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Note

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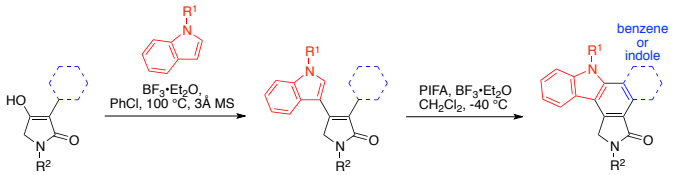
Synthesis of Benzo[*a*]carbazoles and an Indolo[2,3-*a*]carbazole from 3-Aryltetramic Acids

Nathanyal J. Truax, Fernando Banales Mejia, Deborah O. Kwansare, Megan M. Lafferty, Maeve H. Kean, and Erin T. Pelkey*

Department of Chemistry, Hobart and William Smith Colleges, Geneva, NY 14456 USA
*pelkey@hws.edu



ABSTRACT

A simple and flexible approach to 3-pyrrolin-2-one fused carbazoles is disclosed. The key step involves the BF_3-mediated electrophilic substitution of indoles with *N*-alkyl-substituted 3-aryltetramic acids, which provides access to indole-substituted 3-pyrrolin-2-ones. Scholl-type oxidative cyclizations of these materials led to the formation of the corresponding 3-pyrrolin-2-one-fused benzo[*a*]carbazoles and indolo[2,3-*a*]carbazoles. This work represents the first synthesis of the benzo[*a*]pyrrolo[3,4-*c*]carbazol-3(8*H*)-one ring system, while the indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazol-5-one ring system is found in a number of biologically active compounds including the protein kinase C (PKC) inhibitor, staurosporine.

Indolo[2,3-*a*]carbazoles comprise an important class of biologically active heterocycles (Figure 1).[1,2] For example, staurosporine (**1**)[3] is a potent inhibitor of protein kinase C (PKC).[4] Hudkins and co-workers investigated structure-activity relationships by preparing carbocyclic[5] and heterocyclic[6] fused variants of the indolo[2,3-*a*]carbazole ring system. One of these analogs, an indazolo[5,4-*a*]carbazole named CEP-11981 (**2**), was found to be a vascular endothelial growth factor (VEGF) inhibitor[7] and advanced to Phase I clinical trials.[8] Interestingly, the parent benzo[*a*]carbazole **3** has not previously been reported.[9,10]

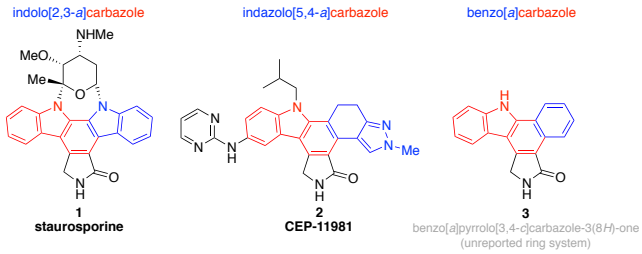
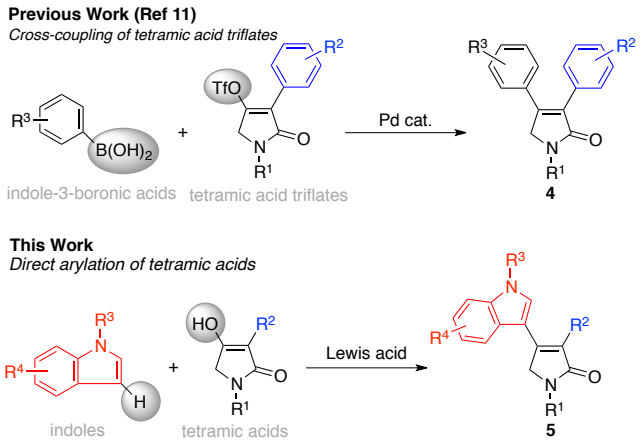


Figure 1. Structures of fused carbazole ring systems.

We are interested in developing synthetic strategies that can be used to prepare indolo[2,3-*a*]carbazoles and new heterocyclic analogs such as **3**. Toward this end, we have explored the use of tetramic acid derivatives to prepare 3,4-diaryl-3-pyrrolin-2-ones (**4**) (Scheme 1).[11-13] Palladium-catalyzed cross-coupling reactions of tetramic acid triflates with arylboronic acids gives **4**. Rather than using costly indolylboronic acids to prepare indole-substituted 3-pyrrolin-2-ones **5**, we became interested in developing a new strategy that takes advantage of the inherent reactivity of the electron-rich indole ring system.[14] We were inspired by a report by Prabhakar and co-workers;[15] they found that treatment of *N*-benzoyltetramic acid with 2,2'-biindole in the presence of BF_3•Et_2O gave a biindole-substituted 3-pyrrolin-2-one with loss of the benzoyl group. To preclude the possibility of *N*-deprotection, we decided to systematically

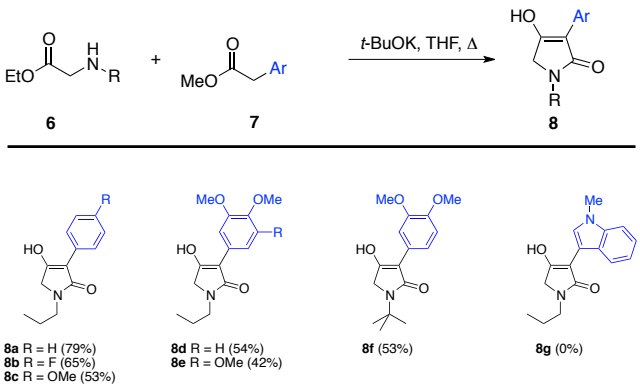
study the synthesis of **5** using *N*-alkyltetramic acids. Realization of this strategy would offer significant advantages over the cross-coupling strategy as it does not require functionalization of the enolic moiety into a triflate nor does it require the use of palladium catalysts or arylboronic acids.

Scheme 1. Arylation Reactions of Tetramic Acids



The requisite *N*-alkyl-3-aryltetramic acids **8** were prepared using the one-pot tandem amidation-Dieckmann cyclization reported by Le Gall and co-workers (Scheme 2).[16,17] The cyclocondensation of ethyl *N*-alkylglycinates **6**[18] and arylacetates **7**[19] by treatment with *t*-BuOK gave tetramic acids **8** in mostly good yields. The latter were conveniently isolated as crystalline materials directly from the work-up of these reactions. We chose to make *N*-tert-butyl tetramic acid **8f** in order to explore the possibility of making the free N-H lactams later by removal of the *tert*-butyl groups.[20] Interestingly, this tandem reaction failed to give indole-substituted tetramic acid **8g**.

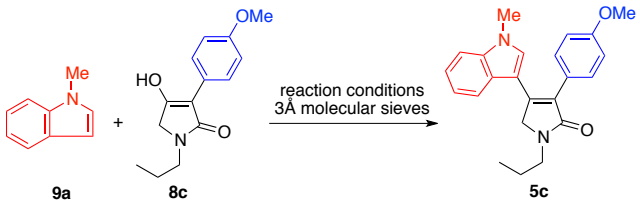
Scheme 2. Synthesis of 3-Aryltetramic acids



We next explored Lewis-acid mediated arylation reactions using *N*-propyltetramic acid **8c** as the electrophilic partner and *N*-methylindole (**9a**) as the nucleophilic partner (Table 1, entry 1). Following similar reaction conditions to that reported by Prabhakar,[15] we treated **8c** and **9a** with BF_3•Et_2O in CH_2Cl_2 and 3Å molecular sieves at rt for 20 h and obtained an 11% yield of indole product **5c**.

To improve the yield of **5c**, we screened different reaction conditions (Table 1). The reactions were analyzed by evaluating the crude ^{1}H NMR spectra and determining the ratio of product **5c** to starting material **8c** based on the relative respective methylene protons (δ3.90 for **8c** and δ4.45 for **5c**). The best conditions obtained included PhMe, 100 °C, and a reaction time of 1 h (Table 1, Entry 14). Longer reaction times gave lower relative amounts of product (Table 1, Entry 12 vs Entry 13) and this result was rationalized by control experiments, which indicated that the product was being degraded over time.[21] We tried a few alternate Lewis acids ($AlCl_3$, $FeCl_3$, $InCl_3$, $Cu(OTf)_2$) to mediate the transformation, but we did not find a better Lewis acid than BF_3•Et_2O.

Table 1. Screening reaction conditions[a]



9a 8c 5c

Entry	Lewis acid	solvent	temp (°C)	time (h)	conversion[b]
1	BF_3•Et_2O	CH_2Cl_2	40	20	13[c]
2	BF_3•Et_2O	THF	65	1	0
3	BF_3•Et_2O	CH_3CN	65	1	0
4	BF_3•Et_2O	DCE	65	1	7
5	BF_3•Et_2O	PhCl	65	1	25
6	BF_3•Et_2O	PhCl	65	4	40
7	BF_3•Et_2O	PhCl	65	24	54
8	BF_3•Et_2O	PhMe	65	1	37
9	BF_3•Et_2O	PhCl	100	0.25	53
10	BF_3•Et_2O	PhCl	100	0.5	70
11	BF_3•Et_2O	PhCl	100	0.75	65
12	BF_3•Et_2O	PhCl	100	1	64
13	BF_3•Et_2O	PhCl	100	4	45
14	BF_3•Et_2O	PhMe	100	1	80
15	$AlCl_3$	PhCl	100	0.5	0
16	$FeCl_3$	PhCl	100	0.5	---[d]
17	$InCl_3$	PhCl	100	0.5	27
18	$Cu(OTf)_2$	PhCl	100	0.5	---[d]

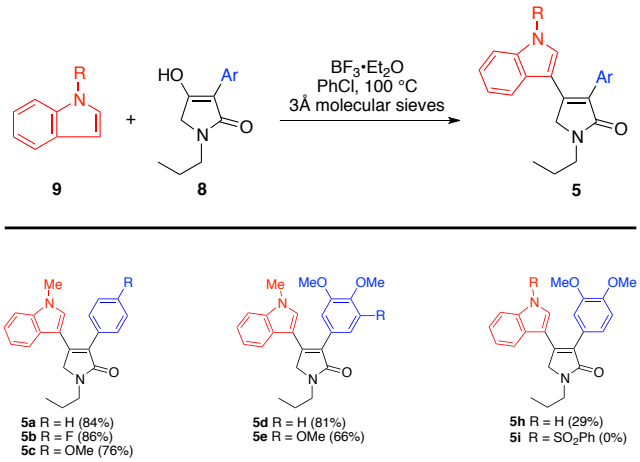
[a]0.40 mmol of **8c**, 0.48 mmol of *N*-methylindole (**9a**), and 0.60 mmol of Lewis acid used; [b]Estimated by using ratio of ring methylene signals (^{1}H NMR) of **5c** and **8c** averaged from at least two trials; [c]Using a 2.0 mmol scale, 11% isolated yield of **5c** was obtained; [d]NMR showed neither **8c** nor **5c**.

Using the best conditions from our screen, we next explored substrate scope (Scheme 3). We quickly found that PhMe was not suitable for larger scale reactions (perhaps due to solubility issues), so we used PhCl as the solvent moving forward (Table 1, Entry 10). Treatment of indoles **9** with tetramic acids **8** gave 3,4-diaryl-3-pyrrolin-2-ones **5**. The indolylation reaction

worked well with *N*-methylindole **9a**; on the other hand, a much lower yield was obtained with parent indole (**9b**) during the preparation of *N*-unsubstituted indole **5h**.

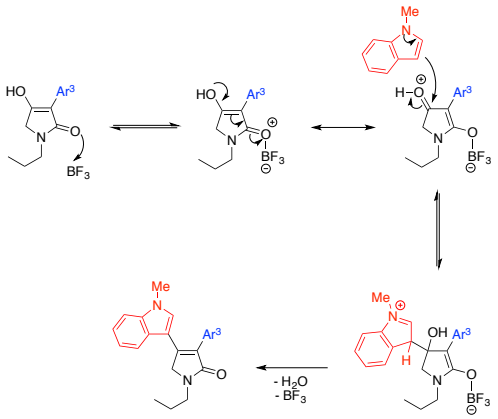
We also tried *N*-(phenylsulfonyl)indole **9c**[22] (R^1 = SO_2Ph) in the indolylation reaction and we did not observe any arylation product **5i** (Scheme 3); this result illustrates that electron-withdrawing groups on indole inhibit the reaction.

Scheme 3. Substrate Scope



A possible mechanism for this transformation is proposed (Scheme 4). Association of BF_3 with the lactam carbonyl promotes the condensation reaction between the tetramic acid and the indole. Loss of water and disassociation of the Lewis acid gives the product. Similar reactions involving indoles and cyclic ketones have been reported by others leading to 3-vinylindoles.[14]

Scheme 4. Possible Mechanism

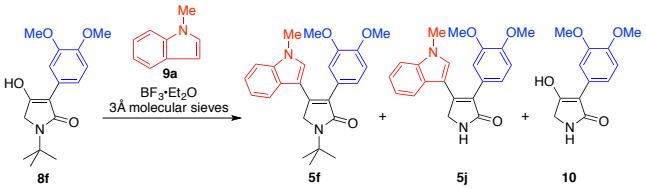


We examined the possibility of preparing *N*-unsubstituted 3-pyrrolin-2-ones. We hypothesized that *tert*-butyl substrate **8f** would undergo the indolylation reaction in a similar fashion to the propyl substrate **8e**, and then subsequently, the *tert*-butyl group of the corresponding indole product **5f** could be removed under acidic conditions (*e.g.*, treatment with TFA). In one of the early runs (Table 2, entry 1: PhCl, 100 °C, 0.5h), the indolylation of **8f** gave a mixture of products that included deprotected product **5j** (31% yield) and deprotected tetramic acid **10** (40% yield). We were pleased to see that the *tert*-butyl group was indeed removable. Subjecting tetramic acid **10** to the PhCl/100 °C reaction conditions did not give product **5j** suggesting that *N*-substitution of the tetramic acid is required for the indolylation to proceed. Under milder conditions (Table 2, entry 2: DCE, 65°C, 12h), the protected product **5f** was obtained in just 17% yield.

To improve upon these results, we next assessed the inherent stability of the *tert*-butyl group of **8f** in the presence of BF_3•Et_2O in PhCl at a range of different temperatures (70°C, 80°C, 90°C, 100°C, 110°C, 120°C). We found that the *tert*-butyl group of **8f** was relatively stable at 70°C and 80°C (only traces of **10** detected after 1h), whereas at higher temperatures, significant amounts of **10** could be detected after 1h in the crude reaction mixtures. Using this

information, we ran the indolylation of **8f** at 80°C followed by heating to 120°C to remove the *tert*-butyl group of the presumed intermediate product **5f**. In addition, to help the indolylation reaction compete with the deprotection, we used 5.0 equiv of **9a**. Under these conditions (Table 2, entry 3), we were able to obtain a 55% yield of **5j**. This result demonstrates that *N*-unprotected 3-pyrrolin-2-ones can be prepared from *tert*-butyl protected tetramic acid substrates.[23]

Table 2. *tert*-Butyl Substrate



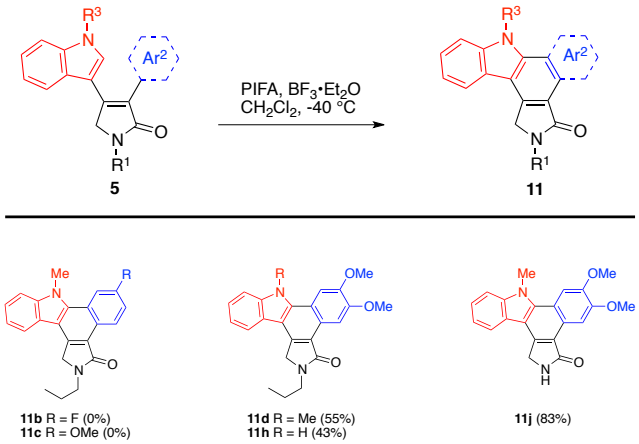
Entry	solvent	temp (°C)	time (h)	**5f** (%)[a]	**5j** (%)[a]	**10** (%)[a]
1	PhCl	100°C	0.5	0	31	40
2	DCE	65°C	12	17	0	---[b]
3[c]	PhCl	80°C/120°C[d]	3/1	---[b]	55	---[b]

[a]Isolated yield; [b]Not determined; [c]5.0 equiv of **9a** used; [d]After heating at 80°C for 3h, reaction mixture was heated to 120°C for 1h

We next turned our attention to preparing fused carbazoles. We recently reported the use of Scholl-type oxidative cyclization reactions to transform 3,4-diaryl-3-pyrrolin-2-ones into the corresponding dibenzo[*e,g*]isoindol-1-ones using the hypervalent iodine reagent, phenyliodine(III) bis(trifluoroacetate) (PIFA).[11c,24] Treatment of 4-indolylpyrrolones **5d**, **5h**, and **5j** with PIFA and BF_3•Et_2O gave the corresponding fused carbazoles **11d**, **11h**, and **11j** (Scheme 5). To our knowledge, these benzo[*a*]carbazoles **11** represent the first reported examples of simple benzo[*a*]pyrrolo[3,4-*c*]carbazol-3-ones. As we observed earlier,[11c] 3,4-dimethoxyphenyl groups are superior to 4-methoxyphenyl groups in promoting the oxidative cyclization. Neither

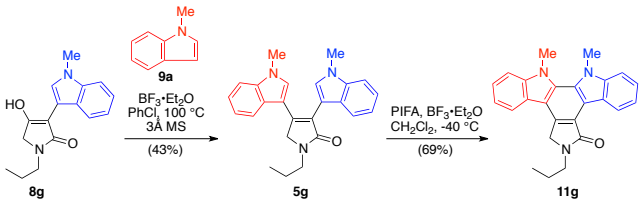
the 4-methoxyphenyl substrate **5c** nor the 4-fluorophenyl substrate **5b** yielded any of the corresponding benzo[*a*]carbazole products **11c** and **11b**.

Scheme 5. Synthesis of Benzo[*a*]carbazoles



Lastly, we applied our methodology to the preparation of the indolo[2,3-*a*]carbazole ring system (Scheme 6).[25] As mentioned earlier, we had tried to prepare tetramic acid **8g** using the same chemistry depicted in Scheme 2 but this failed. We managed to successfully prepare **8g** using an alternate two-step strategy starting from *N*-methylindole-3-acetic acid (see Supporting Information). Treatment of **8g** with **9a** and BF_3•Et_2O in PhCl gave bisindole **5g** in 43% yield. Subsequent oxidative cyclization of **5g** mediated by PIFA and BF_3•Et_2O gave indolo[2,3-*a*]carbazole **11g** in 69% yield. Overall, this result represents a relatively short and potentially flexible strategy to indolocarbazoles.[26]

Scheme 6. Synthesis of Indolo[2,3-*a*]carbazole



In conclusion, we have prepared indole-substituted 3-pyrrolin-2-ones using a direct arylation reaction between tetramic acids and simple indole substrates. The indole-substituted 3-pyrrolin-2-ones proved to be useful building blocks in the preparation of indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazoles and benzo[*a*]pyrrolo[3,4-*c*]carbazoles via Scholl-type oxidative cyclization reactions. The entire synthetic sequence involves only one chromatographic purification per final product and no precious metals or other costly reagents are required.

EXPERIMENTAL SECTION

General Methods.[11c]

General Method A for the Preparation of Ethyl *N*-Alkylglycinates 6.

A modification of a literature procedure was followed.[18b] To a rt stirred solution of primary amine (400. mmol) in ether (200 mL) was added ethyl bromoacetate (5.5 mL, 50. mmol) dropwise via syringe. The reaction mixture was stirred at rt for 24-48 h (as noted) during which time a white precipitate forms. The reaction mixture was filtered to remove precipitate. The organic layer was washed with an saturated solution of sodium bicarbonate (100 mL) and brine (200 mL) and dried over sodium sulfate. Removal of the solvent in vacuo gave the ethyl *N*-alkylglycinates **6** as colorless oils, which were used directly without further purification.

Ethyl *N*-Propylglycinate (6a).[18a]

Using **General Method A,** propylamine (23.6 g, 32.9 mL, 400. mmol), and a reaction time of 24 h gave the title compound **6a** as a colorless oil (6.99 g, 48.2 mmol, 96% yield): IR (ATR, neat) 3332, 1736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.19 (q, *J* = 7.2 Hz, 2H), 3.40 (s, 2H), 2.57 (t, *J* = 7.2 Hz, 2H), 1.73 (br s, 1H), 1.52 (sext, *J* = 7.2 Hz, 2H), 1.28 (t, *J* = 7.2 Hz, 3H), 0.93 (t, *J* = 7.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 61.0, 51.8, 51.3, 23.5, 14.5, 12.0 ppm.

Ethyl *N*-(*tert*-Butyl)glycinate (6b).[18c]

Using **General Method A,** *tert*-butylamine (46.8 g, 67.3 mL, 640. mmol), and a reaction time of 48 h gave the title compound **6b** as a colorless oil (11.53 g, 72.41 mmol, 91% yield): IR (ATR, neat) 3330, 1737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.19 (q, *J* = 7.2 Hz, 2H), 3.39 (s, 2H), 1.59 (br s, 1H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.10 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 61.1, 50.5, 45.2, 29.1, 14.5 ppm.

General Method B for the Preparation of Methyl Arylacetates 7.

To a rt stirred solution of an arylacetic acid (100. mmol) in MeOH (200 mL) was added concentrated H_2SO_4 (5.30 mL, 100. mmol) dropwise. The reaction mixture was heated to reflux for 1-24 h (as noted) and then cooled to 0 °C with the aid of an external ice bath. An aqueous solution of saturated $NaHCO_3$ (100 mL) was added to the reaction mixture dropwise via an addition funnel. The bulk of the MeOH was then removed in vacuo and the residue was extracted with ether (2 x 200 mL). The combined organics were dried over Na_2SO_4. Removal of the solvent in vacuo gave the methyl arylacetates **7**, which were used directly without further purification.

Methyl 2-Phenylacetate (7a).[19c]

Using **General Method B**, phenylacetic acid (10.00 g, 73.45 mmol), and a reaction time of 16 h gave the title compound **7a** as a colorless oil (10.40 g, 69.25 mmol, 94% yield): R_f = 0.80 (1:2 EtOAc/petroleum ether); IR (ATR, neat) 1733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25-7.36 (m, 5H), 3.70 (s, 3H), 3.63 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 134.2, 129.5, 128.9, 127.4, 52.4, 41.5 ppm.

Methyl 2-(4'-Fluorophenyl)acetate (7b).[19e]

Using **General Method B**, 2-(4'-fluorophenyl)acetic acid (10.0 g, 64.9 mmol), and a reaction time of 1.5 h gave the title compound **7b** as a colorless oil (8.77 g, 52.1 mmol, 80% yield): R_f = 0.84 (1:1 EtOAc/petroleum ether); IR (ATR, neat) 1734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.22-7.26 (m, 2H), 6.98-7.04 (m, 2H), 3.70 (s, 3H), 3.60 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2 (d, J = 1.3 Hz), 162.3 (d, J = 244 Hz), 131.1 (d, J = 7.8 Hz), 129.9 (d, J = 3.4 Hz), 115.7 (d, J = 21 Hz), 52.4, 40.6 ppm.

Methyl 2-(3',4'-Dimethoxyphenyl)acetate (7d).[19]

Using **General Method B**, 2-(3',4'-dimethoxyphenyl)acetic acid (5.00 g, 25.5 mmol), and a reaction time of 23 h gave the title compound **7d** as a light yellow oil (4.91 g, 23.4 mmol, 92% yield): R_f = 0.44 (1:2 EtOAc/petroleum ether); IR (ATR, neat) 1732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.82 (s, 3H), 3.88 (s, 3H), 3.87 (s, 3H), 3.70 (s, 3H), 3.57 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 149.2, 148.4, 126.7, 121.7, 112.6, 111.5, 56.2, 56.1, 52.3, 41.0 ppm.

Methyl 2-(2',3',4'-Trimethoxyphenyl)acetate (7e).[19a]

Using **General Method B**, 2-(2',3',4'-dimethoxyphenyl)acetic acid (5.00 g, 22.1 mmol), and a reaction time of 23 h gave the title compound **7d** as a light yellow amorphous solid (4.362 g, 18.16 mmol, 82% yield): mp 35-38 °C (lit.[19a] mp 40.5-41.5 °C); R_f = 0.38 (1:2 EtOAc/petroleum ether); IR (ATR, neat) 1734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.50 (s, 2H), 3.86 (s, 6H), 3.83 (s, 3H), 3.71 (s, 3H), 3.56 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 153.5, 137.3, 129.8, 106.5, 61.1, 56.4, 52.4, 41.7 ppm.

Methyl 1-Methylindole-3-acetate (7g).[19b]

Using a modification of **General Method B** (3 equivalents of H_2SO_4 and room temperature), 1-methylindole-3-acetic acid (3.00 g, 15.9 mmol), and a reaction time of 1 h gave the title compound **7g** as a reddish-brown oil (2.50 g, 12.3 mmol, 77% yield): R_f = 0.60 (1:2 EtOAc/petroleum ether); IR (ATR, neat) 1731, 1616 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.59-7.61 (m, 1H), 7.29-7.32 (m, 1H), 7.22-7.26 (m, 1H), 7.11-7.15 (m, 1H), 7.05 (s, 1H), 3.78 (d, J = 0.8 Hz, 2H), 3.77 (s, 3H), 3.70 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 137.1, 128.0, 127.9, 122.0, 119.4, 119.2, 109.5, 107.0, 52.2, 32.9, 31.3 ppm.

General Method C for the Preparation of 3-Aryltetramic Acids 8.

A modification of a literature procedure by Le Gall and co-workers was followed.[16] To a rt stirred mixture of ethyl *N*-alkylglycinates **6** (30.0 mmol) and methyl arylacetates **7** (30.0 mmol) in THF (150 mL) was added solid *t*-BuOK (4.04 g, 36.0 mmol). The reaction mixture was heated to reflux for 2-24 h as noted. The reaction mixture was then cooled to 0 °C (with the aid of an external ice bath) and treated with an aqueous solution of $KHSO_4$ (1.0 M, 120 mL)

dropwise via addition funnel. After stirring the biphasic mixture for 15 min, the bulk of the THF was removed in vacuo. The resulting residue was extracted with EtOAc (4 x 100 mL).* The combined EtOAc layers were washed with brine (400 mL) and dried over sodium sulfate. The EtOAc layer was concentrated to approximately half the original volume and then placed in a refrigerator. The precipitate that formed was collected by filtration. The concentration/filtration sequence was repeated with the mother liquor 2-3 times and additional precipitate collected. The combined precipitated solids were dried in vacuo giving 3-aryltetramic acids as white (or close to white) powders, which were used without further purification. *In some cases, treatment of the aqueous residue with EtOAc gave a precipitate which turned out to be the desired product; filtration before the drying step then gave an additional crop of product.

4-Hydroxy-3-phenyl-1-propyl-1*H*-pyrrol-2(5*H*)-one (8a).

Using **General Method C**, amine **6a** (4.36 g, 30.0 mmol), ester **7a** (4.51 g, 30.0 mmol), and a reaction time of 11 h gave the title compound **8a** as a white powder (5.18 g, 23.8 mmol, 79% yield): mp 217-222 °C; R_f = 0.38 (2:1 EtOAc/petroleum ether); IR (ATR, neat) 1661, 1584 cm^{-1}; ^1H NMR (400 MHz, D_6-DMSO) δ 11.61 (br s, 1H), 7.97 (dd, *J* = 1.0, 8.4 Hz, 2H), 7.27-7.32 (m, 2H), 7.12-7.16 (m, 1H), 3.93 (s, 2H), 3.28 (t, *J* = 7.2 Hz, 2H), 1.51 (sext, *J* = 7.2 Hz, 2H), 0.85 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, D_6-DMSO) δ 170.8, 166.6, 132.5, 127.7, 126.7, 125.4, 102.9, 48.9, 42.5, 21.3, 11.3 ppm; HRMS (ESI-FTICR) calcd for $C_{13}H_{15}NO_2$•Na 240.0995, found 240.0996.

3-(4'-Fluorophenyl)-4-Hydroxy-1-propyl-1*H*-pyrrol-2(5*H*)-one (8b).

Using **General Method C**, amine **6a** (2.90 g, 20.0 mmol), ester **7b** (3.36 g, 20.0 mmol), and a reaction time of 18 h gave the title compound **8b** as a white powder (2.95 g, 12.5 mmol, 65% yield): mp 220-225 °C; R_f = 0.31 (2:1 EtOAc/petroleum ether); IR (ATR, neat) 1663, 1581, 1560 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 11.71 (br s, 1H), 8.02-8.06 (m, 2H), 7.12-7.17 (m, 2H), 3.93 (s, 2H), 3.28 (t, *J* = 7.2 Hz, 2H), 1.51 (sext, *J* = 7.2 Hz, 2H), 0.84 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 166.4 (d, *J* = 1.4 Hz), 160.0 (d, *J* = 241 Hz), 129.0 (d, *J* = 3.1 Hz), 128.4 (d, *J* = 7.6 Hz), 114.5 (d, *J* = 21.6 Hz), 102.0, 48.9, 42.5, 21.2, 11.3 ppm; HRMS (ESI-FTICR) calcd for $C_{13}H_{14}FNO_2$•Na 258.0901, found 258.0902.

4-Hydroxy-3-(4'-methoxyphenyl)-1-propyl-1*H*-pyrrol-2(5*H*)-one (8c).

Using **General Method C**, amine **6a** (2.18 g, 15.0 mmol), commercially available methyl 2-(4'-methoxyphenyl)acetate (**7c**) (2.70 g, 15.0 mmol), and a reaction time of 6 h gave the title compound **8c** as a white powder (1.97 g, 7.97 mmol, 53% yield): mp 212-220 °C; R_f = 0.35 (2:1 EtOAc/petroleum ether); IR (ATR, neat) 1663, 1582 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 11.40 (br s, 1H), 7.92 (d, *J* = 9.2 Hz, 2H), 6.89 (d, *J* = 9.2 Hz, 2H), 3.90 (s, 2H), 3.74 (s, 3H), 3.27 (t, *J* = 7.2 Hz, 2H), 1.50 (sext, *J* = 7.2 Hz, 2H), 0.84 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 165.0, 157.0, 127.8, 125.0, 113.1, 102.7, 54.9, 48.9, 42.5, 21.3, 11.3 ppm; HRMS (ESI-FTICR) calcd for $C_{14}H_{17}NO_3$•Na 270.1101, found 270.1102.

4-Hydroxy-3-(3',4'-dimethoxyphenyl)-1-propyl-1*H*-pyrrol-2(5*H*)-one (8d).

Using **General Method C**, amine **6a** (2.90 g, 20.0 mmol), ester **7d** (4.20 g, 20.0 mmol), and a reaction time of 18 h gave the title compound **8d** as a light yellow powder (3.00 g, 10.8 mmol, 54% yield): mp 204-210 °C; R_f = 0.18 (2:1 EtOAc/petroleum ether); IR (ATR, neat) 1660, 1582

cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.42 (br s, 1H), 7.72 (d, *J* = 2.0 Hz, 1H), 7.55 (dd, *J* = 2.0, 8.4 Hz, 1H), 6.91 (d, *J* = 8.4 Hz, 1H), 3.90 (s, 2H), 3.74 (s, 3H), 3.28 (t, *J* = 7.2 Hz, 2H), 1.51 (sext, *J* = 7.2 Hz, 2H), 0.85 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 165.1, 147.9, 146.7, 125.4, 119.4, 111.4, 110.6, 102.7, 55.4, 55.3, 48.8, 42.5, 21.3, 11.3 ppm; HRMS (ESI-FTICR) calcd for $C_{15}H_{19}NO_4$•Na 300.1206, found 300.1207.

4-Hydroxy-3-(3',4',5'-trimethoxyphenyl)-1-propyl-1*H*-pyrrol-2(5*H*)-one (8e).

Using **General Method C**, amine **6a** (2.91 g, 20.0 mmol), ester **7e** (4.81 g, 10.0 mmol), and a reaction time of 24 h gave the title compound **8e** as an off-white powder (2.58 g, 8.39 mmol, 42% yield): mp 190-196 °C; R_f = 0.15 (2:1 EtOAc/petroleum ether); IR (ATR, neat) 1662, 1590 cm^{-1}; ^{1}H NMR (400 MHz, D_6-DMSO) δ 11.67 (br s, 1H), 7.42 (s, 2H), 3.92 (s, 2H), 3.74 (s, 6H), 3.65 (s, 3H), 3.28 (t, *J* = 7.2 Hz, 2H), 1.51 (sext, *J* = 7.2 Hz, 2H), 0.84 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 166.4, 152.2, 135.5, 128.2, 104.2, 102.5, 60.0, 55.6, 48.9, 42.5, 21.3, 11.3 ppm; HRMS (ESI-FTICR) calcd for $C_{16}H_{21}NO_5$•Na 330.1312, found 330.1312.

1-(*tert*-Butyl)-4-hydroxy-3-(3',4'-dimethoxyphenyl)-1*H*-pyrrol-2(5*H*)-one (8f).

Using **General Method C**, amine **6b** (2.99 g, 18.8 mmol), ester **7d** (3.95 g, 18.8 mmol), and a reaction time of 22 h gave the title compound **8f** as a white fluffy powder (2.90 g, 9.95 mmol, 53% yield): mp 218-223 °C; R_f = 0.37 (2:1 EtOAc/petroleum ether); IR (ATR, neat) 1677, 1591 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.25 (br s, 1H), 7.68 (d, *J* = 2.0 Hz, 1H), 7.50 (dd, *J* = 2.0, 8.8 Hz, 1H), 6.89 (d, *J* = 8.8 Hz, 1H), 3.95 (s, 2H), 3.73 (s, 3H), 3.72 (s, 3H), 1.39 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 164.5, 147.8, 146.7, 125.4, 119.6, 111.3, 110.7, 103.9,

55.4, 55.3, 52.7, 47.2, 27.7 ppm; HRMS (ESI-FTICR) calcd for $C_{16}H_{21}NO_4$•Na 314.1363, found 314.1364.

General Method D for the Preparation of 3-Aryl-4-(indol-3'-yl)-3-pyrrolin-2-ones 5.

To a rt stirred mixture of tetramic acid **8** (2.00 mmol) and *N*-methylindole **9a** or indole **9b** (2.40 mmol) in PhCl (20 mL) was added 3Å molecular sieves (1.0 g) followed by BF_3•Et_2O (0.43 g, 0.37 mL, 3.0 mmol). The reaction mixture was heated to 100 °C for 0.5 h to 1.5 h (as noted) and then allowed to cool to rt and treated with MeOH (20 mL). The reaction mixture was decanted to remove the molecular sieves and the solvent was removed in vacuo. The residue was treated with CH_2Cl_2 (20 mL) and silica gel (2.0 g) and the solvent was removed in vacuo (dry load). Purification by flash chromatography (EtOAc/petroleum ether gradient) gave the desired products as lightly colored amorphous solids.

4-(1"-Methylindol-3"-yl)- 3-phenyl-1-propyl-1*H*-pyrrol-2(5*H*)-one (5a).

Using **General Method D**, tetramic acid **8a** (0.500 g, 2.30 mmol), *N*-methylindole (**9a**) (0.429 g, 3.27 mmol), and a reaction time of 1 h gave the title compound **5a** as a light yellow amorphous solid (0.640 g, 1.94 mmol, 84% yield): mp 43-47 °C; R_f = 0.44 (1:1 EtOAc/petroleum ether); IR (ATR, neat) 1660, 1597, 1571 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49-7.52 (m, 2H), 7.29-7.36 (m, 4H), 7.16-7.24 (m, 2H), 7.09 (s, 1H), 7.00-7.04 (m, 1H), 4.46 (s, 2H), 3.73 (s, 3H), 3.57 (t, *J* = 7.2 Hz, 2H), 1.74 (sext, *J* = 7.2 Hz, 2H), 1.01 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 143.2, 137.3, 133.9, 129.8, 129.6, 128.6, 128.5, 127.8, 125.7, 122.6, 121.3, 120.7, 110.0, 109.1, 53.4, 44.4, 33.4, 22.3, 11.8 ppm; HRMS (ESI-FTICR) calcd for $C_{22}H_{22}N_2O$•Na 353.1624, found 353.1624.

3-(4'-Fluorophenyl)-4-(1"-methylindol-3"-yl)-1-propyl-1*H*-pyrrol-2(5*H*)-one (5b).

Using **General Method D**, tetramic acid **8b** (0.500 g, 2.13 mmol), *N*-methylindole (**9a**) (0.335 g, 2.55 mmol), and a reaction time of 1 h gave the title compound **5b** as a light yellow amorphous solid (0.638 g, 1.83 mmol, 86% yield): mp 60-63 °C; R_f = 0.44 (1:1 EtOAc/petroleum ether); IR (ATR, neat) 1735, 1661, 1599, 1571 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47-7.52 (m, 2H), 7.31-7.33 (m, 1H), 7.21-7.25 (m, 1H), 7.11-7.13 (m, 1H), 7.10 (s, 1H), 6.98-7.04 (m, 3H), 4.43 (s, 2H), 3.76 (s, 3H), 3.56 (t, *J* = 7.2 Hz, 2H), 1.73 (sext, *J* = 7.2 Hz, 2H), 1.0 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 162.5 (d, *J* = 246 Hz), 143.2, 137.4, 131.6 (d, *J* = 7.9 Hz), 129.8 (d, *J* = 3.4 Hz), 129.4, 127.5, 125.5, 122.7, 121.3, 120.8, 115.6 (d, *J* = 21.3 Hz), 110.0, 109.0, 53.4, 44.4, 33.5, 22.3, 11.7 ppm; HRMS (ESI-FTICR) calcd for $C_{22}H_{21}FN_2O$•Na 371.1530, found 371.1530.

3-(4'-Methoxyphenyl)-4-(1"-Methylindol-3"-yl)-1-propyl-1*H*-pyrrol-2(5*H*)-one (5c).

Using **General Method D**, tetramic acid **8c** (1.00 g, 4.04 mmol), *N*-methylindole (**9a**) (0.636 g, 4.85 mmol), and a reaction time of 1 h gave the title compound **5c** as a yellow powder (1.11 g, 3.08 mmol, 76% yield): mp 132-133 °C; R_f = 0.36 (2:1 EtOAc/petroleum ether); IR (ATR, neat) 1663, 1605 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.8 Hz, 2H), 7.30-7.33 (m, 1H), 7.20-7.24 (m, 2H), 7.12 (s, 1H), 7.01-7.05 (m, 1H), 6.87 (d, *J* = 8.8 Hz, 2H), 4.43 (s, 2H), 3.82 (s, 3H), 3.74 (s, 3H), 3.56 (t, *J* = 7.2 Hz, 2H), 1.72 (sext, *J* = 7.2 Hz, 2H), 1.00 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 159.3, 142.1, 137.3, 131.0, 129.4, 128.1, 126.3, 125.8, 122.5, 121.4, 120.7, 114.1, 110.0, 109.3, 55.5, 53.4, 44.4, 33.4, 22.3, 11.8 ppm; HRMS (ESI-FTICR) calcd for $C_{23}H_{24}N_2O_2$•Na 383.1730, found 383.1728.

3-(3',4'-Dimethoxyphenyl)-4-(1"-methylindol-3"-yl)-1-propyl-1*H*-pyrrol-2(5*H*)-one (5d). Using **General Method D**, tetramic acid **8d** (0.150 g, 0.541 mmol), *N*-methylindole (**9a**) (0.085 g, 0.65 mmol), and a reaction time of 1 h gave the title compound **5d** as a yellow amorphous solid (0.172 g, 0.440 mmol, 81% yield): mp 66-69 °C; R_f = 0.35 (2:1 EtOAc/petroleum ether); IR (ATR, neat) 1654, 1604 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30-7.33 (m, 1H), 7.18-7.25 (m, 2H), 7.08-7.14 (m, 3H), 7.02-7.06 (m, 1H), 6.83 (d, *J* = 9.2 Hz, 1H), 4.43 (s, 2H), 3.88 (s, 3H), 3.75 (s, 3H), 3.70 (s, 3H), 3.56 (t, *J* = 7.2 Hz, 2H), 1.73 (sext, *J* = 7.2 Hz, 2H), 1.00 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 148.9, 148.8, 143.0, 137.3, 129.5, 128.0, 126.5, 125.7, 122.6, 122.5, 121.5, 120.8, 112.9, 111.4, 110.0, 109.3, 56.1, 56.0, 55.4, 44.4, 33.4, 22.3, 11.8 ppm; HRMS (ESI-FTICR) calcd for $C_{24}H_{26}N_2O_3$•Na 413.1836, found 413.1834.

3-(3',4',5'-Trimethoxyphenyl)-4-(1"-methylindol-3"-yl)-1-propyl-1*H*-pyrrol-2(5*H*)-one (5e). Using **General Method D**, tetramic acid **8e** (0.250 g, 0.813 mmol), *N*-methylindole (**9a**) (0.128 g, 0.976 mmol), and a reaction time of 1 h gave the title compound **5e** as a white film (0.224 g, 0.533 mmol, 66% yield): mp 45-50 °C; R_f = 0.26 (2:1 EtOAc/petroleum ether); IR (ATR, neat) 1660, 1620, 1578 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30-7.33 (m, 1H), 7.17-7.25 (m, 2H), 7.15 (s, 1H), 7.03-7.07 (m, 1H), 6.78 (s, 2H), 4.46 (s, 2H), 3.85 (s, 3H), 3.76 (s, 3H), 3.66 (s, 6H), 3.57 (t, *J* = 7.2 Hz, 2H), 1.73 (sext, *J* = 7.2 Hz, 2H), 1.01 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 153.4, 143.0, 137.8, 137.3, 129.7, 129.2, 127.8, 125.5, 122.7, 121.5, 120.9, 110.0, 109.0, 107.0, 61.1, 56.2, 53.3, 44.4, 33.5, 22.3, 11.7 ppm; HRMS (ESI-FTICR) calcd for $C_{25}H_{28}N_2O_4$•Na 443.1941, found 443.1938.

3-(3',4'-Dimethoxyphenyl)-4-(indol-3"-yl)-1-propyl-1*H*-pyrrol-2(5*H*)-one (5h).

Using **General Method D**, tetramic acid **8d** (0.500 g, 1.80 mmol), indole (**9b**) (0.634 g, 5.41 mmol), and a reaction time of 1.5 h gave the title compound **5h** as a light yellow amorphous solid (0.195 g, 0.518 mmol, 29% yield): mp 184-187 °C; R_f = 0.27 (2:1 EtOAc/petroleum ether); IR (ATR, neat) 3351, 3230, 1731, 1647, 1603 cm^{-1}; ^1H NMR (400 MHz, D_6-DMSO) δ 11.54 (br s, 1H), 7.59 (d, *J* = 2.8 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 1H), 7.04-7.09 (m, 1H), 7.01 (dd, *J* = 2.0, 8.4 Hz, 1H), 6.81-6.93 (m, 4H), 4.49 (s, 2H), 3.74 (s, 3H), 3.43 (m, 2H), 3.33 (s, 3H), 1.64 (sext, *J* = 7.2 Hz, 2H), 0.91 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, D_6-DMSO) δ 170.4, 148.02, 148.01, 143.2, 136.4, 126.4, 126.2, 126.0, 124.1, 121.8, 121.7, 120.8, 119.6, 113.0, 111.9, 111.4, 109.0, 55.4, 55.0, 52.5, 43.4, 21.4, 11.4 ppm; HRMS (ESI-FTICR) calcd for $C_{23}H_{24}N_2O_3$•Na 399.1679, found 399.1677.

1-(*tert*-Butyl)-3-(3',4'-dimethoxyphenyl)-4-(1"-methylindol-3"-yl)--1*H*-pyrrol-2(5*H*)-one (5f).

Using a modification of **General Method D** (solvent = DCE; reaction temperature = 65 °C), tetramic acid **8f** (0.200 g, 0.686 mmol), *N*-methylindole (**9a**) (0.108 g, 0.824 mmol), and a reaction time of 12 h gave the title compound as an off-white amorphous solid (46 mg, 0.11 mmol, 17% yield): mp 141-145 °C; R_f = 0.50 (2:1 EtOAc/petroleum ether); IR (ATR, neat) 1654, 1602 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28-7.32 (m, 1H), 7.19-7.24 (m, 1H), 7.15-7.17 (m, 1H), 7.13 (s, 1H), 7.06-7.11 (m, 2H), 7.00-7.04 (m, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 4.47 (s, 2H), 3.87 (s, 3H), 3.75 (s, 3H), 3.68 (s, 3H), 1.58 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 148.9, 148.7, 141.6, 137.3, 129.35, 129.30, 126.4, 125.6, 122.7, 122.5, 121.6, 120.7,

113.0, 111.4, 109.9, 109.3, 56.14, 56.08, 54.3, 51.7, 33.4, 28.4 ppm; HRMS (ESI-FTICR) calcd for $C_{25}H_{28}N_2O_3$•Na 427.1992, found 427.1989.

3-(3',4'-Dimethoxyphenyl)-4-(1"-methylindol-3"-yl)-1*H*-pyrrol-2(5*H*)-one (5j).

Using **General Method D**, tetramic acid **8f** (0.500 g, 1.72 mmol), *N*-methylindole (**9a**) (0.270 g, 2.06 mmol), and a reaction time of 0.5 h gave the title compound **5j** as a light yellow amorphous solid (0.814 g, 0.528 mmol, 31% yield). Trituration (CH_2Cl_2/pentane) gave an analytical sample of **5j** as an off-white powder: mp 83-86 °C; R_f = 0.30 (1:9 MeOH/EtOAc); IR (ATR, neat) 3214, 1731, 1660, 1600 cm^{-1}; ^1H NMR (400 MHz, D_6-DMSO) δ 8.23 (br s, 1H), 7.65 (s, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.10-7.14 (m, 1H), 6.99 (dd, *J* = 2.0, 8.4 Hz, 1H), 6.93 (d, *J* = 2.0 Hz, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), 6.82-6.86 (m, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 4.35 (d, *J* = 1.2 Hz, 2H), 3.79 (s, 3H), 3.74 (s, 3H), 3.42 (s, 3H) D ppm; ^{13}C NMR (100 MHz, D_6-DMSO) δ 173.3, 148.01, 147.95, 144.8, 137.0, 130.3, 126.3, 126.0, 124.4, 121.9, 121.7, 121.0, 119.7, 113.1, 111.4, 110.1, 108.5, 55.4, 55.1, 47.9, 32.8 ppm; HRMS (ESI-FTICR) calcd for $C_{21}H_{20}N_2O_3$•Na 371.1366, found 371.1366. In a subsequent experiment using **General Method D**, tetramic acid **8f** (57 mg, 0.20 mmol), *N*-methylindole (**9a**) (131 mg, 1.00 mmol), in PhCl (5 mL) with heating at 80°C for 3h followed by heating at 120°C for 1h, the title compound **5j** (39. mg, 0.11 mmol) was obtained in 55% yield.

3-(3,4-Dimethoxyphenyl)-4-hydroxy-1*H*-pyrrol-2(5*H*)-one (10).

Using **General Method D**, tetramic acid **8f** (0.500 g, 1.72 mmol), *N*-methylindole (**9a**) (0.270 g, 2.06 mmol), and a reaction time of 0.5 h gave the title compound **10** (after elution of **5j**) as a white amorphous solid (0.164 g, 0.697 mmol, 40% yield): mp 234-237 (dec) °C; R_f = 0.25 (1:9

MeOH/EtOAc); IR (ATR, neat) 3349, 1666, 1613, 1602, 1582 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 11.38 (br s, 1H), 7.70 (d, *J* = 2.0 Hz, 1H), 7.55 (dd, *J* = 2.0, 8.6 Hz, 1H), 7.41 (br s, 1H), 6.90 (d, *J* = 8.6 Hz, 1H), 3.83 (d, *J* = 0.8 Hz, 2H), 3.73 (s, 3H), 3.72 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 167.4, 147.9, 146.7, 125.4, 119.5, 111.3, 110.7, 102.9, 55.4, 55.3, 44.7 ppm; HRMS (ESI-FTICR) calcd for $C_{12}H_{13}NO_4$•Na 258.0737, found 258.0739.

General Method E for the Oxidative Cyclization to Fused Carbazoles 11.

A modification of a literature procedure was followed.[11c] A mixture of 3-pyrrolin-2-one **5** (0.20 mmol) and phenyliodine(III) bis(trifluoroacetate) (PIFA) (95 mg, 0.22 mmol) in CH_2Cl_2 (10 mL) in 20 mL vial with a septum-style cap was cooled to -40 °C using an external cooling bath (acetonitrile/dry ice). To the cooled reaction mixture was added BF_3•Et_2O dropwise via syringe. The reaction mixture was stirred at -40 °C for 3.5-4 h (as noted). The bulk of the solvent was then removed and the crude residue was treated with EtOH (10 mL) and the solution was transferred to a centrifuge tube and placed in a freezer (-20 °C) until a product precipitated. Centrifugation, decantation of the solvent, and drying in vacuo gave the desired products as colored powders.

1,2-Dihydro-5,6-dimethoxy-8-methyl-2-propylbenzo[*a*]pyrrolo[3,4-*c*]carbazol-3(8*H*)-one (11d).

Using **General Method E**, 3-pyrrolin-2-one **5d** (0.100 g, 0.256 mmol), and a reaction time of 3.5 h gave title compound **11d** as a pink powder (54.6 mg, 0.141 mmol, 55% yield): mp 205-210 °C; R_f = 0.63 (2:1 EtOAc/petroleum ether); IR (ATR, neat) 1661, 1629, 1578 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.88 (s, 1H), 8.15 (s, 1H), 8.00 (d, *J* = 7.6 Hz, 1H), 7.83 (d, *J* = 8.4 Hz,

1H), 7.51-7.55 (m, 1H), 7.32-7.36 (m, 1H), 4.87 (s, 2H), 4.43 (s, 3H), 4.04 (s, 3H), 3.95 (s, 3H), 3.59 (t, J = 7.2 Hz, 2H), 1.75 (sext, J = 7.2 Hz, 2H), 0.94 (t, J = 7.2 Hz 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 148.9, 147.9, 140.6, 136.7, 136.2, 124.7, 124.4, 121.1, 120.7, 120.1, 116.7, 116.3, 111.7, 110.0, 103.5, 103.4, 55.3, 55.2, 48.5, 43.3, 33.6, 21.4, 11.4 ppm; HRMS (ESI-FTICR) calcd for $C_{24}H_{24}N_2O_3$•Na 411.1679, found 411.1679.

1,2-Dihydro-5,6-dimethoxy-2-propylbenzo[*a*]pyrrolo[3,4-*c*]carbazol-3(8*H*)-one (11h).

Using **General Method E**, 3-pyrrolin-2-one **5h** (0.116 g, 0.310 mmol), and a reaction time of 4 h gave title compound **11h** as a light brown powder (49.9 mg, 0.133 mmol, 43% yield): mp 179-184 °C; R_f = 0.52 (2:1 EtOAc/petroleum ether); IR (ATR, neat) 3302, 1630, 1584 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.36 (br s, 1H), 8.74 (s, 1H), 8.07 (s, 1H), 8.03 (d, J = 7.6 Hz, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.43-7.48 (m, 1H), 7.27-7.32 (m, 1H), 4.96 (s, 2H), 4.01 (s, 3H), 3.94 (s, 3H), 3.61 (t, J = 7.2 Hz, 2H), 1.75 (sext, J = 7.2 Hz, 2H), 0.94 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 149.5, 148.6, 138.9, 137.4, 136.5, 124.7, 123.2, 122.3, 120.9, 119.9, 116.5, 115.5, 111.4, 111.0, 103.5, 102.6, 55.6, 55.3, 48.6, 43.3, 21.4, 11.4 ppm; HRMS (ESI-FTICR) calcd for $C_{23}H_{22}N_2O_3$•Na 397.1523, found 397.1523.

1,2-Dihydro-5,6-dimethoxy-8-methylbenzo[*a*]pyrrolo[3,4-*c*]carbazol-3(8*H*)-one (11j).

Using **General Method E**, 3-pyrrolin-2-one **5j** (59 mg, 0.17 mmol), and a reaction time of 3.5 h gave title compound **11j** as a brown powder (49 mg, 0.14 mmol, 83% yield): mp >300 °C; R_f = 0.35 (2:1 EtOAc/petroleum ether); IR (ATR, neat) 3382, 1663, 1630, 1579 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (s, 1H), 8.53 (br s, 1H), 8.20 (s, 1H), 7.99 (d, J = 7.6 Hz, 1H), 7.85 (d, J = 8.4 Hz, 1H), 7.50-7.55 (m, 1H), 7.31-7.35 (m, 1H), 4.83 (s, 2H), 4.47 (s, 3H), 4.05 (s, 3H), 3.94

(s, 3H) ppm; ^{13}C NMR (100 MHz, D_6-DMSO) δ 172.3, 148.8, 147.8, 140.5, 138.6, 136.8, 124.6, 121.2, 120.6, 120.0, 116.6, 116.2, 111.8, 109.9, 103.5, 103.2, 55.24, 55.21, 43.9, 33.5 (*missing one peak*) ppm; HRMS (ESI-FTICR) calcd for $C_{21}H_{18}N_2O_3$•Na 369.1210, found 369.1210.

Ethyl 2-(2-(1-Methyl-1*H*-indol-3-yl)-*N*-propylacetamido)acetate (i).

To a rt stirred mixture of commercially available *N*-methylindole-3-acetic acid (3.00 g, 15.9 mmol) and DCC (3.94 g, 19.1 mmol) in CH_2Cl_2 was added amine **6a** (2.53 g, 17.4 mmol) and DMAP (0.194 g, 1.59 mmol). The reaction mixture was stirred at rt for 2.5 h and then the precipitate which formed was removed by filtration (twice). The solution was treated with an aqueous solution of $KHSO_4$ (1.0 M, 100 mL) and the organic layer was separated. The aqueous layer was re-extracted with CH_2Cl_2 (100 mL). The combined organic layers were washed with brine (200 mL) and dried over Na_2SO_4. Removal of the solvent in vacuo gave a crude brown oil (5.4 g) which was purified by flash chromatography (EtOAc/petroleum ether gradient). Fractions containing product were filtered (traces of DCU) and the solvent was removed in vacuo to give the title compound **i** as a pink oil (2.99 g, 9.45 mmol, 60% yield). Upon standing at rt for a week, the oil solidified into a light pink powder: mp 47-49 °C; R_f = 0.47 (1:1 EtOAc/petroleum ether); IR (ATR, neat) 1745, 1636 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (*mixture of rotamers*) 7.55-7.58 (m, 1H), 7.27-7.31 (m, 1H), 7.21-7.25 (m, 1H), 7.09-7.14 (m, 1H), 6.97 and 7.14 (s, 1H), 4.10-4.26 (m, 2H), 4.03 and 4.09 (s, 2H), 3.86 (d, *J* = 0.8 Hz, 2H), 3.75 and 3.77 (s, 3H), 3.31-3.35 (m, 2H), 1.51-1.56 (m, 2H), 1.20-1.30 (m, 3H), 0.84-0.89 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ (*major rotamer*) 172.3, 169.80, 137.1, 127.9, 127.7, 121.9, 119.2, 118.8, 109.5, 107.7, 61.3, 51.5, 47.9, 33.00, 30.8, 22.3, 14.4, 11.4 ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ (*minor rotamer*) 172.0, 169.83, 127.8, 127.6, 122.0, 119.4, 119.0, 110.3,

109.4, 107.4, 61.7, 50.4, 49.5, 32.97, 31.7, 20.9, 14.3, 11.6 ppm HRMS (ESI-FTICR) calcd for $C_{18}H_{24}N_2O_3$•Na 339.1679, found 339.1678.

1-(*tert*-Butyl)-4-hydroxy-3-(1'-methylindol-3'-yl)-1*H*-pyrrol-2(5*H*)-one (8g).

Using **General Method C**, amide **i** (3.46 g, 10.9 mmol), and a reaction time of 2 h gave the title compound **8g** as a white powder (2.445 g, 9.045 mmol, 83% yield): mp 220-228 °C; R_f = 0.31 (2:1 EtOAc/petroleum ether); IR (ATR, neat) 1682, 1595 cm^{-1}; ^1H NMR (400 MHz, D_6-DMSO) δ 10.94 (br s, 1H), 7.95-7.98 (m, 1H), 7.62 (s, 1H), 7.36-7.39 (m, 1H), 7.10-7.14 (m, 1H), 6.97-7.01 (m, 1H), 3.95 (s, 2H), 3.78 (s, 3H), 3.31 (t, *J* = 7.2 Hz, 2H), 1.53 (sext, *J* = 7.2 Hz, 2H), 0.87 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, D_6-DMSO) δ 171.5, 162.1, 136.1, 128.0, 126.4, 122.3, 120.9, 118.2, 109.2, 105.5, 100.7, 49.2, 42.8, 32.4, 21.4, 11.3 ppm; HRMS (ESI-FTICR) calcd for $C_{16}H_{18}N_2O_2$•Na 293.1266, found 293.1261.

3,4-Bis(1'-methylindol-3'-yl)-1-propyl-1*H*-pyrrol-2(5*H*)-one (5g).

Using **General Method D**, tetramic acid **8g** (0.500 g, 1.85 mmol), *N*-methylindole (**9a**) (0.291 g, 2.22 mmol), and a reaction time of 0.5 h gave the title compound **5g** as an off-white film (0.307 g, 0.801 mmol, 43% yield). Trituration (CH_2Cl_2/pentane) gave an analytical sample of **5g** as an off-white powder: mp 195-199 °C; R_f = 0.44 (2:1 EtOAc/petroleum ether); IR (ATR, neat) 1670, 1630, 1608 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62-7.64 (m, 1H), 7.62 (s, 1H), 7.31-7.34 (m, 2H), 7.23-7.28 (m, 1H), 7.12-7.17 (m, 2H), 7.00 (s, 1H), 6.96-6.98 (m, 1H), 6.82-6.86 (m, 1H), 4.63 (s, 2H), 3.87 (s, 3H), 3.61 (t, *J* = 7.2 Hz, 2H), 3.57 (s, 3H), 1.76 (sext, *J* = 7.2 Hz, 2H), 1.01 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 140.2, 137.3, 137.0, 131.2, 130.9, 126.5, 125.4, 122.4, 122.3, 121.5, 120.9, 120.7, 119.1, 110.1, 109.53, 109.50, 107.4, 53.5, 44.6,

33.3, 33.2, 22.3, 11.8 (*missing one peak*) ppm; HRMS (ESI-FTICR) calcd for $C_{25}H_{25}N_3O$•Na 406.1890, found 406.1889.

12,13-Dimethyl-6,7,12,13-tetrahydro-6-propyl-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazol-5-one (11g).

Using **General Method E**, 3-pyrrolin-2-one **5g** (50. mg, 0.13 mmol), and a reaction time of 4 h gave title compound **11g** as a light brown powder (34 mg, 0.89 mmol, 69% yield): mp 258-260 °C; R_f = 0.73 (2:1 EtOAc/petroleum ether); IR (ATR, neat) 1661, 1618, 1589 cm^{-1}; ^1H NMR (400 MHz, D_6-DMSO) δ 9.43 (d, *J* = 7.6 Hz, 1H), 8.10 (d, *J* = 7.6 Hz, 1H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.57-7.61 (m, 1H), 7.52-7.56 (m, 1H), 7.37-7.41 (m, 1H), 7.27-7.31 (m, 1H), 5.06 (s, 2H), 4.29 (s, 3H), 4.25 (s, 3H), 3.65 (t, *J* = 7.2 Hz, 2H), 1.79 (sext, *J* = 7.2 Hz, 2H), 0.96 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 144.3, 144.0, 131.7, 130.6, 129.8, 126.7, 126.3, 125.9, 124.2, 123.8, 121.1, 121.0, 120.8, 120.4, 119.9, 116.9, 110.7, 109.9, 50.3, 44.7, 37.1, 36.9, 22.4, 11.8 ppm; HRMS (ESI-FTICR) calcd for $C_{25}H_{23}N_3O$•Na 404.1733, found 404.1733.

ASSOCIATED CONTENT

Supporting Information

^1H NMR spectra and ^{13}C NMR spectra for all synthesized 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

Notes

The authors declare no competing financial interest.

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