JOC Article

Synthetic Approaches to Indolo[6,7-*a*]pyrrolo[3,4-*c*]carbazoles: Potent Cyclin D1/CDK4 Inhibitors

Margaret M. Faul,*,†,‡ Thomas A. Engler,*,§ Kevin A. Sullivan,‡ John L. Grutsch,‡ Marcella T. Clayton,‡ Michael J. Martinelli,‡ Joseph M. Pawlak,‡ Michael LeTourneau,‡ D. Scott Coffey,‡ Steven W. Pedersen,‡ Stanley P. Kolis,‡ Kelly Furness,§ Sushant Malhotra,§ Rima S. Al-awar,§ and James E. Ray§

Global Chemical Process Research and Development, Indianapolis, Indiana 46285, and Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, Indiana 46285

mfaul@amgen.com; tae@lilly.com

Received October 31, 2003

Synthesis of indolo[6,7-*a*]pyrrolo[3,4-*c*]carbazoles **1**, a new class of cyclin D1/CDK4 inhibitors, by oxidation of the corresponding aryl indolylmaleimides **2**, will be described. Two approaches to the synthesis of **2** were identified that required new methods for the synthesis of 7-substituted indole acetamides **3** and *N*-methyl (indol-7-yl)oxoacetates **6**. The chemistry developed enabled introduction of functionality (−OR, NR_2) at C_{12} and N_{13} facilitating structure−activity relationship (SAR) evaluation of this indolocarbazole platform.

Introduction

The eukaryotic cell division cycle is a tightly controlled process that is regulated by the cyclin/CDK family of protein kinase complexes. Stringent control of this process is essential to ensure that DNA synthesis and subsequent mitotic division is accurately executed. There is now strong evidence that CDKs, their regulators, and substrates are the targets of genetic alteration in many human cancers.[1−4] Their frequent deregulation in human tumors make them attractive targets for the identification of new anti-neoplastic agents.[5] A number of small molecules such as flavopiridol[6,7] and UCN-01[8] have been identified as inhibitors of the CDKs and are currently showing promising results in early clinical trials (Chart 1).

Intensive effort has been expended in recent years to identify novel inhibitors of cyclin D1/CDK4.[9−12] Although most of this effort has focused on the pyrrolo[3,4-*c*]-carbazole alkaloids with [*a*]annulation,[10,13,14] we recently reported a new class of indolo[6,7-*a*]pyrrolo[3,4-*c*]carbazoles represented by **1a**, **1d**, and **1g** that were potent inhibitors of cyclin D1/CDK4 in vitro, in whole cells[12] and in solid tumors upon intravenous administration.[15]

Our initial efforts in this area focused on the potent CDK4 inhibitor **1a**; however, its low aqueous solubility (<1 μg/mL at a variety of pHs) presented a challenge for clinical development. Further evaluation of the indolo-[6,7-*a*]pyrrolo[3,4-*c*]carbazole platform SAR revealed that large substituents were tolerated at C_{12} and N_{13}. For example, **1b** and **1e** both had IC_{50} values ≤75 nM in cyclin D1/CDK4 assays; unfortunately, their aqueous solubilities were only marginally better than **1a**. To improve the aqueous solubility of this platform, we turned our attention to introducing amino-containing substituents at the C_{12} and N_{13} positions as represented

† Current address: Chemical Process Research and Development, Amgen, Inc., One Amgen Center Dr., 29-M-B, Thousand Oaks, CA 91320.

‡ Global Chemical Process Research and Development.

§ Lilly Research Laboratories.

(1) Damiens, E.; Meijer, L. *Pathol. Biol.* **2000**, *48*, 340−351.

(2) Senderowicz, A. M.; Sausville, E. A. *J. Natl. Cancer. Inst.* **2000**, *92*, 376−387.

(3) Kraker, A. J.; Booher, R. N. *Annu. Rep. Med. Chem.* **1999**, *34*, 247−256.

(4) Gray, N.; Detivaud, L.; Doerig, C.; Meijer, L. *Curr. Med. Chem.* **1999**, *6*, 859−875.

(5) Mihal, V.; Hajduch, M.; Noskova, V.; Feketova, G.; Jess, K.; Gojova, L.; Kasparek, I.; Stary, J.; Blazek, B.; Pospisilova, D.; Novak, Z. *Adv. Exp. Med. Biol.* **1999**, *457*, 461−471.

(6) Senderowicz, A. M. *Invest. New Drugs* **1999**, *17*, 313−320.

(7) Motwani, M.; Li, X.-K.; Schwartz, G. K. *Clin. Cancer Res.* **2000**, *6*, 924−932.

(8) Sausville, E. A.; Zaharevitz, D.; Gussio, R.; Meijer, L.; Louarn-Leost, M.; Kunick, C.; Schultz, R.; Lahusen, T.; Headlee, D.; Stinson, S.; Arbuck, S. G.; Senderowicz, A. *Pharmacol. Ther.* **1999**, *82*, 285−292.

(9) Sanchez-Martinez, C.; Shih, C.; Faul, M. M.; Zhu, G.; Paal, M.; Somoza, C.; Li, T.; Krumrich, C.; Winneroski, L.; Xun, Z.; Brooks, H. B.; Patel, P.; Schultz, R. M.; DeHahn, T. D.; Kirmani, K.; Spencer, C. D.; Watkins, S. A.; Considine, E.; Dempsey, J. A.; Ogg, C. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3835−3839.

(10) Zhu, G.; Conner, S. E.; Zhou, X.; Shih, C.; Li, T.; Brooks, H. B.; Considine, E.; Dempsey, J. A.; Faul, M. M.; Ogg, C.; Patel, B.; Schultz, R. M.; Spencer, C. D.; Teicher, B.; Watkins, S. A. *J. Med. Chem.* **2003**, *46*, 2027−2030.

(11) Zhu, G.; Conner, S.; Zhou, X.; Shih, C.; Brooks, H. B.; Considine, E.; Dempsey, J. A.; Ogg, C.; Patel, B.; Schultz, R. M.; Spencer, C. D.; Teicher, B.; Watkins, S. A. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1231−1235.

(12) Engler, T. A.; Furness, K.; Malhotra, S.; Sanchez-Martinez, C.; Shih, C.; Xie, W.; Zhu, G.; Zhou, X.; Conner, S.; Faul, M. M.; Sullivan, K. A.; Kolis, S. P.; Brooks, H. B.; Patel, B.; Schultz, R. M.; DeHahn, T. B.; Kirmani, K.; Spencer, C. D.; Watkins, S. A.; Considine, E. L.; Dempsey, J. A.; Ogg, C. A.; Stamm, N. B.; Anderson, B. D.; Campbell, R. M.; Vasudevan, V.; Lytle, M. L. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2261−2267.

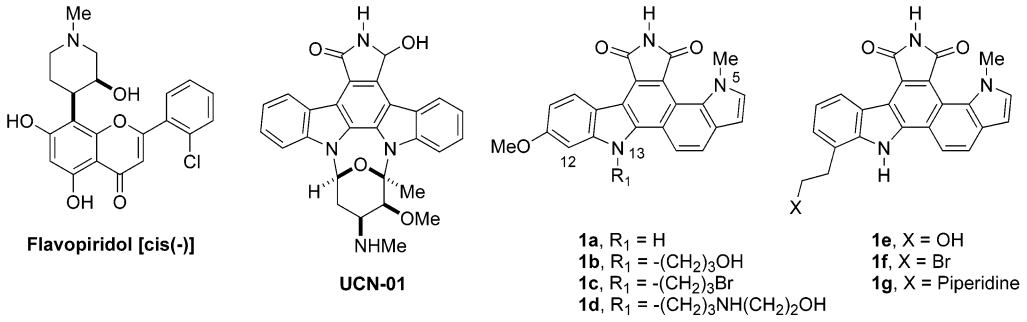
(13) Prudhomme, M. *Current Pharmaceutical Design* **1997**, *3*, 265−290.

(14) Pindur, U.; Kim, Y.-S.; Mehrabani, F. *Curr. Med. Chem.* **1999**, *6*, 29−69.

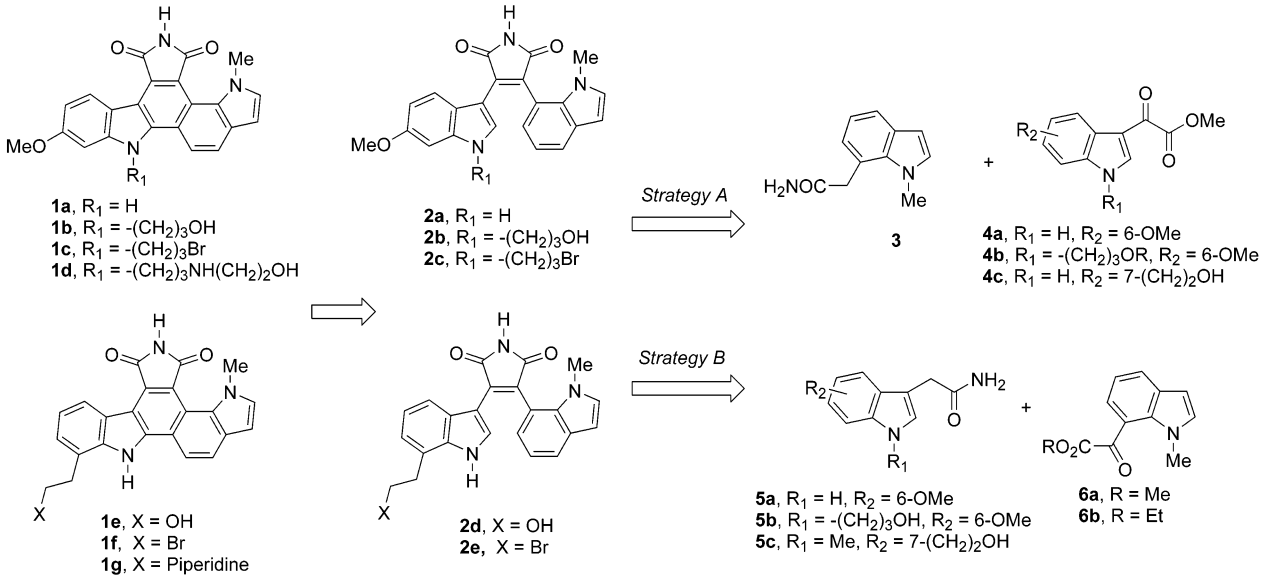
(15) Patel, B. Manuscript in preparation.

10.1021/jo035606v CCC: $27.50
Published on Web 03/31/2004

CHART 1



SCHEME 1



by analogues **1d** and **1g**. The aqueous solubility of **1d** and **1g**, as their mesylate salts was 8.6 and 8.5 mg/mL, respectively. To support toxicological and pharmacological evaluation of these compounds, we required a synthetic route that would afford multigram quantities of material for pre-clinical evaluation. Although numerous synthetic approaches to pyrrolo[3,4-*c*]carbazole alkaloids have been reported,[16−18] no synthetic details have appeared on the synthesis of this new indolo[6,7-*a*]pyrrolo-[3,4-*c*]carbazole class. This manuscript describes the first full disclosure of our synthetic efforts in this area, with **1a**−**g** as representative examples.

Results and Discussion

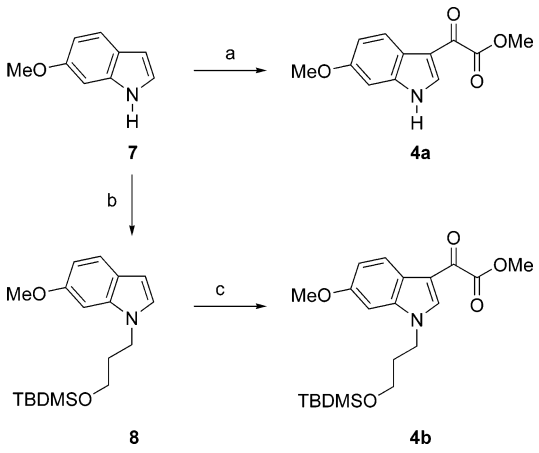
We envisioned that indolo[6,7-*a*]pyrrolo[3,4-*c*]carbazoles **1a**−**g** could be prepared by oxidative cyclization of aryl indolylmaleimides **2a**−**e** (Scheme 1). The aryl indolylmaleimides would be prepared either (i) by condensation of *N*-methylindole-7-acetamide **3** with the substituted glyoxylates **4** (strategy A) or (ii) by condensation of the substituted indole-3-acetamides **5** with alkyl (1-methyl indol-7-yl)oxoacetates **6** (strategy B). At the outset of this work, it was not clear if one set of coupling partners would offer a significant advantage over the other. In addition, a number of synthetic challenges were identified with each of these approaches that included (i) identification of an efficient and scaleable method for the synthesis of 7-substituted indoles **3** and **6**[19] and (ii) development of a robust oxidation procedure for conversion of maleimides **2** to carbazoles **1**. Furthermore, it was critical that a general route to the synthesis of **1** was developed that would enable structure−activity relationship (SAR) evaluation of this platform and allow for the facile introduction of functionality (−OR, NR_2) at C_{12} and N_{13}.[12] This manuscript describes our efforts in achieving these goals.

Indole-Oxoacetate Synthesis. 1-Methyl-α-oxoindole-3-acetates **4a**−**c** were prepared in good yields by treatment of 6-methoxyindoles **7** or **8** with oxalyl chloride, followed by in situ quench of the acid chloride with MeOH or NaOMe at low temperature (←60 °C) (Scheme 2).

The indole required for synthesis of **4c** was not commercially available but was prepared from 2-(2-nitrophenyl)ethanol **9**. Silyl protection of **9** followed by a Bartoli indole synthesis produced the protected 7-hydroxyethylindole **11** in 54% yield (Scheme 3).[20] Glyoxylation via the procedure outlined above afforded, after in situ desilylation, **4c** in three steps and 31% overall yield from **9**.

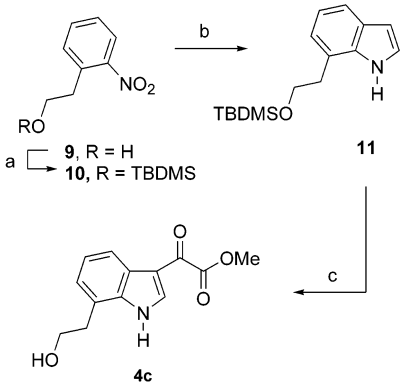
(16) Gribble, G. W.; Berthel, S. J. *Tetrahedron* **1992**, *48*, 8869−8880.
(17) Gribble, G. W.; Berthel, S. J. *Stud. Nat. Prod. Chem.* **1993**, (Stereoselective Synthesis (Pt. H)), 365−409.
(18) Knoelker, H.-J.; Reddy, K. R. *Chem. Rev.* **2002**, *102*, 4303−4427.
(19) Hartung, C. G.; Fecher, A.; Chapell, B.; Snieckus, V. *Org. Lett.* **2003**, *5*, 1899−1902.
(20) Bartoli, G.; Palmieri, G.; Bosco, M.; Dalpozzo, R. *Tetrahedron Lett.* **1989**, *30*, 2129−2132.

SCHEME 2 [a]



[a] Key: (a) (i) $(COCl)_2$, THF, (ii) MeOH, 79%; (b) NaH, DMF, $Br(CH_2)_3OTBDMS$, 100%; (c) (i) $(COCl)_2$, Et_2O, (ii) NaOMe, MeOH, 79%.

SCHEME 3 [a]

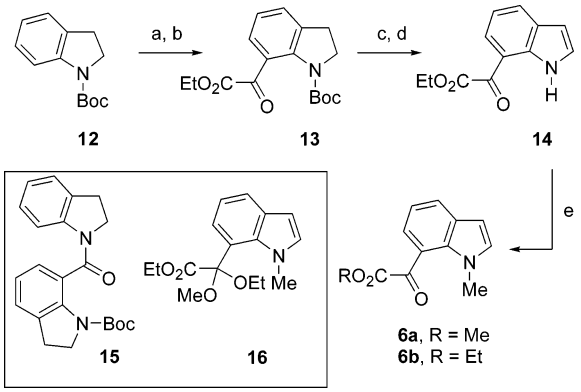


[a] Key: (a) TBDMSCl, imidazole, CH_2Cl_2, 96%; (b) CH_2═$CHMgBr$; −45 °C, THF, 56%; (c) $(COCl)_2$, Et_2O; NaOMe, MeOH, 57%.

Two approaches were evaluated for synthesis of *N*-methyl (indol-7-yl)oxoacetates **6**. Our first approach involved halogen−metal exchange of 7-bromo *N*-methylindole, and treatment of the lithiated intermediate with dimethyl oxalate to afford a 57% yield of **6a**. Although this approach was expedient, the high cost of 7-bromoindole (>$50/g) discouraged application of this chemistry on large scale.

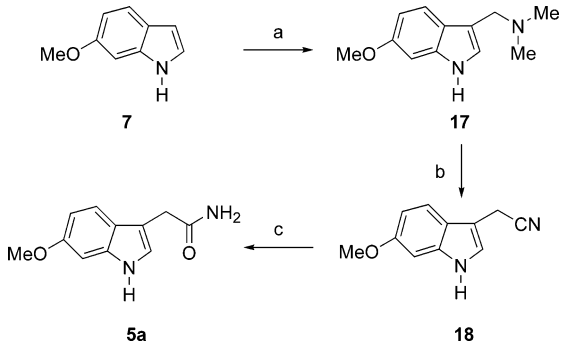
Our second approach to **6** was based upon a directed metalation of the readily available *N*-Boc indoline **12**.[21] Reaction of **12** with *s*-BuLi/TMEDA followed by addition of diethyl oxalate afforded a 59% yield of **13**, which crystallized directly from the reaction mixture (Scheme 4). The major byproduct of this reaction was indoline **15** formed by reaction of the aryllithium with **12**. Although levels of **15** could be controlled by rigorously maintaining the reaction temperature at −78 °C, further improvement in the yield was not realized. Removal of the *N*-Boc protecting group and trifluoroacetic anhydride mediated oxidation of the resultant indoline afforded ethyl (indol-7-yl)-oxo acetate **15** in 81% yield. Methylation of **14** with NaH/MeI in DMF afforded an 85% yield of **6b** that was contaminated with methyl ester **6a** and ketal **16**. Ketal

SCHEME 4 [a]



[a] Key: (a) *s*-BuLi, TMEDA, MTBE; (b) $(EtO_2C)_2$, 59%; (c) TFA; (d) TFAA, DMSO, 81%; (e) NaH, MeI, DMF, 85%.

SCHEME 5 [a]



[a] Key: (a) CH_2═NMe_2Cl, CH_2Cl_2, 100%; (b) NaCN, DMSO, EtOAc, 80 °C, 82%; (c) KOH, *t*-BuOH or *Rhodococcus rhodochrous*, toluene, 88%.

16 was removed by chromatography and although methyl ester **6a** remained as an impurity, it was expected that it would also undergo the condensation reaction to generate **2** and would not pose a problem in the synthesis of **1**.

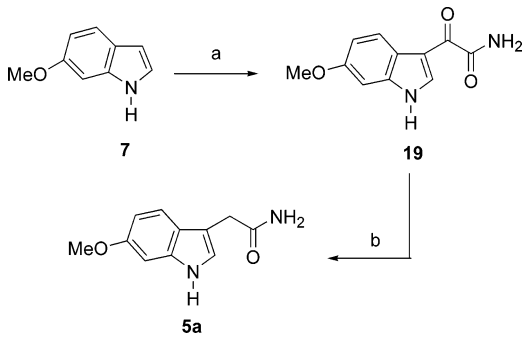
Acetamide Synthesis. Two approaches for the synthesis of 6-methoxyindole-3-acetamides **5a** and **5b** were evaluated. Synthesis via gramine **17** afforded **5a** in four steps and 65% yield (Scheme 5).[22−24] On large scale, hydrolysis of **18** to **5a** was problematic due to competitive formation of the carboxylic acid. Although not widely published, we found that selective hydrolysis of indole-3-acetonitrile **18** to **5a** could be performed in 88% yield using whole cells of *Rhodococcus rhodochrous* J-1 in toluene as a solvent.[25] However, due to the limited availability of the *R. rhodochrous* organism this reaction was not amenable to large scale.

Our second approach to **5a** was based upon development of work previously reported for reduction of indole oxo-acetates to their corresponding indole-3-acetates.[26,27]

(21) Iwao, M.; Kuraishi, T. *Heterocycles* **1992**, *34*, 1031−1038.

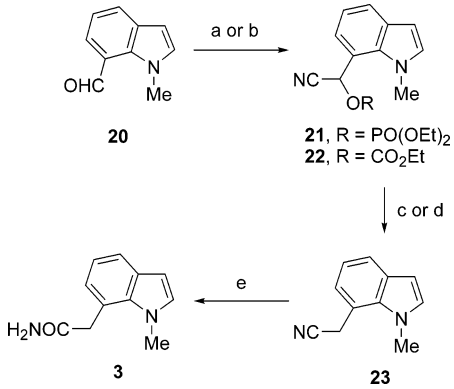
(22) Brewster, J. H.; Eliel, E. L. *Org. React.* **1953**, *VII*, 99−197.
(23) Kozikowski, A. P.; Ishida, H. *Heterocycles* **1980**, *14*, 55−58.
(24) Faul, M. M.; Winneroski, L. L.; Krumrich, C. A. *J. Org. Chem.* **1999**, *64*, 2465−2470.
(25) Mauger, J.; Nagasawa, T.; Yamada, H. *Tetrahedron* **1989**, *45*, 1347−1354.
(26) Demopoulos, V. J. *Synth. Commun.* **1989**, *19*, 2585−2594.
(27) Stiller, E. T.; Diassi, P. A.; Gerschutz, D.; Meikle, D.; Moetz, J.; Principe, P. A.; Levine, S. D. *J. Med. Chem.* **1972**, *15*, 1029−1032.

SCHEME 6 [a]



[a] Key: (a) (i) $(COCl)_2$, THF, (ii) NH_4OH, 90%; (b) $NaH_2PO_2 \cdot xH_2O$, dioxane/H_2O, 81%.

SCHEME 7 [a]

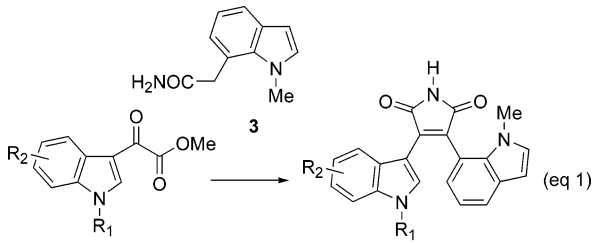


[a] Key: (a) $(EtO)_2P(O)CN$, LiCN; (b) EtOCOCl, NaCN, *n*-Bu_4NCl, THF, 92%; (c) THF, SmI_2, 85% from **21**; (d) H_2 (50 psi), 10% Pd/C, EtOAc, 99%; (e) KOH, *t*-BuOH, reflux, 85% from **23**.

Although not previously reported, we were interested in determining if a similar strategy could be applied to the corresponding indole-3-glyoxylamides. Thus, indole-3-glyoxylamide **19** was prepared in 90% yield by treatment of **7** with oxalyl chloride, followed by in situ quench with NH_4OH at low temperature (−60 °C). Upon reduction of **19** with sodium hypophosphite in dioxane/water at reflux an 81% yield of **5a** was obtained. This approach was very efficient on large scale and provided access to a variety of indole-3-acetamide derivatives (Scheme 6).

For the synthesis of *N*-methylindole-7-acetamide **3**, we envisioned starting from readily available 7-formylindole **20**[28] and proceeding via acetonitrile **23** (Scheme 7). However, this approach presented a significant challenge since few reagents are known to directly homologate aryl aldehydes to aryl acetonitriles in good yield.[29−31] Thus, two new synthetic routes were developed.[32,33] Our initial approach, based upon the work of Kurihara, involved conversion of **20** to **23** via cyanophosphonate **21**. Although this approach was successful it was not attractive for scale-up, as previously described.[33] Therefore, a related sequence via the cyanocarbonate **22** was developed. Hydrogenation of **22** afforded **23**, that upon hydrolysis using KOH/*t*-BuOH at reflux afforded an efficient, robust and practical synthesis of **3** in 3 steps and 78% overall yield from readily available reagents.[33]

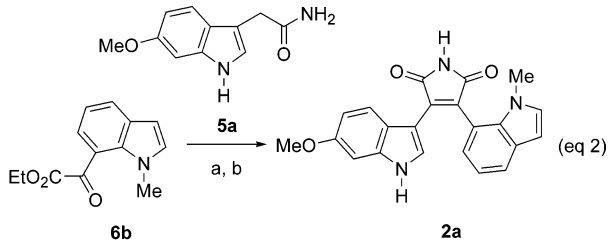
TABLE 1. Synthesis of the Inversed Arylindolyl Maleimides (eq 1)



entry	indole **4**	R_1	R_2	yield, %	product **2**
1	**a**	H	6-OMe	65	**a**
2	**b**	$-(CH_2)_3OH$	6-OMe	62	**b**
3	**c**	H	7-$(CH_2)_2OH$	72	**d**

Arylindolyl Maleimide Synthesis. A number of methods have been reported to prepare 3,3′-bisindolylmaleimides by condensation of α-oxo-indole-3-acetates with indole-3-acetamides.[36,37] This technology was directly applicable to the synthesis of novel 3, 7′-bisindolylmaleimides **2a**, **2b**, and **2d** affording the desired products in 62−72% yield (eq 1, Table 1).

As a comparison, **2a** was obtained in only 52% yield when the reacting partners were reversed (eq 2), demonstrating that the synthesis of **2a** via strategy B was less efficient than strategy A (Scheme 1). The reason for the lower yield was due to competitive hydrolysis of **6b** to its corresponding (indolyl-7-yl)-α-oxoacetic acid, which does not participate in the condensation reaction, but is instead further decarbonylated to *N*-methyl-7-indolecarboxylic acid. A number of conditions (alternative bases, methods of elimination and solvents) were examined to improve the yield of this reaction but were unsuccessful.



Key: (a) t-KOBu, THF; (b) HCl, reflux - 52%.

Carbazole Formation: The final step of the process involved the oxidative cyclization of **2** to **1**. A number of methods to prepare indolocarbazoles by oxidation of the

(28) Dobson, D. R.; Gilmore, J.; Long, D. A. *Synlett* **1992**, 79−80.
(29) Van Leusen, A. M.; Oomkes, P. G. *Synth. Commun.* **1980**, *10*, 399−403.
(30) Schoellkopf, U.; Schroeder, R. *Angew. Chem.* **1973**, *85*, 402−403.
(31) Santiago, B.; Meyers, A. I. *Tetrahedron. Lett.* **1993**, *34*, 5839−5842.
(32) Engler, T. A.; Furness, K.; Malhotra, S.; Diefenbacher, C.; Clayton, J. R. *Tetrahedron Lett.* **2003**, *44*, 2903−2905.
(33) Kolis, S. P.; Clayton, M. T.; Grutsch, J. L.; Faul, M. M. *Tetrahedron Lett.* **2003**, *44*, 5707−5710.
(34) Yoneda, R.; Harusawa, S.; Kurihara, T. *J. Org. Chem.* **1991**, *56*, 1827−1832.
(35) Au, A. T. *Synth. Commun.* **1984**, 743−748.
(36) Faul, M. M.; Winneroski, L. L.; Krumrich, C. A. *J. Org. Chem.* **1998**, *63*, 6053−6058.
(37) Faul, M. M.; Winneroski, L. L.; Krumrich, C. A. *Tetrahedron Lett.* **1999**, *40*, 1109−1112.

TABLE 2. Photochemical Conditions Evaluated for Synthesis of 1 from 2a

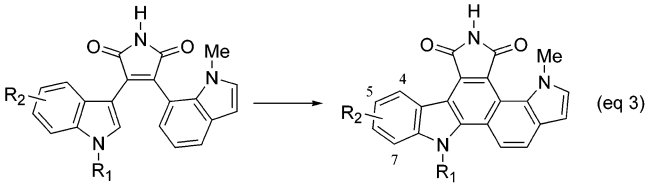
entry	oxidant	volume[a] (mL/g)	yield, %
1	DDQ	1000	92
2	DDQ	500	89
3	DDQ	250	91
4	DDQ	100	incomplete
5	none	1000	47
6	DDQ, cat. *p*-TsOH	1000	dec

[a] All reactions performed in EtOAc.

2,2′-bisindole bond have been reported,[38,39] and although no reports on the oxidation of the 3,7′-bisindolylmaleimide system have been published, a close analogy was reported by our group for the synthesis of aryl- and heteroaryl[*a*]pyrrolo[3,4-*c*]carbazoles via both photochemistry and Heck cyclization strategies.[40] Due to the difficulty in accessing the Heck reaction partners for synthesis of **1**, we focused our efforts on the photocyclization reaction (Table 2). Our initial conditions involved treatment of **2a** with DDQ (1.1 equiv) in EtOAc (1000 mL/g) and afforded a 92% yield of **1a** after 1 h. However, the photochemical reaction presented numerous challenges: (i) it was difficult to perform on large scale; (ii) it required high dilution, minimizing throughput; (iii) removal of the DDQ byproducts by extractive workup was problematic due to the competing insolubility of the indolocarbazole product; and (iv) DDQ in the final product, had to be removed to ppm levels due to its known toxic effects. Thus, a variety of conditions were examined to improve this chemistry.

We initially focused on use of EtOAc as the solvent and determined that the reaction could be performed in 250 mL/g with minimal impact on the yield (Table 2, entries 1−3). For this reaction to be successful, both DDQ and **2a** had to be dissolved in the reaction solvent prior to the start of the reaction. If the concentration of the reaction is increased to 100 mL/g incomplete reaction was observed (entry 4). Attempts to reduce the amount of DDQ were unsuccessful, and in the absence of DDQ, **1a** was isolated in only 47% yield (entry 5). Use of DDQ with cat. *p*-TsOH resulted in decomposition (entry 6). Attempts to perform the reaction in alternative solvents where the solubility of **2a**, DDQ and **1a** could be increased (acetone, dioxane, DMF, xylenes, diphenyl ether, THF) were unsuccessful resulting in either incomplete reaction or decomposition. Alternative oxidants (SeO_2, MnO_2, benzoquinone cat. *p*-TsOH, phenyliodine-(III) bis(trifluoroacetate) (PIFA) with or without BF_3-OEt_2,[41] cat. $FeCl_2/O_2$, $CuCl_2$, $Pd(OTf)_2$,[42] $PdCl_2$, $Pd(OAc)_2$,[43,44] I_2 cat. AIBN) also gave incomplete reaction or decomposition. Although a wide variety of alternative conditions were examined we have been unable to identify a successful alternative to DDQ/*hν* for the synthesis of this class of compounds.

TABLE 3. Synthesis of the Inversed BIMs (eq 3)



entry	BIM **2**	R_1	R_2	yield, %	product **1**
1	**a**	6-OMe	H	87	**a**
2	**b**	6-OMe	$-(CH_2)_3OH$	55	**b**
3	**e**	7-$(CH_2)_2OH$	H	95	**e**
4	**c**	6-OMe	$-(CH_2)_3Br$	87	**c**
5	**f**	7-$(CH_2)_2Br$	H	92	**f**

Fortunately, the optimum conditions for synthesis of **1a** from **2a** could be successfully applied to substrates **2b**−**e** (eq 3, Table 3), as well as a variety of other analogues.[12] For the synthesis of **1d** and **1g**, although oxidation could be performed on **2b** and **2d** prior to bromide formation in good yields, the preferred strategy was to perform the photooxidation reaction on the bromides **2c** and **2e** due to the higher solubility of the resulting carbazoles **1c** and **1f** in organic solvents, which facilitated isolation and chromatographic purification. Bromides **2c** and **2e** were readily prepared from **2b** and **2d** in 69−71% yield via standard conditions (CBr_4/PPh_3, DMF or CH_2Cl_2/THF).

The final steps for the synthesis of **1d** and **1g** involved displacement of the bromide by the desired amine. This was performed via standard S_N2 chemistry, using 2-aminoethanol or piperidine in DMF at 60 °C, to afford **1d** and **1g** in 42 and 95% yield, respectively. The advantage of this approach is that a variety of amines can be incorporated from the key late stage bromide intermediates **1c** and **1f**. By using this chemistry the SAR of **1** was expanded to examine a diverse collection of aminoalkyl-substituted indolocarbazoles as described in our publication detailing the biological activity of this class of compounds.[12]

Conclusions

A new class of indolo[6,7-*a*]pyrrolo[3,4-*c*]carbazoles, exemplified by **1a**, **1d**, and **1g**, have been identified as potent inhibitors of cyclin D1/CDK4. The hitherto optimal synthetic route to these compounds employed *N*-methyl-7-formylindole **20** as the starting material for the synthesis of *N*-methylindole-7-acetamide **3**. Coupling of **3** with (indol-3-yl)oxoacetates **4** afforded the 3,7′-bisindolylmaleimides **2**, which upon DDQ photooxidation in EtOAc yield **1**. The syntheses proceed in six to eight steps and 16−36% overall yield.

Experimental Section

Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. TLC was performed on Kiesegel 60 F254 plates (Merck) using reagent grade

(38) Gallant, M.; Link, J. T.; Danishefsky, S. J. *J. Org. Chem.* **1993**, *58*, 343−349.
(39) Link, J. T.; Gallant, M.; Danishefsky, S. J.; Huber, S. *J. Am. Chem. Soc.* **1993**, *115*, 3782−3783.
(40) Sanchez-Martinez, C.; Faul, M. M.; Shih, C.; Sullivan, K. A.; Grutsch, J. L.; Cooper, J. T.; Kolis, S. P. *J. Org. Chem.* **2003**, *68*, 8008−8014.
(41) Faul, M. M.; Sullivan, K. A. *Tetrahedron. Lett.* **2001**, *42*, 3271−3273.
(42) Ohkubo, M.; Kawamoto, H.; Ohno, T.; Nakano, M.; Morishima, H. *Tetrahedron* **1997**, *53*, 585−592.
(43) Harris, W.; Hill, C. H.; Keech, E.; Malsher, P. *Tetrahedron Lett.* **1993**, *34*, 8361−8364.
(44) Wang, J.; Rosingana, M.; Watson, D. J.; Dowdy, E. D.; Discordia, R. P.; Soundarajan, N.; Li, W.-S. *Tetrahedron. Lett.* **2001**, *42*, 8935−8937.

solvents. Flash chromatography was performed using Merck silica gel 60 (230−400 mesh). ^{1}H NMR was performed at 300 MHz and ^{13}C NMR at 75 MHz in $CDCl_3$ unless otherwise specified. Chemical shifts are in ppm downfield from internal tetramethylsilane. Mass spectral, combustion, and infrared analysis were performed by the Eli Lilly and Co. Physical Chemistry Department.

6-Methoxy-1-methyl-α-oxo-1*H*-indole-3-acetic Acid Methyl Ester (4a). A solution of **7** (25.0 g, 185 mmol) in THF (500 mL) at 0 °C was treated dropwise with oxalyl chloride (25.8 g, 17.8 mL, 203.4 mmol) at such a rate that the reaction temperature did not exceed 1 °C (2−4 min). The reaction was stirred at 0 °C for 2 h and then quenched with MeOH (29.6 g, 37.5 mL, 924.5 mmol). The solid that precipitated was collected and dried to afford 34.1 g (79%) of **4a**: ^{1}H NMR (300 MHz, DMSO-d_6) δ12.26 (s, 1H), 8.35 (d, 1H, J = 3.29 Hz), 8.05 (d, 1H, J = 8.42 Hz), 7.07 (d, 1H, J = 2.19 Hz), 6.94 (d, 0.5H, J = 2.56 Hz), 6.92 (d, 0.5H, J = 2.19 Hz) 3.90 (s, 2H), 3.82 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 178.4, 163.9, 157.0, 137.7, 137.6, 121.7, 119.2, 112.3, 112.5, 95.8, 55.2, 52.4; IR (KBr) ν 3437, 3188, 2954,1729, 1619, 1586, 1521, 1495, 1448, 1415, 1380, 1254, 1230, 1161, 1140, 1115, 1092, 750 cm^{-1}; MS (FD+) m/z calcd for $C_{12}H_{11}NO_4$ 233.2, found 233.1. Anal. Calcd for $C_{12}H_{11}NO_4$: C, 61.8; H, 4.75; N, 6.01. Found: C, 61.4; H, 4.71; N, 5.97.

{1-[3-(*tert*-Butyldimethylsilanyloxy)propyl]-6-methoxy-1*H*-indol-3-yl}oxoacetic Acid Methyl Ester (4b). To a solution of **8** (2.45 g, 7.66 mmol) in Et_2O (40 mL) at 0 °C was added oxalyl chloride (1.07 g, 8.42 mmol). The reaction was stirred for 30 min while warming to rt. The reaction was cooled to −78 °C, and NaOMe (5.25 mL, 22.98 mmol) as a 25 wt % solution in MeOH introduced. The reaction was stirred overnight and allowed to warm to rt. The mixture was poured into EtOAc, washed with H_2O, saturated $NaHCO_3$ (aq), and brine, and dried ($MgSO_4$). The resultant solution was concentrated in vacuo and the crude product purified by silica gel chromatography (75:25 hexane/EtOAc to 65:35 hexane/EtOAc gradient) to give 2.46 g (79%) of **4b** as an oil: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.30 (s, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.14 (d, J = 2 Hz, 1H), 6.93 (dd, J = 2.0, 8.4 Hz, 1H), 4.32 (t, J = 6.8 Hz, 2H), 3.86 (s, 3H), 3.82 (s, 3H), 3.55 (t, J = 6.0 Hz, 2H), 1.98 (app quintet, J = 6.4 Hz, 2H), 0.86 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 177.8, 163.8, 157.2, 139.9, 137.7, 122.1, 119.8, 112.5, 111.6, 94.8, 59.2, 55.4, 52.4, 43.3, 31.9, 25.7, 17.8, −5.56. IR ($CHCl_3$) ν 3022, 1730, 1640 cm^{-1}; MS (electrospray) m/z 406 (M^+ + 1). Anal. Calcd for $C_{21}H_{31}NO_5Si$: C, 62.19; H, 7.70; N, 3.45. Found: C, 61.97; H, 7.57; N, 3.60.

[7-(2-Hydroxyethyl)-1*H*-indol-3-yl]oxoacetic Acid Methyl Ester (4c). A solution of **11** (47.0 g, 170 mmol) in Et_2O (600 mL) was cooled to 4 °C (ice bath), and a 2 M solution of oxalyl chloride in THF (92.0 mL, 184 mmol) was added dropwise. The ice bath was removed and the reaction allowed to warm to rt (1.5 h). The reaction was cooled to −78 °C, and a solution of NaOMe in MeOH (85.1 mL, 25wt %, 357 mmol) was introduced over 5 min. The cold bath was removed, and the reaction was allowed to warm to rt (1 h). The reaction was quenched with H_2O (500 mL) and poured into EtOAc (400 mL). The water layer was separated and extracted with EtOAc (2 × 200 mL). The organic layers were combined, washed with saturated NH_4Cl (aq) (400 mL) and brine (500 mL), and dried ($MgSO_4$). The solution was concentrated in vacuo and the product purified by silica gel chromatography (70:30 hexanes/EtOAc) to give 23.9 g (57%) **4c** as a yellow solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.38 (s, 1H), 8.36 (s, 1H), 8.03 (dd, J = 7.7, 1.5 Hz, 1H), 7.20 (dd, J = 7.7, 7.7 Hz, 1H), 7.14 (dd, J = 7.7, 1.5 Hz, 1H), 4.72 (br s, 1H), 3.88 (s, 3H), 3.70 (t, J = 6.6 Hz, 2H), 3.04 (t, J = 6.6 Hz, 2H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 178.6, 164.0, 137.9, 136.0, 125.4, 124.3, 122.9, 118.9, 112.6, 61.1, 52.4, 34.1 (one signal is not apparent); IR ($CHCl_3$) ν 3622, 3276, 3016, 1731, 1644 cm^{-1}. Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.66. Found: C, 62.87; H, 5.20; N, 5.72.

6-Methoxyindole-3-acetamide (5a). 6-Methoxyindole-3-acetamide **19** (97.35 g) and 10% Pd−C (19.5 g) were taken up in 50:50 H_2O/dioxane (350 mL) and diluted with dioxane (875 mL). The reaction mixture was treated dropwise over 1.5 h with a solution of $NaH_2PO_2 \cdot xH_2O$ in water (325 mL). During the addition, the reaction mixture was heated to reflux and stirred for 9 h. The reaction mixture was cooled to rt, treated with Hyflo (50 g), stirred for 15 min, then filtered through a pad of Hyflo (130 g prepared from 25% dioxane/H_2O). The filter cake was washed with 9:1 dioxane/H_2O (4 × 200 mL) and the filtrate concentrated in vacuo. The wet residue was diluted with water (800 mL) and concentrated in vacuo until 2350 mL of distillate was collected. Water (350 mL) was added to the reaction mixture, which was cooled in an ice−water bath for 20 min. The tan solid that precipitated out of solution was filtered, washed with water, and dried (78.67 g). The isolated material was treated with EtOAc (200 mL), heated to reflux, and then cooled and stirred at 0−5 °C for 30 min. The solution was filtered to afford 73.9 g (81%) **5a** as a light tan solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.63 (s, 1H), 7.42 (d, 1H, J = 8.8 Hz), 7.24 (s, 1H), 7.04 (d, 1H, J = 2.2 Hz), 6.85 (d,1H, J = 2.2 Hz). 6.81 (s, 1H), 6.40 (app dd, 1H, J = 8.59 Hz, 4.8 Hz), 3.74 (s, 3H), 3.43 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.9, 155.4, 136.7, 122.2, 121.6, 119.2 108.9, 108.4, 94.3, 55.1 32.6; IR (KBr) ν 3378, 3189, 1652, 1627, 1580, 1559, 1502, 1456, 1396, 1287, 1266, 1205, 1165, 1128, 1026, 815 cm^{-1}; HRMS (ES+) exact mass calcd for $C_{11}H_{12}N_2O_2$ 204.0899, found 204.0899.

(1-Methyl-1*H*-indol-7-yl)oxoacetic Acid Ethyl Ester (6b). A solution of **14** (3.00 g, 13.8 mmol) dissolved in DMF (12 mL) was added dropwise to a slurry of NaH (60% dispersion in mineral oil, 0.66 g, 16.6 mmol) in DMF (7 mL) under N_2 at 0 °C keeping the temperature of the reaction mixture below 6 °C. The resulting mixture was stirred at 0 °C for 30 min. A solution of CH_3I (9.8 mL, 69.1 mmol) dissolved in DMF (7 mL) was added dropwise by syringe keeping the temperature of the reaction mixture below 14 °C. The resulting mixture was stirred at rt for 18 h, quenched by addition of a 0.1 N HCl solution, and extracted with EtOAc. The organic layer was washed with brine and dried ($MgSO_4$). The solution was concentrated in vacuo and the crude product purified by silica gel chromatography (9:1 hexanes/EtOAc) to give 2.71 g (85%) **6a**/**6b** as an 8:1 mixture. **6b**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.98 (app dd, 1H, J = 7.9 Hz, 0.92 Hz), 7.58 (dd, 1H, J = 7.7 Hz, 1.1 Hz), 7.48 (d, 1H, J = 3.3 Hz), 7.21 (t, 1H, J = 7.7 Hz), 6.67 (d, 1H, J = 2.9 Hz) 4.44 (q, 2H, J = 7.3 Hz), 3.81 (s, 3H), 1.35 (t, 3H, J = 7.1 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 186.1, 164.0, 133.6, 133.0, 131.3, 128.0, 126.9, 118.7, 118.3, 102.2, 62.3, 37.5, 13.8; IR ($CDCl_3$) ν 3688, 3019, 1733, 1677, 1521 cm^{-1}. Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.5; H, 5.67; N, 6.06. Found: C, 67.1; H, 5.49; N, 6.03.

1-[3-(*tert*-Butyldimethylsilanyloxy)propyl]-6-methoxy-1*H*-indole (8). To a solution of **7** (10.0 g, 67.9 mmol) and (3-bromopropoxy)-*tert*-butyldimethylsilane (18.0 g, 71.3 mmol) in DMF (300 mL) was added NaH (60% mineral oil dispersion, 0.353 g, 8.82 mmol). The reaction was stirred for 2 h, quenched with saturated $NaHCO_3$ (aq), diluted with EtOAc (400 mL), washed with saturated $NaHCO_3$ (aq) and brine, and dried ($MgSO_4$). The solution was concentrated in vacuo and the crude oil purified by filtration through a plug of silica gel (85:15 hexane/EtOAc) to give 22.1 g (100%) of **8** that was used without further purification: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.38 (d, J = 8.4 Hz, 1H), 7.15 (d, J = 3.2 Hz, 1H), 6.92 (d, J = 2.0 Hz, 1H), 6.65 (dd, J = 2.4, 8.4 Hz, 1H), 6.32 (d, J = 3.2 Hz, 1H) 4.16 (t, J = 6.4 Hz, 2H), 3.77 (s, 3H), 3.53 (t, J = 6 Hz, 2H), 1.90 (app quintet, J = 6.8 Hz, 2H), 0.87 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 155.5, 136.3, 127.1, 122.2, 120.9, 108.9, 100.4, 93.0, 59.5, 55.2, 41.9, 32.6, 25.7, 17.8, −5.50; MS (electrospray) m/z 320 (M^+ + 1).

***tert*-Butyldimethyl[2-(2-nitrophenyl)ethoxy]silane (10).** A solution of 2-(2-nitrophenyl)ethanol (100 g, 590 mmol) in CH_2Cl_2 (800 mL) was treated with imidazole (117 g, 777 mmol) followed by *tert*-butyldimethylsilyl chloride (562 g, 826 mmol).

A white precipitate formed upon the addition, and the reaction was stirred 2.5 h. The mixture was filtered, diluted with CH_2Cl_2 (300 mL), washed with 0.1 N HCl (300 mL), H_2O (400 mL), saturated $NaHCO_3$ (aq) (400 mL), brine (400 mL), and dried ($MgSO_4$). The solution was concentrated in vacuo to give 160 g (96%) of **10** as a transparent oil that was used without further purification: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.99 (dd, J = 1, 8 Hz, 1H), 7.73 (ddd, J = 1, 6.5, 7 Hz, 1H), 7.5−7.65 (m, 2H), 3.90 (t, J = 6.6 Hz, 2H), 3.14 (t, J = 6.6 Hz, 2H), 0.87 (s, 9H), 0.1 (s, 6H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 149.8, 133.1, 132.8, 132.7, 127.6, 124.0, 62.7, 34.9, 25.6, 17.8, −5.7; HRMS (M^+ + 1) calcd for $C_{14}H_{24}NO_3Si$ 282.1525, found 282.1519.

7-[2-(*tert*-Butyldimethylsilanyloxy)ethyl]-1*H*-indole (11). A solution of **10** (85.6 g, 304 mmol) in THF (1 L) was cooled to −65 °C, and a 1.0 M solution of vinylmagnesium bromide in THF (913 mL, 913 mmol) was introduced while maintaining a temperature below −60 °C. The reaction was stirred for 15 min at −45 °C, additional vinylmagnesium bromide (152 mL, 152 mmol) was added, and the reaction was stirred at −45 °C for 30 min. The cold reaction was poured into saturated NH_4Cl (aq) (800 mL) and diluted with EtOAc (500 mL). The two layers were separated, and the aqueous layer was extracted with EtOAc (2 × 200 mL). The organic layers were combined, washed with brine (400 mL), and dried ($MgSO_4$). The solution was concentrated in vacuo and the product purified by silica gel chromatography (95:5 hexane/EtOAc) to give 47.1 g (56%) **11** as a transparent brown oil that was used without further purification: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.02 (br s, 1H), 7.36 (dd, J = 4.8, 4.8 Hz, 1H), 7.28 (dd, J = 3, 3 Hz, 1H), 6.86−6.92 (m, 2H), 6.39 (dd, J = 1.2, 3.2 Hz, 1H), 3.85 (t, J = 6.8 Hz, 2H), 3.03 (t, J = 6.8 Hz, 2H), 0.80 (s, 9H), −0.11 (s, 6H); MS (electrospray) m/z 276 (M^+ + 1).

Ethyl 1-Boc-indolineglyoxylate (13). *sec*-Butyllithium (1.3 M in cyclohexanes, 42.1 mL, 54.7 mmol) was added dropwise to a solution of 1-*tert*-butyloxycarbonyl-2,3-dihydro-1*H*-indole **12** (10.0 g, 45.6 mmol) and TMEDA (8.26 mL, 54.7 mmol) in dry MTBE (100 mL) at −78 °C under N_2, keeping the temperature of the reaction mixture below −65 °C. After the addition was complete, the reaction mixture was stirred at −78 °C for 3 h. Diethyl oxalate (13.3 g, 91.2 mmol) dissolved in MTBE (25 mL) was then added dropwise keeping the temperature below −65 °C. The reaction mixture was stirred −78 °C for 1 h before being allowed to warm to rt. The reaction was then quenched with saturated NH_4Cl (150 mL) and extracted with EtOAc (3 × 100 mL). The EtOAc portions were combined, washed with brine, and dried ($MgSO_4$). The solution was concentrated in vacuo and the crude product purified by silica gel chromatography (9:1 hexanes/EtOAc) to give 8.53 g (59% yield) of **13**: ^{1}H NMR (DMSO-d_6) δ 7.44 (d, 0.5H, J = 1.46 Hz), 7.42 (d, 0.5H, J = 1.09 Hz), 7.22 (dd, 1H, J = 1.09, 7.69 Hz), 7.09 (m, 1H, J = 6.59 Hz), 4.14 (app q, 2H, J = 6.95 Hz), 4.00 (app t, 2H, J = 8.42 Hz), 3.15 (t, 2H, J = 8.42 Hz), 1.42 (s, 9H), 1.23 (app t, 3H, J = 7.14 Hz); ^{13}C NMR (DMSO-d_6) δ 182.5, 159.8, 153.3, 139.9, 132.9, 128.3, 128.1, 123.2, 122.9, 81.5, 61.3, 47.8, 27.8, 27.6, 27.4, 13.7; IR ($CHCl_3$) ν 3019, 2983, 1733, 1703, 1592, 1453, 1439, 1340, 1395, 1344, 1163, 1148, 1042, 840 cm^{-1}; HRMS (ES) exact mass calcd for $C_{17}H_{21}N_5O$ 319.1420, found 319.1410. Anal. Calcd for $C_{17}H_{21}N_5O$: C, 63.9; H, 6.63; N, 4.39. Found: C, 64.2; H, 6.44; N, 4.69.

(1*H*-Indol-7-yl)-α-oxoacetic Acid Ethyl Ester (14). Trifluoroacetic acid (15.4 mL, 200 mmol) was added to a solution of **13** (15.98 g, 50.0 mmol) in CH_2Cl_2 (182 mL) at rt under N_2. The reaction mixture was stirred at rt for 18 h and then quenched by slow addition of saturated aq $NaHCO_3$ (300 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 50 mL), washed with brine, and dried ($MgSO_4$). The solution was concentrated in vacuo and the crude product purified by silica gel chromatography (85:15 hexanes/EtOAc) to give 8.83 g (81%) of ethyl 7-indolineglyoxylate: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.59 (s, 1H), 7.22 (app d, 1H, J = 7.0 Hz), 7.16 (app dd, 1H, J = 8.2 Hz, 0.9 Hz), 6.48 (app dd, 1H, J = 6.8 Hz), 4.37 (q, 2H, J = 7.0 Hz), 3.72 (app t, 2H, J = 8.2 Hz), 3.00 (app t, 2H, J = 8.6 Hz), 1.31 (t, 3H, J = 7.1 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 185.8, 164.8, 154.9 132.4 129.8 128.0, 115.1, 109.4, 61.6, 46.7, 26.6, 13.8; IR ($CDCl_3$) ν 3692, 3425, 3027, 1732, 1637, 1578 cm^{-1}; HRMS (ES) exact mass calcd for $C_{12}H_{13}NO_3$ M^+ 219.0895, found 219.0895.

Trifluoroacetic anhydride (0.464 mL, 3.28 mmol) was added dropwise to a solution of DMSO (0.466 mL, 6.57 mmol) in CH_2Cl_2 (9 mL) at −78 °C under N_2 keeping the temperature of the reaction mixture below −65 °C. The reaction mixture was stirred at −78 °C for 90 min, and then ethyl 7-indolineglyoxylate (0.48 g, 2.19 mmol) in CH_2Cl_2 (5 mL) was added dropwise. The reaction mixture was stirred under N_2 for 1 h while warming to −30 °C. The reaction mixture was recooled to −78 °C and Et_3N (1.37 mL, 9.85 mmol) added. The reaction mixture was allowed to warm to rt, washed sequentially with water, 1 N HCl, saturated $NaHCO_3$ (aq), and brine, and dried ($MgSO_4$). The solution was concentrated in vacuo to give 0.47 g (99%) of **14**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.68 (s, 1H), 8.07 (d, 1H, J = 7.7 Hz), 7.72 (app dd, 1H, J = 7.3 Hz, 0.7 Hz), 7.50 (t, 1H, J = 2.9 Hz), 7.25 (t, 1H, J = 7.7 Hz), 6.67 (dd, 1H, J = 2.9 Hz, 1.8 Hz), 4.48 (q, 2H, J = 7.0 Hz), 1.38 (app t, 3H, J = 7.1 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 187.3, 164.2 133.2, 129.8, 129.2, 128.1, 127.0, 118.7, 115.3, 102.2, 62.1, 13.9; IR ($CDCl_3$) ν 3454, 3026, 1734, 1652, 1589 cm^{-1}. Anal. Calcd for $C_{12}H_{11}NO_3$ C, 66.4; H, 5.10; N, 6.45. Found: C, 66.2; H, 5.07; N, 6.48.

6-Methoxyindole-3-glyoxamide (19). A solution of **7** (40 g, 0.272 mmol) in THF (600 mL) was cooled to −5 °C and treated dropwise with oxalyl chloride (26.1 mL, 1.1 equiv) at such a rate that the reaction temperature did not exceed 1 °C (2−4 min). The reaction was stirred at −4 °C for 1.5 h and then transferred by cannula to 29% NH_4OH (200 mL) at such a rate that the reaction temperature remained below 10 °C (10 min). The resultant yellow slurry was stirred at −5 °C for 15 min and then filtered (slow). The filter cake was washed with water (3 × 100 mL) and dried to afford 40.2 g of a yellow powder. The filtrate was concentrated in vacuo to a volume of 400 mL, and the brown solid that precipitated was filtered, washed with water (3 × 100 mL), and dried to afford an additional 20.14 g of solid. The isolated solids were combined in acetone (250 mL) and the mixture heated briefly to reflux, then cooled to 0−5 °C and stirred for 10−15 min. The yellow solid obtained was filtered, washed with the minimal amount of acetone, and dried to afford 53.58 g (90%) of **19**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.87 (s, 1H), 8.60 (s, 1H), 8.09 (d, 1H, J = 8.7 Hz), 8.05 (s, 1H), 7.68 (s, 1H), 7.05 (d, 1H, J = 2.2 Hz), 6.91 (app dd, 1H, J = 8.6 Hz, 2.4 Hz), 3.81 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 182.7, 166.0, 156.7 137.4, 137.2, 121.8, 119.9, 112.2 111.9, 95.7 55.2; IR (KBr) ν 3403, 3210, 2832, 1698, 1624, 1587, 1519, 1448, 1396, 1348, 1295, 1260, 1147, 1093, 1023 cm^{-1}; HRMS (ES+) exact mass calcd for $C_{11}H_{10}N_2O_3$ 218.0691, found 218.0694.

3-(6-Methoxy-1*H*-indol-3-yl)-4-(1-methyl-1*H*-indol-7-yl)-pyrrole-2,5-dione (2a). Strategy A. A slurry of **3** (2.0 g, 10.6 mmol) and **4a** (2.73 g, 11.7 mmol) in THF (100 mL) was cooled to 0 °C in an ice−water bath. *t*-BuOK (1.0 M in THF, 43.0 mL, 43 mmol) was added dropwise through an addition funnel while the reaction temperature was maintained <1 °C. The solution was stirred at 0 °C for 30 min and then warmed to 50 °C. Reaction progress was monitored by HPLC, and after ∼2 h no starting material remained. The reaction mixture was cooled to rt and 1.0 M HCl added dropwise over a period of 1 h; during this time, the temperature increased to 31 °C and the color of the reaction mixture changed from purple to orange. The orange solution was transferred to a separatory funnel and diluted with water (200 mL). The aqueous layer was extracted with EtOAc (2 × 200 mL), and the combined organic layers were washed with saturated $NaHCO_3$ (aq) (200 mL) and brine (100 mL) and dried ($MgSO_4$). The solution was concentrated in vacuo to afford a brown solid that was purified by silica gel chromatography (1:2 hexane/EtOAc) to afford 2.56

g (65%) **2a** as an orange solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.65 (s, 1H), 11.11 (s, 1H), 7.85 (s, 1H), 7.63 (dd, 1H, J = 7.7 Hz, 1.09 Hz), 7.24 (d, 1H, J = 2.9 Hz), 7.00 (app t., 1H, J = 15 Hz), 6.92 (dd, 1H, J = 7.3 Hz, 1.1 Hz), 6.85 (d, 1H, J = 2.2 Hz), 6.49 (d, 1H, J = 2.9 Hz), 6.24 (d, 1H, J = 8.8 Hz), 6.15 (app dd, 1H, J = 9.0 Hz, 4.8 Hz), 3.68 (s, 3H), 3.66 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.4 172.4 155.8 137.3, 135.2, 134.2, 131.5 130.4, 129.5, 128.2, 124.0, 121.6 121.4, 118.7 118.6 115.2 109.7 105.3, 100.7 94.9, 55.0, 34.6; IR (KBr) ν 3307, 1751, 1691, 1633, 1616, 1512, 1343, 1298, 1164, 1156 cm^{-1}. Anal. Calcd for $C_{22}H_{17}N_3O_3$: C, 71.14; H, 4.61; N, 11.31. Found: C, 71.34; H, 4.83; N, 11.13.

3-(6-Methoxy-1*H*-indol-3-yl)-4-(1-methyl-1*H*-indol-7-yl)-pyrrole-2,5-dione (2a). Strategy B. Compounds **6b** (7.78 g, 26.91 mol, 80% pure) and **5a** (5 g, 24.48 mol) were charged to a reaction vessel with THF (350 mL). The slurry was cooled to −3 °C (ice/acetone bath) and *t*-KOBu (1.0 M in THF, 110 mL) added dropwise at such a rate as to maintain the temperature below 0 °C. Upon completion of the addition, the reaction temperature was allowed to rise to ambient temperature (over 30 min) and then heated at reflux for 345 min. Upon completion, the reaction mixture was allowed to cool to ambient temperature and partitioned with water (700 mL) and EtOAc (700 mL). The organic layer was washed with brine and dried ($MgSO_4$). The solvent was removed in vacuo to yield 8 g of an orange foam of 80% purity. The crude product was chromatographed by passing it through silica and eluting with 5:1 CH_2Cl_2/EtOAc to afford 5.32 g (52%) of **2a**.

3-[1-(3-Hydroxypropyl)-6-methoxy-1*H*-indol-3-yl]-4-(1-methyl-1*H*-indol-7-yl)-1*H*-pyrrole-2,5-dione (2b). To a solution of **4b** (5.47 g, 13.5 mmol) and **3** (2.55 g, 13.5 mmol) in DMF (250 mL) was added *t*-BuOK (1.0 M solution in THF, 40.5 mL, 40.5 mmol). The reaction was stirred at rt for 24 h, quenched with 1 N HCl, and stirred for 1 h. The reaction mixture was poured into EtOAc (1.5 L), washed with 1 N HCl, saturated $NaHCO_3$ (aq), and brine, and dried ($MgSO_4$). The solution was concentrated in vacuo and the crude red solid triturated and recrystallized with Et_2O/hexane to give 3.6 g (62%) of **2b** as a red solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.10 (s, 1H), 7.94 (s, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.23 (d, J = 3 Hz, 1H), 6.98 (m, 2H), 6.85 (d, J = 7 Hz, 1H), 6.47 (dd, J = 3 Hz, 1H), 6.07 (d, J = 9 Hz, 2H), 6.00 (d, J = 9 Hz, 1H), 4.62 (t, J = 5.2 Hz, 1H), 4.21 (t, J = 7.2 Hz, 2H), 3.67 (s, 3H), 3.65 (s, 3H), 3.34 (app quartet, J = 5.6 Hz, 2H), 1.83 (app quintet, J = 6.8 Hz, 2H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 173.5, 172.4, 155.9, 137.3, 134.6, 134.3, 133.6, 131.6, 129.6, 127.8, 124.2, 121.8, 121.6, 119.1, 118.6, 115.3, 109.7, 104.5, 100.7, 93.9, 57.5, 55.2, 42.8, 34.7, 32.4; IR (KBr) ν 3516, 3176, 1688 cm^{-1}; HRMS (M^+ + 1) calcd for $C_{25}H_{24}N_3O_4$ 430.1767, found 430.1748. Anal. Calcd for $C_{25}H_{23}N_3O_4$: C, 69.92; H, 5.40; N, 9.78. Found: C, 69.55; H, 5.45; N, 9.59.

3-[1-(3-Bromopropyl)-6-methoxy-1*H*-indol-3-yl]-4-(1-methyl-1*H*-indol-7-yl)-1*H*-pyrrole-2,5-dione (2c). To a solution of **2b** (3.0 g, 7.0 mmol) in DMF (300 mL) were added PPh_3 (2.6 g, 10.5 mmol) and CBr_4 (3.3 g, 10.5 mmol). The reaction mixture was stirred at rt under N_2 for 1 h. After 2 h, the reaction mixture was diluted with EtOAc (300 mL) and water (800 mL). The aqueous phase was extracted with EtOAc (3 × 300 mL), and the combined organic phases were washed with saturated $NaHCO_3$ (aq) and brine and dried ($MgSO_4$). The solution was concentrated in vacuo and the crude product purified by silica gel chromatography (3:7 EtOAc/hexanes) gave 2.4 g (71%) **2c** as a red solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.04 (s, 1H), 7.88 (s, 1H), 7.62 (d, J = 6.1 Hz, 1H), 7.19 (d, J = 2.6 Hz, 1H), 7.00−6.91 (m, 2H), 6.84 (d, J = 6.0 Hz, 1H), 6.48 (d, J = 2.5 Hz, 1H), 6.10 (m, 2H), 4.27 (t, J = 5.8 Hz, 2H), 3.71 (s, 3H), 3.62 (s, 3H), 3.32 (t, J = 5.8 Hz, 2H), 2.11 (m, 2H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 173.4, 172.4, 156.1, 137.1, 134.5, 134.2, 133.2, 131.6, 129.6, 128.5, 124.1, 122.0, 121.6, 119.7, 118.6, 115.1, 109.9, 104.8, 100.8, 93.8, 55.3, 44.2, 34.7, 32.4, 31.4; IR (KBr) ν 3186, 1690 cm^{-1}; HRMS (M^+ + 1) calcd for $C_{25}H_{23}BrN_3O_3$ 492.0923, found 492.0920.

3-[7-(2-Hydroxyethyl)-1*H*-indol-3-yl]-4-(1-methyl-1*H*-indol-7-yl)-1*H*-pyrrole-2,5-dione (2d). *t*-BuOK (1.0 M in THF, 6.2 mL, 6.2 mmol) was added dropwise to solution of **3** (1.20 g, 6.35 mmol) in DMF (50 mL) followed after 5 min by a solution of **4c** (1.57 g, 6.35 mmol) in DMF (25 mL) dropwise over 10 min giving a yellow-brown solution. After 90 min, additional *t*-BuOK (6.6 mL, 6.6 mmol) was introduced, and the reaction was stirred for 24 h. The maroon-purple reaction mixture was quenched with 1 N HCl and concentrated to 20−30 mL and the red slurry diluted with EtOAc. The two layers were separated, and the organic layer was washed with H_2O, saturated $NaHCO_3$ (aq), and brine and dried ($MgSO_4$). The resultant solution was concentrated onto SiO_2 in vacuo and the product purified by silica gel chromatography (7:3 EtOAc/hexanes) to give 1.24 g (50%) of **2d** as a red solid. Also a product of chromatography was a mixture of the product and the starting acetamide (10:1, 0.365 g). The yield of the product based on recovered starting material was 72%: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.81 (s, 1H), 11.14 (s, 1H), 7.86 (d, J = 3 Hz, 1H), 7.60 (d, J = 8 Hz, 1H), 7.27 (d, J = 3 Hz, 1H), 6.96 (dd, J = 7, 7 Hz, 1H), 6.87 (d, J = 7 Hz, 1H), 6.81 (d, J = 7 Hz, 1H), 6.49 (d, J = 3 Hz, 1H), 6.43 (dd, J = 8, 8 Hz, 1H), 6.25 (d, J = 8 Hz, 1H), 4.67 (t, J = 5 Hz, 1H), 3.70 (s, 3H), 3.64 (m, 2H), 2.90 (t, J = 6.7 Hz, 2H); HRMS (M^+ + 1) calcd for $C_{23}H_{20}N_3O_3$ 386.1505, found 386.1495. Anal. Calcd for $C_{23}H_{19}N_3O_3$: C, 71.68; H, 4.97; N, 10.90. Found: C, 71.33; H, 5.13; N, 10.83.

3-[7-(2-Bromoethyl)-1*H*-indol-3-yl]-4-(1-methyl-1*H*-indol-7-yl)-1*H*-pyrrole-2,5-dione (2e). Method A. CBr_4 (3.05 g, 9.20 mmol) was added in one portion to a solution of **2d** (2.88 g, 7.47 mmol) and PPh_3 (2.32 g, 8.84 mmol) in DMF (50 mL), and the mixture stirred at rt for 4 h. The solution was concentrated to about 10 mL, poured into EtOAc, washed with water, saturated $NaHCO_3$ (aq), and brine, and dried ($MgSO_4$). The solution was concentrated onto SiO_2 in vacuo and the product purified by silica gel chromatography (30 to 50% EtOAc/hexanes) to afford 2.31 g (69%) of **2e** as an orange solid: ^{1}H NMR (400 MHz, acetone-d_6) δ 11.13 (s, 1H), 9.90 (s, 1H), 8.30 (d, J = 3 Hz, 1H), 7.62 (m, 1H), 7.17 (d, J = 3 Hz, 1H), 6.92−6.98 (m, 3H), 6.44−6.55 (m, 3H), 3.82 (s, 3H), 3.68 (t, J = 8 Hz, 2H), 3.39 (t, J = 8 Hz, 2H); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 173.5, 172.4, 135.2, 134.2, 131.6, 131.0, 129.5, 129.2, 125.0, 124.0, 122.6, 122.4, 121.5, 120.1, 119.5, 118.6, 115.1, 105.5, 100.7, 34.7, 33.9, 33.1 (one aromatic signal is buried); IR (KBr) ν 3430, 1756, 1699 cm^{-1}; HRMS (M^++1) calcd for $C_{23}H_{19}BrN_3O_2$ 448.0661, found 448.0665. Anal. Calcd for $C_{23}H_{18}BrN_3O_2$: C, 61.62; H, 4.05; N, 9.37. Found: C, 61.60; H, 4.20; N, 9.08.

Method B. To a solution of **2d** (0.5 g, 1.3 mmol) in CH_2Cl_2/THF (40/30 mL) were added PPh_3 (0.3 g, 1.3 mmol) and CBr_4 (0.4 g, 1.3 mmol). The reaction mixture was stirred at rt and under N_2 for 1 h. Another 1 equiv of PPh_3 (0.3 g, 1.3 mmol) was added followed by 1 equiv of CBr_4 (0.4 g, 1.3 mmol). This operation was repeated one more time after 1 h. The reaction was monitored by TLC and was completed after 1 h. The reaction mixture was diluted with EtOAc (100 mL), washed with saturated $NaHCO_3$ (aq) and brine, and dried ($MgSO_4$). The solution was concentrated in vacuo and the product purified by silica gel chromatogprahy (1:1 EtOAc/hexanes) to give 0.5 g (87%) **2e** as a red solid.

9-Methoxy-3-methyl-3*H*-indolo[6,7-*a*]pyrrolo[3,4-*c*]carbazole-4,6(5*H*,11*H*)-dione (1a). A solution of **2a** (3.00 g, 8.08 mmol) and DDQ (1.83 g, 8.08 mmol) in EtOAc (1 L) was irradiated in a 1 L photolysis reactor using a Hanovia medium-pressure Hg lamp through a Pyrex filter at 25−45 °C for ∼3 h. The reaction solution was washed with aqueous 0.1 N NaOH (4 × 150 mL) and brine (150 mL) and dried ($MgSO_4$). The solution was concentrated in vacuo and the solid triturated with CH_2Cl_2 (150 mL), filtered, and dried to afford 2.59 g (87%) **1a** as an orange-red solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.60 (s, 1H), 11.07 (s, 1H), 8.86 (d, 1H, J = 8.8 Hz), 8.25 (d, 1H, J = 8.8 Hz), 8.04 (d, 1H, J = 8.4 Hz), 7.57 (d, 1H, J = 2.9

Hz), 7.20 (d, 1H, J = 2.2 Hz), 7.02 (dd, 1H, J = 8.8, 2.2 Hz), 6.85 (d, 1H, J = 2.9 Hz). 3.95 (s, 3H), 3.93 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 170.6, 159.1, 142.0, 141.6, 132.4, 131.8, 127.4, 126.3, 125.1, 123.1, 120.4, 117.4, 115.2, 114.0, 113.2, 112.0, 109.6, 103.5, 94.8, 55.3, 38.4; IR ($CHCl_3$) ν 3363, 3194, 3042, 2978, 2931, 2828, 1746, 1707, 1630, 1615 cm^{-1}; HRMS (ES+) calcd for $C_{22}H_{15}N_3O_3$ 369.1110, found 369.1108.

11-(3-Hydroxypropyl)-9-methoxy-3-methyl-3*H*-indolo-[6,7-*a*]pyrrolo[3,4-*c*]carbazole-4,6(5*H*,11*H*)-dione (1b). A solution of **2b** (2.0 g, 4.65 mmol) and DDQ (1.06 g, 4.65 mmol) in EtOAc (1 L) was photolyzed with 450 W Hanovia lamp through a Pyrex filter for 2.25 h. The mixture was purified by plug filtration through silica gel eluting with EtOAc and recrystallized from toluene/MeOH/hexane to give 1.1 g (55%) of **1b** as a red solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.07 (s, 1H), 8.98 (d, J = 8.4 Hz, 1H), 8.36 (d, J = 8.8 Hz, 1H), 7.97 (d, J = 8.8 Hz, 1H), 7.56 (d, J = 3.2 Hz, 1H), 7.40 (d, J = 1.6 Hz, 1H), 7.04 (dd, J = 2.4, 8.6 Hz, 1H), 6.81 (d, J = 3.2 Hz, 1H), 4.90 (t, J = 7.2 Hz, 2H), 4.86 (br s, 1H), 3.94 (s, 3H), 3.83 (s, 3H), 3.57 (t, J = 5.2 Hz, 2H), 2.14 (app quintet, J = 6 Hz, 2H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 170.4, 170.2, 159.3, 143.7, 140.1, 132.4, 131.7, 126.4, 125.3, 125.2, 122.6, 120.7, 117.9, 114.5, 114.2, 114.1, 113.4, 109.8, 102.9, 93.9, 57.8, 55.4, 43.1, 38.2, 32.3; IR (KBr) ν 3560, 3178, 1744, 1696 cm^{-1}. Anal. Calcd for $C_{25}H_{21}N_3O_4$: C, 70.25; H, 4.95; N, 9.83. Found: C, 70.58; H, 5.06; N, 9.58.

11-(3-Bromopropyl)-9-methoxy-3-methyl-3*H*-indolo-[6,7-*a*]pyrrolo[3,4-*c*]carbazole-4,6(5*H*,11*H*)-dione (1c). A solution of **2c** (0.7 g, 1.4 mmol) and DDQ (0.3 g, 1.4 mmol) in EtOAc/dioxane (600/400 mL) was irradiated with a 450 W Hanovia medium-pressure lamp through a Pyrex filter. After 1 h, the reaction mixture was washed with 0.1 N NaOH (500 mL) and brine (500 mL) and dried ($MgSO_4$). The solution was concentrated in vacuo and the product purified by silica gel chromatography (EtOAc) to afford 0.6 g (87%) of **1c** as a red solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.09 (s, 1H), 8.99 (d, J = 8.7 Hz, 1H), 8.30 (d, J = 8.9 Hz, 1H), 7.99 (d, J = 8.9 Hz, 1H), 7.58 (d, J = 3.0 Hz, 1H), 7.41 (d, J = 1.8 Hz, 1H), 7.06 (dd, J = 8.7, 2.1 Hz, 1H), 6.83 (d, J = 3.0 Hz, 1H), 4.96 (t, J = 7.2 Hz, 2H), 3.96 (s, 3H), 3.84 (s, 3H), 3.70 (t, J = 6.1 Hz, 2H), 2.51 (m, 2H); HRMS (M^+ + 1) calcd for $C_{25}H_{21}N_3O_3$ 490.0766, found 490.0764.

3,5-Dihydro-11-[3-[(2-hydroxyethyl)amino]propyl]-9-methoxy-3-methyl-3*H*-indolo[6,7-*a*]pyrrolo[3,4-*c*]carbazole-4,6(5*H*,11*H*)-dione (1d). A mixture of**1c** (150 mg, 0.30 mmol), 2-aminoethanol (0.25 mL, 3.81 mmol), and DMF (10 mL) was heated at 65 °C overnight. The reaction was allowed to cool and concentrated to a red oil. The oil was taken up in EtOAc, washed with H_2O, saturated $NaHCO_3$ (aq), and brine, and dried ($MgSO_4$). The solution was concentrated in vacuo, and a 0.154 mM solution of methansulfonic acid in CH_3CN (1.95 mL) was added to the crude product. The resultant organic layer was extracted with H_2O (10 and 5 mL), and the combined aqueous solutions were freeze-dried. The salt was obtained dissolved in H_2O (2 mL) and 0.1 N NaOH (3 mL) added. The product that precipitated was collected by filtration, rinsed with H_2O, and freeze-dried to give 73 mg (42%) of **1d**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.98 (d, J = 8 Hz, 1H), 8.37 (d, J = 9 Hz, 1H), 7.98 (d, J = 9 Hz, 1H), 7.57 (d, J = 3 Hz, 1H), 7.42 (d, J = 2 Hz, 1H), 7.03 (dd, J = 8, 2 Hz, 1H), 6.81 (d, J = 3 Hz, 1H), 4.91 (t, J = 7 Hz, 2H), 4.48 (br s, 1H), 3.95 (s, 3H), 3.83 (s, 3H), 3.48 (t, J = 6 Hz, 2H), 2.64 (t, J = 6 Hz, 2H), 2.58 (t, J = 6 Hz, 2H), 2.07 (m, 2H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 170.4, 170.2, 159.3, 143.7, 140.1, 132.5, 131.7, 126.4, 125.3, 125.2, 122.7, 120.8, 118.0, 114.5, 114.12, 114.10, 113.4, 110.0, 102.9, 94.0, 60.3, 55.5, 51.7, 45.9, 44.0, 38.2, 29.3; IR (KBr) ν 3371, 1742, 1694 cm^{-1}; HRMS (M^+ + 1) calcd for $C_{27}H_{27}N_4O_4$ 471.2032, found 471.2035.

10-(2-Hydroxyethyl)-3-methyl-3*H*-indolo[6,7-*a*]pyrrolo-[3,4-*c*]carbazole-4,6(5*H*,11*H*)-dione (1e). A solution of **2d** (0.80 g, 2.0 mmol) and DDQ (0.50 g, 2.0 mmol) in EtOAc (1000 mL) was irradiated with a 450 W Hanovia medium-pressure lamp through a Pyrex filter for 0.5 h. The dark red mixture was washed with 0.1 N NaOH (500 mL) and brine (500 mL) and dried ($MgSO_4$). The resultant solution was concentrated in vacuo and purified by silica gel chormatopgraphy (30:70 EtOAc/hexanes) to afford 0.70 g (95%) of **1e** as a red solid: ^{1}H (400 MHz, DMSO-d_6) δ 12.15 (s, 1H), 11.07 (s, 1H), 8.85 (d, J = 8 Hz, 1H), 8.57 (d, J = 8 Hz, 1H), 8.05 (d, J = 8 Hz, 1H), 7.58 (d, J = 3 Hz, 1H), 7.38 (d, J = 8 Hz, 1H), 7.29 (dd, J = 8 Hz, 1H), 6.84 (d, J = 3 Hz, 1H), 4.81 (t, J = 5 Hz, 1H), 3.88 (s, 3H), 3.84 (m, 2H), 3.30 (t, J = 7 Hz, 2H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 170.6, 170.5, 141.6, 139.5, 132.6, 131.8, 127.7, 127.1, 127.0, 123.1, 122.9, 122.0, 121.5, 120.7, 120.5, 117.8, 114.8, 113.6, 112.1, 103.4, 61.2, 38.4, 34.3; IR (KBr) ν 3455, 3187, 1734, 1696 cm^{-1}; HRMS (M^+ + 1) calcd for $C_{23}H_{18}N_3O_3$ 384.1348, found 384.1347.

10-(2-Bromoethyl)-3-methyl-3*H*-indolo[6,7-*a*]pyrrolo-[3,4-*c*]carbazole-4,6(5*H*,11*H*)-dione (1f). A solution of **2e** (2.23 g, 4.98 mmol) and DDQ (1.13 g, 4.98 mmol) in dioxane (800 mL) was irradiated with a 450W Hanovia mercury arc lamp through a Pyrex filter for 2.5 h. The dark solution was concentrated to about 40 mL and poured into EtOAc. The EtOAc solution was washed with 0.1 N NaOH, saturated $NaHCO_3$ (aq), and brine, dried ($MgSO_4$), and concentrated to about 50 mL. Hexanes (2−3 mL) were added and the solution allowed to stand 4 h. Filtration afforded 1.41 g (64%) of **1f** as a red solid that was dried under vacuum at 75 °C. The mother liquor was concentrated onto silica gel and purified (30:70 EtOAc/hexanes) to afford an additional 0.62 g (28%) of **1f**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.24 (s, 1H), 11.10 (s, 1H), 8.91 (d, J = 8 Hz, 1H), 8.55 (d, J = 8 Hz, 1H), 8.07 (d, J = 8 Hz, 1H), 7.60 (d, J = 3 Hz, 1H), 7.47 (d, J = 8 Hz, 1H), 7.33 (dd, J = 8, 8 Hz, 1H), 6.85 (d, J = 3 Hz, 1H), 3.92 (t, J = 7.5 Hz, 2H), 3.88 (s, 3H), 3.70 (t, J = 7.5 Hz, 2H). Anal. Calcd for $C_{23}H_{16}BrN_3O_2$: C, 61.90; H, 3.61; N, 9.42. Found: C, 61.61; H, 3.55; N, 9.48.

3-Methyl-10-[2-(1-piperidinyl)ethyl]-3*H*-indolo[6,7-*a*]-pyrrolo[3,4-*c*]carbazole-4,6(5*H*,11*H*)-dione (1g). A solution of **1f** (100 mg, 0.22 mmol) and piperidine (0.21 mL, 2.2 mmol) in DMF (5 mL) was heated at 60 °C overnight. The mixture was cooled and the product separated by directly injecting the mixture in two 2.5 mL portions onto a 7 μm C18 reversed-phase HPLC column (19 × 300 mm) with gradient elution with 95:5 H_2O (0.1% HCl)/CH_3CN to 5:95 H_2O (0.1% HCl):CH_3CN. Fractions containing product where passed through an SCX column, washing first with MeOH and EtOAc, and then a 1:1 mixture of 2 M NH_3 in MeOH and EtOAc. Concentration of the latter afforded 95 mg (95%) of **1g** as an orange solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.32 (br s, 1H), 11.07 (s, 1H), 8.83 (d, J = 7 Hz, 1H), 8.55 (d, J = 8 Hz, 1H), 8.03 (d, J = 8 Hz, 1H), 7.57 (d, J = 3 Hz, 1H), 7.35 (d, J = 7 Hz, 1H), 7.28 (dd, J = 7, 7 Hz, 1H), 6.83 (d, J = 3 Hz, 1H), 3.87 (s, 3H), 3.32 (br t, J = 7.6 Hz, 4H), 2.74 (m, 2H), 2.59 (m, 2H), 1.60 (m, 4H), 1.45 (m, 2H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 170.5, 170.5, 141.6, 139.3, 132.6, 131.8, 127.7, 127.0, 126.3, 124.2, 122.9, 121.9, 121.5, 120.63, 120.57, 117.8, 114.8, 113.5, 112.2, 103.4, 59.2, 54.2, 38.4, 28.2, 25.5, 24.1; IR (KBr) ν 3214, 1744, 1695 cm^{-1}; HRMS (M^+ + 1) calcd for $C_{28}H_{27}N_4O_2$ 451.2134, found 451.2158.

Acknowledgment. We thank Professors Marvin Miller, Bill Roush, Peter Wipf, Ted Taylor, Paul Wender, and Leo Paquette for helpful discussions during the course of this work. Mr. Paul Dodson and Mr. Michael Henshaw are acknowledged for their analytical support for this project. Dr. Sam Wendel is acknowledged for his help in developing the enzymatic hydrolysis of **18**. We thank Drs. Walter Xie, C. Richard King, Bruno Geithlen, Julia L. Barkin, Michael K. Hilinski, and Gene Kogut for help with scale-up and synthesis of intermediates.

JO035606V