Synthesis of Polysubstituted Indoles and Indolines by Means of Zirconocene-Stabilized Benzyne Complexes

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Abstract: The development of a new method for the regiospecific synthesis of polysubstituted indoles and indolines is reported. The key steps involve the generation of zirconocene-stabilized benzyne complexes and subsequent intramolecular olefin insertion reactions to provide tricyclic indoline zirconacycles. The zirconacyclic intermediates were cleaved with iodine to yield diiodo indolines, which were converted to a wide variety of indole and indoline products, such as analogs of tryptamine, serotonin, tryptophan, and the pharmacophore of CC-1065.

Introduction

The indole nucleus is a common feature of a variety of natural products.[1] Many of these compounds and their analogs possess potent biological activity and are therefore attractive synthetic targets. Among indoles, those which are substituted at the 3- and 4-positions, such as the ergot alkaloids,[2] indolactam V,[3] chuangxinmycin,[4] and CC-1065,[5] have recently received attention by synthetic chemists due to their biological activity and synthetically interesting structures.

Although a large number of methods exist for the synthesis of substituted indoles,[1] the synthesis of 3,4-disubstituted indoles still represents a formidable task. The main difficulty is that the 4-position of the indole ring system is much less electron-rich than other positions, rendering "traditional" strategies, such as electrophilic aromatic substitution, less effective than in other heterocyclic ring systems.[6] For this reason, special methods have been developed for the synthesis of these important compounds, and they can be divided into two broad categories. The first approach is to construct the pyrrole ring using an annelation method onto an appropriately substituted aromatic precursor. Among these methods are the Fischer,[7] Madelung,[8] Reissert,[9] and Batcho–Leimgruber[10] indole syntheses. More recently, organometallic methods have played an increasingly important role in this annelation approach.[11] Some of the more successful methods involve catalysis by Ni(0), Pd(0), or Pd(II) species as developed by Ban,[12] Larock,[13] Hegedus,[14] and Stille.[15] The advantages of these methods are that they generally require only a catalytic amount of a metal complex and that they are tolerant of a range of functional groups. One drawback of these approaches, however, is the need for polysubstituted benzenoid starting materials which can be either difficult to prepare or expensive.

The second approach to the synthesis of 3,4-di-substituted indoles is to introduce a substituent directly into the 4-position of an existing indole framework. Among the most successful

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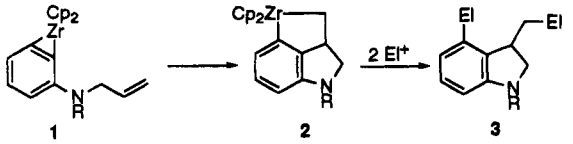
Scheme 1



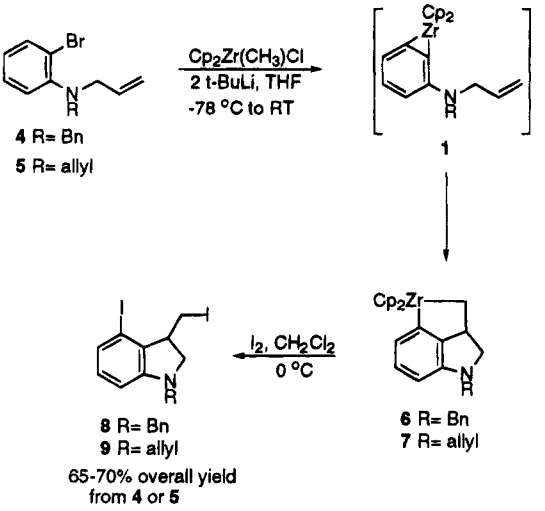
methods in this category are the use of chromium tricarbonyl complexes of indoles introduced by Kozikowski and further developed by Widdowson,[16] the thallation/palladation method of Somei,[17] and the lithiation of gramine by Iwao.[18] These methods have been successfully used in the synthesis of several natural products, including indolactam V.[4] In some cases, however, the regiochemistry of the substitution reaction is difficult to control, resulting in regioisomeric mixtures of products. In addition, the use of highly toxic metals such as chromium or thallium can present safety and waste-disposal problems.

The present work describes the development of a methodology which we feel is complementary to those discussed above. This technique is based on the regioselective generation and coupling reactions of zirconocene-stabilized benzyne complexes.[19] The use of these complexes provides a general means for the synthesis of polysubstituted aromatic compounds with essentially complete regiochemical control. Until recently, our work has dealt with the intermolecular insertion reactions of benzyne complexes. We reasoned, however, that the intramolecular insertion reaction of an *N*-allylaniline which contains a suitably disposed benzyne complex **1** would produce a 3,4-disubstituted indoline zirconacycle **2** (Scheme 1). Cleavage of the zirconacycle with electrophiles would then afford a regiochemically pure 3,4-disubstituted indoline **3** that could be used for the synthesis of more complex indolines and indoles.[20]

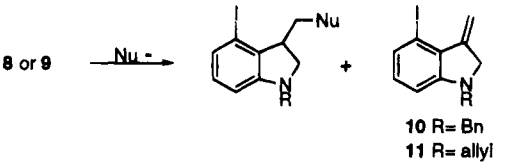
Results and Discussion

The first example of this intramolecular insertion reaction was realized (Scheme 2) when a mixture of *N*-allyl-*N*-benzyl-2-bromoaniline (**4**) and bis(cyclopentadienyl)zirconium methyl chloride was treated with 2 equiv of *tert*-butyllithium in THF at −78 °C to afford zirconacycle **6**, presumably via benzyne complex **1** (R = benzyl). Treatment of zirconacycle **6** with 2 equiv of iodine effected cleavage of both carbon−zirconium bonds to give diiodo indoline **8** in 67% yield (based on **4**). Two important goals were realized in the transformation of **4** to **8**. First, the indole skeleton was constructed from readily prepared materials. Second, and most importantly, the 3- and 4-positions of the indole skeleton were functionalized in a *regiospecific* manner. Initially we used a benzyl group as a nitrogen protecting group for the *N*-allyl-2-bromoaniline precursor **4**.[20a] We later found that a second allyl group could function equally well without affecting either the formation or the electrophilic

Scheme 2



Scheme 3



cleavage of the metallacycle.[20b] Additionally, we found that *N*,*N*-diallyl-2-bromoaniline (**5**) is more convenient to prepare than **4**. For instance, **5** has been prepared on a 90 mmol scale in 78% yield by heating 2-bromoaniline with allyl bromide in the presence of Na_2CO_3 in DMF. Due to the ease of preparation of **5**, we began using diallyl substrates almost exclusively later in our studies to give 1-allyl-4-iodo-3-(iodomethyl)indolines such as **9**. Although zirconacycles **6** and **7** have been isolated in pure form and spectroscopically characterized, we found that it is not necessary to isolate any organometallic intermediates in order to obtain **8** or **9** in good yield (typically 60−70%) and in pure form.

Nucleophilic Substitution Reactions of 9. We were interested in using diiodo indolines such as **8** and **9** as intermediates for the synthesis of more highly functionalized indole derivatives. We began by investigating whether nucleophilic substitution reactions of the alkyl iodide could be used to further functionalize **8** and **9**. We found that when either **8** or **9** was treated with nucleophiles, two competing reactions occurred. The first reaction was one in which the alkyl iodide was displaced to give the desired substitution product. In the second reaction, dehydrohalogenation occurred to yield 3-methyleneindolines **10** and **11** (Scheme 3). For most nucleophilic reagents such as sodium methoxide, sodium acetate, and Grignard reagents, olefins **10** and **11** were the sole products. However, if either **8** or **9** was treated with "soft" carbon nucleophiles such as malonate anion, both the desired substitution product and the olefin were produced. When the malonate anion was generated before the addition of **8** or **9** to the reaction mixture, olefins **10** and **11** were the only observed products. However, if the malonate anion was generated in the presence of **9** using either sodium or potassium carbonate, both the substitution product and the elimination product were observed in approximately equal amounts, as estimated by ^1H NMR. The addition of a phase-transfer catalyst, such as tetra-*n*-butyl ammonium chloride,[21] to the reaction mixture improved the yield of the substitution product only slightly, even when a stoichio-

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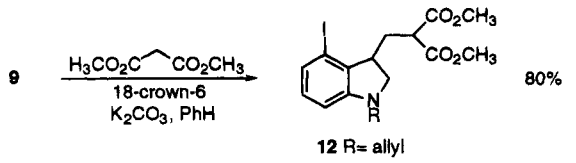
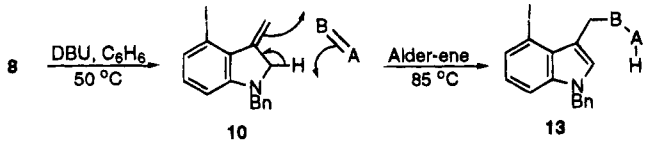
Scheme 4



Scheme 5

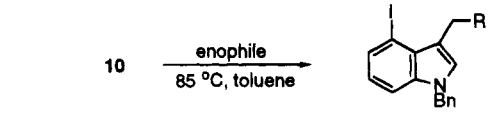


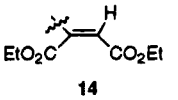
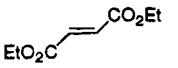
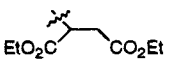
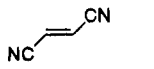
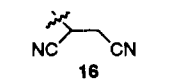
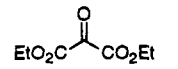
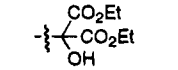
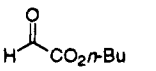
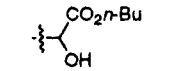
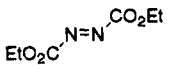
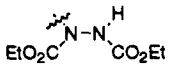
metric amount was employed. However, the addition of a *stoichiometric* amount of 18-crown-6[22] when K_2CO_3 was employed significantly improved the yield of the desired substitution product. Of the solvents investigated, we found benzene to give the highest yield of substitution product. Under these conditions, dimethyl malonate derivative **12** was obtained in 80% isolated yield (Scheme 4). It is important to note in this case that the purity of isolated **12** was >95% as determined by ^{1}H NMR and GC, and that olefin **11** was not a contaminant. However, olefin **11** did comprise 10−15% of the crude reaction material under these conditions, as estimated by ^{1}H NMR.

Reactions of 3-Methyleneindolines with Enophiles and Electrophiles. We found that olefins **10** or **11** were efficiently produced if **8** or **9** was allowed to react with DBU at 45−60 °C in either benzene or toluene. Although we were unable to obtain either **10** or **11** in pure form due to their tendency to isomerize to the more stable 3-methylindole derivatives, they proved to be surprisingly stable to the conditions in which they were produced. Due to the relationships of **10** and **11** to their aromatic isomers, we postulated that they would undergo Alder−ene reactions[23] with activated enophiles to give indole derivatives (Scheme 5). The ene reactions of **10** with a variety of doubly-activated enophiles were effected under relatively mild conditions (Table 1). For example, the reaction of **10** with diethyl acetylenedicarboxylate at 85 °C gave olefin **14** (Table 1, entry 1) in 53% yield, based on diiodide **8**. We subsequently found that Achmatowicz and co-workers had observed that 4-(*N*,*N*-dimethylamino)styrene derivatives, which are structurally related to olefins **10** and **11**, underwent thermal ene reactions under similarly mild conditions. In contrast, 4-nitrostyrene derivatives, which are more electron poor, failed to undergo ene reactions under the same conditions.[23b]

Deprotection of Diiodoindolines. We desired to utilize a nitrogen protecting group on aniline precursors **4** and **5** that could be removed under mild conditions from either diiodoindolines such as **8** or **9** or an indole product. After much experimentation, we discovered that, for the zirconocene-mediated benzyne coupling reaction, benzyl and allyl groups gave the highest yield of the desired metallacycles. However, the removal of these groups from indolines such as **8** and **9** proved to be troublesome. Attempted removal of the benzyl group from **8** by hydrogenolysis, using Pd/C and H_2 or ammonium formate as the hydrogen source,[24] gave only unchanged starting material. A second approach that we studied

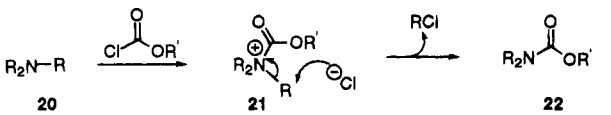
Table 1



Entry	Enophile	Product (R)	Yield(%)[a]
1	$EtO_2C-\equiv-CO_2Et$	 **14**	53
2		 **15**	56
3		 **16**	60
4		 **17**	76
5		 **18**	72
6		 **19**	83

[a] Yields refer to isolated yields of purified products based on diiodide precursor **8**.

Scheme 6



was isomerization/hydrolysis of the allyl group in **9**. Wilkinson's catalyst[25] gave only starting material, and the use of $(Ph_3P)_4RhH$[26] required the addition of 25 mol % catalyst in order to force the reaction to completion. Eventually we found that the best method for the deprotection of either the *N*-benzyl- or *N*-allylindolines, **8** or **9**, was dealkylation using haloformates. Olofson and co-workers have shown that tertiary amines can be selectively dealkylated using chloroformates to provide intermediate carbamates,[27] which are cleaved under mild conditions to give secondary amines in good yields. The proposed reaction mechanism in the production of the carbamates involves initial attack of the amine on the chloroformate to produce an ammonium chloride salt **21** (Scheme 6). Alkyl group R is then cleaved by attack of chloride ion to give carbamate **22** and an

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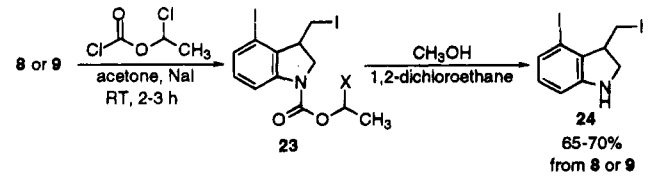
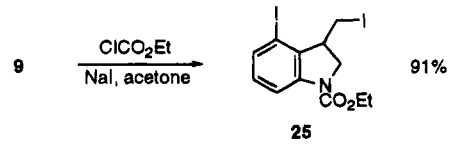
(26) Sundberg, R. J.; Hamilton, G. S.; Laurino, J. P. *J. Org. Chem.* **1988**, *53*, 976.
(27) (a) Olofson, R. A. *Pure Appl. Chem.* **1988**, *60*, 1715. (b) Olofson, R. A.; Abbott, D. E. *J. Org. Chem.* **1984**, *49*, 2795. (c) Olofson, R. A.; Martz, J. T.; Senet, J. P.; Piteau, M.; Malfroot, T. *J. Org. Chem.* **1984**, *49*, 2081.

Scheme 7



Scheme 8



alkyl chloride (RCl). Alternatively, chloride can attack R′, fragmenting the chloroformate, giving CO_2 and an alkyl chloride (R′Cl). The most useful chloroformate for this type of reaction has proven to be 1-chloroethyl chloroformate (ACE-Cl).[27b] Although there are literature reports detailing the dealkylation of aromatic amines using ACE-Cl, the reactions require a large excess of the chloroformate, high temperatures (>150 °C), and long reaction times.[28] When we used ACE-Cl with either **8** or **9** according to the original conditions reported by Olofson, no dealkylation occurred and only unchanged starting materials were recovered. Upon increasing the number of equivalents of the chloroformate and heating the reaction mixture to higher temperatures, only decomposition of the starting materials was observed. We reasoned that the problem was due to the low nucleophilicity of the aromatic amine which retarded the formation of the required ammonium salt **21**. The solution that we found was to make the chloroformate more reactive by converting it *in situ* to an iodoformate.[29] This was accomplished by conducting the dealkylation reaction in acetone with 2 equiv of ACE-Cl and 3 equiv of sodium iodide. Under these conditions, the dealkylation of either **8** or **9** took place readily at *room temperature* to give the desired intermediate carbamate **23** (Scheme 7). We propose that the first step is acyl halide exchange to produce a more reactive iodoformate, which is attacked by the amine to produce an ammonium iodide salt. In addition, since iodide is more nucleophilic than chloride,[30] the cleavage of either the benzyl or allyl group from the salt takes place readily to give carbamate **23** and benzyl or allyl iodide. Under these conditions, either the benzyl or allyl group was selectively cleaved, and no ring fragmentation was observed. Unfortunately, experiments using mass spectroscopy were inconclusive as to whether the second halide in the chloroformate was also exchanging under the reaction conditions. Carbamate **23** was cleaved using methanol and 1,2-dichloroethane (DCE) as cosolvent to give secondary amine **24** in 65–70% overall yield from either **8** or **9**. This modification of Olofson's method was used to successfully prepare a variety of carbamates by utilizing different chloroformates. For example, reaction of diiodide **9** with ethyl chloroformate and NaI in acetone gave ethyl carbamate **25** in 91% yield (Scheme 8). One limitation of the method is that R′ (Scheme 6) must be less prone to undergo nucleophilic attack by iodide than R; otherwise fragmentation of the chloroformate becomes the dominant reaction pathway.

Synthesis of Tryptamine Analogs. We felt that olefins **10** and **11** would be useful not only in the Alder–ene reaction but also as nucleophiles as shown in Scheme 9. We further

Scheme 9

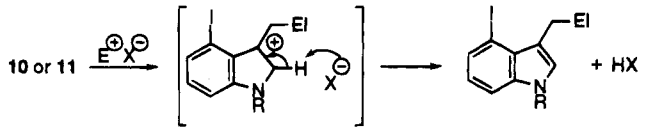
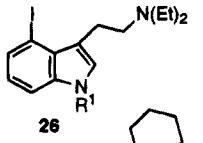
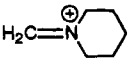
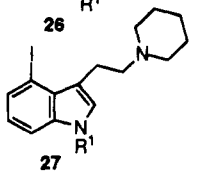
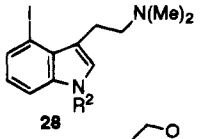
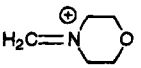
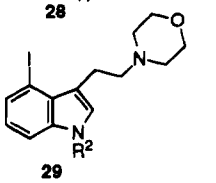
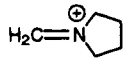
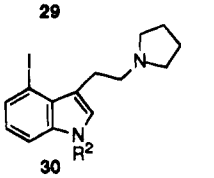


Table 2

Entry	Iminium Salt	Product[a]	Yield[b]
1	$H_2C{=}\overset{\oplus}{N}(Et)_2$	 **26**	85%
2		 **27**	70%
3	$H_2C{=}\overset{\oplus}{N}(Me)_2$	 **28**	85%
4		 **29**	84%
5		 **30**	79%

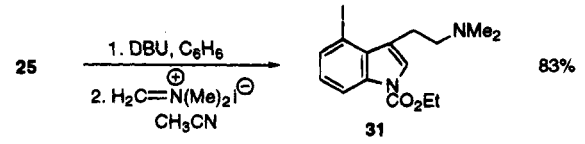
[a] R_1 = Bn, R_2 = allyl. [b] Yield refers to isolated yields based on diiodide precursors **8** or **9**.

reasoned that iminium salts could act as electrophiles, providing a simple synthesis of tryptamine analogs. Further, since a wide variety of iminium salts can be readily prepared,[31] a wide range of tryptamine analogs would be readily available. Typically, the preparation of dialkyl tryptamine analogs involves multistep syntheses, the yields of which can vary widely, depending upon the substituents on the indole ring.[32] The reaction of olefins **10** and **11** with iminium salts in CH_3CN proceeded under extremely mild conditions (45 °C, 2 h) to give 4-iodotryptamine derivatives in excellent yield (Table 2). For example, reaction of **10** with *N*,*N*-diethyl-*N*-methyleneammonium chloride gave diethyltryptamine derivative **26** in 85% yield based on diiodide **8**. It is worth noting that the use of 3-methyleneindolines protected as carbamates, such as **25**, gives the desired tryptamine products in yields comparable to those protected with alkyl groups (Scheme 10).

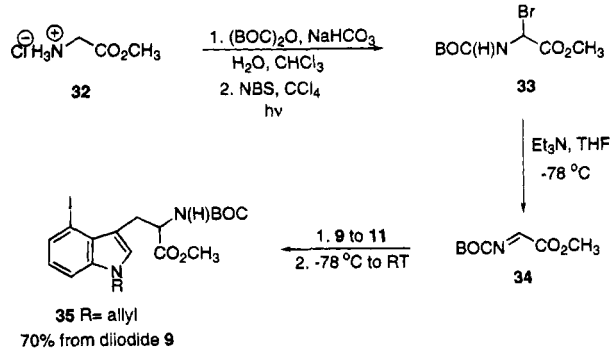
Synthesis of Tryptophan Analogs. On the basis of our success in preparing tryptamine derivatives, we were interested in using a similar methodology for the synthesis of 4-iodotryptophan derivatives. Since tryptophan is the biogenetic precursor of many important indolic natural products, such as the ergot

(28) Bachelet, J. P.; Caubere, P. *J. Org. Chem.* **1982**, *47*, 234.
(29) Hobson, J. D.; McCluskey, J. G. *J. Chem. Soc. C* **1967**, 2015.
(30) March, J. *Advanced Organic Chemistry*, 3rd ed.; Wiley-Interscience: New York, 1985.
(31) (a) Rochin, C.; Babot, O.; Dunogues, J.; Duboudin, F. *Synthesis* **1986**, 228. (b) Bohme, H.; Mundlos, E.; Lehners, W.; Herboth, O. R. *Chem. Ber.* **1957**, *90*, 2008.
(32) For example, see: (a) Macor, J. E.; Post, R.; Ryan, K. *Synth. Commun.* **1993**, *23*, 65. (b) Macor, J. E.; Fox, C. B.; Johnson, C.; Koe, B. K.; Lebel, L. A.; Zorn, S. H. *J. Med. Chem.* **1992**, *35*, 3625. (c) Macor, J. E.; Ryan, K.; Newman, M. E. *Tetrahedron* **1992**, *48*, 1039.

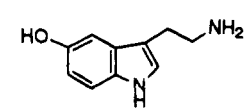
Scheme 10



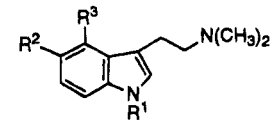
Scheme 11



alkaloids[2] and the teleocidins,[3] the preparation of regiochemically and optically pure polysubstituted tryptophan derivatives is an area of considerable interest.[33] In order to prepare tryptophan derivatives from an olefin such as **10** or **11**, an electrophilic glycine equivalent was required. It is well-known that such species react with nucleophiles such as Grignard reagents, carbanions, electron-rich aromatics, enamines, allylic organometallic reagents, enolates, tin acetylides, and silyl enol ethers.[34] However, to our knowledge, a simple olefin has never served as the nucleophilic component of the reaction. Further, while there are no reported examples of the synthesis of tryptophan derivatives using a glycine cation equivalent, the use of glycine anion equivalents with 3-(halomethyl)indoles is well established.[35] For our initial studies we chose to use (*N*-(*tert*-butoxycarbonyl)imino)acetate **34** as the glycine cation equivalent (Scheme 11).[36] Compounds such as **34** can be prepared by bromination of protected glycine esters with NBS, followed by dehydrohalogenation using a tertiary amine base. Bromoacetate **33** was prepared by reaction of glycine methyl ester hydrochloride with $(BOC)_2O$ followed by photolysis in the presence of NBS.[36] Imine **34** was generated by the addition of triethylamine to a THF solution of **33** at −78 °C. Olefin **11** was then added to the imine to provide 4-iodotryptophan derivative **35** in 70% isolated yield after workup and purification by flash chromatography. We are unsure whether this reaction proceeds through a concerted Alder−ene type or a stepwise, zwitterionic mechanism. However, regardless of mechanism, this reaction can be considered to be an ene reaction.[23b] As such, it is one of the few known intermolecular ene reactions in which an imino substrate acts as the enophile[37] and, to our knowledge, is the first ene reaction involving an imino enophile that proceeds at or below room temperature in the absence of a Lewis acid catalyst.



5-hydroxytryptamine
36



37

Figure 1.

Synthesis of Serotonin Analogs. Another area in which we have been interested is the preparation of serotonin analogs. Serotonin, or 5-hydroxytryptamine (**36**) (Figure 1), is a neurotransmitter that has been implicated in playing either a primary or a modulatory role in many physiological processes,[38] such as hunger, memory, thermoregulation, sleep, sexual behavior, anxiety, and depression. The family of serotonin receptors in mammals has been divided into four groups: 5-HT_1, 5-HT_2, 5-HT_3, and 5-HT_4, with each group containing many subtypes. The structure, binding requirements, and function of many of these receptor sites remain unknown. For these reasons there exists a significant research effort to identify small molecules that bind selectively to one or more types of serotonin receptor. There are several different classes of small molecules that have been studied with respect to their binding to serotonin receptors. Among these ligands are aminotetralines, arylpiperazines, phenylalkylamines, ergolines, and (indolylalkyl)amines.[38] Although serotonin itself is an (indolylalkyl)amine, this structural class of ligands has not been well-studied with respect to its binding characteristics. In addition, only recently have 4-substituted indole derivatives been studied with respect to their 5-HT receptor binding, most notably by Macor and coworkers.[32] The target structures that we were interested in preparing are represented by **37** (Figure 1), where R_2 = functional groups that are capable of acting as hydrogen-bond acceptors. This design is based on the work of Street and coworkers, who showed that the critical pharmacophoric element for binding to a 5-HT_1 receptor is a hydrogen-bond acceptor at the 5-position of the indole ring.[39] We were successful in preparing compounds in which R_2 = methoxy, fluoro, and diallylamino. We also prepared the compound in which R_3 = methyl, since we envisioned that the methyl group could be transformed into a functional group capable of acting as a hydrogen-bond acceptor.

The first analog that we prepared was **41**, in which R_2 = methoxy (Scheme 12). The starting material, 2-bromo-4-methoxyaniline (**38**),[40] was prepared in 42% yield by bromination of *p*-aniside with tetra-*n*-butylammonium tribromide.[41] In this reaction, we found it critical that a 1:1 mixture of CH_3OH/CH_2Cl_2 be used as the solvent system. If either CH_3OH or CH_2Cl_2 was used alone, a mixture of all possible regioisomers was the result. Amine **38** was diallylated using allyl bromide and Na_2CO_3 in DMF to give *N,N*-diallyl-2-bromo-4-methoxyaniline (**39**) in 88% yield. Treatment of a mixture of **39** and bis(cyclopentadienyl)zirconium methyl chloride with 2 equiv

(33) (a) Nagarathnam, D.; Johnson, M. E. *Synth. Commun.* **1993**, *23*, 2011. (b) Jeschke, T.; Wensbo, D.; Annby, U.; Gronowitz, S. *Tetrahedron Lett.* **1993**, *34*, 6471. (c) Allen, M. S.; Hamaker, L. K.; LaLoggia, A. J.; Cook, J. M. *Synth. Commun.* **1992**, *22*, 2077. (d) Schöllkopf, U.; Lonsky, R.; Lehr, P. *Liebigs Ann. Chem.* **1985**, 413.

(34) Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon: Oxford, 1989.

(35) (a) Schöllkopf, U.; Lonsky, R.; Lehr, P. *Liebigs Ann. Chem.* **1985**, 413. (b) Gander-Coquoz, M.; Seebach, D. *Helv. Chim. Acta* **1988**, *71*, 224. (c) Allen, M. S.; Hamaker, L. K.; LaLoggia, A. J.; Cook, J. M. *Synth. Commun.* **1992**, *22*, 2077. (d) Nagarantham, D.; Johnson, M. E. *Synth. Commun.* **1993**, *23*, 2011.

(36) (a) Bretschneider, T.; Miltz, W.; Munster, P.; Steglich, W. *Tetrahedron* **1988**, *44*, 5414. (b) Munster, P.; Steglich, W. *Synthesis* **1987**, 223.

(37) (a) Lin, J.-M.; Koch, K.; Fowler, F. W. *J. Org. Chem.* **1986**, *51*, 167. (b) Tschaen, D. M.; Turos, E.; Weinreb, S. M. *J. Org. Chem.* **1984**, *49*, 5058. (c) Koch, K.; Lin, J.-M.; Fowler, F. W. *Tetrahedron Lett.* **1983**, *24*, 1581. (d) Tschaen, D. M.; Weinreb, S. M. *Tetrahedron Lett.* **1982**, *23*, 3015. (e) Achmatowicz, O.; Pietraszkiewicz, M. J. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2680.

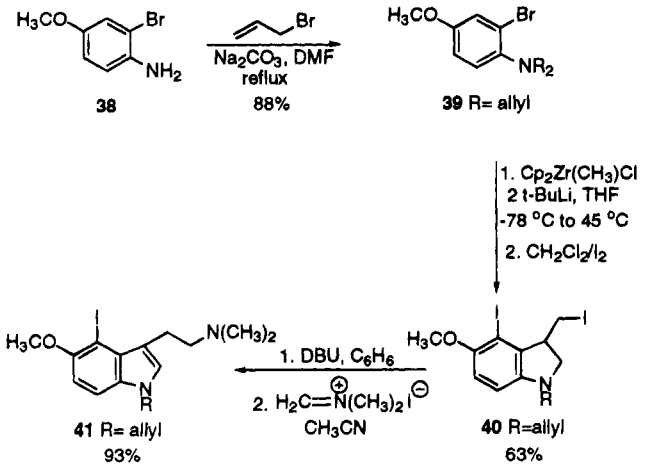
(38) (a) Glennon, R. A. *J. Med. Chem.* **1987**, *30*, 1. (b) Peroutka, S. J. *Pharmacol. Toxicol.* **1990**, *67*, 373.

(39) Street, L. J.; Baher, R.; Castro, J. L.; Chambers, M. S.; Guiblin, A. R.; Hobbs, S. C.; Matassa, V. G.; Reeve, A. J.; Beer, M. S.; Middlemiss, D. N.; Noble, A. J.; Stanton, J. A.; Scholey, K.; Hargreaves, R. J. *J. Med. Chem.* **1993**, *36*, 1529.

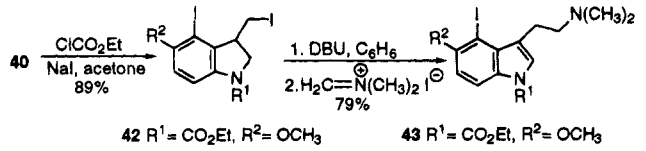
(40) Kelley, W. S.; Monack, L.; Rogge, P. T. Schwartz, R. N.; Varimbi, S. R.; Walter, R. I. *Liebigs Ann. Chem.* **1971**, *744*, 129.

(41) Kajigaeshi, S.; Kakinami, T.; Okamoto, T.; Fujisaki, S. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1159.

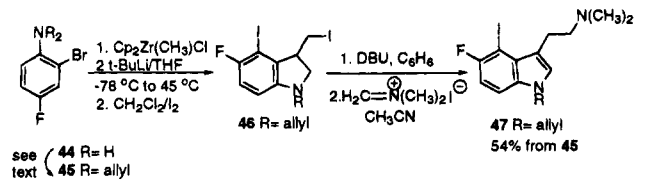
Scheme 12



Scheme 13



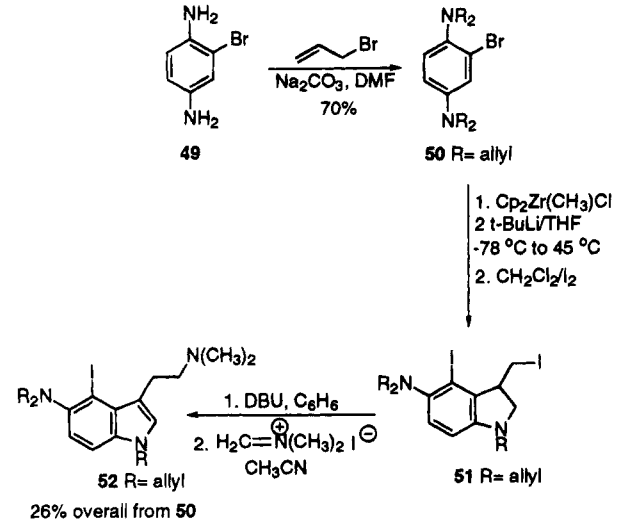
Scheme 14



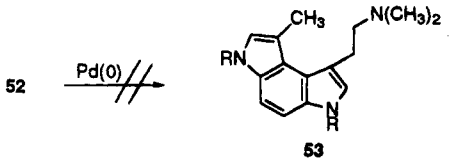
of *t*-BuLi in THF at −78 °C, allowing the solution to warm to room temperature, followed by briefly heating the mixture to 45 °C, gave the desired zirconacycle cleanly (as evidenced by ^{1}H NMR). Cleavage of the zirconacycle with I_2 in CH_2Cl_2 gave diiodide **40** in 63% yield (based on **39**). Indoline **40** was converted to serotonin analog **41** in 93% yield as previously described for similar compounds: treatment of **40** with DBU followed by reaction of the resulting olefin with Eschenmoser's salt. Alternatively, the allyl protecting group was cleaved with ethyl chloroformate and NaI in acetone to give 1-carbethoxy derivative **42** in 89% yield (Scheme 13). The carbamate was then allowed to react with DBU and Eschenmoser's salt to give **43** in 79% yield. Conversion of **40** to the corresponding carbamate **42** before reaction with Eschenmoser's salt should allow the nitrogen in the indole product to be deprotected. Although we have not attempted this transformation with any of the indole carbamates that we have prepared, Kozikowski has demonstrated that 1-carbethoxy-protected indoles can be deprotected by reaction with alcoholic NaOH.[42]

The 5-fluoro analog was prepared beginning with 2-bromo-4-fluoroaniline (**44**) (Scheme 14). Allylation of **44** with allyl bromide and Na_2CO_3 in DMF gave *N,N*-diallyl-2-bromo-4-fluoroaniline (**45**) in 94% yield. Metallacycle formation under standard conditions proceeded as expected (^{1}H NMR). However, the course of the electrophilic cleavage reaction of the metallacycle with I_2 proved to be sensitive to the solvent employed.[43] When THF was used, the result was a complex mixture of products in which the desired product **46** was only a minor component. However, when CH_2Cl_2 was employed, the iodination reaction proved to be cleaner, giving diiodide **46** in approximately 70% yield (estimated by ^{1}H NMR). Unlike other diiodo indolines that we had prepared, we were unable to isolate **46** in pure form. We reasoned that if **46** were converted to the more polar tryptamine derivative, it could be purified by flash chromatography. Crude diiodide **46** was allowed to react with DBU and Eschenmoser's salt to give 5-fluorotryptamine derivative **47**, which was easily obtained in pure form in 54% overall yield from **45**.

Scheme 15



Scheme 16

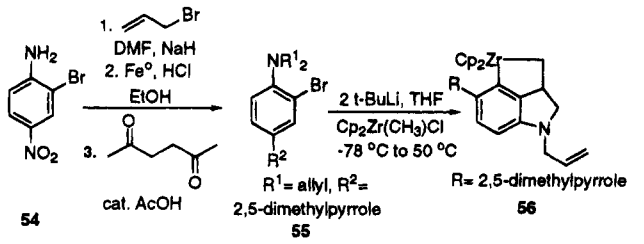


We next turned our attention to a substrate with an amino substituent in the 5-position. 4-Nitroaniline was brominated with Bu_4NBr_3 in a 1:1 mixture of CH_2Cl_2 and CH_3OH to give 2-bromo-4-nitroaniline in 96% yield (Scheme 15). The nitro group was reduced using Fe^0/HCl, and the crude diamine **49** was converted to the tetraallylic diamine **50** (70%). The zirconacycle formed cleanly under the usual conditions, but the iodination again proved to be troublesome. Although iodination of the metallacycle to provide **51** was cleaner in CH_2Cl_2 than in THF, the reaction proceeded with low efficiency. As with fluoro analog **46**, we were unable to obtain **51** in pure form. Conversion of the crude material to the desired tryptamine derivative was accomplished as previously described to give **52** in overall yield of 26% from **50**. Attempted Heck arylation[44] of the allyl amino group in compound **52** using conditions developed by Larock[13] and Hegedus failed to give the desired [3,2-*e*]pyrroloindole skeleton (Scheme 16). Similar results were observed by Hegedus in his study on the preparation of pyrroloquinones.[45,46]

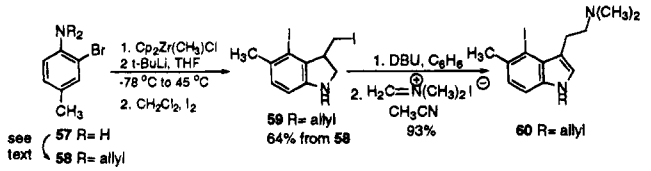
We were also interested in preparing an analog of **50** in which the two amino groups were differentially protected. To this end we prepared aniline derivative **55** (Scheme 17). Bromination of 4-nitroaniline gave 2-bromo-4-nitroaniline (**54**). Allylation of the amino group with allyl bromide and NaH in DMF, followed by reduction of the nitro group and acid-catalyzed

(42) Kozikowski, A. P.; Greco, M. N. *J. Org. Chem.* **1984**, *49*, 2310.
(43) For a similar solvent dependence in zirconocene chemistry, see: Houri, A. F.; Didiuk, M. T.; Xu, Z.; Horan, N. R.; Hoveyda, A. A. *J. Am. Chem. Soc.* **1993**, *115*, 6614.
(44) (a) Heck, R. F. *Org. React. (N.Y.)* **1982**, *27*, 345. (b) Heck, R. F. *Acc. Chem. Res.* **1979**, *12*, 146.
(45) Amatore, C.; Pflüger, F. *Organometallics* **1990**, *9*, 2276.

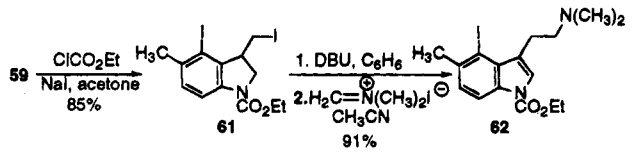
Scheme 17



Scheme 18



Scheme 19



pyrrole formation with 1,5-hexanedione,[47] gave **55**. Although metallacycle formation occurred cleanly (^{1}H NMR), we were unable to find conditions in which iodination of the metallacycle proceeded to give the desired diiodo indoline in reasonable yield.

The last substrate that we studied was *N,N*-diallyl-2-bromo-4-methylaniline (**58**), which was prepared from 2-bromo-4-methylaniline (**57**) in 95% yield (Scheme 18). Metallacycle formation and cleavage proceeded as expected to give diiodide **59** in 64% overall yield from **58**. Reaction of **59** with DBU and Eschenmoser's salt gave tryptamine derivative **60** in 87% yield. Alternatively, the allyl protecting group was cleaved (85%), followed by treatment with DBU and Eschenmoser's salt to give the carbethoxy-protected indole **62** in 91% yield (Scheme 19).

Synthesis of an Analog of the CC-1065/Duocarmycin A Pharmacophore. Recently we developed a synthesis of an analog of the common pharmacophore of CC-1065[5] (**63**) and duocarmycin A (**64**), two important antitumor antibiotics (Figure 2).[20b] Although both of these compounds have proven to be very potent antibiotics, they also display some toxic effects in laboratory animals. Consequently, there has been interest in preparing analogs of these compounds in which the left-hand, middle, and right-hand portions are altered in the hope that these analogs retain the same antibiotic activity, while showing reduced toxicity. Most of the synthetic work in this area has involved preparing analogs of the entire left-hand segment of the molecule. In comparison, the synthesis of the parent spirocyclic CI subunit (**65**), which contains the 1,2,7,7a-tetrahydrocycloprop[1,2-*c*]indol-4-one subunit, has received little attention. The initial synthesis of the left-hand segment of CC-1065 was completed in 1981 by Wierenga at Upjohn.[48] He reported that preparation of the pharmacophore required an efficient, regiospecific synthesis of 6-hydroxyindolines such as **66** (Figure 3). Because the methodology that we had developed permitted the regiospecific synthesis of an indoline such as **66**

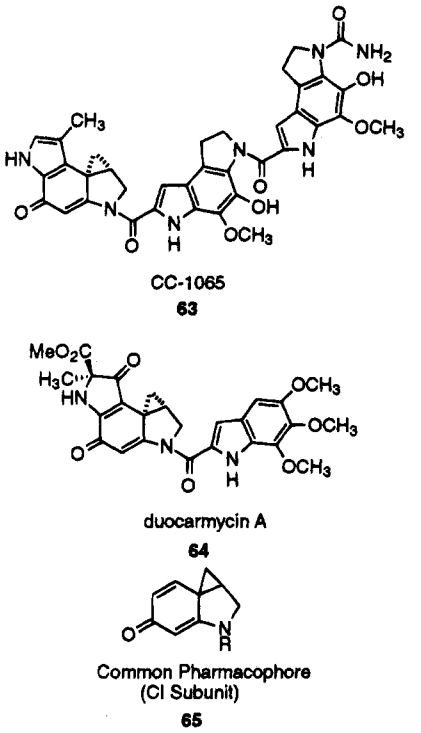


Figure 2.

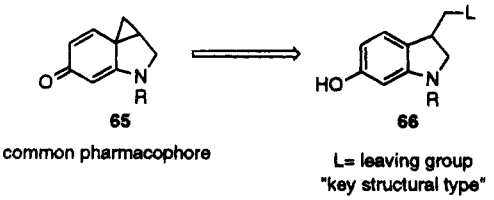
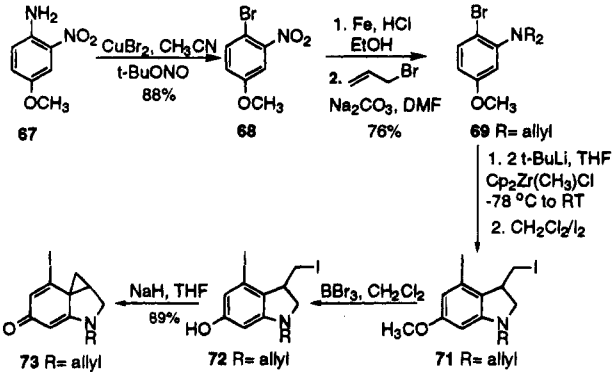


Figure 3.

Scheme 20



in which L = iodide, we reasoned that the synthesis of the pharmacophore would be a useful application of the method.

Our synthesis began with 4-methoxy-2-nitroaniline, which was converted to the corresponding aryl bromide **68** in 88% yield using copper(II) bromide and *tert*-butyl nitrite (Scheme 20).[49] Reduction of the nitro group and allylation of the resulting amine gave *N,N*-diallyl-2-bromo-5-methoxyaniline (**69**). Treatment of a mixture of **69** and bis(cyclopentadienyl)zirconium methyl chloride in THF with 2 equiv of *t*-BuLi provided the desired metallacycle. Electrophilic cleavage of the zirconacycle with I_2 in CH_2Cl_2 gave diiodide **71** in 65% yield. The methyl phenyl ether was selectively cleaved by

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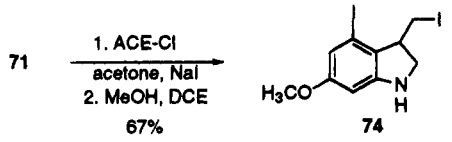
(47) Bruekelman, S. P.; Meakins, G. D.; Tirel, M. D. *J. Chem. Soc., Chem. Commun.* **1982**, 800.
(48) Weirenga, W. *J. Am. Chem. Soc.* **1981**, *103*, 5621.
(49) Doyle, M. P.; Siegfried, B.; Dellaria, J. F. *J. Org. Chem.* **1977**, *42*, 2426.

Scheme 21



reaction with BBr_3 in CH_2Cl_2[50] to give phenol **72**. Phenol **72** was unstable for long periods of time and was therefore used immediately after purification. The addition of **72** to a suspension of NaH in THF[51] gave the desired tetrahydrocyclopropa[1,2-*c*]indol-4-one analog **73** in 89% yield. Like phenol **72**, spirocycle **73** also proved to be unstable. As a solid it was stable for approximately 1 h, but in solution it afforded insoluble material after 30 min. Boger reported the same type of instability with several structurally related CI analogs.[51]

Boger has also demonstrated that secondary indolines that are precursors to the CI subunit can be coupled with phosphodiesterase dimer (PDE-1) to provide CC-1065 analogs that show some binding selectivity with B-DNA.[51] In order to allow for the synthesis of functional CC−1065 analogs from our material, it was required that the allyl protecting group in **71** be removed to provide the corresponding secondary amine (Scheme 21). The dealkylation was carried out as described previously, by allowing **71** to react with ACE-Cl and NaI in acetone, giving the intermediate carbamate. The carbamate was subsequently cleaved with CH_3OH and 1,2-dichloroethane as cosolvent to give secondary amine **74** in 67% overall yield from **71**. After the completion of our work, two reports appeared from Tietze and Grote in which zirconocene-stabilized benzyne complexes were used for the preparation of the left-hand segment of CC−1065 and a pharmacophore analog.[52]

In summary, a novel method for the regiospecific synthesis of polysubstituted indoles and indolines from readily available materials has been developed. The key step of the synthesis involves the regiospecific generation of a zirconocene-stabilized benzyne complex which undergoes an intramolecular olefin insertion reaction to provide a tricyclic indoline zirconacycle. The zirconacycle can be treated, without isolation, with iodine to yield a diiodo indoline. These diiodo indolines have proven to be very versatile intermediates for the synthesis of a wide variety of indoles and indolines. Further investigations of the use of this and related chemistry for the synthesis of related heterocycles, including natural products, are currently underway in our laboratories.

Experimental Section

All reactions involving organometallic reagents were conducted under an atmosphere of purified argon using standard Schlenk techniques or under nitrogen in a Vacuum Atmospheres Co. drybox. The argon was purified and deoxygenated by passage through a column of activated R3-11 catalyst obtained from Schweizer-Hall, Plainfield, NJ. It was then dried by passage through a column of activated 3 Å molecular sieves. All organic reactions were performed under an atmosphere of argon or nitrogen. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian XL-300 or VXR-500 or a Bruker AC250 FT spectrometer. Infrared (IR) spectra were recorded on either a Mattson Cygnus Starlab 100 or a Perkin-Elmer Series 1600 FT spectrometer. Gas chromatography analyses were performed on a Hewlett-Packard Model 5890 GC with a 3392A integrator and FID detector using a 25 m capillary column with cross-linked SE-30 as a stationary phase. Liquid chromatography analyses were performed on a Hewlett-Packard Model 1050 HPLC equipped with a Hewlett-Packard Model 1040A diode array detector using an Alltech 250 mm × 4.6 mm 5 μm silica column. Electron impact mass spectra and high-resolution mass determinations (HRMS) were recorded on a Finnegan MAT System 8200. Tetrahydrofuran, benzene, and diethyl ether were dried and deoxygenated by continuous refluxing over sodium/benzophenone ketyl under nitrogen or argon followed by distillation. Hexane was deolefinated by stirring over H_2SO_4, from which it was decanted and then stored over CaH_2. The deolefinated hexane thus obtained was dried and deoxygenated by refluxing over sodium/benzophenone ketyl followed by distillation. Alternatively, HPLC grade hexane was dried and deoxygenated by continuous refluxing over sodium/benzophenone ketyl under nitrogen or argon followed by distillation. Methylene chloride was dried by refluxing over CaH_2, followed by distillation. Acetonitrile was stored over activated 3 Å molecular sieves prior to use. Anhydrous *N,N*-dimethylformamide (DMF) was purchased from Aldrich Chemical Co. and was used without further purification. Cp_2ZrCl_2 was purchased from Boulder Scientific Inc., Mead, CO. All other reagents were prepared according to published procedures or were available from commercial sources and used without further purification. Unless otherwise stated, preparative flash chromatography was performed on E. M. Science Kieselgel 60 (230−400 mesh). Yields refer to isolated yields of compounds estimated to be ≥95% pure (unless otherwise noted) as determined by ^1H NMR and either capillary GC or HPLC analysis. All reported yields are representative.

***N*-Allyl-*N*-benzyl-2-bromoaniline (4).** A flame-dried Schlenk flask was charged with a stir bar, THF (150 mL), and 2-bromoaniline (8.56 g, 49.7 mmol). The solution was cooled to −78 °C, and *n*-butyllithium (19.0 mL of a 2.68 M solution in hexane, 50.9 mmol) was added dropwise. The solution was stirred for 15 min at −78 °C, after which time benzyl bromide (5.90 mL, 49.6 mmol) was added via syringe. The solution was kept at −78 °C for 15 min and then allowed to warm to room temperature. After 2 h, the solution was again cooled to −78 °C, and another portion of *n*-butyllithium (19.0 mL of a 2.68 M solution in hexane, 50.9 mmol) was added. After 15 min at −78 °C, allyl bromide (4.32 mL, 50.0 mmol) was added, and the solution was kept at −78 °C for 15 min and then allowed to warm to room temperature. After stirring for 2 h, the THF was removed using a rotary evaporator to leave a dark oil. Vacuum distillation (0.2 mmHg, 140−145 °C, using a 15 cm Vigreux column) gave **4** as a yellow oil (11.7 g, 78%). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.56 (d, J = 7.86 Hz, 1H), 7.4−7.1 (m, 6H), 7.0 (d, J = 7.85 Hz, 1H), 6.85 (t, J = 7.50 Hz, 1H), 5.83 (m, 1H), 5.17 (m, 2H), 4.23 (s, 2H), 3.62 (d, J = 5.93 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 148.9, 138.1, 134.5, 133.7, 128.5, 128.1, 127.5, 126.9, 124.5, 124.2, 121.3, 117.8, 56.3, 55.0. IR (film, cm^{-1}): 1028, 1474, 1494, 1584, 2837, 2926, 3027, 3062, 3083. HRMS (EI) calcd for $C_{16}H_{16}BrN$: 301.0461. Found: 301.0465.

***N,N*-Diallyl-2-bromoaniline (5).** Into a flask were placed 2-bromoaniline (15.22 g, 88.46 mmol), allyl bromide (19.0 mL, 26.56 g, 219.56 mmol), Na_2CO_3 (104.0 g, 0.98 mol), and DMF (250 mL). The mixture was heated to reflux for 3 h, after which time it was allowed to cool and was then poured into a separatory funnel containing ether (500 mL) and water (300 mL). The organic layer was collected, washed with water (3 × 300 mL) and brine (300 mL), dried over $MgSO_4$, and filtered, and the solvents were removed to leave a brown oil. The product was isolated by Kugelrohr distillation (109−115 °C, 1 mmHg) to give 17.35 g (78%) of a yellow oil. ^1H NMR ($CDCl_3$, 250 MHz): δ 7.56 (d, J = 7.0 Hz, 1H), 7.20 (t, J = 7.0 Hz, 1H), 7.03 (d, J = 7.0 Hz, 1H). 6.87 (t, J = 7.0 Hz, 1H), 5.9−5.7 (m, 2H), 5.15 (m, 4H), 3.68 (d, J = 5.93 Hz, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 148.9, 134.7, 133.8, 127.4, 124.3, 124.0, 121.1, 117.6, 55.3. IR (neat, cm^{-1}): 3076, 2817, 1585, 1474, 1417, 1275, 1217, 1029, 921. HRMS (EI) calcd for $C_{12}H_{14}BrN$: 251.0310. Found: 251.0312.

1-Benzyl-4-iodo-3-(iodomethyl)indoline (8). A flame-dried Schlenk flask was charged with a stir bar, THF (50 mL), bis(cyclopentadienyl)zirconium methyl chloride (4.06 g, 15 mmol), and **4** (4.53 g, 15 mmol). The solution was cooled to −78 °C, and *tert*-butyllithium (17.8 mL of a 1.69 M solution in hexane, 30 mmol) was added. Stirring was continued at −78 °C for 15 min, after which time the solution was allowed to warm to room temperature and was stirred for an additional 2 h. The THF was then removed *in vacuo*, and the residue was dissolved in CH_2Cl_2 (50 mL). Into a separate Schlenk flask were placed a stir bar, I_2 (9.75 g, 38.4 mmol), and CH_2Cl_2 (50 mL). The I_2

(50) McOmie, J. F. W.; West, D. E. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 412.

(51) Boger, D. L.; Wysocki, R. J. *J. Org. Chem.* **1989**, *54*, 1238.

(52) (a) Tietze, L. F.; Grote, T. *J. Org. Chem.* **1994**, *59*, 192. (b) Tietze, L. F.; Grote, T. *Chem. Ber.* **1993**, *126*, 2733.

solution was cooled to 0 °C and transferred into the solution of the metallacycle via cannula. Stirring was continued at 0 °C for 4 h, after which time the CH_2Cl_2 was removed using a rotary evaporator, and the residue was dissolved in ether (150 mL). The organic layer was washed with aqueous Na_2SO_3 (3 × 50 mL), water (3 × 50 mL) and brine, dried over $MgSO_4$, filtered, and concentrated to leave a dark brown oil. Flash chromatography (99:1 hexane/ether) yielded 4.61 g (65%) of a yellow oil. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.4−7.2 (m, 5H), 7.01 (d, J = 7.89 Hz, 1H), 6.79 (t, J = 7.67 Hz, 1H), 6.40 (d, J = 7.91 Hz, 1H), 4.34 (d, J = 15.4 Hz, 1H), 4.15 (d, J = 15.4 Hz, 1H), 3.58 (dd, J = 9.13, 1.59 Hz, 1H), 3.47−3.41 (m, 3H), 3.17 (t, J = 9.91 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 151.9, 137.2, 134.1, 130.6, 128.6, 127.5, 127.3, 126.7, 107.1, 93.2, 57.9, 52.3, 47.5, 9.0. IR ($CHCl_3$, cm^{-1}): 3065, 3033, 3009, 2926, 1591, 1566, 1451. HRMS (EI) calcd for $C_{16}H_{15}NI_2$: 474.9288. Found: 474.9292.

1-Allyl-4-iodo-3-(iodomethyl)indoline (9). To a flame-dried Schlenk flask were added *N,N*-diallyl-2-bromoaniline (**5**) (2.52 g, 10.0 mmol), bis(cyclopentadienyl)zirconium methyl chloride (2.77 g, 10.19 mmol), and THF (50 mL). The mixture was cooled to −78 °C, and *tert*-butyllithium (11.22 mL of a 1.81 M solution in pentane, 20.31 mmol) was added dropwise from a syringe. Stirring was continued at −78 °C for 15 min, after which time it was allowed to warm to room temperature and was stirred for an additional 1 h. The THF was removed *in vacuo*, and CH_2Cl_2 (15 mL) was added to the remaining residue. Into a separate Schlenk flask were placed I_2 (6.42 g, 25.30 mmol) and CH_2Cl_2 (45 mL). Both solutions were cooled to 0 °C, and the I_2 was added to the metallacycle via cannula. The resulting solution was stirred at 0 °C for 4 h, after which time it was poured into a separatory funnel containing ether (150 mL) and Na_2SO_3 solution (150 mL). The organic layer was collected, washed with water (2 × 150 mL) and brine (150 mL), dried over $MgSO_4$, and filtered, and the solvents were removed by rotary evaporation. The product was isolated by flash chromatography (95:5 hexane/ethyl acetate) followed by heating to 100 °C at 2 mmHg for 10 min to remove any remaining volatile impurities to give 2.76 g (65%) of a yellow oil. ^1H NMR ($CDCl_3$, 250 MHz): δ 6.97 (d, J = 8.0 Hz, 1H), 6.79 (t, J = 7.8 Hz, 1H), 6.39 (d, J = 7.8 Hz, 1H), 5.80 (m, 1H), 5.20 (m, 2H), 3.83−3.35 (m, 6H), 3.11 (t, J = 10.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 151.3, 134.0, 132.4, 130.1, 126.3, 117.4, 106.9, 92.6, 57.1, 50.5, 47.2, 8.34. IR (neat, cm^{-1}): 3073, 3007, 2976, 2917, 2833, 1589, 1566, 1478, 1447, 1241, 781. HRMS (EI) calcd for $C_{12}H_{13}NI_2$: 424.9141. Found: 424.9140.

1-Benzyl-4-iodo-3-methyleneindoline (10). A flame-dried round-bottom flask equipped with a stir bar was charged with toluene (8 mL), **8** (0.481 g, 1.01 mmol), and DBU (0.173 mL, 176 mg, 1.16 mmol). The reaction mixture was heated to 60 °C for 2 h, after which time it was filtered to remove the precipitated DBU salts. Removal of the solvents by rotary evaporation left a viscous, yellow oil. ^1H NMR (C_6D_6, 250 MHz): δ 7.2−6.9 (m, 6H), 6.52 (t, J = 3.06 Hz, 1H), 6.42 (t, J = 7.93 Hz, 1H), 6.14 (d, J = 7.93 Hz, 1H), 4.66 (t, J = 2.75 Hz, 1H), 3.77 (s, 2H), 3.67 (t, J = 3.00 Hz, 2H).

12. Into a flask were placed 1-allyl-4-iodo-3-(iodomethyl)indoline (**9**) (160 mg, 0.38 mmol), 18-crown-6 (125 mg, 0.473 mmol), K_2CO_3 (89 mg, 0.644 mmol), dimethyl malonate (0.08 mL, 102 mg, 0.722 mmol), and benzene (5.5 mL). The reaction mixture was heated to reflux overnight and then allowed to cool. It was filtered through a plug of silica which was washed with benzene (2 × 20 mL). The solvents were removed and the product was isolated by flash chromatography (9:1 hexane/ethyl acetate) to give 128 mg (80%) of a clear oil. ^1H NMR ($CDCl_3$, 250 MHz): δ 6.98 (d, J = 7.83 Hz, 1H), 6.74 (d, J = 7.83 Hz, 1H), 6.40 (d J = 7.80 Hz, 1H), 5.75 (m, 1H), 5.20 (m, 2H), 3.76 (s, 3H), 3.70 (m, 1H), 3.64 (s, 3H), 3.53 (m, 2H), 3.27 (m, 2H), 3.10 (m, 1H), 2.25 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.4, 151.9, 135.5, 133.1, 129.8, 127.0, 117.7, 107.0, 93.1, 56.1, 52.5, 51.3, 49.5, 42.1, 30.8. IR (neat, cm^{-1}): 3073, 3003, 2951, 1732, 1591, 1567, 1446, 1234, 1159, 916, 764, 732. HRMS (EI) calcd for $C_{17}H_{20}NO_4I$: 429.0438. Found: 429.0434.

Ene Reactions: General Procedure I. A flame-dried round-bottom flask was charged with a stir bar, toluene or benzene (10 mL/mmol **8**), and **8**. The solution was heated to 50−60 °C, at which time 1 equiv of DBU was added dropwise via syringe. The reaction mixture was stirred at 50−60 °C for 2 h, after which time the solution was filtered to remove the precipitated DBU salts. The ene substrate was then added to the solution, and the reaction mixture was heated to 85 °C for 8 h. Isolation of the reaction product was accomplished by dilution of the mixture with ether, extracting the organic layer with water and brine, drying over $MgSO_4$, filtering, and concentrating *in vacuo*. Flash chromatography was used when further purification was necessary.

General Procedure II. A flame-dried round-bottom flask was charged with a stir bar, toluene or benzene (10 mL/mmol **8** or **9**), and **8** or **9**. The solution was heated to 50−60 °C, at which time 1 equiv of DBU was added dropwise via syringe. The reaction mixture was kept at 50−60 °C for 2 h, after which time the solution was filtered to remove the precipitated DBU salts. The solvent was removed *in vacuo*, and the remaining residue was dissolved in CH_3CN (10 ml). The resulting solution was heated to 50−60 °C, and the iminium salt was added in one portion. The reaction was generally complete after 2 h. Isolation of the reaction product was accomplished by diluting the mixture with ether, extracting the organic layer with 2 N NaOH, water (3×), and brine (1×), drying over $MgSO_4$, filtering, and concentrating *in vacuo*. Flash chromatography was used when further purification was necessary.

14 (Table 1, Entry 1). Indoline **8** (0.51 g, 1.06 mmol), DBU (0.16 mL, 163 mg, 1.07 mmol), and diethyl acetylenedicarboxylate (0.375 mL, 2.3 mmol) were employed according to general procedure I. Flash chromatography (4:1 hexane/ethyl acetate) yielded **14** as a yellow oil (0.260 g, 53%). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.55 (d, J = 7.13 Hz, 1H), 7.30−7.26 (m, 4H), 7.06 (m, 3H), 6.85 (t, J = 7.64 Hz, 1H), 5.58 (m, J = 1.79 Hz, 1H), 5.23 (s, 2H), 4.23 (q, J = 6.90 Hz, 2H), 4.13 (q, J = 7.40 Hz, 2H), 4.09 (s, 2H), 1.2 (m, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.7, 165.3, 150.1, 136.9, 136.6, 131.4, 129.9, 128.9, 127.8, 126.7, 123.3, 121.6, 110.3, 110.1, 84.6, 61.3, 60.6, 50.1, 30.3, 29.9, 14.1, 13.9. IR (film, cm^{-1}): 1732, 1736, 2954, 3029. HRMS (EI) calcd for $C_{24}H_{24}O_4NI$: 517.0750. Found: 517.0748.

15 (Table 1, Entry 2). Indoline **8** (0.541 g, 1.06 mmol), DBU (0.16 mL, 163 mg, 1.07 mmol), and diethyl fumarate (0.26 mL, 273 mg, 1.59 mmol) were employed according to general procedure I. Flash chromatography (4:1 hexane/ethyl acetate) yielded **15** as a yellow oil (0.278 g, 56%). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.56 (d, J = 7.71 Hz, 1H), 7.25 (m, 3H), 7.21 (d, J = 8.14 Hz, 1H), 7.04 (d, J = 7.73 Hz, 2H), 7.00 (s, 1H), 6.80 (t, J = 7.06 Hz, 1H), 5.21 (s, 2H), 4.04 (m, 4H), 3.45 (m, 2H), 3.15 (m, 1H), 2.71−2.50 (m, 2H), 1.20 (m, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 174.7, 171.8, 137.0, 136.8, 131.2, 129.3, 128.8, 128.4, 127.7, 126.6, 122.9, 112.9, 110.0, 85.1, 60.42, 60.41, 49.9, 43.5, 35.8, 27.1, 14.09, 14.08. IR (film, cm^{-1}): 1723, 2905, 2935, 2981. HRMS (EI) calcd for $C_{24}H_{26}O_4NI$: 519.0906. Found: 519.0903.

16 (Table 1, Entry 3). Indoline **8** (0.265 g, 0.56 mmol), DBU (0.11 mL, 112 mg, 0.6 mmol), and fumaronitrile (0.052 g, 0.67 mmol) were used according to general procedure I. Flash chromatography (4:1 hexane/ethyl acetate) yielded **16** as a yellow oil (0.143 g, 60%). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.59 (d, J = 7.64 Hz, 1H), 7.40−7.25 (m, 5H), 7.10 (dd, J = 8.11, 2.40 Hz, 2H), 6.88 (t, J = 7.67 Hz, 1H), 5.28 (s, 2H), 3.50 (m, 2H), 3.35 (m, 1H), 2.80 (dd, J = 17.13, 4.83 Hz, 1H), 2.70 (dd, J = 17.13, 6.12 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 137.2, 136.3, 131.4, 130.4, 128.0, 127.7, 126.7, 123.5, 118.9, 115.6, 110.6, 109.5, 84.4, 60.3, 50.3, 31.3, 27.4, 20.0. IR ($CHCl_3$, cm^{-1}): 2249, 2959, 3050, 3054, 3068. HRMS (EI) calcd for $C_{20}H_{16}N_3I$: 425.0388. Found: 425.0387.

17 (Table 1, Entry 4). Indoline **8** (0.456 g, 0.97 mmol), DBU (0.16 mL, 163 mg, 1.07 mmol), and diethyl ketomalonate (0.09 mL, 101 mg, 0.580 mmol) were used according to general procedure I. Flash chromatography (4:1 hexane/ethyl acetate) yielded **17** as a light yellow oil (0.378 g, 76%). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.56 (d, J = 7.73 Hz, 1H), 7.27 (m, 4H), 7.18 (d, J = 8.21 Hz, 1H), 7.0 (dd, J = 7.77, 1.72 Hz, 2H), 6.77 (t, J = 7.77 Hz, 1H), 5.23 (s, 2H), 4.15 (m, 4H), 4.04 (s, 2H), 3.97 (s, 1H), 1.25 (t, J = 7.15 Hz, 3H), 1.17 (t, J = 7.16 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.0, 170.3, 136.8, 136.3, 131.8, 129.9, 128.7, 127.6, 126.5, 122.6, 110.0, 109.3, 85.1, 79.4, 62.3, 60.3, 49.9, 29.0, 21.0, 14.1, 13.9. IR ($CHCl_3$, cm^{-1}): 1430, 1546, 1736, 1741, 2984, 3032, 3509 (br). HRMS (EI) calcd for $C_{23}H_{25}O_5NI$: 522.0777. Found: 522.0774.

18 (Table 1, Entry 5). Indoline **8** (1.87 g, 3.93 mmol), DBU (0.6 mL, 611 mg, 4.01 mmol), and butyl glyoxalate (0.698 g, 3.9 mmol) were used according to general procedure I. Flash chromatography

(4:1 hexane/ethyl acetate) yielded **18** as a yellow oil (1.34 g, 72%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.56 (d, J = 7.70 Hz, 1H), 7.18 (d, J = 8.22 Hz, 1H), 7.13 (s, 1H), 7.03 (dd, J = 7.03, 1.76 Hz, 2H), 6.67 (t, J = 7.67 Hz, 1H), 5.17 (s, 2H), 4.60 (m, 1H), 4.12 (t, J = 6.54 Hz, 2H), 3.80 (dd, J = 14.8, 4.29 Hz, 1H), 3.20 (dd, J = 14.8, 8.41 Hz, 1H), 2.97 (d, J = 5.74 Hz, 1H), 1.54 (m, 2H), 1.28 (m, 2H), 0.86 (t, J = 7.50 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 174.7, 136.7, 131.1, 129.7, 129.6, 128.6, 128.3, 127.6, 126.5, 122.7, 111.0, 109.9, 84.8, 71.1, 65.7, 65.2, 49.8, 30.4, 18.9, 13.5. IR ($CHCl_3$, cm^{-1}): 1727, 2962, 3010, 3031, 3540 (br). HRMS (EI) calcd for $C_{22}H_{24}NO_3I$: 477.0800. Found: 477.0800.

19 (Table 1, Entry 6). Indoline **8** (0.480 g, 1.0 mmol), DBU (0.15 mL, 153 mg, 1.0 mmol), and diethyl azodicarboxylate (0.235 mL, 1.49 mmol) were used according to general procedure I. Flash chromatography (3:2 hexane/ethyl acetate) yielded **52** as a light yellow oil (0.432 g, 83%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.55 (d, J = 7.71 Hz, 1H), 7.3 (m, 5H), 7.05 (m, 2H), 6.80 (t, J = 7.94 Hz, 1H), 5.23 (s, 2H), 5.16 (br s, 2H), 4.20 (q, J = 6.93 Hz, 2H), 4.05 (q, J = 6.93 Hz, 2H), 1.25 (t, J = 6.93 Hz, 3H), 1.14 (t, J = 6.93 Hz, 3H). ^{13}C NMR (acetone-d_6, 75 MHz): δ 158.2, 157.8, 138.4, 138.0, 131.9, 131.6, 129.7, 129.3, 128.9, 128.2, 127.6, 123.5, 111.6, 111.2, 84.7, 62.3, 61.5, 50.3, 14.9, 14.8. IR ($CHCl_3$, cm^{-1}): 1712, 1743, 3019, 3027, 3418 (br). HRMS (EI) calcd for $C_{22}H_{24}N_3O_4I$: 521.0811. Found: 521.0812.

4-Iodo-3-(iodomethyl)indoline (24). To a flask were added 1-allyl-4-iodo-3-(iodomethyl)iodoline (**9**) (128 mg, 0.301 mmol), NaI (90 mg, 0.600 mmol), 1-chloroethyl chloroformate (0.06 mL, 80 mg, 0.556 mmol), and acetone (4 mL). The resulting mixture was stirred at room temperature for 3 h, after which time the solvent was removed, leaving a brown oil and a white solid. The oil was dissolved in a minimum amount of ether and was eluted down a flash column using 9:1 hexane/ether as eluent. All of the UV-active compounds were collected, and the solvent was removed to leave a clear oil, which was dissolved in 1,2-dichloroethane (3 mL) and placed in a flask to which methanol (3 mL) was added. The solution was heated to reflux for 90 min, cooled to room temperature, and poured into a separatory funnel containing ether (25 mL) and $NaHCO_3$ solution (25 mL). The organic layer was collected, washed with water (25 mL) and brine (25 mL), dried over $MgSO_4$, and filtered, and the solvents were removed by rotary evaporation. The product was isolated by flash chromatography (95:5 hexane/ether) to give 78 mg (68%) of a yellow oil that turned green upon exposure to air. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.02 (d, J = 7.2 Hz, 1H), 6.76 (t, J = 7.7 Hz, 1H), 6.54 (d, J = 7.7 Hz, 1H), 3.8–3.5 (m, 5H), 3.17 (t, J = 9.22 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 151.2, 133.9, 130.4, 127.9, 109.5, 92.9, 52.1, 49.0, 8.7. IR (neat, cm^{-1}): 3385, 2934, 2863, 1594, 1569, 1474, 1443, 1286, 764, 735, 635. HRMS (EI) calcd for $C_9H_9NI_2$: 384.8828. Found: 384.8830.

1-Carbethoxy-3-(iodomethyl)-4-iodoindoline (25). Into a flask were placed 1-allyl-4-iodo-3-(iodomethyl)indoline (**9**) (1.00 g, 2.35 mmol), NaI (1.10 g, 7.34 mmol), ethyl chloroformate (0.67 mL, 760 mg, 7.01 mmol), and acetone (15 mL). The mixture was heated to reflux for 6 h, after which time it was allowed to cool and was then poured into a separatory funnel containing ether (50 mL) and water (50 mL). The organic layer was collected, washed with water (2 × 50 mL) and brine (50 mL), dried over $MgSO_4$, and filtered, and the solvents were removed to leave a dark oil. The product was isolated by flash chromatography (95:5 hexane/ethyl acetate) to give 972 mg (91%) of a yellow oil. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.8 (br, 1H), 7.31 (d, J = 8.4 Hz, 1H), 6.95 (t, J = 8.4 Hz, 1H), 4.26 (br q, J = 7.0 Hz, 2H), 4.10 (m, 2H), 3.6 (m, 2H), 3.12 (t, J = 9.8 Hz, 1H), 1.35 (t, J = 7.0 Hz, 3H). ^{13}C NMR (C_6D_6, 125 MHz, 60 °C): δ 152.7, 143.6, 135.8, 132.2, 130.7, 115.4, 92.5, 61.7, 53.7, 46.2, 14.6, 9.0. IR (neat, cm^{-1}): 2979, 1713, 1472, 1448, 1380, 1327, 1307, 1191, 773. HRMS (EI) calcd for $C_{12}H_{13}NO_2I_2$: 456.9039. Found: 456.9035.

26 (Table 2, Entry 1). Indoline **8** (0.483 g, 1.10 mmol), DBU (0.170 mL, 173 mg, 1.14 mmol), and *N,N*-diethyl-*N*-methyleneammonium chloride (0.153 g, 1.26 mmol) were used according to general procedure II. Flash chromatography (1:1 hexane/ether, 3% triethylamine) yielded **26** as a yellow oil (0.372 g, 85%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.07 (t, J = 7.23 Hz, 6H), 2.65 (q, J = 7.23 Hz, 4H), 2.80 (t, J = 8.10 Hz, 2H), 3.17 (t, J = 8.10 Hz, 2H), 5.17 (s, 2H), 6.75 (t, J = 7.87 Hz, 1H), 7.01 (m, 3H), 7.15 (d, J = 8.37 Hz, 1H), 7.23 (m, 3H), 7.53 (d, J = 7.41 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 11.9, 23.1, 46.9, 49.8, 55.1, 85.3, 109.8, 115.3, 122.7, 126.5, 127.6, 128.1, 128.5, 128.7, 130.8, 136.8, 136.9. IR (film, cm^{-1}): 1355, 1429, 1446, 1490, 2805, 2930, 2968, 3030, 3063. HRMS (EI) calcd for $C_{21}H_{25}N_2I$: 432.1062. Found: 432.1060.

27 (Table 2, Entry 2). Indoline **8** (0.481 g, 1.01 mmol), DBU (0.17 mL, 173 mg, 1.16 mL), and *N*-methylenepiperidinium chloride (155 mg, 1.16 mmol) were used according to general procedure II. Spinning-plate chromatography (1:1 hexane/ether with 3% Et_3N) gave **27** as a yellow oil (0.312 g, 70%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.53 (d, J = 7.74 Hz, 1H), 7.35–7.2 (m, 3H), 7.17 (d, J = 8.18 Hz, 1H), 7.05 (m, 3H), 6.77 (t, J = 6.93 Hz, 1H), 5.20 (s, 2H), 3.23 (t, J = 8.20 Hz, 2H), 2.69 (t, J = 8.20 Hz, 2H), 2.54 (br s, 4H), 1.62 (m, 4H), 1.47 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 137.0, 136.8, 130.9, 128.8, 128.6, 128.2, 127.6, 126.6, 122.7, 115.3, 109.8, 85.3, 61.5, 54.7, 49.9, 26.1, 24.5, 22.9. IR (film, cm^{-1}): 1116, 1323, 1429, 1453, 2799, 2932, 2970, 3063. HRMS (EI) calcd for $C_{22}H_{25}N_2I$: 444.1057. Found: 444.1063.

28 (Table 2, Entry 3). 1-Allyl-4-iodo-3-(iodomethyl)indoline (**9**) (318 mg, 0.748 mmol), DBU (0.12 mL, 122 mg, 0.802 mmol), and *N,N*-dimethyl-*N*-methyleneammonium iodide (153 mg, 0.827 mmol) were employed according to general procedure II. The product was isolated by flash chromatography (3:2 hexane/ethyl acetate followed by 60:35:5 hexane/ethyl acetate/triethylamine) to yield 225 mg (85%) of a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.55 (d, J = 7.51 Hz, 1H), 7.22 (d, J = 8.1 Hz, 1H), 6.98 (s, 1H), 6.82 (t, J = 7.8 Hz, 1H), 5.90 (m, 1H), 5.16 (d, J = 10.5 Hz, 1H), 5.06 (d, J = 10.5 Hz, 1H), 4.61 (d, J = 5.70 Hz, 2H), 3.18 (t, J = 8.1 Hz, 2H), 2.64 (t, J = 8.1 Hz, 2H), 2.36 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 136.7, 132.9, 130.8, 128.4, 127.7, 122.5, 117.3, 114.6, 109.7, 85.2, 61.8, 48.6, 45.6, 23.8. IR (neat, cm^{-1}): 2939, 2857, 2817, 1545, 1469, 1430, 1418, 1324, 925, 734. HRMS (EI) calcd for $C_{15}H_{19}N_2I$: 354.0595. Found: 354.0592.

29 (Table 2, Entry 4). 1-Allyl-4-iodo-3-(iodomethyl)indoline (**9**) (313 mg, 0.737 mmol), DBU (0.12 mL, 122 mg, 0.802 mmol), and *N*-methylenemorpholinium chloride (117 mg, 0.863 mmol) were employed according to general procedure II. The product was isolated by flash chromatography (4:1 hexane/ethyl acetate followed by 80:15:5 hexane/ethyl acetate/triethylamine) to give 246 mg (84%) of a viscous, yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.54 (d, J = 7.5 Hz, 1H), 7.22 (d, J = 8.1 Hz, 1H), 6.98 (s, 1H), 6.81 (t, J = 7.95 Hz, 1H), 5.92 (m, 1H), 5.18 (d, J = 10.0 Hz, 1H), 5.05 (d, J = 10.0 Hz, 1H), 4.60 (d, J = 5.10 Hz, 2H), 3.25 (t, J = 8.1 Hz, 2H), 2.81 (t, J = 8.1 Hz, 2H), 2.65 (m, 4H), 1.81 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 136.6, 133.0, 130.7, 128.4, 127.6, 122.5, 117.4, 115.0, 109.6, 85.3, 58.6, 54.2, 48.6, 25.1, 23.5. IR (neat, cm^{-1}): 2960, 2926, 2789, 1544, 1469, 1429, 1325, 1178, 1123, 736. HRMS (EI) calcd for $C_{17}H_{21}N_2OI$: 396.0700. Found: 396.0700.

30 (Table 2, Entry 5). 1-Allyl-4-iodo-3-(iodomethyl)indoline (**9**) (323 mg, 0.760 mmol), DBU (0.12 mL, 122 mg, 0.802 mmol), and *N*-methylenepyrrolidinium chloride (105 mg, 0.878 mmol) were employed according to general procedure II. The product was isolated by flash chromatography (4:1 hexane/ethyl acetate followed by 80:15:5 hexane/ethyl acetate/triethylamine) to yield 228 mg (79%) of a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.55 (d, J = 7.8 Hz, 1H), 7.23 (d, J = 8.1 Hz, 1H), 6.99 (s, 1H), 6.84 (t, J = 7.95 Hz, 1H), 5.92 (m, 1H), 5.18 (d, J = 10.5 Hz, 1H), 5.01 (d, J = 10.5 Hz, 1H), 4.63 (d, J = 5.10 Hz, 2H), 3.75 (t, J = 4.65 Hz, 4H), 3.21 (t, J = 8.1 Hz, 2H), 2.71 (t, J = 8.1 Hz, 2H), 2.60 (t, J = 4.65 Hz, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 136.7, 133.0, 130.8, 128.4, 127.8, 122.6, 117.4, 114.4, 109.7, 85.2, 67.1, 61.0, 53.8, 48.6, 22.7. IR (neat, cm^{-1}): 2957, 2920, 2810, 1470, 1444, 1430, 1324, 1116, 909, 733. HRMS (EI) calcd for $C_{17}H_{21}N_2I$: 380.0751. Found: 380.0751.

31. 1-Carbethoxy-4-iodo-3-(iodomethyl)indoline (**25**) (720 mg, 1.58 mmol), DBU (0.240 mL, 244 mg, 1.60 mL), and *N,N*-dimethyl-*N*-methyleneammonium iodide (370 mg, 2.0 mmol) were employed according to general procedure II. The product was purified by flash chromatography (7:3 hexane/ethyl acetate followed by 60:35:5 hexane/ethyl acetate/triethylamine) to yield 506 mg (83%) of a clear, viscous oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.21 (d, J = 8.1 Hz, 1H), 7.67 (d, J = 8.1 Hz, 1H), 7.47 (s, 1H), 6.94 (t, J = 7.8 Hz, 1H), 4.43 (q, J = 6.9 Hz, 2H), 3.11 (t, J = 7.5 Hz, 2H), 2.63 (t, J = 7.5 Hz, 2H), 2.34 (s, 6H), 1.43 (t, J = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 150.2, 136.4, 134.7, 131.1, 125.5, 124.6, 120.4, 115.2, 84.7, 63.3, 60.4,

45.6, 24.3, 14.4. IR (neat, cm^{-1}): 2975, 2939, 2816, 2765, 1740, 1462, 1419, 1377, 1350, 1290, 1249, 1093. HRMS (EI) calcd for $C_{15}H_{19}N_2O_2I$: 386.0491. Found: 386.0488.

35. Into a flask were placed 1-allyl-4-iodo-3-(iodomethyl)indole (**9**) (412 mg, 0.970 mmol), DBU (0.16 mL, 163 mg, 1.07 mmol), and benzene (3 mL). The solution was heated to 50 °C for 90 min and then allowed to cool to room temperature. The DBU salts were filtered away, and the benzene was removed by rotary evaporation. Into a separate flask were placed bromoacetate **33** (669 mg, 2.5 mmol) and THF (4 mL). The solution was cooled to −78 °C, and Et_3N (0.370 mL, 269 mg, 2.65 mmol) was added, causing the immediate formation of a precipitate. The mixture was allowed to stir at −78 °C for 30 min, after which time a THF solution of olefin **11** was added. The resulting mixture was allowed to stir and slowly warm to room temperature overnight. It was then poured into a separatory funnel containing ether (50 mL) and water (50 mL). The organic layer was collected, washed with water (2 × 50 mL) and brine (50 mL), dried over $MgSO_4$, and filtered, and the solvents were removed. The product was isolated by flash chromatography (85:15 hexane/ethyl acetate) to give 328 mg (70%) of a white solid, mp = 127−130 °C. An analytically pure sample was prepared by recrystallization from ethanol/hexane to give white needles, mp = 128−130 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.55 (d, J = 7.5 Hz, 1H), 7.23 (d, J = 8.1 Hz, 1H), 7.00 (br s, 1H), 6.82 (t, J = 7.8 Hz, 1H), 5.92 (m, 1H), 5.17 (d, J = 10.2 Hz, 1H), 5.03 (br m, 2H), 4.71 (m, 1H), 4.63 (d, J = 5.7 Hz, 2H), 3.70 (br s + m, 4H), 3.40 (br m, 1H), 1.4−1.1 (br s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 28.2, 48.6, 52.1, 54.7, 54.9, 79.6, 85.0, 109.9, 110.9, 117.5, 122.9, 128.4, 128.7, 131.3, 132.7, 136.8, 155.2, 173.2. IR (neat, cm^{-1}): 3378 (br), 2976, 1739, 1709. Anal. Calcd for $C_{20}H_{25}N_2O_4I$: C, 49.6; H, 5.2; N, 5.78. Found: C, 49.9; H, 4.95; N, 5.67.

Tetra-*n*-butylammonium Tribromide. Into a flask were placed tetra-*n*-butylammonium bromide (15.15 g, 46.98 mmol) and CH_2Cl_2 (100 mL). Bromine (2.40 mL, 7.44 g, 46.58 mmol) was added last via syringe, causing the solution to turn orange. The solution was allowed to stir at room temperature for 30 min, and then it was poured into a flask containing ether (300 mL), causing the product to crystallize. The orange crystals were collected using a Büchner funnel and were dried *in vacuo*, giving 22.45 g (99%) of an orange solid, mp = 72−74 °C (lit.[40] mp = 74−76 °C). This compound is also available from Aldrich Chemical Co. (catalog no. 30, 159-0).

(38) 2-Bromo-4-methoxyaniline. Into a flask were placed *p*-aniside (2.47 g, 20.05 mmol), methanol (40 mL), and CH_2Cl_2 (80 mL). To the colorless solution was added *n*-Bu_4NBr_3 (9.68 g, 20.07 mmol) in one portion, causing the reaction mixture to turn purple. The resulting mixture was allowed to stir at room temperature for 35 min and was then poured into a separatory funnel containing saturated aqueous Na_2SO_3 (100 mL) and ether (100 mL). The organic layer was collected, washed with water (2 × 100 mL) and brine (100 mL), dried over $MgSO_4$, and filtered through a short plug of silica, and the solvents were removed to leave a dark, red oil. The product was isolated by flash chromatography (4:1 hexane/ethyl acetate) to yield 1.72 g (42%) of a brown oil. ^1H NMR ($CDCl_3$, 300 MHz): δ 6.98 (d, J = 2.4 Hz, 1H), 6.69 (m, 2H), 3.78 (br s, 2H), 3.69 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 152, 138, 117, 116, 115, 109, 56. IR (neat, cm^{-1}): 3442, 3358, 3203, 2999, 2949, 2832, 1623, 1600, 1499, 1440, 1275, 1230, 1212, 1037, 865.

***N,N*-Diallyl-2-bromo-4-methoxyaniline (39).** To a flask were added 2-bromo-4-methoxyaniline (3.75 g, 18.56 mmol), allyl bromide (4.0 mL, 5.59 g, 46.22 mmol), Na_2CO_3 (5.92 g, 55.85 mmol), and DMF (30 mL). The mixture was heated to reflux for 1 h, allowed to cool to room temperature, and poured into a separatory funnel containing ether (60 mL) and water (60 mL). The organic layer was collected, washed with water (2 × 60 mL) and brine (60 mL), and dried over $MgSO_4$, and the solvents were removed to leave a dark, brown oil. The product was isolated by Kugelrohr distillation (T = 120−130 °C, P = 0.1 mmHg) to give 4.58 g (88%) of a yellow oil. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.13 (d, J = 3.3 Hz, 1H), 6.97 (d, J = 9.0 Hz, 1H), 6.77 (dd, J = 3.3, 9.0 Hz, 1H), 5.79 (m, 2H), 5.10 (m, 4H), 3.75 (s, 3H), 3.60 (d, J = 6.0 Hz, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 155.9, 141.9, 134.9, 124.8, 122.4, 118.5, 117.3, 113.2, 56.2, 55.6. IR (neat, cm^{-1}): 3076, 3005, 2977, 2938, 2834, 1601, 1563, 1495, 1463, 1440, 1418, 1286, 1209, 1040, 992, 921, 810, 740, 675. HRMS (EI) calcd for $C_{13}H_{16}BrNO$: 281.0416. Found: 281.0415.

1-Allyl-4-iodo-3-(iodomethyl)-5-methoxyindoline (40). Into a Schlenk flask were placed *N,N*-dially-2-bromo-4-methoxyaniline (**39**) (544 mg, 1.93 mmol), bis(cyclopentadienyl)zirconium methyl chloride (580 mg, 2.13 mmol), and THF (6 mL). The solution was cooled to −78 °C, and *t*-BuLi (2.0 mL of a 1.96 M solution in pentane, 3.92 mmol) was added dropwise. The resulting solution was allowed to stir at −78 °C for 15 min and was then allowed to warm to room temperature and was heated to 45 °C for an additional 1 h. The THF was removed *in vacuo* leaving an orange foam, to which CH_2Cl_2 (3 mL) was added. Into a separate Schlenk flask were placed iodine (1.22 g, 4.81 mmol) and CH_2Cl_2 (3 mL). Both solutions were cooled to 0 °C, and the iodine solution was added by cannula to the solution of the metallacycle. The resulting dark mixture was allowed to stir at 0 °C for 4 h and then at room temperature for an additional 10 h. The whole mixture was poured into a separatory funnel containing saturated aqueous Na_2SO_3 solution (50 mL) and ether (50 mL). The organic layer was collected, washed with water (2 × 50 mL) and brine (50 mL), and dried over $MgSO_4$, and the solvents were removed to leave a dark oil. The product was isolated by flash chromatography (95:5 hexane/ethyl acetate) to yield 553 mg (63%) of a yellow oil. ^1H NMR ($CDCl_3$, 250 MHz): δ 6.62 (d, J = 8.5 Hz, 1H), 6.39 (d, J = 8.5 Hz, 1H), 5.85 (m, 1H), 5.24 (m, 2H), 3.79 (m, 2H), 3.75 (m, 1H), 3.7−3.5 (m, 4H), 3.32 (t, J = 8.25 Hz, 1H), 3.15 (t, J = 9.47 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 150.9, 146.2, 136.7, 133.2, 117.6, 111.7, 108.0, 86.2, 58.3, 57.4, 52.3, 48.5, 8.4. IR (neat, cm^{-1}): 2931, 2830, 1599, 1474, 1459, 1432, 1258, 1236, 1063, 796, 758. HMRS (EI) calcd for $C_{13}H_{15}I_2NO$: 454.9246. Found: 454.9245.

41. 1-Allyl-4-iodo-3-(iodomethyl)-5-methoxyindoline (**40**) (320 mg, 0.703 mmol), DBU (0.11 mL, 112 mg, 0.736 mmol), and *N,N*-dimethyl-*N*-methyleneammonium iodide (156 mg, 0.843 mmol) were employed according to general procedure II. The product was isolated by flash chromatography (95:5 ethyl acetate/triethylamine) to yield 250 mg (93%) of a viscous, yellow oil. ^1H NMR ($CDCl_3$, 250 MHz): δ 7.15 (d, J = 8.8 Hz, 1H), 6.98 (s, 1H), 6.83 (d, J = 8.8 Hz, 1H), 5.9 (m, 1H), 5.15 (m, 2H), 4.62 (m, 2H), 3.88 (s, 3H), 3.21 (t, J = 8.1 Hz, 2H), 2.63 (t, J = 8.1 Hz, 2H), 2.36 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 151.9, 132.9, 132.6, 129.2, 128.6, 117.1, 114.4, 109.9, 108.2, 77.3, 61.9, 58.3, 48.7, 45.6, 24.1. IR (neat, cm^{-1}): 2936, 2855, 2815, 2768, 1644, 1610, 1461, 1426, 1249, 1066, 784. HRMS (EI) calcd for $C_{16}H_{21}N_2OI$: 384.0700. Found: 384.0696.

1-Carbethoxy-4-iodo-3-(iodomethyl)-5-methoxyindoline (42). Into a flask were placed 1-allyl-4-iodo-3-(iodomethyl)-5-methoxyindoline (**40**) (1.29 g, 2.83 mmol), sodium iodide (1.49 g, 10 mmol), ethyl chloroformate (1.0 mL, 1.14 g, 10.46 mmol), and acetone (20 mL). The mixture was heated to reflux for 90 min, cooled to RT, and poured into a separatory funnel containing ether (50 mL) and water (50 mL). The organic layer was collected, washed with water (2 × 50 mL) and brine (50 mL), and dried over $MgSO_4$, and the solvents were removed to leave a dark oil. The product was isolated by flash chromatography (9:1 hexane/ethyl acetate) to yield 1.22 g (89%) of a yellow, viscous oil. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.8 (br, 1H), 6.71 (d, J = 9.0 Hz, 1H), 4.29 (br, 2H), 4.05 (m, 2H), 3.86 (s, 3H), 3.61 (m, 2H), 3.15 (t, J = 10.2 Hz, 1H), 1.37 (t, J = 7.0 Hz, 3H). ^{13}C NMR (C_6D_6, 75 MHz, 65 °C): δ 154.5, 152.9, 137.9, 137.2, 115.8, 111.3, 85.4, 61.5, 56.5, 54.0, 46.9, 14.6, 8.9. IR (neat, cm^{-1}): 2977, 1699, 1595, 1463, 1398, 1327, 1309, 1261, 1220, 1173, 1152, 1060. HRMS (EI) calcd for $C_{13}H_{15}NO_3I_2$: 486.9145. Found: 486.9146.

43. 1-Carbethoxy-4-iodo-3-(iodomethyl)-5-methoxyindoline (**42**) (243 mg, 0.500 mmol), DBU (0.08 mL, 81 mg, 0.534 mmol), and *N,N*-dimethyl-*N*-methyleneammonium iodide (120 mg, 0.649 mmol) were employed according to general procedure II. The product was isolated by flash chromatography (7:2:1 hexane/ethyl acetate/triethylamine) to yield 165 mg (79%) of a viscous, yellow oil. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.13 (br d, J = 9.3 Hz, 1H), 7.49 (s, 1H), 6.88 (d, J = 9.3 Hz, 1H), 4.47 (q, J = 6.9 Hz, 2H), 3.92 (s, 3H), 3.17 (t, J = 7.8 Hz, 2H), 2.66 (t, J = 7.8 Hz, 2H), 2.36 (s, 6H), 1.45 (t, J = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 154.3, 150.2, 132.5, 131.6, 125.5, 120.7, 115.6, 108.8, 77.2, 63.1, 60.4, 57.6, 45.6, 24.6, 14.4. IR (neat, cm^{-1}): 3120, 2975, 2938, 2857, 2817, 2767, 1732, 1603, 1583, 1557, 1455,

1417, 1379, 1252, 1105, 1058, 842, 795, 732. HRMS (EI) calcd for $C_{16}H_{20}N_2O_3I$ ($M - H^+$): 415.0521. Found: 415.0523.

***N,N*-Diallyl-2-bromo-4-fluoroaniline (45).** Into a flask were placed 2-bromo-4-fluoroaniline (4.581 g, 24.11 mmol), allyl bromide (6.30 mL, 8.81 g, 72.90 mmol), Na_2CO_3 (6.97 g, 65.76 mmol), and DMF (50 mL). The mixture was heated to reflux for 3 h, after which time it was allowed to cool and then poured into a separatory funnel containing ether (200 mL) and water (200 mL). The organic layer was collected, washed with water (3 × 200 mL) and brine (200 mL), dried over $MgSO_4$, and filtered, and solvents were removed to leave a brown oil. The product was isolated by Kugelrohr distillation (100–110 °C, 0.1 mmHg) to give 6.06 g (94%) of a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.29 (dd, J = 2.7, 8.4 Hz, 1H), 6.95 (m, 2H), 5.78 (m, 2H), 5.12 (m, 4H), 3.61 (d, J = 6.0 Hz, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.5 (d, $^1J_{C-F}$ = 243 Hz), 145.1, 134.6, 124.8 (d, $^3J_{C-F}$ = 7.9 Hz), 121.9 (d, $^3J_{C-F}$ = 9.07 Hz), 120.5 (d, $^2J_{C-F}$ = 23.6 Hz), 117.7, 114.2 (d, $^2J_{C-F}$ = 20 Hz), 55.8. IR (neat, cm^{-1}): 4332, 3417, 3077, 3009, 2979, 2926, 2815, 1643, 1596, 1485, 1418, 1262, 1193, 992, 923, 871, 814, 578. HRMS (EI) calcd for $C_{12}H_{13}BrFN$: 269.0216. Found: 269.0212.

47. To a Schlenk flash were added *N,N*-diallyl-2-bromo-4-fluoroaniline (**45**) (270 mg, 1 mmol), bis(cyclopentadienyl)zirconium methyl chloride (285 mg, 1.05 mmol), and THF (4 mL). The solution was cooled to −78 °C, and *tert*-butyllithium (1.10 mL of a 1.89 M solution in pentane, 2.08 mmol) was added dropwise from a syringe. The resulting orange solution was stirred at −78 °C for 15 min and was then allowed to warm to room temperature and stir for an additional 1 h. The THF was removed *in vacuo* leaving an orange foam, to which CH_2Cl_2 (4 mL) was added. Into a separate Schlenk flask were placed I_2 (636 mg, 2.51 mmol) and CH_2Cl_2 (4 mL). Both solutions were cooled to 0 °C, and the I_2 solution was added to the solution of the metallacycle via cannula. The resulting dark mixture was allowed to stir at 0 °C for 4 h, after which time it was poured into a separatory funnel containing ether (75 mL) and Na_2SO_3 solution (75 mL). The organic layer was collected, washed with water (2 × 75 mL) and brine (75 mL), dried over $MgSO_4$, and filtered, and the solvents were removed to leave a dark, brown oil. The oil was dissolved in benzene (5 mL) and was placed into a flask to which DBU (0.164 mL, 0.167 g, 1.10 mmol) was added, and the mixture was heated to 50 °C for 1 h. The DBU salts were filtered away, and the benzene was evaporated to leave a brown oil, which was dissolved in CH_3CN (4 mL). To this solution was added *N,N*-dimethyl-*N*-methyleneammonium iodide (237 mg, 1.28 mmol), and the mixture was heated to 45 °C for 2 h. It was then allowed to cool and poured into a separatory funnel containing ether (25 mL) and 2 N NaOH (25 mL). The organic layer was collected, washed with water (25 mL) and brine (25 mL), dried over $MgSO_4$, and filtered, and the solvents were removed. The product was isolated by flash chromatography (65:35 hexane/ethyl acetate followed by 60:35:5 hexane/ethyl acetate/triethylamine) to give 201 mg (54%) of a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.08 (dd, J = 4.2, 9.0 Hz, 1H), 7.01 (s, 1H), 6.87 (t, J = 8.4 Hz, 1H), 5.9 (m, 1H), 5.10 (m, 2H), 4.6 (d, J = 5.4 Hz, 2H), 3.16 (t, J = 8.1 Hz, 2H), 2.61 (t, J = 8.1 Hz, 2H), 2.34 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.2 (d, $^1J_{C-F}$ = 230 MHz), 145.2, 133.1, 132.8, 129.1, 128.5, 117.5, 115.1, 110.4 (d, $^3J_{C-F}$ = 9.23 Hz), 109.2 (d, $^2J_{C-F}$ = 28 Hz), 71.3 (d, $^2J_{C-F}$ = 28 Hz), 61.7, 48.9, 45.6, 23.8. IR (neat, cm^{-1}): 3084, 2940, 2858, 2819, 1466, 1429, 1235, 1040, 925, 909, 789. HRMS (EI) calcd for $C_{15}H_{18}FN_2I$: 372.0501. Found: 372.0496.

***N,N*-Diallyl-2-bromo-4-(*N,N*-diallylamino)aniline (50).** Into a flask were placed 2-bromo-4-nitroaniline (2.35 g, 10.83 mmol), iron powder (2.78 g, 49.78 mmol), concentrated HCl (8.5 mL of a 37% solution, 3.77 g, 103.5 mmol), and ethanol (35 mL). The mixture was heated to reflux for 1 h, then allowed to cool, and poured into a separatory funnel containing ether (100 mL) and 2 N NaOH (50 mL). The organic layer was collected, washed with water (2 × 50 mL) and brine (50 mL), dried over $MgSO_4$, and filtered, and the solvents were removed to leave a brown oil, which was used without further purification. The oil was added to a flask containing allyl bromide (5.60 mL, 7.82 g, 64.70 mmol), Na_2CO_3 (9.16 g, 86.40 mmol), and DMF (70 mL). The mixture was heated to reflux for 3 h, allowed to cool, and poured into a separatory funnel containing ether (100 mL) and water (100 mL). The organic layer was collected, washed with water (2 × 100 mL) and brine (100 mL), dried over $MgSO_4$, and filtered, and the solvents were removed by rotary evaporation. The product was isolated by Kugelrohr distillation (135–140 °C, 0.1 mmHg) to give 2.62 g (70%) of a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.89 (m, 2H), 6.55 (dd, J = 3.15, 8.75 Hz, 1H), 5.82 (m, 4H), 5.13 (m, 8H), 3.85 (d, J = 4.8 Hz, 4H), 3.56 (d, J = 6.6 Hz, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 146.2, 138.0, 135.4, 133.7, 124.8, 123.2, 117.0, 116.8, 116.2, 111.6, 56.3, 52.9. IR (neat, cm^{-1}): 3076, 2978, 2814, 1642, 1603, 1501, 1417, 1227, 992, 919. HRMS (EI) calcd for $C_{18}H_{23}BrN_2$: 346.1045. Found: 346.1047.

52. To a Schlenk flask were added *N,N*-diallyl-4-(diallylamino)-2-bromoaniline (368 mg, 1.06 mmol), bis(cyclopentadienyl)zirconium methyl chloride (300 mg, 1.10 mmol), and THF (4 mL). The solution was cooled to −78 °C, and *tert*-butyllithium (1.13 mL of a 1.89 M solution in pentane, 2.14 mmol) was added dropwise via syringe. The resulting mixture was stirred at −78 °C for 15 min, after which time it was heated to 60 °C for 30 min, then it was allowed to cool to room temperature and stir for an additional 1 h. The THF was removed *in vacuo* to leave an orange foam, to which CH_2Cl_2 (4 mL) was added. Into a separate Schlenk flask were placed iodine (662 mg, 2.61 mmol) and CH_2Cl_2 (10 mL). Both solutions were cooled to 0 °C, and the iodine solution was added to the solution of the metallacycle via cannula. The resulting dark solution was allowed to stir at 0 °C for 4 h and an additional 12 h at room temperature. The mixture was then poured into a separatory funnel containing ether (25 mL) and Na_2SO_3 solution (25 mL). The organic layer was collected, washed with water (25 mL) and brine (25 mL), dried over $MgSO_4$, and filtered, and the solvents were removed to leave a dark oil. The oil was dissolved in benzene (5 mL) and placed in a flask to which DBU (0.180 mL, 183 mg, 1.20 mmol) was added, and the mixture was heated to 50 °C for 1 h. The DBU salts were filtered away, and the benzene was removed via rotary evaporation to leave a brown oil, which was dissolved in CH_3CN (4 mL). To the CH_3CN solution was added *N,N*-dimethyl-*N*-methyleneammonium iodide (240 mg, 1.30 mmol), and the mixture was heated to 45 °C for 2 h. The solution was allowed to cool and was poured into a separatory funnel containing ether (25 mL) and 2 N NaOH (25 mL). The organic layer was collected, washed with water (25 mL) and brine (25 mL), dried over $MgSO_4$, and filtered, and the solvents were removed. The product was purified by flash chromatography (7:3 hexane/ethyl acetate followed by 65:35:5 hexane/ethyl acetate/triethylamine) to give 124 mg (26%) of a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.14 (d, J = 9.0 Hz, 1H), 6.96 (s, 1H), 6.92 (d, J = 9.0 Hz, 1H), 5.90 (m, 3H), 5.15 (m, 6H), 4.59 (d, J = 5.41 Hz, 2H), 3.56 (d, J = 6.0 Hz, 4H), 3.23 (t, J = 7.8 Hz, 2H), 2.63 (t, J = 7.8 Hz, 2H), 2.35 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 143.7, 135.6, 134.4, 133.2, 129.5, 127.9, 117.9, 117.4, 117.0, 115.3, 109.4, 94.3, 62.0, 57.7, 48.9, 45.7, 24.5. IR (neat, cm^{-1}): 3075, 2975, 2937, 2814, 1457, 1417, 1040, 992, 919, 733. HRMS (EI) calcd for $C_{21}H_{28}N_3I$: 449.1330. Found: 449.1331.

2-Bromo-4-nitroaniline (54). Into a flask were placed 4-nitroaniline (4.32 g, 31.28 mmol), CH_2Cl_2 (120 mL), and CH_3OH (70 mL). Bu_4NBr_3 (16.94 g, 35.13 mmol) was added as a solid and in one portion at RT causing the solution to turn orange. After 5 min at RT, the mixture was poured into a separatory funnel containing CH_2Cl_2 (50 mL) and aqueous Na_2SO_3 solution (100 mL). The organic layer was collected, washed with water (2 × 100 mL) and brine (100 mL), dried over $MgSO_4$, and filtered through a short plug of silica gel, and the solvents were removed to leave 6.51 g (96%) of a yellow solid, mp = 102–104 °C (lit. mp[13] = 104 °C). The spectral data were consistent with literature values. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 8.37 (d, J = 2.5 Hz, 1H), 8.03 (dd, J = 2.5, 8.8 Hz, 1H), 6.75 (d, J = 8.8 Hz, 1H), 4.85 (br s, 2H).

***N,N*-Diallyl-2-bromo-4-methylaniline (58).** Into a round-bottom flask were placed 2-bromo-4-methylaniline (3.76 g, 20.21 mmol), allyl bromide (4.0 mL, 5.59 g, 46.22 mmol), Na_2CO_3 (6.53 g, 61.61 mmol), and DMF (50 mL). The mixture was heated to reflux for 90 min, allowed to cool to room temperature, and then poured into a separatory funnel containing ether (250 mL) and water (250 mL). The organic layer was collected, washed with water (2 × 250 mL) and brine (250 mL), and dried over $MgSO_4$, and the solvents were removed to leave a yellow oil. The product was purified by Kugelrohr distillation (T = 100–105 °C, P = 0.1 mmHg) to give 5.88 g (95%) of a clear oil. ^{1}H

NMR ($CDCl_3$, 300 MHz): δ 7.24 (d, J = 1.8 Hz, 1H), 6.84 (dd, J = 1.8, 7.8 Hz, 1H), 6.75 (d, J = 7.8 Hz, 1H), 5.64 (m, 2H), 4.95 (m, 4H), 3.49 (d, J = 6.0 Hz, 4H), 2.10 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 146.3, 134.9, 134.1, 134.0, 128.1, 123.8, 121.2, 117.4, 55.6, 20.3. IR (neat, cm^{-1}): 3416, 3076, 3008, 2978, 2921, 2814, 1642, 1603, 1518, 1491, 1417, 1221, 1160, 1048, 992, 920. HRMS (EI) calcd for $C_{13}H_{16}BrN$: 265.0467. Found: 265.0466.

1-Allyl-4-iodo-3-(iodomethyl)-5-methylindoline (59). Into a Schlenk flask were placed *N,N*-diallyl-2-bromo-4-methylaniline (565 mg, 2.12 mmol), bis(cyclopentadienyl)zirconium methyl chloride (640 mg, 2.35 mmol), and THF (6 mL). The mixture was cooled to −78 °C, and *t*-BuLi (2.20 mL of a 1.96 M solution in pentane, 4.31 mmol) was added dropwise, causing the solution to turn orange. The resulting mixture was stirred at −78 °C for 15 min, allowed to warm to room temperature, and then heated to 45 °C for 1 h. The THF was removed *in vacuo* leaving an orange foam, to which CH_2Cl_2 (3 mL) was added. Into a separate Schlenk flask were placed iodine (1.35 g, 5.31 mmol) and CH_2Cl_2 (4 mL). Both solutions were cooled to 0 °C, and the iodine solution was transferred via cannula into the solution of the metallacycle. The resulting dark solution was stirred for 4 h at 0 °C and for an additional 2 h at room temperature. The mixture was poured into a separatory funnel containing ether (50 mL) and saturated Na_2SO_3 solution (50 mL). The organic layer was collected, washed with water (2 × 50 mL) and brine (50 mL), and dried over $MgSO_4$, and solvents were removed to leave a dark oil. The product was purified via flash chromatography (95:5 hexane/ethyl acetate) to give 600 mg (64%) of a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.97 (d, J = 8.1 Hz, 1H), 6.36 (d, J = 8.1 Hz, 1H), 5.83 (m, 1H), 5.23 (m, 2H), 3.74 (dd, J = 6.1, 15 Hz, 1H), 3.65−3.5 (m, 4H), 3.35 (t, J = 9.9 Hz, 1H), 3.10 (dd, J = 9.4, 11 Hz, 1H), 2.32 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 149.5, 135.6, 133.1, 130.0, 129.6, 117.8, 107.8, 100.1, 57.9, 51.6, 49.1, 26.9, 8.7. IR (neat, cm^{-1}): 3074, 3008, 2917, 2830, 1643, 1595, 1570, 1477, 1455, 1417, 1308, 1271, 1247, 1174, 924, 801. HRMS (EI) calcd for $C_{13}H_{15}NI_2$: 438.9298. Found: 438.9298.

60. 1-Allyl-4-iodo-3-(iodomethyl)-5-methylindoline (**59**) (231 mg, 0.526 mmol), DBU (0.09 mL, 92 mg, 0.602 mmol), and *N,N*-diethyl-*N*-methyleneammonium iodide (122 mg, 0.659 mmol) were employed according to general procedure II. The product was isolated by flash chromatography (60:35:5 hexane/ethyl acetate/triethylamine) to yield 168 mg (87%) of a viscous, yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.11 (d, J = 8.3 Hz, 1H), 6.96 (s, 1H), 5.92 (m, 1H), 5.05 (m, 2H), 4.60 (d, J = 5.4 Hz, 2H), 3.22 (t, J = 7.8 Hz, 2H), 2.65 (t, J = 7.8 Hz, 2H), 2.54 (s, 3H), 2.36 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 134.9, 133.0, 132.2, 129.2, 127.8, 122.9, 117.2, 114.6, 109.3, 92.1, 62.1, 48.7, 45.7, 28.9, 24.6. IR (neat, cm^{-1}): 2967, 2938, 2855, 2814, 2765, 1551, 1461, 1417, 1294, 1262, 1206, 1038, 789, 606. HRMS (EI) calcd for $C_{16}H_{21}N_2I$: 368.0751. Found: 368.0748.

1-Carbethoxy-4-iodo-3-(iodomethyl)-5-methylindoline (61). To a flask were added 1-allyl-4-iodo-3-(iodomethyl)-5-methylindoline (**59**) (516 mg, 1.18 mmol), sodium iodide (531 mg, 3.54 mmol), ethyl chloroformate (0.28 mL, 0.32 g, 2.95 mmol), and acetone (13 mL). The mixture was heated to reflux for 3 h, cooled to room temperature, and poured into a separatory funnel containing ether (30 mL) and water (30 mL). The organic layer was collected, washed with water (2 × 30 mL) and brine (30 mL), and dried over $MgSO_4$, and the solvents were removed to leave a dark oil. The product was isolated by flash chromatography (9:1 pentane/ether) to yield 472 mg (85%) of a clear, viscous oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.70 (br, 1H), 7.11 (d, J = 8.4 Hz, 1H), 4.29 (br q, J = 7.2 Hz, 2H), 4.10−3.95 (m, 2H), 3.65 (dd, J = 1.95, 10.1 Hz, 1H), 3.54 (t, J = 8.2 Hz, 1H), 3.11 (t, J = 10.1 Hz, 1H), 2.39 (s, 3H), 1.37 (t, J = 7.2 Hz, 3H). ^{13}C NMR (C_6D_6, 125 MHz, 65 °C): δ 152.9, 140.9, 136.6, 135.3, 130.0, 115.2, 99.5, 61.5, 53.8, 47.6, 27.2, 14.6, 8.9. IR (neat, cm^{-1}): 2977, 2251, 1710, 1591, 1475, 1460, 1324. HRMS (EI) calcd for $C_{13}H_{15}NO_2I_2$: 470.9190. Found: 470.9190.

62. 1-Carbethoxy-4-iodo-3-(iodomethyl)-5-methylindoline (**61**) (300 mg, 0.637 mmol), DBU (0.1 mL, 102 mg, 0.669 mmol), and *N,N*-dimethyl-*N*-methyleneammonium iodide (143 mg, 0.773 mmol) were employed according to general procedure II. The product was purified by flash chromatography (60:35:5 hexane/ethyl acetate/triethylamine) to give 230 mg (91%) of a yellow, viscous oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.10 (d, J = 8.1 Hz, 1H), 7.46 (s, 1H), 7.16 (d, J = 8.1 Hz, 1Hz), 4.45 (q, J = 7.1 Hz, 2H), 3.17 (t, J = 8.1 Hz, 2H), 2.64 (t, J = 8.1 Hz, 2H), 2.53 (s, 3H), 2.36 (s, 6H), 1.45 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 150.3, 136.5, 134.3, 132.7, 126.4, 125.3, 121.6, 115.7, 92.1, 63.8, 61.2, 46.5, 29.1, 25.8, 14.7. IR (neat, cm^{-1}): 2977, 2942, 2818, 2733, 1739, 1459, 1434, 1379, 1259, 1099, 909, 838, 801, 733. HRMS (EI) calcd for $C_{16}H_{21}N_2O_2I$: 400.0650. Found: 400.0647.

4-Bromo-3-nitroanisole (68). Into a flask under a nitrogen atmosphere were placed copper(II) bromide (1.70 g, 7.61 mmol), *tert*-butyl nitrite (1.25 mL, 1.08 g, 10.51 mmol), and acetonitrile (15 mL). The solution was heated to 65 °C, and 4-methoxy-2-nitroaniline (**67**) (1.03 g, 6.10 mmol) in 15 mL of CH_3CN was added dropwise to the copper(II) bromide solution over 10 min. After the addition was complete, the solution was left at 65 °C for 1 h, after which time it was allowed to cool to room temperature and was then poured into a flask containing 20% aqueous HCl (100 mL). The aqueous solution was extracted with ether (3 × 100 mL), the ether layers were combined, washed with water (3 × 100 mL), and brine (1 × 100 mL), and dried over $MgSO_4$, and the solvents were removed to leave a dark red oil. The product was purified via Kugelrohr distillation (T = 120−125 °C, P = 0.01 mmHg) to give 1.24 g (88%) of a bright yellow solid: mp = 32−34 °C (lit. mp[13] = 32−34 °C). ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.59 (d, J = 8.9 Hz, 1H), 7.37 (d, J = 2.95 Hz, 1H), 6.98 (dd, J = 2.95, 8.9 Hz, 1H), 3.86 (s, 3H). IR (neat, cm^{-1}): 3099, 3012, 2969, 2939, 2896, 2840, 1526, 1481, 1354, 1306, 1274, 1236, 1021, 801.

2-Bromo-5-methoxyaniline. To a flask were added **68** (3.45 g, 14.84 mmol), iron powder (2.48 g, 44.48 mmol), ethanol (50 mL), and concentrated HCl (6.15 mL of a 37% solution). The reaction mixture was heated to reflux and the reaction was shown by TLC analysis to be complete after 3 h. The solution was allowed to cool to RT, and solid Na_2CO_3 was added until no more bubbling occurred. The solution was then extracted with ether (200 mL). The ether layer was collected, washed with water (3 × 100 mL) and brine (1 × 100 mL), and dried over $MgSO_4$, and the solvents were removed to leave a dark oil. The product was further purified via Kugelrohr distillation (T = 110 °C, P = 0.01 mmHg) to leave 2.79 g (93%) of a yellow oil. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.16 (d, J = 8.7 Hz, 1H), 6.21 (d, J = 2.8 Hz, 1H), 6.12 (dd, J = 2.8, 8.7 Hz, 1H), 4.04 (br s, 2H), 3.63 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.9, 144.8, 132.8, 105.5, 101.2, 100.4, 55.3. IR (neat, cm^{-1}): 3502, 3407, 3254, 3130, 2984, 2857, 1586, 1529, 1457, 1451, 1426, 1321, 1234, 1157, 972, 810, 725.

***N,N*-Diallyl-2-bromo-5-methoxyaniline (69).** A two-neck, round-bottom flask equipped with a reflux condenser and a stir bar was placed under a nitrogen atmosphere. To the flask were added 2-bromo-5-methoxyaniline (2.60 g, 12.8 mmol), Na_2CO_3 (5.42 g, 51.1 mmol), allyl bromide (4.00 mL, 5.59 g, 46.2 mmol), and DMF (55 mL). The reaction mixture was heated to reflux, and the reaction was shown by TLC analysis to be complete after 4 h. The solution was allowed to cool to room temperature and was extracted with ether (200 mL). The ether layer was collected, washed with water (3 × 100 mL) and brine (1 × 100 mL), and dried over $MgSO_4$, and the solvents were removed to leave a dark oil. Further purification of the product was accomplished by Kugelrohr distillation (T = 100 °C, P = 0.01 mmHg) to give 2.97 g (82%) of a yellow oil. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.30 (d, J = 8.8 Hz, 1H), 6.47 (d, J = 2.8 Hz, 1H), 6.33 (dd, J = 2.8, 8.8 Hz, 1H), 5.71 (m, 2H), 5.05 (m, 4H), 3.63 (s, 3H), 3.56 (d, J = 6.0 Hz, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.2, 149.9, 134.7, 133.8, 117.6, 111.4, 110.7, 109.2, 55.4, 55.2. IR (neat, cm^{-1}): 3040, 2990, 2968, 2946, 1627, 1578, 1449, 1429, 1322, 1277, 1186, 1144, 1046, 1007, 947, 845. HRMS (EI) calcd for $C_{13}H_{16}BrNO$: 281.0416. Found: 281.0415.

1-Allyl-4-iodo-3-(iodomethyl)-6-methoxyindoline (71). Into a Schlenk flash equipped with a stir bar and under an argon atmosphere were placed **69** (2.85 g, 10.08 mmol), bis(cyclopentadienyl)zirconium methyl chloride (3.08 g, 11.34 mmol), and THF (60 mL). The solution was cooled to −78 °C, and *t*-BuLi (12.23 mL of a 1.74 M solution in pentane, 21.33 mmol) was added dropwise from a syringe. The resulting solution was left at −78 °C for 15 min and was then slowly warmed to 45 °C. When the solution reached 45 °C, it began to bubble and darken considerably. The resulting solution was left at 45 °C until the bubbling ceased (15 min) and was then allowed to cool to room temperature and stir for 2 h. The THF was removed *in vacuo* to leave

an orange foam, to which CH_2Cl_2 (30 mL) was added. Into a separate Schlenk flask were placed iodine (7.06 g, 27.81 mmol) and CH_2Cl_2 (50 mL). Both solutions were cooled to 0 °C, and the iodine solution was added via cannula to the solution of the metallacycle. The resulting dark solution was maintained at 0 °C for 4 h, after which time it was added to a separatory funnel containing ether (200 mL) and a saturated Na_2SO_3 solution (100 mL). The ether layer was collected, washed with water (3 × 100 mL) and brine (1 × 100 mL), and dried over $MgSO_4$, and the solvents were removed to leave a dark brown oil. Further purification was accomplished by flash chromatography (95:5 hexane/ethyl acetate) to give 2.96 g (65%) of a yellow, viscous oil. ^1H NMR ($CDCl_3$, 300 MHz): δ 6.50 (d, J = 1.6 Hz, 1H), 5.96 (d, J = 1.6 Hz, 1H), 5.80 (m, 2H), 5.22 (m, 2H), 3.72 (m, 1H), 3.50 (m, 5H), 3.08 (t, J = 9.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 162, 152, 133, 128, 118, 111, 95, 93, 58, 56, 51, 47, 10. IR (neat, cm^{-1}): 3077, 3000, 2954, 2933, 2832, 1608, 1568, 1478, 1335, 1208, 1171, 1039, 629. HRMS (EI) calcd for $C_{13}H_{15}I_2NO$: 454.9246. Found: 454.9243.

1-Allyl-6-hydroxy-4-iodo-3-(iodomethyl)indoline (72). Into a Schlenk flask equipped with a stir bar and under an argon atmosphere were placed **71** (256 mg, 0.563 mmol) and CH_2Cl_2 (3 mL). The solution was cooled to −78 °C, and BBr_3 (1.5 mL of a 1.0 M solution in CH_2Cl_2, 1.50 mmol) was added dropwise from a syringe. The resulting yellow solution was maintained at −78 °C for 30 min, after which time it was allowed to slowly warm to room temperature, and stirring was continued overnight. The solution was then cooled to 0 °C, and methyl alcochol (3 mL) was slowly added. The whole mixture was then poured into a separatory funnel containing ethyl acetate (60 mL) and water (50 mL). The ethyl acetate layer was collected, washed with water (3 × 100 mL) and brine (1 × 100 mL), and dried over $MgSO_4$, and the solvents removed to leave a brown oil. Further purification was accomplished by flash chromatography (4:1 hexane/ethyl acetate) to give 214 mg (86%) of a yellow oil. The ^1H NMR indicated that the sample contained approximately 2% ethyl acetate that could not be removed *in vacuo* without considerable decomposition due to the short half-life of the compound. HPLC analysis of the sample showed that the sample was >95% pure with respect to UV-active compounds. On the basis of this data, we estimated the sample to be 95% pure. ^1H NMR ($CDCl_3$, 250 MHz): δ 6.48 (d, J = 1.92 Hz, 1H), 5.83 (d, J = 1.92 Hz, 1H), 5.75 (m, 1H), 5.23 (m, 2H), 4.81 (br s, 1H), 3.80−3.40 (m, 5H), 3.08 (t, J = 9.47 Hz, 1H). ^{13}C NMR (d_8-THF, 75 MHz): δ 163.6, 156.3, 134.2, 126.7, 117.8, 114.6, 97.0, 92.9, 58.9, 51.7, 48.0, 9.8. IR (neat, cm^{-1}): 3250 (br), 3080, 2975, 2872, 2680, 2237, 1603, 1578, 1479, 1452, 1336, 1287, 1190, 1170, 991, 821. HRMS (EI) calcd for $C_{12}H_{13}I_2NO$: 440.9090. Found: 440.9090.

1-Allyl-4-iodo-1,2,7,7a-tetrahydrocycloprop[1,2-*c*]indol-4-one (73). Into a Schlenk flask under an argon atmosphere were placed a stir bar and sodium hydride (22 mg of a 60% suspension in oil, 0.55 mmol), which was washed with hexane (1 × 5 mL) and suspended in THF (2 mL). A solution of **72** (65 mg, 0.147 mmol in 1.5 mL THF) was added dropwise to the sodium hydride suspension at room temperature. The resulting solution was maintained at room temperature for 15 min, after which time it was filtered and the solvent removed to leave an off-white foam (41 mg, 89%). Compound **73** was estimated to be reasonably pure by ^1H NMR. Compound **73** was unstable to chromatography and was only sparingly soluble in most solvents, making an estimate of the purity difficult. ^1H NMR (d_8-THF, 250 MHz): δ 6.76 (s, 1H), 5.76 (m, 1H), 5.32 (s, 1H), 5.15 (m, 2H), 3.75−3.48 (m, partially obscured by solvent, 4H), 2.50 (dt, J = 5.4, 7.9 Hz, 1H), 1.75 (dd, J = 4.6, 7.9 Hz, 1H), 1.03 (t, J = 4.6 Hz, 1H). ^{13}C NMR (d_8-THF, 75 MHz): δ 183.9, 167.5, 143.0, 132.8, 118.3, 96.2, 68.2, 55.1, 49.4, 41.9, 28.0, 27.0. IR (neat, cm^{-1}): 2922, 2360, 1611, 1535, 1455, 1394, 1349, 1240, 1022, 988, 918, 868, 807. HRMS (EI) calcd for $C_{12}H_{12}NOI$: 312.9965. Found: 312.9962.

4-Iodo-3-(iodomethyl)-6-methoxyindoline (74). Into a flask under a nitrogen atmosphere were placed **71** (121 mg, 0.266 mmol), sodium iodide (120 mg, 0.8 mmol), and acetone (4.5 mL). 1-Chloroethyl chloroformate (0.07 mL, 0.09 g, 0.649 mmol) was added via syringe to the reaction mixture at room temperature, immediately causing a precipitate to form. The mixture was then heated to reflux, and the progress of the reaction was followed by TLC analysis. After conversion to the intermediate carbamate was complete, the reaction mixture was allowed to cool to room temperature and filtered, and the solvents were removed to leave a dark oil. The oil was dissolved in 9:1 hexane/ethyl acetate and filtered through a column of silica gel, collecting all of the UV-active compounds, and the solvents were removed to leave a yellow oil. The oil was dissolved in 1,2-dichloroethane (3 mL) and was added to a flask under a nitrogen atmosphere that contained an equal volume of methyl alcohol. The mixture was heated to reflux until conversion of the carbamate to the amine was approximately 80% complete as judged by TLC analysis. As the reaction proceeds past this point, significant amounts of side products begin to form. In order to obtain optimal yields for this reaction, it is best not to let it proceed until all of the intermediate carbamate has been consumed. The solution was cooled to room temperature and extracted with ether (1 × 75 mL). The ether layer was collected, washed with water (3 × 100 mL) and brine (1 × 100 mL), and dried over $MgSO_4$, and the solvents were removed. The product was purified via flash chromatography (using 85:15 hexane/ethyl acetate) to give 74 mg (67%) of a yellow oil that later solidified upon standing at −10 °C. Like compound **72**, compound **74** was not stable for long periods of time. The purity of **74** was estimated to be approximately 95% by both ^1H NMR and HPLC analysis. ^1H NMR ($CDCl_3$, 300 MHz): δ 6.59 (d, J = 2.10 Hz, 1H), 6.12 (d, J = 2.10 Hz, 1H), 3.72 (s, 3H), 3.70−3.4 (m, 5H), 3.16 (t, J = 9.30 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 161.3, 152.0, 126.9, 113.0, 96.5, 92.5, 55.6, 52.7, 48.1, 9.3. IR (neat, cm^{-1}): 3388 (br), 2935, 2864, 1600, 1567, 1484, 1436, 1331, 1297, 1197, 1169, 1112, 1035, 908, 821, 731. HRMS (EI) calcd for $C_{10}H_{11}NOI_2$: 414.8934. Found: 414.8931.

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