  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- $d_6$ )  $\delta$  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- $d_6$ )  $\delta$  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- $d_6$ )  $\delta$  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- $d_6$ )  $\delta$  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- $d_6$ )  $\delta$  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- $d_6$ )  $\delta$  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.<sup>38</sup> 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- $d_6$ )  $\delta$  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- $d_6$ )  $\delta$  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- $d_6$ )  $\delta$  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- $d_6$ )  $\delta$  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- $d_6$ )  $\delta$  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-

$d_6$ )  $\delta$  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- $d_6$ )  $\delta$  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- $d_6$ )  $\delta$  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- $d_6$ )  $\delta$  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- $d_6$ )  $\delta$  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- $d_6$ )  $\delta$  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- $d_6$ )  $\delta$  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- $d_6$ )  $\delta$  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- $d_6$ )  $\delta$  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- $d_6$ )  $\delta$  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- $d_6$ )  $\delta$  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- $d_6$ )  $\delta$  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- $d_6$ )  $\delta$  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- $d_6$ )  $\delta$  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- $d_6$ )  $\delta$  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- $d_6$ )  $\delta$  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- $d_6$ )  $\delta$  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>.

## ■ AUTHOR INFORMATION

### Corresponding Author

\*E-mail: [pelkey@hws.edu](mailto:pelkey@hws.edu).

### Notes

The authors declare no competing financial interest.

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## ■ REFERENCES

- Yasuzawa, T.; Iida, T.; Yoshida, M.; Hirayama, N.; Takahashi, M.; Shirahata, K.; Sano, H. *J. Antibiot.* **1986**, *39*, 1072–1078.
- (a) Nakanishi, S.; Matsuda, Y.; Iwahashi, K.; Kase, H. *J. Antibiot.* **1986**, *39*, 1066–1071. (b) Horton, P. A.; Longley, R. E.; McConnell, O. J.; Ballas, L. M. *Experientia* **1994**, *50*, 843–845.
- Indolocarbazole (1) is the aglycone of staurosporine, a nanomolar inhibitor of protein kinase C (PKC) and lead compound in a large number of studies: Omura, S.; Sasaki, Y.; Iwai, Y.; Takeshima, H. *J. Antibiot. Chem.* **1995**, *48*, 535–548.
- Selected total syntheses of staurosporinone (1): (a) Sarstedt, B.; Winterfeldt, E. *Heterocycles* **1983**, *20*, 469–476. (b) Hughes, I.; Nolan, W. P.; Raphael, R. A. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2475–2480. (c) Moody, C. J.; Rahimtoola, K. F.; Porter, B.; Ross, B. C. *J. Org. Chem.* **1992**, *57*, 2105–2214. (d) Harris, W.; Hill, C. H.; Keech, E.; Malsher, P. *Tetrahedron Lett.* **1993**, *34*, 8361–8364. (e) Xie, G.; Lown, J. W. *Tetrahedron Lett.* **1994**, *35*, 5555–5558. (f) Wood, J. L.; Stoltz, B. M.; Dietrich, H.-J.; Pflum, D. A.; Petsch, D. T. *J. Am. Chem. Soc.* **1997**, *119*, 9641–9651. (g) Beccalli, E. M.; Gelmi, M. L.; Marchesini, A.



- Tetrahedron* **1998**, *54*, 6909–6918. (h) Eils, S.; Winterfeldt, E. *Synthesis* **1999**, 275–281. (i) Gaudencio, S. P.; Santos, M. M. M.; Lobo, A. M.; Prabhakar, S. *Tetrahedron Lett.* **2003**, *44*, 2577–2578. (j) Wada, Y.; Nagasaki, H.; Tokuda, M.; Orito, K. *J. Org. Chem.* **2007**, *72*, 2008–2014. (k) Rajeshwaran, G. G.; Mohanakrishnan, A. K. *Org. Lett.* **2011**, *13*, 1418–1421.
- (5) Selected reports of nonglycosidic indolocarbazole-based analogues of (1): (a) Kleinschroth, J.; Hartenstein, J.; Rudolph, C.; Schächtele, C. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 55–60. (b) Xie, G.; Nagata, H.; Tamaoki, T.; Lown, J. W. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2841–2844. (c) Yang, S.-M.; Malaviya, R.; Wilson, L. J.; Argentieri, R.; Chen, X.; Yang, C.; Wang, B.; Cavender, D.; Murray, W. V. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 326–331. (d) Wilson, L. J.; Yang, C.; Murray, W. V. *Tetrahedron Lett.* **2007**, *48*, 7399–7403. (e) Wilson, L. J.; Malaviya, R.; Yang, C.; Argentieri, R.; Wang, B.; Chen, X.; Murray, W. V.; Cavender, D. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3333–3338.
- (6) (a) Kleinschroth, J.; Hartenstein, J.; Rudolph, C.; Schächtele, C. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1959–1964. (b) Martiny-Baron, G.; Kazanietz, M. G.; Mischak, H.; Blumberg, P. M.; Kochs, G.; Hug, H.; Marmé, D.; Schächtele, C. *J. Biol. Chem.* **1993**, *268*, 9194–9197.
- (7) Qatsha, K. A.; Rudolph, C.; Marmé, D.; Schächtele, C.; May, W. S. *Proc. Natl. Acad. Sci. U. S. A.* **1993**, *90*, 4674–4678.
- (8) (a) Rotella, D. P.; Glicksman, M. A.; Prantner, J. E.; Neff, N. T.; Hudkins, R. L. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1167–1170. (b) Gingrich, D. E.; Reddy, D. R.; Iqbal, M. A.; Singh, J.; Aimone, L. D.; Angeles, T. S.; Albom, M.; Yang, S.; Ator, M. A.; Meyer, S. L.; Robinson, C.; Ruggeri, B. A.; Dionne, C. A.; Vaught, J. L.; Mallamo, J.; Hudkins, R. L. *J. Med. Chem.* **2003**, *46*, 5375–5388. (c) Tao, M.; Park, C. H.; Bihovsky, R.; Wells, G. J.; Husten, J.; Ator, M. A.; Hudkins, R. L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 938–942. (d) Tao, M.; Park, C. H.; Josef, K.; Hudkins, R. L. *J. Heterocycl. Chem.* **2009**, *46*, 1185–1189.
- (9) Hudkins, R. L.; Diebold, J. L.; Tao, M.; Josef, K. A.; Park, C. H.; Angeles, T. S.; Aimone, L. D.; Husten, J.; Ator, M. A.; Meyer, S. L.; Holskin, B. P.; Durkin, J. T.; Fedorov, A. A.; Fedorov, E. V.; Almo, S. C.; Mathiasen, J. R.; Bozyczko-Coyne, D.; Saporito, M. S.; Scott, R. W.; Mallamo, J. P. *J. Med. Chem.* **2008**, *51*, 5680–5689.
- (10) (a) Hudkins, R. L.; Johnson, N. W. *J. Heterocycl. Chem.* **2001**, *38*, 591–597. (b) Hudkins, R. L.; Johnson, N. W.; Angeles, T. S.; Gessner, G. W.; Mallamo, J. P. *J. Med. Chem.* **2007**, *50*, 433–441.
- (11) Ma, D.-W.; Zhang, Y.-D.; Zhang, X.-R.; Wu, S.-H.; Feng-Gang, T. *Chin. J. Chem.* **2001**, *19*, 489–492.
- (12) Conchon, E.; Anizon, F.; Aboab, B.; Prudhomme, M. *Synthesis* **2008**, 2569–2574.
- (13) (a) Yakushijin, K.; Kozuka, M.; Furukawa, H. *Chem. Pharm. Bull.* **1980**, *28*, 2178–2184. (b) Lewis, F. D.; Burch, E. L. *J. Photochem. Photobiol. A* **1996**, *96*, 19–23. (c) Klumpp, D. A.; Zhang, Y.; O'Connor, M. J.; Esteves, P. M.; de Almeida, L. S. *Org. Lett.* **2007**, *9*, 3085–3088. (d) Kim, Y. H.; Lee, H.; Kim, Y. J.; Kim, B. T.; Heo, J.-N. *J. Org. Chem.* **2008**, *73*, 495–501. (e) Yamashita, S.; Kurono, N.; Senboku, H.; Tokuda, M.; Orito, K. *Eur. J. Org. Chem.* **2009**, 1173–1180.
- (14) (a) Coffin, A. R.; Roussell, M. A.; Tserlin, E.; Pelkey, E. T. *J. Org. Chem.* **2006**, *71*, 6678–6681. (b) Dorward, K. M.; Guthrie, N. J.; Pelkey, E. T. *Synthesis* **2007**, 2317–2322. (c) Yoon-Miller, S. J. P.; Dorward, K. M.; White, K. P.; Pelkey, E. T. *J. Heterocycl. Chem.* **2009**, *46*, 447–454. (d) Greger, J. G.; Yoon-Miller, S. J. P.; Bechtold, N. R.; Flewelling, S. A.; MacDonald, J. P.; Downey, C. R.; Cohen, E. A.; Pelkey, E. T. *J. Org. Chem.* **2011**, *76*, 8203–8214.
- (15) (a) Kovacic, P.; Jones, M. B. *Chem. Rev.* **1987**, *87*, 357–359. (b) King, B. T.; Kroulik, J.; Robertson, C. R.; Rempala, P.; Hilton, C. L.; Korinek, J. D.; Gortari, L. M. *J. Org. Chem.* **2007**, *72*, 2279–2288. (c) Zhai, L.; Shukla, R.; Wadumethrige, S. H.; Rathore, R. *J. Org. Chem.* **2010**, *75*, 4748–4760.
- (16) (a) Fabre, S.; Prudhomme, M.; Sancelme, M.; Rapp, M. *Bioorg. Med. Chem.* **1994**, *2*, 73–77. (b) Link, J. T.; Raghavan, S.; Gallant, M.; Danishefsky, S. J.; Chou, T. C.; Ballas, L. M. *J. Am. Chem. Soc.* **1996**, *118*, 2825–2842. (c) See also reference 8c.
- (17) (a) Wood, C. S.; Mallory, F. B. *J. Org. Chem.* **1964**, *29*, 3373–3377. (b) Padwa, A.; Hartman, R. *J. Am. Chem. Soc.* **1966**, *88*, 3759–3765. (c) Quin, L. D.; Middlemas, E. D.; Rao, N. S.; Miller, R. W.; McPhail, A. T. *J. Am. Chem. Soc.* **1982**, *104*, 1893–1900. (d) Smith, P. A. S.; Friar, J. J.; Resemann, W.; Watson, A. C. *J. Org. Chem.* **1990**, *55*, 3351–3362. (e) Trost, B. M.; Krische, M. J.; Berl, V.; Grenzer, E. M. *Org. Lett.* **2002**, *4*, 2005–2008. (f) Nikolaev, V. A.; Galkina, O. S.; Sieler, J.; Rodina, L. L. *Tetrahedron Lett.* **2010**, *51*, 2713–2716. (g) Chang, M.-Y.; Lee, N.-C. *Synlett* **2011**, 1875–1881. (h) Lu, Z.; Cui, W.; Xia, S.; Bai, Y.; Luo, F.; Zhu, G. *J. Org. Chem.* **2012**, *77*, 9871–9877. (i) Chang, M.-Y.; Wu, M.-H. *Tetrahedron* **2013**, *69*, 129–136.
- (18) VOF<sub>3</sub>: (a) Liepa, A.; Summons, R. E. *J. Chem. Soc., Chem. Comm.* **1977**, 826–827. (b) Halton, B.; Maiment, A. I.; Officer, D. L.; Warnes, J. M. *Aust. J. Chem.* **1984**, *37*, 2119–2128. (c) Comins, D. L.; Chen, X.; Morgan, L. A. *J. Org. Chem.* **1997**, *62*, 7435–7438. (d) Wang, K.; Wang, Q.; Huang, R. *J. Org. Chem.* **2007**, *72*, 8416–8421. (e) Ambrosini, L. M.; Cernak, T. A.; Lambert, T. H. *Tetrahedron* **2010**, *66*, 4882–4887. (f) Leighty, M. W.; Georg, G. I. *ACS Med. Chem. Lett.* **2011**, *2*, 313–315. (g) Pansare, S. V.; Lingampally, R.; Dyapa, R. *Eur. J. Org. Chem.* **2011**, 2235–2238.
- (19) FeCl<sub>3</sub>: (a) Borner, R. C.; Jackson, R. F. W. *J. Chem. Soc., Chem. Commun.* **1994**, 845–846. (b) Brenna, E.; Fuganti, C.; Serra, S. *J. Chem. Soc., Perkin Trans 1* **1998**, 901–904. (c) Wang, K.-L.; Lü, M.-Y.; Wang, Q.-M.; Huang, R.-Q. *Tetrahedron* **2008**, *64*, 7504–7510. (d) Wang, K.; Lü, M.; Yu, A.; Zhu, X.; Wang, Q. *J. Org. Chem.* **2009**, *74*, 935–938. (e) Mysliwiec, D.; Donnio, B.; Chmielowski, P. J.; Heinrich, B.; Stepien, M. *J. Am. Chem. Soc.* **2012**, *134*, 4822–4833. (f) Zhou, C.; Chen, X.; Lu, P.; Wang, Y. *Tetrahedron* **2012**, *68*, 2844–2850.
- (20) MnO<sub>2</sub>: Wang, K.; Hu, Y.; Li, Z.; Wu, M.; Liu, Z.; Su, B.; Yu, A.; Liu, Y.; Wang, Q. *Synthesis* **2010**, 1083–1091.
- (21) Ti(OCOCF<sub>3</sub>)<sub>2</sub>: (a) Taylor, E. C.; Andrade, J. G.; McKillop, A. J. *J. Chem. Soc., Chem. Comm.* **1977**, 538–539. (b) Cragg, J. E.; Herbert, R. B. *J. Chem. Soc., Perkin Trans 1* **1982**, 2487–2490. (c) Pansare, S. V.; Dyapa, R. *Org. Biomol. Chem.* **2012**, *10*, 6776–6784.
- (22) 2-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ): (a) Zhai, L.; Shukla, R.; Rathore, R. *Org. Lett.* **2009**, *11*, 3474–3477. (b) Navale, T. S.; Thakur, K.; Rathore, R. *Org. Lett.* **2011**, *13*, 1634–1637. (c) See also references 15c and 17i.
- (23) *m*-Chloroperbenzoic acid (*m*-CPBA): Wang, K.; Hu, Y.; Meng, W.; Li, Z.; Liu, Z.; Su, B.; Yu, A.; Liu, Y.; Wang, Q. *Tetrahedron* **2010**, *66*, 9135–9140.
- (24) Phenyliodine(III) bis(trifluoroacetate) (PIFA): (a) Olivera, R.; SanMartin, R.; Pascual, S.; Herrero, M.; Domínguez, E. *Tetrahedron Lett.* **1999**, *40*, 3479–3480. (b) Moreno, I.; Tellitu, I.; SanMartín, R.; Badía, D.; Carrillo, L.; Domínguez, E. *Tetrahedron Lett.* **1999**, *40*, 5067–5070. (c) Moreno, I.; Tellitu, I.; SanMartin, R.; Domínguez, E. *Synlett* **2001**, 1161–1163. (d) Olivera, R.; SanMartin, R.; Tellitu, I.; Domínguez, E. *Tetrahedron* **2002**, *58*, 3021–3037. (e) Churruca, F.; SanMartin, R.; Carril, M.; Urriaga, M. K.; Solans, X.; Tellitu, I.; Domínguez, E. *J. Org. Chem.* **2005**, *70*, 3178–3187. (f) Churruca, F.; SanMartin, R.; Tellitu, I.; Domínguez, E. *Eur. J. Org. Chem.* **2005**, 2481–2490.
- (25) (a) Pingaew, R.; Ruchirawat, S. *Synlett* **2007**, 2363–2366. (b) Niphakis, M. J.; Georg, G. I. *J. Org. Chem.* **2010**, *75*, 6019–6022. (c) Barrett, T. N.; Braddock, D. C.; Monta, A.; Webb, M. R.; White, A. J. P. *J. Nat. Prod.* **2011**, *74*, 1980–1984. (d) See also reference 15b.
- (26) (a) Kita, Y.; Gyoten, M.; Ohtsubo, M.; Tohma, H.; Takada, T. *Chem. Commun.* **1996**, 1481–1482. (b) Takada, T.; Arisawa, M.; Gyoten, M.; Hamada, R.; Tohma, R.; Kita, Y. *J. Org. Chem.* **1998**, *63*, 7698–7706. (c) Hamamoto, H.; Anilkumar, G.; Tohma, H.; Kita, Y. *Chem. Commun.* **2002**, 450–451.
- (27) Casiraghi, G.; Rassu, G.; Spanu, P.; Pinna, L. *J. Org. Chem.* **1992**, *57*, 3760–3763.
- (28) We also attempted to prepare a nitro-substituted substrate **9d** from **8d** (Ar<sup>3</sup> = 4'-nitrophenyl), but this reaction inexplicably failed; the synthesis of **9d** was not pursued further.
- (29) (a) Andrews, M. D.; Brewster, A. G.; Chuhan, J.; Ibbett, A. J.; Moloney, M. G.; Watkin, D. *Synthesis* **1997**, 305–308. (b) Ito, M.; Okui, H.; Nakagawa, H.; Mio, S.; Iwasaki, T.; Iwabuchi, J. *Heterocycles*

2002, 57, 881–894. (c) Miyazaki, H.; Ogiku, T.; Sai, H.; Moritani, Y.; Ohtani, A.; Ohmizu, H. *Chem. Pharm. Bull.* **2009**, 57, 979–985.

(d) Mallinger, A.; Nadal, B.; Chopin, N.; Le Gall, T. *Eur. J. Org. Chem.* **2010**, 1142–1148.

(30) We had previously encountered a similar lability of the Boc group in tetramic acid triflate **11** ( $\text{Ar}^3 = \text{Ph}$ ); see reference 14c.

(31) (a) Li, W.-R.; Lin, S. T.; Hsu, N.-M.; Chern, M.-S. *J. Org. Chem.* **2002**, 67, 4702–4706. (b) Boukouvalas, J.; McCann, L. C. *Tetrahedron Lett.* **2010**, 51, 4636–4639.

(32) Le Gall and co-workers also reported a low yield in their synthesis of 3-(4'-methoxyphenyl)tetramic acid using a different method; see reference 29d.

(33) Erhardt, P. W.; Woo, C. M.; Gorczynski, R. J.; Anderson, W. G. *J. Med. Chem.* **1982**, 25, 1402–1407.

(34) Gynther, M.; Laine, K.; Ropponen, J.; Leppänen, J.; Mannila, A.; Nevalainen, T.; Savolainen, J.; Järvinen, T.; Rautio, J. *J. Med. Chem.* **2008**, 51, 932–936.

(35) Although amidoesters **8** apparently have not been reported in the literature, structurally related methyl esters have appeared in the patent literature: Xiao, Z.; Deng, R.; Zeng, Q. *Faming Zhuanli Shenqing*, CN 103483321, 2014. *Chem. Abstr.* **2014**, 160, 190111.

(36) Storgaard, M.; Dörwald, F. Z.; Peschke, B.; Tanner, D. *J. Org. Chem.* **2009**, 74, 5032–5040.

(37) 3-Pyrrolin-2-one **15bb** has recently been prepared via a double Suzuki cross-coupling of a 3,4-dibromo-3-pyrrolin-2-one: Awuah, E.; Capretta, A. *J. Org. Chem.* **2011**, 76, 3122–3130.

(38) Zhang, P. Y.; Wong, I. L. K.; Yan, C. S. W.; Zhang, X. Y.; Jiang, T.; Chow, L. M. C.; Wan, S. B. *J. Med. Chem.* **2010**, 53, 5108–5120.