RECENT ADVANCES IN INDOLE ARYNE CYCLOADDITION CHEMISTRY. PART I: TOTAL SYNTHESIS OF (±)-CIS-TRIKENTRIN B. PART II: INVESTIGATION INTO THE REGIOSELECTIVITY OF 6,7-INDOLE ARYNE CYCLOADDITIONS. PART III: SYNTHESIS AND REACTIONS OF NOVEL TRIBROMOINDOLES

A DISSERTATION IN
Chemistry
and
Pharmaceutical Sciences

Presented to the Faculty of the University of Missouri-Kansas City in partial fulfillment of the requirements for the degree

DOCTOR OF PHILOSOPHY

by

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ABSTRACT

Since their discovery in the Buszek laboratories in 2007, the indole arynes and their cycloaddition chemistry has demonstrated its significance in achieving the total synthesis of biologically active indole alkaloid natural products such as the trikentrins and herbindoles in a facile manner. The application of 6,7-indole aryne cycloaddition methodology towards the total synthesis of (±)-cis-trikentrin B, one of the representative members of the trikentrin family of natural products is described.

The 5,6,7-tribromoindole served as the 6,7-indole aryne precursor which was synthesized via an adapted Leimgruber-Batcho synthetic protocol. The success with achieving annulation at the 6,7-position of the indole nucleus in (±)-cis-trikentrin B relied heavily on one crucial question i.e., whether the key intermediate 5,6,7-tribromo-N-TBS-indole would undergo selective metal-halogen exchange at C-7. Gratifyingly the indole underwent selective metal-halogen exchange at C-7 and subsequent elimination to give exclusively the 6,7-indole aryne which underwent Diels-Alder cycloaddition with
cyclopentadiene. To complete the synthesis, the remaining unreacted C-5 bromo position was subjected to Stille cross-coupling to install the trans-buteryl side chain at this site.

The original regiochemical observations in 6,7-indole aryne cycloadditions were made with N-Me-4-phenyl-6,7-dibromoindole resulting predominantly in the contrasteric regiosiomer. This phenomenon was observed by the virtue of the polarized nature of the 6,7-indole aryne as revealed by computational studies involving ab initio calculations.

In order to probe further into the regioselective cycloadditions of 6,7-indole arynes, a series of 6,7-dibromoindoles were synthesized to investigate the effect of 2-, 3-, 4- and 5-substitution on the regioselectivity of 6,7-indole aryne cycloadditions with 2-tert-butylfuran. The results of this investigation indicated that the degree of polarization of the 6,7-indole aryne bond depends on electronic nature and the positions of the various substituents on the pyrrole and benzene rings of the indole which in turn is responsible for imparting regioselectivity in the 6,7-indole aryne cycloadditions.

The Buszek laboratories have previously demonstrated the exclusive generation of 6,7-indole arynes from 4,6,7- and 5,6,7-tribromoindoles via a remarkable selective metal-halogen exchange at C-7 for use in natural products total synthesis and library development. In connection to these previous efforts, synthesis of the 4,5,6- and 4,5,7-tribromoindoles, the remaining two members of the tribromoindole series, is described. Treatment with n-BuLi followed by quenching with various electrophiles reveals a strong preference for initial metal-halogen exchange at the C-7 position in the case of 4,5,7-tribromoindoles, and at the C-4 position in the case of the 4,5,6-tribromoindole scaffold. Exclusive generation of the 4,5-indole aryne in either system followed by cycloaddition with 2-tert-butylfuran shows only a modest regiochemical preference in the cycloadducts. Finally, the 4,5-benzannulated
scaffolds were subjected to Negishi cross-coupling with dimethyl and diethylzinc to demonstrate the proof-of-concept for library development.
The faculty listed below, appointed by the Dean of the School of Graduate Studies, have examined a dissertation titled “Recent Advances in Indole Aryne Cycloaddition Chemistry. Part I: Total Synthesis of (±)-cis-Trikentrin B. Part II: Investigation into the Regioselectivity of 6,7-Indole Aryne Cycloadditions. Part III: Synthesis and Reactions of Novel Tribromoindoles.” presented by Alok Nerurkar, candidate for the Doctor of Philosophy degree, and certify that in their opinion it is worthy of acceptance.

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Dedicated to my biggest support system, my beloved fiancé,

Komal Dasani
CHAPTER 1
INTRODUCTION AND BACKGROUND

1.1 Arynes and Hetarynes: Discovery and Significance

Arynes and hetarynes (aka heteroarynes) have emerged as versatile and effective tools in organic synthesis for the construction of complex natural products of biological importance and for the design and development of novel architecturally unique scaffolds for drug discovery (Gampe and Carreira, 2012; Tadross and Stoltz, 2012; Goetz, Shah et al., 2014). The prototypical aryne is benzyne itself, 1.11 (Roberts, Simmons et al., 1953). Hetarynes are arynes that are derived from heteroaromatic systems, most commonly those in which a heteroatom such as nitrogen, oxygen or sulfur is a part of the aromatic nucleus. The area of aryne and hetaryne chemistry has certainly come a long way since the discovery of benzyne in 1953, where a myriad of novel hetarynes have been discovered and reported. This comprehensive list of hetarynes that have been reported in the literature include 2,3-pyridyne, 1.12 (Martens and den Hertog, 1962); 3,4-pyridyne, 1.13 (Kauffman and Boettcher, 1962); 2,3-thiophyne (Reinecke, Newsom et al., 1981); 1.14, 3,4-thiophyne, 1.15 (Reinecke, Newsom et al., 1981), 1-Boc-3,4-pyrine, 1.16 (Liu, Chan et al., 1999); 2,3-quinolyne, 1.17 (Fleet and Fleming, 1969); 3,4-quinolyne, 1.18 and 5,6-quinolyne, 1.19 (Kauffman, Fischer et al., 1967); 7,8-quinolyne, 1.20 (Collis and Burrell, 2005); 1,2-didehydrobenzothiophene, 1.21 (Reinecke, Newsom et al., 1981); 1,2-carbazolyne, 1.22 (Brown, Choi et al., 1997); 5,6-carbazolyne, 1.23 (Goetz, Silberstein et al., 2014); 4,5-indolyne, 1.24, 5,6-indolyne, 1.25 and 6,7-indolyne, 1.26 (Buszek, Luo et al., 2007); 4,5-didehydrobenzofuran, 1.27, 5,6-didehydrobenzofuran, 1.28 and 6,7-didehydrobenzofuran, 1.29 (Brown and Buszek, 2012).
Although numerous aforementioned novel hetarynes have been discovered since 1953, the related published reports reveal that most of these reactive intermediates were studied for their structure and reactivity rather than their applications. It was only in the last two decades that there has been a resurgence in the area of aryne and hetaryne chemistry where these intermediate species have been extensively used in the total synthesis of several important natural products. Some of the recent examples include the usage of benzyne as demonstrated by Stoltz in the total synthesis of the tetrahydroisoquinoline alkaloid, (-)-quinocarcin, 1.30 (Allan and Stoltz, 2008) and in the synthesis of (-)-curvularin, 1.31, a naturally occurring benzannulated macrolactone (Tadross, Virgil et al., 2010). The 3,4-pyridyne cycloaddition methodology was instrumental in the concise syntheses of naturally occurring alkaloids such as (s)-macrostomine, 1.32 (Enamorado, Ondachi et al., 2010) and ellipticine, 1.34 (Diaz, Cobas et al., 2001). Intermolecular nucleophilic additions to the 4,5-indole arynes have been successfully utilized in the total syntheses of the members of the welwitindolinone family of natural products such as N-methylwelwitindolinone C isothiocyanate, 1.35 (Quasdorf, Huters et al., 2011), N-methylwelwitindolinone D isonitrile,
1.36 (Styduhar, Huters et al., 2013) and (-)-N-methylwewitindolinone B isothiocyanate, 1.37 (Weires, Styduhar et al., 2014). Similarly, (+)-tubingensin A, 1.38, a carbazole-containing alkaloid was readily accessed via intramolecular carboxalyne cyclization strategy (Goetz, Silberstein et al., 2014). Finally, the advantages of the 6,7-indole aryne chemistry in particular have been successfully exploited by the Buszek laboratories for the total synthesis of the trikentrins, 1.39-1.40 (Buszek, Brown et al., 2009; Chandrasoma, Brown et al., 2013) and the herbindoles, 1.41-1.42 (Buszek, Brown et al., 2009).

![Chemical Structures](image)

**Figure 1.2.** Examples of natural products that used the aryne and hetaryne methodologies in their total synthesis.

### 1.2 Indole Arynes and their Cycloaddition Chemistry

Arynes derived from all the benzenoid positions of the ubiquitous indole nucleus namely, the 4,5-, 5,6 and the 6,7-indole aryne (Figure 1.3), were not known until their discovery in the Buszek laboratories in 2007. The Buszek laboratories developed and
reported the first ever general approach for the generation of the three isomeric indole arynes via facile metal-halogen exchange and elimination of the corresponding o-dibromoindoles (Scheme 1.1).

![Figure 1.3. The three isomeric indole arynes.](image)

**Scheme 1.1.** Generation of 4,5-, 5,6- and 6,7-indole arynes and trapping with furan.

The 6,7-indole aryne cycloaddition chemistry soon culminated in the successful total syntheses of (±)-cis-trikentrin A and (±)-herbindole A, two representative members of a rare class of benzannulated indole alkaloid natural products namely, the trikentrins and the herbindoles. In 1986, Capon and co-workers isolated the members of the trikentrin family of natural products namely, (+)-cis-trikentrin A, (+)-cis-trikentrin B, (+)-trans-trikentrin A, (-)-trans-trikentrin B and iso-trans-trikentrin B from the marine sponge *Trikentrion flabelliforme*, collected off of the Australian coast in Darwin (Capon, Macleod et al., 1986).
These newly discovered compounds were found to exhibit growth inhibitory activity towards gram-positive bacteria, *Bacillus subtilis* but, no activity levels were provided.

The structurally related herbindoles were isolated four years later in 1990 by Scheuer and co-workers from the Australian sponge *Axinella sp.* (Herb, Carroll *et al.*, 1990). Similar to the trikentrins, the members of this family namely, herbindole A, herbindole B and herbindole C were also found to possess potent biological significance i.e. cytotoxicity against KB cells as well as fish antifeedant properties.

In the first generation synthesis of (+)-*cis*-trikentrin A, the N-TBS-4-ethyl-6,7-dibromoindole, 1.55 was subjected to the metal-halogen exchange and elimination protocol to generate the 4-ethyl-6,7-indole aryne, 1.56 (Scheme 1.2). The reactive aryne intermediate underwent a [4 + 2] cycloaddition reaction with cyclopentadiene to yield the cycloadduct, 1.57 thus, achieving annulation at the 6,7-position of the indole nucleus eventually leading to the target molecule, 1.59 (Buszek, Brown *et al.*, 2009).

![Scheme 1.2. First generation total synthesis of (+)-*cis*-trikentrin A](image-url)
In a similar manner, the 6,7-indole aryne cycloaddition methodology was exploited by the Buszek laboratories towards the total synthesis of (±)-herbindole A, 1.67 (Buszek, Brown et al., 2009) (Scheme 1.3).

Scheme 1.3. First generation total synthesis of (±)-herbindole A.

Subsequently, the Buszek laboratories reported the second-generation total synthesis of (±)-cis-trikentrin A which involved the use of N-TBS-4,6,7-tribromoindole, 1.68 as the 6,7-indole aryne precursor (Brown, Luo et al., 2009).

Scheme 1.4. Second generation total synthesis of (±)-cis-trikentrin A

Treatment of 1.68 with a slight excess of n-BuLi at -78 °C induced a selective metal-halogen exchange at C-7 to yield the 7-lithiated intermediate, 1.69 (Scheme 1.4). Subsequently, warming up the reaction mixture to -40 to -30 °C resulted in an elimination of
LiBr to generate exclusively the 6,7-indole aryne, 1.70 which was further trapped with cyclopentadiene to afford 4-bromo-6,7-benzannulated scaffold 1.71. The unreacted C-4 bromine was subjected to Negishi cross-coupling protocol with Et₂Zn to install the desired ethyl substituent at the 4-position thus, providing the late-stage intermediate, 1.72.

Indeed, the 6,7-indole aryne, 1.73 has proved to be an extremely powerful and versatile intermediate in the total synthesis of biologically active, complex natural products such as the trikentrins, 1.76-1.77 and the herbindoles, 1.74; 1.75; and 1.78 (Figure 1.4). The 6,7-annulation in each of these target molecules was readily accessed via facile 6,7-indole aryne generation and its subsequent cycloaddition reaction with cyclopentadiene thus, demonstrating the first successful applications of the intermolecular 6,7-indole aryne cycloaddition methodology in total synthesis.

![Figure 1.4. 6,7-benzannulated indole alkaloid natural products.](image)

The 6,7-indole aryne cycloaddition methodology has also demonstrated its significance in the development of small molecule libraries of biological relevance. Recently,
the Buszek laboratories constructed an unprecedented 93-membered library of polycyclic, 4-substituted-6,7-benzannulated indoles structurally inspired from the trikentrins and herbindoles (Thorton, Brown et al., 2011). The 6,7-indole aryne precursor, 1.79 was subjected to selective metal-halogen exchange at C-7 to produce the 7-lithiated intermediate, 1.80 (Scheme 1.5). Subsequently, elimination of LiBr resulted in the generation of the 4-bromo-6,7-indole aryne, 1.81 which was further trapped with furan and cyclopentadiene to afford the corresponding 6,7-cycloadducts, 1.82a and 1.82b. The strained olefin in the cycloadduct was reduced with diimide prior to subjecting the remaining unreacted 4-bromo position to a series of Pd-catalyzed cross-coupling reactions with a collection of boronic acids and secondary amines to yield a suite of 4-substituted-6,7-benzannulated indole library members structurally represented by 1.83 and 1.84. The reduction step was necessary as it was found that the presence of this strained alkene resulted in significantly reduced cross-coupled yields.

Scheme 1.5. Examples of diverse library construction using a 6,7-indole aryne cycloaddition and cross-coupling tactic.
The newly synthesized benzannulated indole scaffolds were found to exhibit anti-proliferative activities at micromolar and sub-micromolar concentrations in the L1210 leukemia and HL-60 promyelocytic leukemia cell based assays (Perchellet, Waters et al., 2012). The proposed mechanism of action of these library members in L1210 leukemia cell lines was apoptotic DNA degradation and nuclear fragmentation. Furthermore, in a subsequent HL-60 cell based study these compounds inhibited the proliferation of tumor cells through microtubule de-stabilization, a mode of action that resembles that of an established anti-cancer drug, vincristine (Perchellet, Waters et al., 2014). Additionally, the annulated indoles mimicked the effect of jasplakinolide by remarkably increasing the rate and level of actin polymerization, suggesting that they might also stabilize the cleavage furrow to block cytokinesis. Apparently, the annulated indoles interact with both tubulin to decrease microtubule assembly and with actin to block cytokinesis, thereby inducing bi- and multinucleation resulting in genomic instability and apoptosis. The compelling biological results obtained in the cell-based assays helped to validate the significance of 6,7-indole aryne chemistry in library development and drug discovery.

During the course of our investigations into the cycloadditions reactions of indole arynes, we observed a remarkable regioselectivity preference in the 6,7-indole aryne cycloadditions with 2-substituted furans (Brown, Luo et al., 2009). For example, when the 6,7-indole aryne generated from N-methyl-3-phenyl-6,7-dibromoindole was trapped with 2-tert-butylfuran, the contrasteric (more sterically crowded) regioisomer was formed about 50 folds excess over the non-contrasteric regioisomer. By contrast, no such regiochemical preference was observed in the case of 4,5- and 5,6-indole aryne cycloadditions, where the two regioisomers were obtained in a 1:1 ratio (Scheme 1.6).
Scheme 1.6. Regioselectivity in 4,5-, 5,6- and 6,7-indole aryne cycloadditions with 2-tert-butylfuran.

These observations were rationalized on the basis of ab initio DFT methods performed by the Buszek laboratories in collaboration with the Cramer research group at the University of Minnesota (Garr, Luo et al., 2009). Technically, the 6,7-indole aryne can be represented either as a cummulene, 1.85; an alkyne, 1.86 or alternatively, as a polarized structure, 1.87. The computational studies revealed that the polarized form of the 6,7-indole aryne is the major resonance contributor possessing an electrophilic site at C-6 and a nucleophilic site at C-7 thus, existing as a zwitterionic structure (Figure 1.5).

Figure 1.5. Polarized nature of the 6,7-indole aryne.
The regioselectivity of 6,7-indole aryne cycloadditions was further explored by trapping the 6,7-indole aryne with a series of 2-substituted furans (Table 1).

![Chemical structure](image)

**Table 1.** Regioselective 6,7-indolyne cycloadditions with 2-substituted furans.

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>A</th>
<th>B</th>
<th>Yield, %</th>
</tr>
</thead>
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<td>80</td>
<td>20</td>
<td>89</td>
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<tr>
<td>2</td>
<td>Et</td>
<td>84</td>
<td>16</td>
<td>90</td>
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<tr>
<td>3</td>
<td>i-Pr</td>
<td>94</td>
<td>6</td>
<td>88</td>
</tr>
<tr>
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<tr>
<td>5</td>
<td>Ph</td>
<td>&gt;99</td>
<td>&lt;1</td>
<td>92</td>
</tr>
<tr>
<td>6</td>
<td>SO_2Ph</td>
<td>&lt;1</td>
<td>&gt;99</td>
<td>83</td>
</tr>
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In this study, it was observed that as the electron density at the 2-position of the furan increases, the regiochemical preference favoring the contrasteric regioisomer, 1.89 increases as well. This effect is exactly reversed in the presence of an electron-withdrawing group such as phenylsulfonyl at the 2-position of the furan where none of the contrasteric regioisomer was obtained.

The putative mechanism governing these fascinating reaction profiles is shown in Figure 1.6. In presence of an electron-donating group at the 2-position of the furan, the canonical form of furan, 1.92 is the major resonance contributor thus resulting in the formation of the contrasteric regioisomer, 1.93 as the predominant product. On the other hand, in the presence of an electron-withdrawing group at the 2-position of the furan, the canonical form of furan, 1.95 is the major resonance contributor thus, affording the non-contrasteric regioisomer, 1.96 as the major product. Thus, dipolar effects can induce
regioselection with asymmetrically substituted dienes when polarization of the benzyne triple bond imparts substantial asynchronous electrophilic substitution character to the initial bond forming step.

**Figure 1.6.** Putative mechanism for the 6,7-indole aryne cycloadditions with 2-substituted furans.
CHAPTER 2
APPLICATION OF 6,7-INDOLE ARYNE CYCLOADDITION METHODOLOGY IN TOTAL SYNTHESIS OF (±)-cis-TRIKENTRIN B

2.1 Retrosynthetic Analysis of (±)-cis-trikentrin B

Encouraged by the versatile synthetic utility of 4,5,6-tribromoindole towards the second-generation total synthesis of (±)-cis-trikentrin A and furthermore in the construction of structurally-related libraries of biological significance, we envisioned that a similar strategy involving a novel tribromoindole scaffold could be adapted to achieve the total synthesis of yet another representative member of the trikentrin family namely, (±)-cis-trikentrin B. (±)-cis-trikentrin A and (±)-cis-trikentrin B share a common structural feature i.e., the cis-1,3-dimethyl-cyclopentanoid ring at the 6,7-position of the indole nucleus however, differ only in the substitution pattern at the other positions on the benzene ring. (±)-cis-trikentrin A possesses an ethyl substituent at the C-4 position whereas (±)-cis-trikentrin B bears a trans-butenyl side chain at the C-5 position of the indole system. Hence, we devised a rational retrosynthetic scheme for (±)-cis-trikentrin B that paralleled the total synthesis of (±)-cis-trikentrin A (Scheme 2.1).

We envisioned that the trans-butenyl side chain at the C-5 position could be installed by subjecting the aryl-bromide bond in 2.10 to Pd-catalyzed Stille cross-coupling reaction. The cis-1,3-dimethyl-cyclopentanoid motif in 2.10 could be achieved by converting the primary alcohols in 2.11 to their corresponding mesylates followed Fujimoto reduction protocol. The primary alcohols in turn, could result via a series of transformations on the olefin bond of the 6,7-cycloadduct in 2.12. These include, cis-dihydroxylation followed by oxidative cleavage of the diols to the corresponding dialdehydes and eventually, the
reduction of the dialdehydes to the primary alcohols. The 6,7-cycloadduct, 2.12 could be obtained by trapping the 5-bromo-6,7-indole aryne in a [4 + 2] cycloaddition reaction with cyclopentadiene. 2.13 could be generated via a selective and exclusive metal-halogen exchange at the C-7 bromine of the 5,6,7-tribromoindole scaffold to give 2.14 followed by elimination of LiBr to generate exclusively the 6,7-indole aryne. The 6,7-indole aryne precursor 2.15 could be obtained via Bartoli indole synthesis starting from 1,2,3-tribromo-4-nitrobenzene to yield 5,6,7-tribromoindole followed by silyl protection of the indole nitrogen. Nitration of 1,2,3-tribromobenzene, 2.17 could yield the Bartoli precursor, 2.16 and finally, 2.17 could result from diazotization and further bromination of 2,6-dibromoaniline, 2.18.

Scheme 2.1. Retrosynthetic analysis of (±)-cis-trikentrin B

The success of our synthetic approach relied heavily on one most crucial question i.e., will 2.15 undergo a selective metal-halogen exchange at C-7 and on subsequent elimination, result in the generation of exclusively the 6,7-indole aryne, 2.13 which can be further trapped with cyclopentadiene to achieve the desired 6,7-annulation? It was of intrinsic importance to
address this issue since the occurrence of metal-halogen exchange at any positions other than C-7 would result in undesired outcomes.

Scheme 2.2. Potential sites for metal-halogen exchange in 5,6,7-tribromoindole and the corresponding arynes.

For example, if metal-halogen exchange occurred at the 5-bromo position then it would result in the 5-lithio-6,7-dibromoindole intermediate, 2.20 which upon elimination would generate the undesired 5,6-indole aryne, 2.21 (Scheme 2.2). Similarly, occurrence of metal-halogen exchange at C-6 would result in the formation of 6-lithiated intermediate, 2.22 and subsequently generate either the 5,6-indole aryne, 2.21 or the desired 6,7-indole aryne, 2.23 or alternatively, the mixture of both thus, complicating matters. Ideally, it was desirable to induce metal-halogen exchange selectively and exclusively at C-7 to provide 2.24 in order to generate the 5-bromo-6,7-indole aryne as the sole intermediate for further cycloaddition reaction with cyclopentadiene as planned in the retrosynthetic scheme.
2.2 Synthesis of 5,6,7-Tribromoindole

With the issue of selective metal-halogen exchange in sight, our initial efforts were directed towards designing practical, scalable synthetic routes for the desired 6,7-indole aryne precursor namely, the 5,6,7-tribromoindole. Previously, the Buszek research group had already experienced success with the Bartoli reaction in the synthesis of 4,6,7-tribromoindole which served as the 6,7-indole aryne precursor in the second-generation total synthesis of (±)-cis-trikentrin A and more recently, a versatile scaffold for the construction of 6,7-benzannulated-4-substituted indole libraries of biological importance. Hence, the logical first step was to adapt the Bartoli synthetic protocol (Bartoli, Palmieri et al., 2005) to access the desired 5,6,7-tribromoindole (Scheme 2.3).

Thus, starting from commercially available 2,6-dibromoaniline, 2.18 was subjected to diazotization with tBuONO followed by bromination with CuBr₂ in MeCN at 60 °C to afford 1,2,3-tribromobenzene, 2.17 in 80% yield. Subsequent nitration of 2.17 was achieved with fuming nitric acid to provide in 82%, 2,3,4-tribromonitrobenzene, 2.16 which served as the precursor to the Bartoli synthetic step. 2.16 was treated with vinylmagnesium bromide under typical Bartoli reaction conditions (-40 °C, THF, 1 h) to yield the desired 5,6,7-
tribromoindole, 2.25 in 32%. Although we could successfully synthesize the desired tribromoindole scaffold, despite several attempts to enhance the yield of the Bartoli step, it never rose above 32%. This prompted us to explore alternate synthetic routes that would enable us to obtain the 5,6,7-tribromindole is much improved yields. Consequently, we turned our attention to yet another well-known indole forming reaction namely, the Leimgruber-Batcho indole synthesis (Batcho and Leimgruber, 1985).

**Scheme 2.4.** Leimgruber-Batcho synthesis of 5,6,7-tribromoindole

Commercially available and very inexpensive ($ 0.029/1g), p-toluidine 2.26 was brominated in situ (HBr, 3.0 eq.; H₂O₂, 2.0 eq.; MeOH) to quantitatively yield 2.27 which was subjected to diazotization and subsequent bromination protocol as described earlier to afford 3,4,5-tribromotoluene 2.28 in 80% yield (Scheme 2.4). Nitration of 2.28 was achieved with fuming nitric acid in 89% to provide the Leimgruber-Batcho precursor 2.29. Treatment of 2.29 with tri(piperidin-1-yl)methane (1.5 eq.) at 105 °C under vacuum (105 torr) for 3 h resulted in the enamine intermediate 2.30 which could be isolated however, we chose to carry it forward as it is in the subsequent step which involved FeCl₃·6H₂O-catalyzed reductive
cyclization in the presence of NH$_2$NH$_2$·H$_2$O to afford the desired 5,6,7-tribromoindole in 61% yield over 2 steps, a much better improvement over the Bartoli reaction.

### 2.3 Selective Metal-Halogen Exchange and Cycloaddition

With the required 5,6,7-tribromoindole in hand, we were back to addressing the issue of inducing a selective metal-halogen exchange at the C-7 position of this scaffold.

![Scheme 2.5](image.png)

**Scheme 2.5.** Selective metal-halogen exchange and quenching in N-Me-5,6,7-tribromoindole.

The tribromoindole, 2.25 was N-alkylated by treatment with MeI (2.0 eq) and NaH (2.0 eq) in THF to obtain N-Me-5,6,7-tribromoindole 2.31 in 86% yield. To our delight, when 2.31 was treated with a slight excess of n-BuLi at -78 °C in PhMe, the metal-halogen exchange occurred selectively and exclusively at the C-7 site to provide the 7-lithiated intermediate 2.32 which upon quenching with water at low temperature installed a proton at the same position to yield N-Me-5,6-dibromoindole 2.33 (Scheme 2.5). The formation of 2.33 as the sole product of this reaction provided evidence for the occurrence of selective and exclusive metal-halogen exchange at the C-7 site of the N-Me-5,6,7-tribromoindole scaffold.
which was extremely essential for the generation of the desired 6,7-indole aryne in the subsequent steps of the synthetic scheme.

With the issue of selective metal-halogen exchange addressed, we next attempted to generate the desired 6,7-indole aryne in 2.31 and trap the resulting aryne with cyclopentadiene to achieve annulation at the 6,7-position of the indole nucleus. Thus, 2.31 was subjected to a facile and selective metal-halogen exchange protocol by treatment with n-BuLi in PhMe at -78 °C. Warming up the reaction mixture to -40 to -30 °C resulted in the elimination of LiBr to generate N-Me-5-bromo-6,7-indole aryne which readily underwent a Diels-Alder [4 + 2] cycloaddition reaction with cyclopentadiene to provide the 6,7-cycloadduct, 2.35 in 72% yield (Scheme 2.6). Notably, no metal-halogen exchange whatsoever was observed at the 5-bromo position thus, the C-5 Ar-Br bond remaining completely unaffected and now available for performing cross-coupling chemistry as proposed in the original retrosynthetic strategy.

Scheme 2.6. Exclusive 6,7-indole aryne generation and trapping in N-Me-5,6,7-tribromoindole.

Although N-Me-5,6,7-tribromindole served as an appropriate template for investigating the site of regioselective metal-halogen exchange, this scaffold by itself was not
quite suitable to proceed towards the final target molecule. According to our synthetic strategy, we required a protecting group that could be readily installed and removed in the final stages of the synthesis. One such protecting group that we believed would work was the tert-butyldimethyl silyl (TBS) group since it was previously employed by the Buszek laboratories in the total synthesis of cis-trikentrin A and herbindole A. Initially we attempted the conventional conditions to protect the indole nitrogen as its TBS ether. Thus, the 5,6,7-tribromoindole was reacted with TBS-Cl (2.0 eq.) in the presence of NaH in THF at 0 °C. These efforts did not result in successful installation of the protecting group. However changing from TBSCl to TBSOTf (3.0 eq.) in the presence of NaH (4.0 eq.) and Et3N (2.0 eq.) in THF at 0 °C, provided the desired N-TBS-5,6,7-tribromindole, 2.15 consistently in 78% yield (Scheme 2.7). Gratifyingly, similar to the N-Me-5,6,7-tribromoindole, when N-TBS-5,6,7-tribromoindole was subjected to metal-halogen exchange and elimination protocol, it resulted in a selective and exclusive lithium-bromine exchange at the C-7 site and eventually generating the 6,7-indole aryne which was trapped with cyclopentadiene to obtain the desired 6,7-benzannulated intermediate 2.12 in 83% yield.

![Scheme 2.7. 6,7-indole aryne generation and trapping in N-TBS-5,6,7-tribromoindole.](image)

With the required cycloadduct, 2.12 in hand, we turned our attention towards transforming this cyclopentadiene adduct into the cis-1,3-dimethylcyclopentanoid ring at the 6,7-position. Our initial efforts involved a protocol that was identical to the one previously
employed by our group in the total synthesis of (±)-cis-trikentrin A and (±)-herbindole A (Scheme 2.8). 2.12 was subjected to cis-dihydroxylation (OsO₄, 0.1 eq.; NMO, 5.0 eq.; THF/H₂O, 1.5:1) to afford the diol intermediate 2.36. Subsequently, the diols were oxidatively cleaved NaIO₄ (15 eq.; THF/H₂O, 3.3:1) to provide the 1,3-cis-dialdehyde 2.37 in almost quantitative (99%) yield. Treatment of 2.37 with excess of ethanethiol converted the dialdehydes into their corresponding bisdithioacetals 2.38 and resulted in the deprotection of the indole nitrogen in the same step. Our initial attempts to execute hydrogenolysis of the C-S bond of the bisdithioacetal in order to install the methyl groups with Raney nickel (grade 2800, Aldrich) in refluxing ethanol, as was done in our previous synthesis of racemic cis-trikentrin A, only gave 2.40 as the major product. Changing the solvent to acetone gave a mixture of the desired 5-bromoindole 2.39 in only 16-31% yield, accompanied by varying amounts of the fully reduced undesired indole 2.40.

Scheme 2.8. Installation of 1,3-cis-dimethyl-cyclopentanoid ring via Raney Ni reduction.

These complications in accessing 2.39, prompted us to investigate an alternate route namely, the Fujimoto reduction protocol since Kerr and co-workers had recently shown that similar results could be obtained employing the aforementioned synthetic procedure
(Jackson, Banfield et al., 2005). Thus, the late stage intermediate 2.37 was reduced with NaBH₄, (30 eq., THF, 0 °C) to obtain the primary diols 2.11 (86%), which were further mesylated with MsCl (2.2 eq., Et₃N, 4.0 eq.; CH₂Cl₂) to afford the bismesylate 2.41 in 82% yield (Scheme 2.9). The Fujimoto reduction (NaI, 15 eq.; Zn dust, 60 eq.; glyme, 90 °C) was carried out in a sealed tube to provide the 1,3-cis-dimethyl-cyclopentanoid 2.10 in 58% yield. Desilylation (TBAF, 2.0 eq.; THF) afforded the desired 5-bromoindole 2.39 in 82% yield with the C-5 bromine still intact (Scheme 2.9).

![Scheme 2.9. Fujimoto reduction protocol.](image)

The final step of the synthesis involved subjecting the bromine at the C-5 position to Pd-catalyzed Stille cross-coupling reaction with vinyl tin reagent 2.42 to install the trans-butenyl side chain in the final target molecule. Our initial attempts using conventional Stille cross-coupling conditions failed to give the desired result. However, changing the ligand from triphenylphosphine to triphenylarsine and employing microwave heating readily afforded (±)-cis-trikentrin B in 73% yield thus completing the total synthesis of this natural product (Scheme 3.0).
In conclusion, we have successfully achieved the total synthesis of (±)-cis-trikentrin B using intermolecular cycloaddition of the 6,7-indole aryne with cyclopentadiene coupled with Pd-catalyzed Stille cross-coupling reaction. Finally, this project clearly highlights the following advantages of 6,7-indole aryne cycloaddition methodology in natural products total synthesis:

- Facile generation of the indole aryne from readily available o-dibromides
- Mild reaction conditions (-78 °C to rt)
- High yielding, clean reactions
- Scalable (50+ g scale)
- Adaptable to other benzannulated indole natural products
- Adaptable to library synthesis
3.1 Preliminary 6,7-Indole Aryne Regioselectivity Studies

As mentioned in Chapter 1, during the course of our investigations into the cycloaddition reactions of indole arynes, we observed a remarkable regioselectivity preference in the [4 + 2] Diels-Alder cycloaddition reactions of 6,7-indole arynes with 2-substituted furans. The original regiochemical observations were made with N-Me-3-phenyl-6,7-dibromoindole where it was found that the aryne generated from this precursor upon trapping with 2-tert-butylfuran resulted in the formation of the contrasteric or more sterically crowded regiosomer about 50 folds excess over the non-contrasteric regioisomer. On the other hand, under identical reaction conditions, no such regiochemical preference was observed in the 4,5- and 5,6-indole aryne cycloadditions with 2-tert-butylfuran where the two regioisomers were formed in a 1:1 ratio (Scheme 3.1).

Scheme 3.1. Regioselectivity in 6,7-indole aryne cycloadditions with 2-tert-butylfuran
In order to investigate the fundamental electronic and steric parameters that account for these fascinating reaction profiles, the Buszek laboratories performed *ab initio* calculations using DFT methods in collaboration with the Cramer group at the University of Minnesota. These computational studies revealed that the exceptional regioselectivity observed with the 6,7-indole arynes is by the virtue of the polarized nature of this intermediate species. The 6,7-indole aryne can be more appropriately viewed as a zwitterionic species, possessing an electrophilic site at C-6 and a nucleophilic site at C-7 (Figure 3.1).

![Figure 3.1. Polarized nature of the 6,7-indole aryne](image)

The regioselectivity of 6,7-indole aryne cycloadditions was further explored by trapping the 6,7-indole aryne with a series of 2-substituted furans (Table 3.1).

![Figure 3.1. Polarized nature of the 6,7-indole aryne](image)

**Table 3.1.** Regioselective 6,7-indolyne cycloadditions with 2-substituted furans.

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>A</th>
<th>B</th>
<th>Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>80</td>
<td>20</td>
<td>89</td>
</tr>
<tr>
<td>2</td>
<td>Et</td>
<td>84</td>
<td>16</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>i-Pr</td>
<td>94</td>
<td>6</td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td>t-Bu</td>
<td>98</td>
<td>2</td>
<td>91</td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>&gt;99</td>
<td>&lt;1</td>
<td>92</td>
</tr>
<tr>
<td>6</td>
<td>SO₂Ph</td>
<td>&lt;1</td>
<td>&gt;99</td>
<td>83</td>
</tr>
</tbody>
</table>
In this study, it was observed that as the electron density at the 2-position of the furan increases, the regiochemical preference favoring the contrasteric regioisomer, A increases as well. This effect is exactly reversed in the presence of an electron-withdrawing group such as phenylsulfonyl at the 2-position of the furan where none of the contrasteric regioisomer was obtained.

Intrigued by these results, we were prompted to embark on an empirical study to investigate the effect of various substituents at different positions of the indole system on the regioselectivity of 6,7-indole aryne cycloadditions with 2-tert-butylfuran. Thus, a collection of 2-,3-,4-, and 5-substituted-6,7-dibromoindole precursors were synthesized using adapted Bartoli, Fischer and Leimgruber-Batcho protocols.

### 3.2 Synthesis of 2- and 3-substituted-6,7-dibromoindoles

2,3-dibromophenylhydrazine hydrochloride 3.11 was treated with a collection of aldehydes and ketones 3.12 under Fischer conditions (EtOH, 100 °C, 3 h) to yield a series of 2- and 3-substituted-6,7-dibromoindoles 3.13 a-g. The newly synthesized indoles were N-methylated with MeI (2.0 eq.) in presence of NaH (2.0 eq.) to afford the desired 2- and 3-substituted-6,7-indole aryne precursors 3.14 a-g in excellent yields (Scheme 3.2).

**Scheme 3.2.** Fischer synthesis of 2- and 3-substituted-6,7-dibromoindoles
3.3 Synthesis of 4-substituted-6,7-dibromoindoles

The Bartoli indole synthesis was employed to access 6,7-dibromoindoles possessing various halogens at the 4-position of the indole system. For example, commercially available 4-fluoroaniline \(3.15a\) was nitrated with fuming nitric acid to give the 4-fluoro-2-nitroaniline \(3.16a\) in 89% yield. This was brominated in situ with HBr and \(\text{H}_2\text{O}_2\) to afford \(3.17a\) (89%) which was subsequently diazotized and brominated to yield 1,2-dibromo-5-fluoro-3-nitrobenzene \(3.18a\). Bartoli indole reaction with \(\text{CH}_2=\text{CHMgBr}\) (3.5 eq.) in THF at -78 °C gave the 6,7-dibromo-4-fluoro-1H-indole \(3.19a\) (31%). N-alkylation was achieved with MeI (NaH, THF, 0 °C) to give the 6,7-dibromo-4-fluoro-1-methyl-1H-indole \(3.20a\) in 77% yield. Similarly, Bartoli protocol was implemented to synthesize 4-iodo-, 4-bromo- and 4-ethyl-6,7-dibromoindole precursors \(3.20b-d\).

Scheme 3.3. Bartoli synthesis of 4-substituted-6,7-dibromoindoles.

In order to synthesize 4- and 5-substituted-6,7-dibromoindoles bearing substitution at the C-3 site, Fischer indole synthesis was used (Scheme 3.4).
Scheme 3.4. Fischer synthesis of 4- and 5-substituted-6,7-dibromoindoles with substitution at C-3

The tribromonitrobenzene 3.21.a was subjected to iron catalyzed reduction (activated carbon, NH$_2$NH$_2$•H$_2$O, MeOH) to give the corresponding aniline 3.22.a (83%) which was subsequently converted to the hydrazine salt 3.23.a (6M HCl, NaNO$_2$, SnCl$_2$•2H$_2$O, conc. HCl). Reaction of hydrazine salt with phenyl acetaldehyde (EtOH, 100 °C, seal tube) gave the 3-phenyl-4,6,7-tribromoindole 3.24.a in 67% yield which was N-alkylated as before with MeI. The 3-phenyl-5,6,7-trimibromoindole 3.24.b was synthesized following a similar sequence of reactions.

With the required 6,7-dibromoindole precursors in hand, each of them were subjected to metal-halogen exchange and elimination protocol to generate the corresponding 6,7-indole arynes in these systems which were subsequently trapped with 2-tert-butyliurane to afford the cycloadducts in a specific regiochemical distribution, details of which are described in the following section.
3.4 Regioselective 6,7-Indole Aryne Cycloadditions

We first examined the effect of substituted aryl and other groups at the 3-position of the indole on the regioselectivity of the 6,7-indole aryne cycloadditions (Table 3.2).

![Chemical structure image]

**Table 3.2.** Regioselective 3-Substituted 6,7-Indole Aryne Cycloadditions with 2-**tert**-Butylfuran

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>3.27</th>
<th>3.28</th>
<th>Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>49</td>
<td>1</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>4-MeOPh</td>
<td>&gt;99</td>
<td>&lt;1</td>
<td>76</td>
</tr>
<tr>
<td>3</td>
<td>4-F-Ph</td>
<td>15.7</td>
<td>1</td>
<td>59</td>
</tr>
<tr>
<td>4</td>
<td>CH₂Ph</td>
<td>10</td>
<td>1</td>
<td>58</td>
</tr>
<tr>
<td>5</td>
<td>Et</td>
<td>6.1</td>
<td>1</td>
<td>64</td>
</tr>
<tr>
<td>6</td>
<td>H</td>
<td>3.0</td>
<td>1</td>
<td>60</td>
</tr>
</tbody>
</table>

It can be seen that a highly electron-rich 4-methoxyphenyl substituent (Table 3.2, entry 2) gave within our limits of detection and analysis, exclusively the contrasteric regioisomer 3.27. None of the alternate regioisomer 3.28 was obtained. This was a significant increase over the 3-phenyl substituent where the regioisomeric ratio was 49:1 in favor of 3.27. On the other hand, the less electron-rich 4-fluorophenyl case exhibited somewhat lower degree of regiocontrol where the ratio dropped to 15:1 (Table 3.2, entry 3). There clearly appears to be a definitive trend over here i.e., as the electron density at the 3-position of the indole decreases from 4-methoxyphenyl to phenyl to 4-fluorophenyl, the regioselectivity in these cycloadditions decrease as well.
We next examined the issue of aromatic conjugation at the C-3 site and its effect on the regioselectivity. Thus, by breaking the conjugation at this site i.e., by incorporating a benzyl substituent, there was a significant diminution of regiocontrol, the regioisomeric ratio being 10:1 as compared to 49:1 in presence of a conjugated aromatic phenyl group at this position. This data point clearly suggests that the presence of conjugation at the C-3 site favors the contrasteric regioisomer to a significant degree. Furthermore, a simple alkyl group such as an ethyl group at this site resulted in further diminished yet a significant degree of regiocontrol (6.1:1). It is evident from the data in entries 1-5 that the presence of any substitution at the C-3 position of the indole is beneficial for the regiochemistry of the 6,7-indole aryne cycloadditions with 2-substituted furans. It is the total electron density at this site either due to conjugative or inductive effects that is responsible for imparting the regioselectivity. This point is further strengthen by the data in entry 6 where there is no substituent present at the C-3 position (R = H). In this case, we observed the lowest proportion of the contrasteric regioisomer (3:1).

Subsequently, we turned our attention to the effect of aromatic conjugation at the other position on the pyrrole ring i.e., the C-2 site (Table 3.3). In this case, we observed a significant diminution of regiocontrol where the ratio dropped to 9.1:1 as compared to 49:1 in presence of the same phenyl substituent at the C-3 position, this was a five times decrease in the regioselectivity. Interestingly, incorporating two aromatic conjugated phenyl groups at C-2 and C-3 resulted in further diminished selectivity with the distribution of 6.7:1. of the indole that is responsible for same site. This observation could be rationalized on the basis of the assumption that the steric hindrance between the two phenyl rings at the adjacent positions on the pyrrole ring prevents effective conjugation at this site and thus, reduces the
effect of conjugation on the regioselectivity. Also, the phenyl ring at the 2-position is almost certainly in a non-planar orientation by virtue of which its electronic contributions are more likely to be inductive rather than conjugative. However, even in these cases, the regioselectivity observed was much better than having no substituents present at either C-2 and C-3 (Table 3.3, entry 4).

![Chemical structure](image)

**Table 3.3.** Regioselective 2-Phenyl- and 2,3-Diphenyl-6,7-indole Aryne Cycloadditions with 2-**tert**-Butylfuran

<table>
<thead>
<tr>
<th>entry</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>3.30</th>
<th>3.31</th>
<th>Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>H</td>
<td>49</td>
<td>1</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>Ph</td>
<td>9.1</td>
<td>1</td>
<td>61</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>Ph</td>
<td>6.7</td>
<td>1</td>
<td>62</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>H</td>
<td>3</td>
<td>1</td>
<td>60</td>
</tr>
</tbody>
</table>

After examining the effect of various substituents on the pyrrole side of the indole, we turned our attention towards investigating the impact of different substitution patterns on the benzene ring. The effect of a halogen such as Br at the C-4 position on the regioselectivity was initially gauged. In this case, the regioselectivity ratio was 3.4:1 in favor of the contrasteric regioisomer (Table 3.4, entry 1). This regiochemical outcome was almost similar to the one obtained in case of no substitution at the C-3 site (3:1). Incorporating an aromatic conjugated phenyl group at this site resulted in a slight enhancement of regioselectivity ratio to 4.6:1 (Table 3.4, entry 2). This indicates that in this case, aromatic
conjugation at the C-3 site does impart some beneficial effect to the regioselectivity of these cycloaddition reactions.

![Reaction Scheme](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>R¹</th>
<th>R²</th>
<th>3.33</th>
<th>3.34</th>
<th>Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Br</td>
<td>H</td>
<td>3.4</td>
<td>1</td>
<td>76</td>
</tr>
<tr>
<td>2</td>
<td>Br</td>
<td>Ph</td>
<td>4.6</td>
<td>1</td>
<td>76</td>
</tr>
</tbody>
</table>

However, a much more dramatic effect was observed when bromine was adjacent to the site of the 6,7-indole aryne i.e., at C-5 (Table 3.5)

![Reaction Scheme](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>R¹</th>
<th>R²</th>
<th>3.36</th>
<th>3.37</th>
<th>Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>Br</td>
<td>1.4</td>
<td>1</td>
<td>68</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>Br</td>
<td>1.4</td>
<td>1</td>
<td>62</td>
</tr>
</tbody>
</table>
In this case, there was virtually no regioselectivity observed with the two regioisomers formed in a 1.4:1 ratio (Table 3.5, entry 1). Even the installation of a supposedly beneficial aromatic conjugation at the C-3 site did alter the regiochemical outcome with the isomers still obtained in an identical ratio (1.4:1).

Finally, a collection of 6,7-dibromoindoles possessing halogens and other substituents at the 4-position were synthesized to study the effect of these groups on the regioselectivity of 6,7-indole aryne cycloadditions with 2-tert-butylfuran (Table 3.6).

![Chemical Structures](image)

**Table 3.6.** Regioselective 4-Substituted 6,7-Indole Aryne Cycloadditions with 2-tert-Butylfuran

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>3.39</th>
<th>3.40</th>
<th>Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>2.3</td>
<td>1</td>
<td>71</td>
</tr>
<tr>
<td>2</td>
<td>Br</td>
<td>3.4</td>
<td>1</td>
<td>76</td>
</tr>
<tr>
<td>3</td>
<td>I</td>
<td>15.7</td>
<td>1</td>
<td>65</td>
</tr>
<tr>
<td>4</td>
<td>Et</td>
<td>11.5</td>
<td>1</td>
<td>63</td>
</tr>
</tbody>
</table>

It can be seen that a fluorine substituent at the C-4 position gave a regioselectivity ratio of 2.3:1 in favor of the contrasteric regioisomer as compared to 3.4:1 in case of a bromine at the same site. Furthermore, the presence of iodine at this position resulted in a significant enhancement in the regioselectivity with the distribution being 15.7:1. Thus, there
appears to be a definitive trend over here i.e., as the electronegativity at the 4-position of the indole decreases from fluorine to bromine to iodine, the regioselectivity in these cycloaddition reactions increase. Finally, an inductively electron-donating alkyl substituent such as an ethyl group at this site also provided a significant degree of regiocontrol (11.5:1).

In conclusion, the experimental data reveal that different substituents affect the degree of polarization of 6,7-indole aryne bond which in turn controls the degree of regioselectivity. The presence of electron donating (e.g., p-OMe) conjugated phenyl substituents at the C-3 site provides the greatest degree of regiocontrol. The introduction of non-conjugated substituents at C-3 exhibits diminished but still significant regioselectivity thus suggesting that the presence of any electron rich group at this site benefits the regiochemistry in 2-substituted furan cycloadditions. The regioselectivity is significantly suppressed in the presence of a conjugated phenyl group at C-2 (9.1:1) as compared to having the same substituent at the C-3 site of the indole nucleus (49:1). Phenyl substitution at both C-2 and C-3 results in further diminution of regiocontrol (6.7:1), possibly due to the absence of a planar conformer. However, in these cases, the overall effect on regioselectivity is better than having no substitution at both sites (3:1). Substitution on the benzene side of the indole system results in most cases in a markedly reduced selectivity. The presence of C-4 Br exhibits higher regiocontrol (3.4:1) as compared to virtually no selectivity in case of C-5 Br (1.4:1). Phenyl conjugation at C-3 slightly enhances the regioselectivity in the C-4 Br case (4.6:1); however, it has no impact on the regiochemical distribution in case of a C-5 Br. As the electronegativity decreases from F to I at the C-4 site, the regioselectivity increases (e.g., F, 2.3:1; Br, 3.4:1; I, 15.7:1) in those cases where a C-3 phenyl substituent is absent. Finally,
the inductively electron-rich ethyl group also displays a significant degree of regiocontrol even without a C-3 phenyl substituent (11.5:1).
CHAPTER 4

TRIBROMOINDOLES AS VERSATILE SYNTETIC INTERMEDIATES FOR REGIOSELECTIVE METAL-HALOGEN EXCHANGE, INDOLE ARYNE FORMATION, AND FURTHER REACTIONS: SYNTHESIS AND REACTIONS OF 4,5,6- AND 4,5,7-TRIBROMOINDOLES.

4.1 Background: Tribromoindoles as versatile intermediates for Natural Products Total Synthesis and Library Development

The Buszek research group has previously demonstrated the synthetic utility of two tribromoindoles namely, the 4,6,7- and the 5,6,7-tribromoindole in the total synthesis of biologically active, complex indole alkaloid natural products such as the trikentrins and the herbindoles and furthermore, in the construction of libraries of biological significance inspired from these natural products.

![Scheme 4.1](image_url)

**Scheme 4.1.** The second-generation total synthesis of (±)-cis-trikentrin A.

For example, the 4,6,7-tribromoindole was shown to undergo a selective metal-halogen exchange at C-7 and subsequent elimination to generate exclusively the 6,7-indole aryne. The remaining unreacted C-4 bromine readily underwent Pd(0)-catalyzed Negishi cross-coupling to complete the total synthesis of (±)-cis-trikentrin A (Scheme 4.1).

Furthermore, the 4,6,7-tribromindole served as a versatile template for the construction of an unprecedented 93-membered library of polycyclic, benzannulated indoles exhibiting provocative biological activities (Scheme 4.2).
Similarly, the 5,6,7-tribromoindole resulted in exclusively the 6,7-indole aryne via a highly regioselective metal-halogen exchange at C-7 followed by elimination. Subsequently, the C-5 bromo position was subjected to Stille cross-coupling protocol to successfully achieve the total synthesis of (±)-cis-trikentrin B (Scheme 4.3).

Thus, it can be seen that both the 4,6,7- and 5,6,7-tribromoindoles were found to undergo a highly selective and exclusive metal-halogen exchange at C-7 to subsequently generate solely the 6,7-indole aryne intermediate upon elimination. None of the other bromo positions i.e., the C-4 and C-6 sites in the 4,6,7-tribromoindole were affected by n-BuLi.
Likewise, the 5- and 6-bromo positions in the 5,6,7-tribromoindole scaffold remained unreacted on treatment with n-BuLi.

### 4.2 The Tetrad of Tribromoindoles

In connection with our ongoing total synthesis and indole library programs, and in order to better understand the proclivity for selective metal-halogen exchange in related polybromoindole systems, we decided to synthesize the remaining two members of the tribromoindole family, namely, 4,5,6- and 4,5,7-tribromoindoles (Figure 4.1), both of which were unknown in the literature. With these compounds in hand, we could examine the metal-halogen exchange in these cases, as well as study the regioselective [4+2] cycloaddition behavior of the indole arynes produced in this manner.

![Diagram of tribromoindoles](image)

**Figure 4.1.** The members of the tribromoindole family.

Investigating the issue of metal-halogen exchange in these novel tribromoindole scaffolds was of intrinsic importance because the site of metal-halogen exchange would dictate the position of aryne formation in these systems.

For example, if metal-halogen exchange in the 4,5,6-tribromoindole scaffold occurred at the 4-bromo position then it would result in the 4-lithio-5,6-dibromoindole intermediate, **4.12** which upon elimination would generate the 6-bromo-4,5-indole aryne, **4.13** (Scheme 4.4). Similarly, occurrence of metal-halogen exchange at C-5 would result in the formation of 5-lithiated intermediate, **4.14** and subsequently generate either the 4,5-indole aryne, **4.13** or
the 5,6-indole aryne, 4.15 or alternatively, the mixture of both. Finally, in event of a metal-halogen exchange at the C-6 bromine, the 4-bromo-5,6,-indole aryne, 4.15 would be obtained as the sole aryne.

\[ \text{Scheme 4.4. The potential sites of metal-halogen exchange in 4,5,6-tribromoindole.} \]

Likewise, in case of a metal-halogen exchange at the C-4 site in 4,5,7-tribromoindole, 4.18 would be obtained which upon elimination would result in the formation of 7-bromo-4,5-indole aryne, 4.19 (Scheme 4.5). The same aryne intermediate will result from a metal-halogen exchange at the 6-bromo position. However, if the bromine at C-7 exchanges with n-BuLi then it would not result in the generation of any indole aryne and unfortunately, under such circumstances, the 4,5,7-tribromoindole would fail to serve as a substrate for indole aryne generation.
Scheme 4.5. The potential sites of metal-halogen exchange in 4,5,7-tribromoindole.

4.3 Synthesis of 4,5,6- and 4,5,7-Tribromoindoles

The synthesis of 4,5,6-tribromoindole commenced with commercially available and inexpensive 3-methylaniline (m-toluidine), which was first acetylated (Ac₂O, 1.0 eq.; 1,2-DCE, 84 °C, 1 h) in 94% yield (Scheme 4.6). Nitration (conc. H₂SO₄, conc. HNO₃, 0 °C, 1 h, 75%), followed by amide hydrolysis (conc. HCl, glyme, 85 °C, 3 h, 84%) proceeded uneventfully and afforded 3-methyl-4-nitroaniline. In situ bromination (HBr, 3.0 eq.; 30% H₂O₂, 2.0 eq.; MeOH, rt, 12 h) gave 2,6-dibromo-3-methyl-4-nitroaniline in 91% yield. This aniline was subjected to diazotization and bromination (CuBr₂, 1.3 eq.; tBuONO, 1.6 eq.; CH₃CN, 60 °C, 1 h), providing the 3,4,5-tribromo-2-methylnitrobenzene indole precursor in 77% yield. Subjecting this intermediate to the one-pot Leimgruber-Batcho indole conditions (tripiperidinylmethane, 1.5 eq., 105 °C, 15 torr, 3 h; then, FeCl₃•6H₂O, 0.065 eq.; activated carbon, 3.3 eq.; H₂NNH₂•H₂O, 3.95 eq., 52% for two steps) gave the desired 4,5,6-
tribromoindole in seven steps from \textit{m}-toluidine. The indole was methylated (NaH, 3.0 eq.; then CH\textsubscript{3}I, 3.0 eq., THF, 0 °C) in 92\% yield and \textbf{4.30} used in our subsequent studies.

\textbf{Scheme 4.6.} Synthesis of 4,5,7-tribromoindole via Leimgruber-Batcho protocol.

In a similar manner, the 4,5,7-tribromoindole was also prepared via the Leimgruber-Batcho route (Scheme 4.7). Thus 2-methyl-3-nitroaniline was initially brominated as described above (91\%), diazotized and further brominated (78\%), and then converted to the desired indole \textbf{4.29} in only three steps (56\%, one-pot, two steps). Methylation as before (94\%) provided the compound \textbf{4.30} needed for our study.
4.4 Metal-Halogen Exchange Studies in N-Me-4,5,6- and 4,5,7-Tribromoindoles

With the required tribromoindoles in hand, we first examined the site of metal-halogen exchange in these systems. When N-Me-4,5,6-tribromoindole was treated with n-BuLi at -78 °C, the metal-halogen exchange occurred selectively and exclusively at the C-4 site (Scheme 4.8). The other bromo positions i.e., the C-5 and C-6 sites remained unaffected with n-BuLi. The evidence for the metal-halogen exchange at C-4 was obtained by quenching the 4-lithiated intermediate with water at low temperatures to provide N-Me-5,6-dibromoindole in 62% yield.

However, when N-Me-4,5,7-tribromoindole on treatment with n-BuLi at -78 °C in PhMe did not exhibit exclusive metal-halogen exchange at a single site. In this case, it was observed that the C-7 bromine has a 4 times greater propensity than the bromine at the C-4 site to exchange with n-BuLi (Scheme 4.9).

Scheme 4.9. Metal-halogen exchange studies in N-Me-4,5,7-tribromoindole.

Consequently, on quenching the lithiated intermediates with water at low temperatures, N-Me-4,5-dibromoindole and N-Me-5,7-dibromoindole were obtained in a 4:1 ratio. This data suggests that N-Me-4,5,7-tribromoindole may not be a very useful substrate for indole aryne generation since the C-7 bromo site is more susceptible to metal-halogen exchange as compared to the C-4 site. Although, the 4-lithiated intermediate would result in the formation of 4,5-indole aryne upon elimination, this aryne would not be a major product of this reaction.

4.5 Indole Aryne Cycloadditions in N-Me-4,5,6- and 4,5,7-Tribromoindoles

With the sites of metal-halogen exchange in N-Me-4,5,6- and N-Me-4,5,7-tribromoindoles established, we next attempted to generate arynes in these systems and subsequently trap them with a diene to provide evidence for the existence of these
intermediates. Thus, N-Me-4,5,6-tribromoindole was treated with a slight excess of n-BuLi at -78°C in PhMe to induce a selective and exclusive metal-halogen exchange at C-4. Upon warming up the reaction mixture to -40 to -35°C, the 4-lithiated intermediate underwent an elimination of LiBr to generate the 6-bromo-4,5-indole aryne which was subsequently trapped with cyclopentadiene in a [4 + 2] Diels-Alder cycloaddition reaction to yield the corresponding 6-bromo-4,5-benzannulated product in 65% yield (Scheme 4.10).

**Scheme 4.10.** Indole aryne generation and trapping in N-Me-4,5,6-tribromoindole.

Surprising results were obtained when N-Me-4,5,7-tribromoindole was subjected to metal-halogen exchange and elimination protocol. The metal-halogen exchange studies for this scaffold had suggested the 7-lithiated species to be the major product of this reaction. Thus, the result of this reaction would have been the formation of N-Me-4,5-dibromoindole as the predominant product whereas, the 4,5-indole aryne cycloaddition product to be the minor one. However, when N-Me-4,5,7-tribromoindole was subjected to metal-halogen exchange and elimination protocol, the 4,5-indole aryne cycloaddition product **4.46** was formed as the sole product, none of the N-Me-4,5-dibromoindole **4.41** was observed (Scheme 4.11).

**Scheme 4.11.** Indole aryne generation and trapping in N-Me-4,5,7-tribromoindole.
This intriguing observation could be rationalized on the basis of a hypothesis that the initial metal-halogen exchange occurs at C-7 as demonstrated however, this 7-lithiated species 4.39 itself acts as a lithiating reagent and performs a subsequent metal-halogen exchange at the C-4 site of an unreacted N-Me-4,5,7-tribromoindole to give exclusively 4.40. This intermediate upon elimination forms exclusively the 6-bromo-4,5-indole aryne 4.45 which undergoes cycloaddition with cyclopentadiene (Scheme 4.12).

![Scheme 4.12. Plausible mechanism for C-4 lithiation in N-Me-4,5,7-tribromoindole.](image)

4.6 Regioselectivity in 4,5-Indole Aryne Cycloadditions in N-Me-4,5,6- and 4,5,7-Tribromoindoles

Subsequently, we investigated the regioselectivity in the 4,5-indole aryne cycloadditions in these scaffolds with 2-substituted furans. Thus, when the 4,5-indole aryne generated in N-Me-4,5,6-tribromoindole was trapped with 2-tert-butylfuran, virtually no regioselectivity was observed (1.3:1) with the two regioisomers formed in almost equal proportions (Scheme 4.13).
Scheme 4.13. Regioselective cycloadditions of 6-bromo-4,5-indole aryne with 2-tert-butylfuran.

This observation is consistent with the regiochemical outcome in the N-Me-5,6,7-tribromoindole case where the regioselectivity ratio was comparable (1.4:1). Apparently, the presence of a bromine adjacent to the site of aryne formation is not very beneficial for the regioselectivity of these cycloaddition reactions.

On the other hand, when 7-bromo-4,5-indole aryne was trapped with 2-tert-butylfuran, the regiochemical distribution was slightly enhanced with the two regioisomers formed in a 2:1 ratio (Scheme 4.13). Again, this observation is consistent with the regiochemical outcome in the N-Me-4,6,7-tribromoindole case where the regioselectivity ratio was comparable (3:1). It appears that in both these systems, as the bromine moves one carbon atom away from the site of aryne formation, there is a slight improvement in the regioselectivity of these cycloaddition reactions.

4.7 N-Me-4,5,6- and 4,5,7-Tribromoindoles as Templates for Library Construction

The Buszek laboratory has a long-standing interest in the development of new chemotypes (new chemical entities) based on heteroaromatic systems, especially indoles. The compelling biological results obtained from our previously synthesized 4-substituted-6,7-benzannulated indoles have already validated the significance of annulated indoles in library development. In connection to these previous efforts, we were prompted to exploit the newly synthesized N-Me-4,5,6- and N-Me-4,5,7-tribromoindole scaffolds toward library construction. We envisioned that the 4,5-region of these scaffolds would serve as the aryne cycloaddition region whereas, the remaining unreacted 6- and 7-bromo positions could be subjected to Pd(0)-catalyzed cross-coupling chemistry to install various adornments at these sites. However, the important question was whether or not the bromine substituents in these scaffolds would serve as good partners in cross-coupling reactions.

To demonstrate the proof-of-concept, the remaining unreacted 6-bromo position in 4.44 was subjected to Pd(0)-catalyzed Negishi cross-coupling reaction with dimethylzinc. Gratifyingly, the C-6 bromo position readily underwent the cross-coupling protocol to install
a methyl substituent at this site in 72% yield (Scheme 4.14). Likewise, under identical Negishi conditions, an ethyl group was successfully incorporated at the C-6 site to yield 4.54 in 75% yield thus, providing the first ever examples of 6-substituted-4,5-benzannulated indoles.

![Scheme 4.15](image)

**Scheme 4.15.** Negishi cross-coupling reactions in 6-bromo-4,5-benzannulated indoles.

In a similar manner, the remaining unreacted 7-bromo position in 4.46 was subjected to Pd(0)-catalyzed Negishi cross-coupling reactions with dimethylzinc and diethylzinc to install substitution patterns at these sites in excellent yield thus, providing the first ever examples of 7-substituted-4,5-benzannulated indoles (Schemes 4.15).

![Scheme 4.16](image)

**Scheme 4.16.** Negishi cross-coupling reactions in 7-bromo-4,5-benzannulated indoles.
4.8 Future Directions

With the proof-of-concept already established, the future efforts will be directed towards subjecting the keys scaffolds 4.44 and 4.46 to a series of Pd(0)-catalyzed cross-coupling reactions involving Buchwald-Hartwig, Suzuki-Miyaura, Negishi, Sonogashira, Stille and Heck to construct a collection of structurally diverse 6- and 7-substituted-4,5-benzannulated indole library members (Schemes 4.16 and 4.17).

Scheme 4.17. Various cross-coupling reactions in 6-bromo-4,5-benzannulated indoles.

These newly synthesized library members will be screened in various cell-based assays to ascertain their biological activities.
Scheme 4.18. Various cross-coupling reactions in 7-bromo-4,5-benzannulated indoles.
CHAPTER 6

EXPERIMENTAL SECTION

6.1 General Details

$^1$H-NMR (400 MHz) and $^{13}$C-NMR (100 MHz) were performed in CDCl$_3$ unless otherwise noted with reference to residual solvent at $\delta$ 7.26 ppm and 77.0 ppm respectively. Melting points reported are uncorrected. Unless otherwise noted, all commercially obtained starting materials were used as received. n-Butyllithium was titrated against 2-butanol in anhydrous THF with 1,10-phenanthroline as an indicator prior to use. Tetrahydrofuran and diethyl ether were distilled from sodium and benzophenone under nitrogen prior to use. Toluene was distilled from calcium hydride under nitrogen prior to use. Temperatures of -78 °C were obtained through use of a dry-ice acetone cold bath. Microwave reactions were carried out using a Biotage Initiator microwave reactor at the times and temperatures indicated.
1,2,3-Tribromobenzene (2.17): In a 500-mL round-bottom flask was dissolved 5.78 g (25.9 mmol) of CuBr$_2$ in 200 mL of dry CH$_3$CN and the mixture heated to 60 °C. To this warm solution was added 3.80 mL (31.9 mmol) tert-butyl nitrite, followed by a solution of 5.01 g (19.9 mmol) of commercially available 2,6-dibromoaniline 2.18 in 50 mL CH$_3$CN. The mixture was stirred at 60 °C for 1 h, then cooled to room temperature and poured into 200 mL 20% aqueous ammonia. The mixture was extracted with hexane (2 x 200 mL) and the combined organic phase was washed sequentially with 20% aqueous ammonia (100 mL), water (100 mL), brine (50 mL), and then dried over anhydrous magnesium sulfate. The contents were filtered and concentrated under reduced pressure. The resulting crude material was recrystallized from ethanol to give 5.12 g (80%) of 1,2,3-tribromobenzene 2.17 as an off-white solid, mp = 88-90 °C. $^1$H NMR (CDCl$_3$): δ 7.58 (d, $J = 8.0$ Hz, 2 H), 7.03 (t, $J = 8.0$ Hz, 1 H); $^{13}$C NMR (CDCl$_3$): δ 132.6, 129.2, 127.7, 126.2.

1,2,3-Tribromo-4-nitrobenzene (2.16): In a 250-mL round-bottom flask was dissolved 5.00 g (15.9 mmol) of 2.17 in 100 mL of 1,2-dichloroethane and the mixture cooled to 0 °C. To the vigorously stirred solution at 0 °C was added 7.00 mL (159 mmol) of fuming HNO$_3$
dropwise over 15 minutes. The mixture was stirred at 0 °C for 1 h and then poured over 500 mL of ice. After 30 minutes, 100 mL of CH₂Cl₂ was added and the organic layers extracted with water (3 x 100 mL), saturated NaHCO₃ (3 x 100 mL), brine (100 mL), and then dried over anhydrous magnesium sulfate. The contents were filtered and concentrated under reduced pressure. The crude material was recrystallized from hexanes to give 4.74 g (82%) of 2,3,4-tribromonitrobenzene **2.16** as an off-white solid: mp = 82-84 °C. **1H** NMR (CDCl₃): δ 7.76 (d, J = 8.6 Hz, 1 H), 7.51 (d, J = 8.6 Hz, 1 H); **13C** NMR (CDCl₃): δ 132.6, 132.5, 131.1, 130.1, 123.7, 118.7; HRMS (EI) m/e calcd for C₆H₂Br₃NO₂ 356.7635, found 356.7633.

![Chemical structure](image)

**5,6,7-Tribromoindole (2.25) via Bartoli route:** In 250-mL round-bottom flask was dissolved 2.01 g (5.55 mmol) of **2.16** in 20 mL of dry THF and cooled to -40 °C. To the vigorously stirred solution was added 16.7 mL (16.7 mmol) of 1 M vinyl magnesium bromide via syringe at once. The mixture was stirred for 1 h. The mixture was quenched with 100 mL saturated NH₄Cl and then extracted with diethyl ether (2 x 100 mL) and the combined organic phase was washed sequentially with water (100 mL), brine (50 mL), and dried over anhydrous magnesium sulfate. The material was filtered and concentrated under reduced pressure. The crude material was then purified via flash column chromatography on silica gel using 10% EtOAc (ethyl acetate) in hexanes as the eluent to give 0.628 g (32%) of **2.25** as a white solid, mp = 132-134 °C. **1H**-NMR (CDCl₃): δ 8.36 (bs, 1 H, NH); 7.89 (s, 1 H); 7.27 (dd, J = 3.3, 3.3 Hz, 1 H); 6.57 (dd, J = 3.3, 3.3 Hz, 1 H). **13C**-NMR (CDCl₃): δ
134.8, 128.2, 126.4, 124.0, 119.2, 115.5, 107.9, 103.5; HRMS (EI) m/e calcd for C₈H₄Br₃N 350.7893, found 350.7891.

2,6-Dibromo-4-methylaniline (2.27): In 500-mL round-bottom flask was dissolved 10.7 g (100 mmol) 2.26 in 300 mL of dry methanol. To the vigorously stirred solution was carefully added 50.6 mL (300 mmol) concentrated aqueous HBr (47% wt/wt) followed by 22.7 mL (200 mmol) 30% aqueous H₂O₂ dropwise over 15 minutes. The mixture was stirred overnight. The mixture was poured into 1.0 L of 1 M NaOH and the resulting suspension was filtered and washed with water until neutral. Dried under vacuum at 50 °C gave 26.2 g (99%) of 2.27 as a purple amorphous solid (mp = 74-76 °C) whose physical properties were identical to that of the commercially available compound.

3,4,5-Tribromotoluene (2.28): In a 1-L round-bottom flask was dissolved 11.6 g (52.0 mmol) CuBr₂ in 300 mL of dry CH₃CN and heated to 60 °C. To the warm solution was added 7.6 mL (64 mmol) tert-butyl nitrite followed by a solution of 10.6 g (40.0 mmol) of 2.27 in 100 mL of CH₃CN. The mixture was stirred at 60 °C for 1 h. The solution was cooled to room temperature and poured into 400 mL of 20% aqueous ammonia. The mixture was extracted with hexane (2 x 400 mL) and the combined organic layers were washed
sequentially with 20% aqueous ammonia (200 mL), water (200 mL), brine (100 mL), and then dried over anhydrous magnesium sulfate. The solution was filtered and concentrated under reduced pressure. The crude material was recrystallized from ethanol to give 11.3 g (80%) of 2.28 as off-white needles, mp = 92-94 °C. $^1$H-NMR (CDCl$_3$): $\delta$ 7.38 (s, 2 H), 2.24 (s, 3 H); $^{13}$C-NMR (CDCl$_3$): $\delta$ 139.4, 133.0, 125.4, 123.8, 20.4.

1,2,3-Tribromo-5-methyl-4-nitrobenzene (2.29): In a 250-mL round-bottom flask was dissolved 10.0 g (30.9 mmol) of 2.28 in 100 mL of 1,2-dichloroethane and cooled to 0 °C. To the vigorously stirred solution at 0 °C was added 13.5 mL (309 mmol) of fuming HNO$_3$ dropwise over 15 minutes. The mixture was stirred at 0 °C for 1 h and then poured into 500 mL of ice. After 30 minutes 100 mL of CH$_2$Cl$_2$ was added and extracted. The organic layer was washed sequentially with water (3 x 200 mL), saturated NaHCO$_3$ (3 x 100 mL), brine (100 mL), dried over anhydrous magnesium sulfate. The solution was filtered and concentrated under reduced pressure. The crude material was recrystallized from hexanes to give 9.46 g (82%) of 2.29 as off-white solid, mp = 106-108 °C. $^1$H NMR (CDCl$_3$): $\delta$ 7.58 (s, 1 H), 2.26 (s, 3 H); $^{13}$C NMR (CDCl$_3$): $\delta$ 151.6, 134.4, 130.8, 127.3, 126.7, 117.0, 17.1; HRMS (EI) m/e calcd for C$_7$H$_4$Br$_3$NO$_2$ 370.7791, found 370.7790.
5,6,7-Tribromoindole (2.25) via Leimgruber-Batcho route: In a 50-mL round-bottom flask a mixture of 6.52 g (17.4 mmol) 2.29 and 6.92 g (26.1 mmol) TPM was heated to 105 °C under water-aspirator vacuum with vigorous stirring. After 3 h an aliquot of the mixture showed complete reaction by TLC (20% dichloromethane in hexane). Cooled to room temperature and passed through a plug of silica gel eluting with 50% tert-butyl methyl ether in hexanes and concentrated under reduced pressure to give 8.15 g of crude intermediate which was then suspended in 150 mL methanol in a 250 mL round-bottom flask and heated to reflux. To the red solution was added 0.305 g (1.13 mmol) FeCl$_3$•6H$_2$O and 0.689 g (57.4 mmol) activated carbon. The mixture was refluxed for 5 minutes, and then 3.35 mL (68.7 mmol) NH$_2$NH$_2$•H$_2$O was added via a syringe over 10 minutes and refluxed for 1 h. The mixture was cooled to room temperature and filtered through a 1-cm pad of Celite, washing with methanol. The filtrate was concentrated under reduced pressure to about 5 mL, then diluted with 1M HCl (250 mL), extracted with CH$_2$Cl$_2$ (3 x 75 mL). The combined organic phases were washed with water (2 x 100 mL), brine (50 mL), and dried over anhydrous magnesium sulfate. The solution was filtered and concentrated under reduced pressure. The crude material was then purified via column chromatography on silica gel using 10% CH$_2$Cl$_2$ in hexanes as eluent to give 3.68 g (61%) of 2.25 as a white solid, mp = 132-134 °C. $^1$H-NMR (CDCl$_3$): $\delta$ 8.36 (bs, 1 H, NH); 7.89 (s, 1 H); 7.27 (dd, $J$ = 3.3, 3.3 Hz, 1 H); 6.57 (dd, $J$ = 3.3, 3.3 Hz, 1 H). $^{13}$C-NMR (CDCl$_3$): $\delta$ 134.8, 128.2, 126.4, 124.0, 119.2, 115.5, 107.9, 103.5. HRMS (EI) m/e calcld for C$_8$H$_4$Br$_3$N 350.7893, found 350.7891.
5,6,7-tribromo-1-methyl-1H-indole (2.31): In a 100 mL flame dried round bottom flask under argon was added 35 mg (0.10 mmol) of 5,6,7-tribromoindole 2.25. This was dissolved in 10 mL of dry THF and to this solution was added 5 mg (0.20 mmol) of dry sodium hydride. The solution was stirred at room temperature for 30 min, and then 13 µL (0.20 mmol) of iodomethane was added via syringe. The resulting solution was stirred for 1 h, and then quenched by dropwise addition of aq. NH₄Cl (20 mL). The aqueous mixture was extracted with diethyl ether (3 x 20 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified via flash column chromatography on silica gel using 1% TBME (tert-butyl methyl ether) in hexanes as eluent to give 32 mg (86%) of 5,6,7-tribromo-1-methyl-1H-indole 2.31 as a white solid, mp = 147-149°C. ¹H-NMR: δ 7.87 (s, 1 H), 7.04 (d, J = 3.1 Hz, 1 H), 6.65 (d, J = 3.1 Hz, 1 H), 3.76 (s, 3 H); ¹³C-NMR: δ 136.21, 131.70, 126.61, 123.98, 120.85, 120.63, 109.77, 99.13, 35.70.

5,6-dibromo-1-methyl-1H-indole (2.33): In a flame-dried 50 mL round-bottom flask under argon was added a solution of 30 mg (0.08 mmol) 2.31 in 10 mL dry toluene and cooled to -78 °C, then 64 µL (0.16 mmol) of a 2.5 M solution of n-butyllithium in hexanes was added dropwise via syringe over 15 min. The solution was stirred at -78 °C for 30 min and
The reaction mixture was diluted with water (5 mL) and extracted with diethyl ether (3 x 10 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude material was then purified via column chromatography on silica gel using 1% TBME in hexanes as eluent to give 13 mg of 2.33 as a yellow oil. $^1$H-NMR (CDCl$_3$): $\delta$ 7.88 (s, 1 H); 7.61 (d, $J$ = 1.0 Hz, 1 H); 7.04 (d, $J$ = 3.1 Hz, 1 H); 6.40 (dd, $J$ = 1.0, 3.1 Hz, 1 H); 3.75 (s, 3 H).

5-bromo-1-methyl-6,9-dihydro-1H-6,9-methanobenzo[g]indole (2.35): In a flame-dried 25 mL round-bottom flask under argon was added a solution of 30 mg (0.08 mmol) 2.31 in 10 mL dry toluene. To this was added 135 µL (1.6 mmol) of freshly cracked cyclopentadiene. The resulting solution was cooled to -78 °C, then 64 µL (0.16 mmol) of a 2.5 M solution of n-butyllithium in hexanes was added dropwise via syringe over 15 min. The solution was stirred at -78 °C for 30 min then allowed to slowly warm to room temperature. The reaction was then quenched by addition of saturated NH$_4$Cl (10 mL). After stirring for 5 minutes, the mixture was diluted with water (10 mL) and extracted with diethyl ether (3 x 20 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude material was then purified via column chromatography on silica gel using 1% TBME in hexanes as eluent to give 16 mg (72%) of 2.35 as a yellow oil. $^1$H-NMR (CDCl$_3$): $\delta$ 7.34 (d, $J$ = 0.6 Hz, 1 H); 6.98 (dd, $J$ = 3.1, 5.3 Hz, 1 H); 6.90 (d, $J$ = 3.1 Hz, 1 H); 6.88 (dd, $J$ = 3.1, 5.3 Hz, 1 H); 6.33 (dd,
\( J = 0.6, \ 3.1 \text{ Hz}; \ 4.60 (\text{m}, \ 1 \text{ H}); \ 4.26 (\text{m}, \ 1 \text{ H}); \ 2.39 (\text{m}, \ 2 \text{ H}). \)  
\( ^{13}\text{C}-\text{NMR} \ (\text{CDCl}_3): \ \delta \ 145.69, \ 144.30, \ 143.06, \ 135.35, \ 131.95, \ 130.70, \ 129.87, \ 118.52, \ 108.81, \ 100.45, \ 71.01, \ 51.21, \ 49.39, \ 35.17. \)

5,6,7-Tribromo-1-(tert-butyldimethylsilyl)-1H-indole (2.15): In a flame-dried 250-mL three-neck round bottom flask under argon was added a solution of 1.00 g (2.82 mmol) 2.25 in 50 mL dry THF. To this was added 0.271 g (11.3 mmol) of NaH followed by 0.80 mL (5.6 mmol) Et\(_3\)N. The resulting suspension was cooled to 0 °C for 15 min then 0.92 mL (5.6 mmol) of tert-butyldimethylsilyl trifluoromethanesulfonate diluted in 5 mL pentane was added dropwise via syringe over 5 min. The solution was stirred at 0 °C for an additional 20 minutes. The reaction was then diluted with diethyl ether (50 mL) and quenched by addition of saturated NH\(_4\)Cl (100 mL). Then the mixture was extracted with diethyl ether (3 x 100 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude material was then purified via column chromatography on silica gel using 1% TBME in hexanes as the eluent to give 1.03 g (78%) of 2.15 as a colorless oil which solidified to a glass at room temperature. \(^1\text{H}-\text{NMR} \ (\text{CDCl}_3): \ \delta \ 7.85 (\text{s}, \ 1 \text{ H}), \ 7.41 (\text{d}, \ J = 3.3 \text{ Hz}, \ 1 \text{ H}), \ 6.57 (\text{d}, \ J = 3.3 \text{ Hz}, \ 1 \text{ H}), \ 0.97 (\text{s}, \ 9 \text{ H}), \ 0.72 (\text{s}, \ 6 \text{ H}); \ ^{13}\text{C}-\text{NMR} \ (\text{CDCl}_3): \ \delta \ 140.5, \ 136.2, \ 133.8, \ 123.7, \ 121.3, \ 116.3, \ 109.7, \ 105.0, \ 27.4, \ 19.9, \ 2.2; \ \text{HRMS (EI)} \ m/e \ \text{calcd for C}_{14}\text{H}_{18}\text{Br}_3\text{NSi} \ 464.8758, \ \text{found} \ 464.8755. \)
5-Bromo-1-(tert-butyldimethylsilyl)-6,9-dihydro-1H-6,9-methanobenzol[g]indole (2.12):

In a flame-dried 250 mL three-necked round-bottom flask under argon was added a solution of 0.610 g (1.30 mmol) 2.15 in 60 mL dry toluene. To this was added 1.72 g (26.0 mmol) of freshly cracked cyclopentadiene. The resulting solution was cooled to -78 °C, then 1.04 mL (2.60 mmol) of a 2.5 M solution of n-butyllithium in hexanes was added dropwise via syringe over 15 min. The solution was stirred at -78 °C for 30 min then allowed to slowly warm to room temperature. The reaction was then quenched by addition of saturated NH₄Cl (50 mL). After stirring for 5 minutes, the mixture was diluted with water (100 mL) and extracted with diethyl ether (3 x 100 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude material was then purified via column chromatography on silica gel using 1% methyl tert-butyl ether in hexanes as eluent to give 0.35 g (72%) of 2.12 as a colorless liquid which solidifies to a glass below room temperature. ^1H NMR (CDCl₃): δ 7.37 (s, 1 H); 7.16 (d, J = 3.5 Hz, 1 H); 6.98 (dd, J = 5.3, 5.3 Hz, 1 H); 6.85 (dd, J = 5.3, 5.3 Hz, 1 H); 6.48 (d, J = 3.3 Hz, 1 H); 4.58 (bs, 1 H); 4.26 (bs, 1 H); 2.30 (m, 2 H); 1.20 (s, 9 H); 0.67 (s, 3 H); 0.59 (s, 3 H). ^13C NMR (CDCl₃): δ 145.9, 144.8, 142.4, 136.9, 136.0, 133.2, 133.1, 118.6, 109.6, 104.5, 69.8, 52.0, 51.8, 26.6, 19.4, -1.4, -1.8. HRMS (El) m/e calcd for C₁₉H₂₄BrNSi 373.0862, found 373.0864.
5-bromo-1-(tert-butyldimethylsilyl)-6,7,8,9-tetrahydro-1H-6,9-methanobenzo[g]indole-7,8-diol (2.36): In a 250 mL round-bottom flask was added 0.310 g (0.830 mmol) 2.12 and this was dissolved in 62.5 mL THF/water (1.5:1). To the solution was added 117 mg (0.863 mmol) NMO hydrate. The mixture was stirred at room temperature, and one small crystal of OsO₄ was added and the reaction was followed by TLC. After 6 h the TLC showed complete reaction. The reaction mixture was quenched by addition of saturated aq. NaHSO₃ (10 mL), and the subsequent mixture was stirred rapidly for 30 min. The mixture was then extracted with ethyl acetate (3 x 75 mL), the combined organic phase was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude material was purified via column chromatography on silica gel using 25% ethyl acetate in hexanes as eluent to give 0.26 g (75%) of 2.36 as colorless oil which solidified at room temperature. ¹H-NMR (CDCl₃): δ 7.52 (d, J = 1.4 Hz, 1 H); 7.23 (dd, J = 3.3, 3.3 Hz, 1 H); 6.51 (dd, J = 3.3, 3.3 Hz, 1 H); 3.90 (m, 1 H); 3.85-3.79 (m, 2 H); 3.56 (s, 1 H); 2.25 (d, J = 9.8 Hz, 1 H); 1.96 (d, J = 9.8 Hz, 1 H); 0.98 (s, 9 H); 0.71 (s, 3 H); 0.59 (s, 3 H). ¹³C-NMR (CDCl₃): δ 138.3, 135.1, 133.9, 133.2, 129.8, 121.0, 109.5, 104.6, 70.9, 70.0, 51.6, 51.1, 41.9, 26.5, 19.4, -1.6, -1.9. HRMS (El) m/e calcd for C₁₉H₂₆BrNO₄Si 407.0916, found 407.0918.
(6R,8S)-5-bromo-1-(tert-butyldimethylsilyl)-1,6,7,8-tetrahydrocyclopenta[g]indole-6,8-dicarbaldehyde (2.37): In a 250 mL round-bottom flask was added a solution of 0.200 g (0.490 mmol) 2.36 in 40 mL THF. To the stirred solution was added water (12 mL) followed by 1.57 g (7.35 mmol) NaIO₄. The mixture was stirred at room temperature until TLC analysis indicated complete reaction, about 2 h. The mixture was diluted with ethyl acetate (150 mL) and water (150 mL). The phases were separated and the organic layer was washed with brine (25 mL) and dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude material was passed through a plug of silica gel, eluting with 40% ethyl acetate in hexanes to give 0.198 g (99%) of 2.37 as pale yellow solid, mp = 101-103 °C. ¹H-NMR (CDCl₃): δ 9.84 (s, 1 H); 9.62 (s, 1 H); 7.78 (s, 1 H); 7.32 (d, J = 3.5 Hz, 1 H); 6.62 (d, J = 3.3 Hz, 1 H); 4.56 (d, J = 9.2 Hz, 1 H); 4.20 (d, J = 9.2 Hz, 1 H); 2.96 (d, J = 13.3 Hz, 1 H); 2.56 (m, 1 H); 0.76 (s, 9 H); 0.61 (s, 3 H); 0.59 (s, 3 H). ¹³C-NMR (CDCl₃): δ 199.7, 199.0, 138.14, 135.6, 134.8, 133.3, 125.3, 123.9, 111.8, 105.2, 57.5, 56.9, 27.9, 26.1, 20.0, -1.7, -1.6. HRMS (EI) m/e calcd for C₁₉H₂₄BrNO₂Si 405.0760, found 405.0766.

(6R,8S)-6,8-bis(bis(ethylthio)methyl)-5-bromo-1,6,7,8-tetrahydrocyclopenta[g]indole (2.38): In a flame-dried 100 mL round-bottom flask under argon was added a solution of
0.180 g (0.443 mmol) 2.37 in 5 mL ethanethiol. This stirring solution was cooled to -78 °C and added 4 drops of BF$_3$•OEt$_2$ and the mixture was stirred at -78 °C for 15 min. The solution was then warmed to room temperature and followed by TLC. After a further 45 min, saturated sodium bicarbonate (20 mL) was added, and the mixture was extracted with dichloromethane (3 x 50 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified via column chromatography on silica gel using 5% methyl tert-butyl ether in hexanes as eluent to give 0.16g (74%) of 2.38 as pale yellow solid, mp = 73-75 °C. $^1$H-NMR (CDCl$_3$): δ 10.40 (bs, 1 H); 7.54 (s, 1 H); 7.22 (t, $J$ = 2.7 Hz, 1 H); 6.46 (dd, $J$ = 2.9, 2.7 Hz, 1 H); 5.20 (d, $J$ = 3.3 Hz, 1 H); 4.64 (d, $J$ = 8.4 Hz, 1 H); 3.98 (m, 1 H); 3.73 (m, 1 H); 2.96-2.22 (series of m, 8 H); 1.42-1.34 (m, 6 H); 1.14-1.08 (m, 6 H). $^{13}$C-NMR (CDCl$_3$): δ 136.7, 133.0, 129.8, 128.7, 125.0, 123.5, 110.9, 102.0, 55.8, 52.9, 51.24, 50.6, 34.0, 27.4, 26.8, 26.2, 25.6, 15.1, 14.8, 14.7, 14.6. HRMS (EI) $m/e$ calcd for C$_{21}$H$_{30}$BrNS$_4$ 503.0447, found 442.0333 (M$^-$ C$_2$H$_5$S).

(6R,8S)-5-bromo-6,8-dimethyl-1,6,7,8-tetrahydrocyclopenta[g]indole (3.1) and (6R,8S)-6,8-dimethyl-1,6,7,8-tetrahydrocyclopenta[g]indole (2.39): In a 100 mL round-bottom flask was added a solution of 44 mg (0.087 mmol) of 2.38 in 10 mL acetone. To the stirring solution was added 2.0 g of Raney-Nickel (2800, Aldrich). The resulting suspension was heated to reflux and monitored by TLC. After 1 h, TLC analysis showed no starting material
and the mixture was cooled to room temperature and filtered through a pad of celite. The residue was washed with acetone (3 x 10 mL) and diethyl ether (1 x 50 mL). The combined filtrate was concentrated under reduced pressure. The crude material was purified via column chromatography on silica gel using 5% methyl tert-butyl ether in hexanes as eluent to give 7.1 mg (31%) of 2.39 as colorless oil and 5.8 mg (36%) of 2.40 as colorless oil.

\[ ^1H-NMR \text{(CDCl}_3\text{): } (2.39) \; 7.63 \text{ (s, 1 H); 7.25 (d, } J = 3.3 \text{ Hz, 1 H); 6.55 (d, } J = 3.3 \text{ Hz, 1 H); 3.86–3.74 \text{ (m, 1 H); 3.47–3.36 \text{ (m, 1 H); 2.65–2.54 \text{ (m, 1 H); 1.63 (d, } J = 13.0 \text{ Hz, 1 H); 1.51 (d, } J = 7.2 \text{ Hz, 3 H); 1.29 (d, } J = 7.0 \text{ Hz, 3 H); 0.74 (s, 3 H); 0.68 (s, 9 H); 0.61 (s, 3 \text{).}} \]

\[ ^13C-NMR \text{(CDCl}_3\text{): } \delta \; 140.8, 131.7, 131.0, 129.0, 124.5, 122.2, 111.4, 102.5, 41.1, 41.0, 37.9, 23.0, 22.5. \text{HRMS (El) } m/e \text{ calcd for C}_{13}H_{14}BrN 263.0310, \text{ found 263.0310.}} \]

\[ ^1H-NMR \text{(CDCl}_3\text{): } (2.40) \; 8.08 \text{ (bs, 1 H, NH); 7.53 (d, } J = 8.0 \text{ Hz, 1 H); 7.17 (dd, } J = 3.1, 3.1 \text{ Hz, 1 H); 7.03 (d, } J = 8.0 \text{ Hz, 1 H); 6.60–6.56 \text{ (m, 1 H); 3.53–3.44(m, 1 H); 3.33–3.22 \text{ (m, 1 H); 2.66 (dt, } J = 7.4, 12.3 \text{ Hz, 1 H); 1.53 (d, } J = 6.8 \text{ Hz, 3 H); 1.40 (d, } J = 6.8 \text{ Hz, 3 H); 1.38–1.33 \text{ (m, 1 H).} ^13C-NMR \text{(CDCl}_3\text{): } \delta \; 132.6, 129.2, 127.2, 123.3, 119.0, 115.6, 102.9, 44.5, 38.8, 37.3, 21.0, 20.7. \text{HRMS (El) } m/e \text{ calcd for C}_{13}H_{15}N 185.1205, \text{ found 185.1204.}} \]

\[ \text{((6R,8S)-5-bromo-1-(tert-butyldimethylsilyl)-1,6,7,8-tetrahydrocyclopenta[g]indole-6,8-diyl)dimethanol (2.11): In a 100 mL round-bottom flask was added a solution of 0.130 g (0.319 mmol) 2.37 in 30 mL THF. To the stirred solution was added 0.123 g (3.19 mmol) 2.37 as colorless oil and 5.8 mg (36%) of 2.40 as colorless oil.} \]
NaBH₄ in small portions at 0 °C. The mixture was stirred at 0 °C for 15 minutes. Water (50 mL) was added to the mixture and extracted with ethyl acetate (3 x 50 mL). The combined organic phase was washed with brine (25 mL) and dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude material was recrystallized from hexanes (2 times) to give 0.112 g (86%) of 2.11 as white solid, mp = 168-170 °C.

¹H-NMR (DMSO-d₆): δ 7.71 (d, J = 3.51 Hz, 1 H); 7.54 (s 1 H); 6.93 (d, J = 3.5 Hz, 1 H); 5.23 (t, J = 4.7 Hz, 1 H); 5.15 (t, J = 4.9 Hz, 1 H); 4.45 (t, J = 5.7 Hz, 1 H); 4.15-4.06 (m, 1 H); 4.00-3.92 (m, 1 H); 3.86-3.58 (m, 1 H); 3.57-3.49 (dt, J = 4.5, 10.6 Hz, 1 H); 2.88-2.8 0 (m, 2 H); 5.23 (t, J = 4.7 Hz, 1 H); 1.11 (s, 3 H); 0.96 (s, 9 H); 1 H); 0.95 (s, 3 H). ¹³C-NMR (DMSO-d₆): δ 137.9, 136.2, 135.1, 134.5, 131.0, 122.4, 111.9, 105.1, 64.6, 64.1, 48.7, 48.0, 28.8, 26.3, 20.4, -1.6, -2.8. HRMS (EI) m/e calcd for C₁₉H₂₈BrNO₂Si 409.1073, found 409.1074.

((6R,8S)-5-bromo-1-(tert-butyldimethylsilyl)-1,6,7,8-tetrahydrocyclopenta[g]indole-6,8-diyl)bis(methylene) dimethanesulfonate (2.41): In a flame-dried 100 mL round-bottom flask under argon was added a solution of 0.112 g (0.273 mmol) 2.11 in 30 mL dry CH₂Cl₂. To this stirring solution was added 0.17 mL (1.091 mmol) Et₃N followed by 0.05 mL (0.600 mmol) methanesulfonyl chloride at 0 °C. The reaction mixture was stirred overnight (12 h). Water was added and extracted with CH₂Cl₂ (3 x 25 mL). The combined organic phase was washed with brine (25 mL) and dried over anhydrous magnesium sulfate, filtered and
concentrated under reduced pressure. The crude material was purified via column chromatography on silica gel using 25% EtOAc in hexanes as eluent to give 0.126 g (82%) of 2.41 as colorless oil. $^1$H-NMR (CDCl$_3$):

$\delta$ 7.69 (s, 1 H); 7.29 (d, $J = 3.3$ Hz, 1 H); 6.56 (d, $J = 3.3$, 9.8 Hz, 1 H); 4.54 (dd, $J = 8.0$, 9.8 Hz, 1 H); 4.43–4.38 (m, 1 H); 4.20–4.10 (m, 1 H); 4.00 (t, $J = 9.6$, 1 H); 3.82-3.76 (m, 1 H); 2.98 (s, 3 H); 2.96 (s, 3 H); 2.61-2.50 (m, 1 H); 2.36 (d, $J = 14.5$ Hz, 1 H); 0.79 (s, 3 H); 0.65 (s, 9 H); 0.63 (s, 3 H). $^{13}$C-NMR (CDCl$_3$): $\delta$ 138.0, 135.7, 135.4, 133.6, 127.8, 124.5, 111.8, 105.6, 71.4, 71.3, 60.3, 45.1, 44.5, 36.9, 29.6, 26.2, 20.7, -1.5, -2.6. HRMS (EI) m/e calcd for C$_{21}$H$_{32}$BrNO$_6$S$_2$Si 565.0624, found 470.0825 (M – CH$_3$SO$_3$).

(6R,8S)-5-bromo-1-(tert-butyldimethylsilyl)-6,8-dimethyl-1,6,7,8-tetrahydrocyclopent[a]g]indole (2.10): In a 15 mL sealed tube was added a solution of 0.120 g (0.211 mmol) 2.41 in dry glyme. To this was added 0.514 g (3.40 mmol) NaI followed by 0.891 g (13.625 mmol) Zn powder. The mixture was heated to 90 ºC for 6 h. The mixture was cooled to room temperature, diluted with ethyl acetate (150 mL) and washed with water (5 x 50 mL), brine (25 mL), dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude material was purified via column chromatography on silica gel using 1% TBME in hexanes as eluent to give 0.046 g (58%) of
2.10 as colorless oil. \(^1\)H-NMR (CDCl\(_3\)): \(\delta\) 7.63 (s, 1 H); 7.25 (d, \(J = 3.3\) Hz, 1 H); 6.55 (d, \(J = 3.3\) Hz, 1 H); 3.86–3.74 (m, 1 H); 3.47–3.36 (m, 1 H); 2.65–2.54 (m, 1 H); 1.63 (d, \(J = 13.0\) Hz, 1 H); 1.51 (d, \(J = 7.2\) Hz, 3 H); 1.29 (d, \(J = 7.0\) Hz, 3 H); 0.74 (s, 3 H); 0.68 (s, 9 H); 0.61 (s, 3 H).

\(^13\)C-NMR (CDCl\(_3\)): \(\delta\) 140.8, 137.5, 134.9, 134.4, 133.9, 122.5, 112.5, 105.2, 40.4, 40.0, 39.9, 30.9, 26.4, 24.2, 22.2, 20.8, -1.3, -2.5.

HRMS (EI) \(m/e\) calcd for C\(_{19}\)H\(_{28}\)BrNSi 377.1175, found 377.1174.

\(\text{(6R,8S)-5-bromo-6,8-dimethyl-1,6,7,8-tetrahydrocyclopenta[}g\text{]indole (2.39):}\) In a 50 mL round-bottom flask was added a solution of 0.040 g (0.105 mmol) 2.10 in dry THF. To the stirred solution at 0 °C was added 0.21 mL (0.210 mmol) of 1.0 M TBAF in THF dropwise. The mixture was stirred at room temperature until TLC analysis indicated complete reaction, about 1 h. Water was added (25 mL) and extracted with ether (3 x 25 mL). The combined organic phase was washed with brine (15 mL) and dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude material was purified via column chromatography on silica gel using 5% TBME in hexanes as eluent to give 0.023 g (82%) of 2.39 as colorless oil. \(^1\)H-NMR: \(\delta\) 8.01(bs, 1 H, NH); 7.65 (s, 1 H); 7.17 (d, \(J = 3.1\) Hz, 1 H); 6.50 (d, \(J = 3.3\) Hz, 1 H); 3.58–3.38 (m, 2 H); 2.76–2.66 (m, 1 H); 1.61–1.55 (m, 1 H); 1.46 (d, \(J = 7.4\) Hz, 3 H); 1.44 (d, \(J = 7.3\) Hz, 3 H); \(^13\)C-NMR: \(\delta\) 140.8, 131.7, 131.0, 129.0, 124.5, 122.2, 111.4, 102.5, 41.1, 41.0, 37.9, 23.0, 22.5.
HRMS (EI) m/e calcd for C_{13}H_{14}BrN 263.0310, found 263.0311.

(±)-cis-Trikentrin B: To a 5-mL Biotage microwave vial was added 20 mg (0.076 mmol) of 2.39, 39 mg (0.11 mmol) of the vinyl tin reagent 2.42, 1.7 mg (2.5 mol%) Pd_{2}(dba)_{3} and 2.3 mg (10 mol%) AsPh_{3} in dry tetrahydrofuran (4.0 mL). At this point the vial was sealed and placed in the microwave reactor. The contents of the vial were heated to 150 °C for a total time of 23 min (set time = 20 min; ramp and cool time = 3 min; power setting = high). After cooling, the vial was opened and the contents transferred to a 25-mL round-bottom flask, the vial rinsed with diethyl ether (10 mL), ethyl acetate (5 mL), and the combined organic solutions concentrated under reduced pressure. The residue was purified via flash chromatography using 10% EtOAc in hexanes to give 13 mg (73%) of (±)-cis-trikentrin B as a pale yellow oil. ^1H-NMR (CDCl_3): δ 8.00 (bs, 1 H, NH), 7.62 (s, 1 H), 7.15 (dd, J = 3.1, 2.2 Hz, 1 H), 6.60 (d, J = 15.8 Hz, 1 H), 6.55 (dd, J = 3.1, 2.2 Hz, 1 H), 6.18 (dt, J = 15.8, 6.8 Hz, 1 H), 3.55-3.40 (m, 2 H), 2.72 (ddd, J = 13.1, 9.0, 9.0 Hz, 1 H), 2.30-2.20 (m, 2 H), 1.56 (m, 1 H), 1.45 (d, J = 7.0 Hz, 3 H), 1.35 (d, J = 6.8 Hz, 3 H), 1.12 (t, J = 7.2 Hz, 3 H). ^13C-NMR (CDCl_3): δ 140.6, 131.9, 131.1, 129.1, 127.6, 127.4, 127.3, 123.7, 115.6, 103.0, 41.8, 38.4, 37.1, 26.3, 24.2, 22.5, 14.0.

HRMS (EI) m/e calcd for C_{17}H_{21}N 239.1675, found 239.1674.
Regioselective studies

![Image of chemical structures]

**6,7-dibromo-3-(4-methoxyphenyl)-1H-indole (3.13.b):** In a sealed tube was added 500 mg of (2,3-dibromophenyl)hydrazine hydrochloride 3.11 (1.65 mmol). This was dissolved in 20 mL of ethanol. To this was added 0.20 mL (2.31 mmol, 1.4 eq) of 2-(4-methoxyphenyl)acetaldehyde. The mixture was heated to 100 °C for 2 h, then cooled to room temperature and concentrated under reduced pressure. The residue was diluted with TBME (50 mL) and the organic layer was washed with aq. NaHCO₃ (20 mL), water (20 mL) and brine (10 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified via flash column chromatography on silica gel using 20% TBME in hexanes as eluent to give 6,7-dibromo-3-(4-methoxyphenyl)-1H-indole 3.13.b in 62% as yellow oil. $^1$H-NMR: $\delta$ 8.08 (bs, 1 H), 7.79 (s, 1 H), 7.61 (dd, $J = 2.0, 6.8$ Hz, 2 H), 7.53 (dd, $J = 2.5, 7.2$ Hz, 1 H), 7.12 (m, 1 H), 6.92 (dd, $J = 2.0, 6.8$ Hz, 2 H), 3.84 (s, 3 H). $^{13}$C NMR: $\delta$ 158.41, 136.34, 128.74, 128.62, 126.94, 124.78, 122.73, 122.04, 119.88, 117.56, 114.32, 113.89, 55.34

**6,7-Dibromo-3-(4-fluorophenyl)-1H-indole (3.13.c):** Obtained as above from the reaction between 2,3-dibromophenylhydrazine and 4-fluorophenylacetaldehyde as orange oil. Yield:
263 mg (38%); \(^1\)H-NMR: \(\delta 8.46 \text{ (bs, 1 H)}\), 7.65 (dd, \(J = 0.7, 8.4 \text{ Hz, 1 H})\), 7.55 (dd, \(J = 5.5, 8.9 \text{ Hz, 2 H})\), 7.41 (d, \(J = 8.4 \text{ Hz, 1 H})\), 7.36 (d, \(J = 2.7 \text{ Hz, 1 H})\), 7.16 (apparent triplet, \(J = 8.9 \text{ Hz, 2 H})\); \(^13\)C-NMR: \(\delta 162.98, 160.53, 130.49 \text{ (d, } J = 3.7 \text{ Hz)}\), 129.07 (d, \(J = 3.7 \text{ Hz, 2 H})\), 125.41, 125.10, 122.43, 119.71, 119.01, 117.87, 115.91 (d, \(J = 22.1 \text{ Hz, 1 H})\), 107.52; HRMS (EI) \(m/e\) calcd for C\(_{14}\)H\(_8\)FBr\(_2\)N 366.9007, found 366.9000.

3-Benzyl-6,7-dibromo-1H-indole (3.13.d): Obtained as above from the reaction between 2,3-dibromophenylhydrazine and 2-phenylpropionaldehyde as brown oil. Yield: 281 mg (40%); \(^1\)H-NMR: \(\delta 8.12 \text{ (bs, 1 H)}\), 7.32-7.20 (m, 7 H), 6.94 (s, 1 H), 4.06 (s, 2 H); \(^13\)C-NMR: \(\delta 140.37, 136.21, 128.48, 128.40, 127.06, 126.08, 124.13, 123.39, 119.34, 117.33, 117.23, 107.07, 31.43\); HRMS (EI) \(m/e\) calcd for C\(_{15}\)H\(_{11}\)Br\(_2\)N 362.9258, found 362.9261.

3-Benzyl-6,7-dibromo-1H-indole (3.13.e): Obtained as above from the reaction between 2,3-dibromophenylhydrazine and butyraldehyde as yellow oil. Yield: 281 mg (48%); \(^1\)H-NMR: \(\delta 8.04 \text{ (bs, 1 H)}\), 7.34 (d, \(J = 7.9 \text{ Hz, 1 H})\), 7.22 (d, \(J = 7.9 \text{ Hz, 1 H})\), 7.09 (s, 1 H), 2.68 (q, \(J = 8.2 \text{ Hz, 2 H})\), 1.25 (t, \(J = 8.2 \text{ Hz, 3 H})\); \(^13\)C-NMR: \(\delta 136.16, 126.92, 123.84, 121.57, 120.36, 119.02, 117.15, 106.98, 18.36, 14.35\); HRMS (EI) \(m/e\) calcd for C\(_{10}\)H\(_8\)Br\(_2\)N 300.9101, found 300.9111.
**6,7-Dibromo-2-phenyl-1H-indole (3.13.f):** In a 50 mL round bottom flask under argon was added 500 mg of 2,3-dibromophenylhydrazine (1.88 mmol). This was dissolved in 5 mL ethanol. To this were added 0.22 mL of acetophenone (1.88 mmol, 1.0 eq) and few drops of glacial acetic acid. The reaction mixture was heated to reflux for 2 h, then cooled to room temperature and concentrated under reduced pressure to get the hydrazone intermediate. The hydrazone was added to 5 g of polyphosphoric acid and heated to 120 °C for 2 h. The reaction mixture was then cooled to room temperature and poured over ice. The aqueous mixture was extracted with CH$_2$Cl$_2$ (3 x 25 mL). The combined organic layers were neutralized with 2M NaOH, washed with water (20 mL) and brine (20 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified via flash column chromatography on silica gel using 20% TBME in hexanes as eluent to give 271 mg (41%) of 6,7-dibromo-2-phenyl-1H-indole as a yellow foam. $^1$H-NMR: $\delta$ 8.47 (bs, 1 H), 7.71 (d, $J = 9.7$ Hz, 1 H), 7.51-7.34 (m, 6 H), 6.87 (s, 1 H); $^{13}$C-NMR: $\delta$ 139.13, 136.58, 131.33, 129.14, 128.72, 128.40, 125.33, 125.05, 120.59, 117.29, 106.88, 101.03; HRMS (EI) $m$/e calcd for C$_{14}$H$_9$Br$_2$N 348.9102, found 348.9106.

**6,7-Dibromo-2,3-diphenyl-1H-indole (3.13.g):** Obtained as above from the reaction of 2,3-dibromophenylhydrazine and deoxybenzoin as light yellow foam. Yield: 312 mg (39%); $^1$H-NMR: $\delta$ 8.46 (bs, 1 H), 7.45 (m, 4 H), 7.38-7.29 (m, 8 H); $^{13}$C-NMR: $\delta$ 137.88, 135.98, 133.85, 132.86, 130.46, 129.34, 128.75, 128.58, 128.30, 127.23, 126.04, 125.29, 121.70, 121.15, 116.52, 111.33; HRMS (EI) $m$/e calcd for C$_{20}$H$_{13}$Br$_2$N 424.9415, found 424.9406.
6,7-Dibromo-3-(4-methoxyphenyl)-1-methyl-1H-indole (3.14.b): In a 50 mL flame dried round bottom flask under argon was added 300 mg (0.79 mmol) of 6,7-dibromo-3-(4-methoxyphenyl)-1H-indole. This was dissolved in 20 mL of dry THF and to this solution was added 38 mg (1.56 mmol, 2.0 eq) of dry sodium hydride. The solution was stirred at room temperature for 30 min, and then 0.10 mL (1.56 mmol, 2.0 eq) of iodomethane was added via syringe. The resulting solution was stirred for 1 h, and then quenched by dropwise addition of aq. NH₄Cl. The aqueous mixture was extracted with diethyl ether (3 x 25 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified via flash column chromatography on silica gel using 20% TBME in hexanes as eluent to give 268 mg (86%) of 6,7-dibromo-3-(4-methoxyphenyl)-1-methyl-1H-indole as a yellow oil. ¹H-NMR: δ 7.60 (d, J = 8.6 Hz, 1 H), 7.45 (d, J = 8.4 Hz, 2 H), 7.36 (d, J = 8.6 Hz, 1 H), 7.05 (s, 1 H), 6.99 (d, J = 8.4 Hz, 2 H), 4.19 (s, 3 H), 3.86 (s, 3 H); ¹³C-NMR: δ 158.34, 130.05, 129.68, 128.82, 128.09, 126.67, 124.81, 119.88, 119.82, 116.40, 114.28, 106.79, 55.32, 37.77; HRMS (EI) m/e calcd for C₁₆H₁₃Br₂NO 392.9364, found 392.9366.

6,7-Dibromo-3-(4-fluorophenyl)-1-methyl-1H-indole, (3.14.c): Obtained as above from 6,7-dibromo-3-(4-fluorophenyl)-1H-indole as orange oil. Yield: 336 mg (81%); ¹H-NMR: δ 7.58 (d, J = 8.4 Hz, 1 H), 7.48 (dd, J = 5.5, 8.9 Hz, 2 H), 7.38 (d, J = 8.4 Hz, 1 H), 7.14 (apparent triplet, J = 8.9 Hz, 2 H), 7.09 (s, 1 H), 4.20 (s, 3 H); ¹³C-NMR: δ 162.55, 161.08,
6,7-Dibromo-1-methyl-3-benzyl-1H-indole, (3.13.d): Obtained as above as an orange solid. Yield: 394 mg (98%); mp: 78-81 °C; \(^1^H\)-NMR: \(\delta 7.35-7.24\) (m, 7 H), 6.67 (s, 1 H), 4.03 (s, 2 H), 4.00 (s, 3 H); \(^{13}C\)-NMR: \(\delta 140.37, 134.59, 130.77, 129.26, 128.40, 128.27, 125.95, 123.87, 119.33, 119.14, 113.85, 106.38, 37.15, 30.94\); HRMS (EI) \(m/e\) calcd for C\(_{16}\)H\(_{13}\)Br\(_2\)N 376.9415, found 376.9418.

6,7-Dibromo-3-ethyl-1-methyl-1H-indole, (3.14.e): Obtained as above from 6,7-dibromo-3-ethyl-1H-indole as yellow oil. Yield: 343 mg (82%); \(^1^H\)-NMR: \(\delta 7.35\) (d, \(J = 8.2\) Hz, 1 H), 7.31 (d, \(J = 8.2\) Hz, 1 H), 6.76 (s, 1 H), 4.09 (s, 3 H), 2.71 (q, \(J = 7.4\) Hz, 2 H), 1.31 (t, \(J = 7.4\) Hz, 3 H); \(^{13}C\)-NMR: \(\delta 134.63, 129.41, 129.19, 123.65, 119.24, 116.97, 119.48, 106.38, 37.21, 17.77, 14.30\); HRMS (EI) \(m/e\) calcd for C\(_{11}\)H\(_{11}\)Br\(_2\)N 314.9258, found 314.9264.

6,7-Dibromo-1-methyl-2-phenyl-1H-indole, (3.14.f): Obtained as above from 6,7-dibromo-2-phenyl-1H-indole as yellow foam. Yield: 327 mg (79%); \(^1^H\)-NMR: \(\delta 7.41-7.20\) (m, 7 H), 6.42 (s, 1 H), 3.93 (s, 3 H); \(^{13}C\)-NMR: \(\delta 144.69, 136.69, 132.05, 129.75, 129.59, 128.56, 128.38, 125.20, 120.56, 119.65, 107.00, 102.62, 35.49\); HRMS (EI) \(m/e\) calcd for C\(_{15}\)H\(_{11}\)Br\(_2\)N 362.9258, found 362.9266.
6,7-Dibromo-1-methyl-2,3-diphenyl-1H-indole, (3.14.g): Obtained as above from 6,7-dibromo-2,3-diphenyl-1H-indole as light yellow foam. Yield: 323 mg (78%); \textsuperscript{1}H-NMR: $\delta$ 7.52 (d, $J = 8.6$ Hz, 1 H), 7.49 (d, $J = 8.6$ Hz, 1 H), 7.37 (m, 4 H), 7.29-7.24 (m, 4 H), 7.19 (m, 3 H), 4.01 (s, 3 H); \textsuperscript{13}C-NMR: $\delta$ 140.72, 135.78, 133.93, 131.19, 131.16, 129.91, 128.45, 128.43, 128.41, 128.25, 126.09, 125.28, 120.15, 119.65, 115.82, 106.95, 35.24; HRMS (EI) $m/e$ calcd for C$_{21}$H$_{15}$Br$_2$N 438.9572, found 438.9568.

4-fluoro-2-nitroaniline (3.16.a): In a 250 mL round-bottom flask was added 11.12 g (115 mmol) acetic anhydride and 100 mL 1,2-dichloroethane. To this was added 11.1 g (100 mmol) 4-fluoroaniline (3.15.a) and the solution was heated to 50 °C for 30 min. To the mixture, 10.1 mL (240 mmol) of fuming nitric acid was added dropwise over 45 min. The solution was then stirred at 50 °C for 3 h. The mixture was poured over ice. The mixture was diluted with CH$_2$Cl$_2$ (200 mL) and washed with 1M NaOH until neutral. The organic phase was washed with water (100 mL) and brine (50 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated. In a 250 mL round-bottom flask the crude mixture was dissolved in 100 mL of glyme. To the stirring solution was added conc. HCl (25 mL) dropwise and the mixture was heated to reflux. After 2 h, TLC analysis showed complete hydrolysis of the intermediate amide and the mixture was cooled to room
temperature. The crude reaction mixture was extracted with ethyl acetate (3 x 100 mL), the organic layer was then washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 13.88 g (98%) of the title compound as an yellow crystalline solid, mp = 90-92 °C whose physical properties were identical to that of the commercially available compound.

2-bromo-4-fluoro-6-nitroaniline (3.17.a): In 500-mL round-bottom flask was dissolved 7.8 g (50 mmol) 3.16.a in 150 mL of methanol. To the vigorously stirred solution was carefully added 25.3 mL (150 mmol) concentrated aqueous HBr (47% wt/wt) followed by 11.4 mL (100 mmol) 30% aqueous H₂O₂ dropwise over 15 minutes. The mixture was stirred overnight. The mixture was poured into 1.0 L of 1 M NaOH and the resulting suspension was filtered and washed with water until neutral. Dried under vacuum at 50 °C gave 10.46 g (89%) of 3.17.a as a yellow solid, mp = 70-72 °C whose physical properties were identical to that of the commercially available compound.

1,2-dibromo-5-fluoro-3-nitrobenzene (3.18.a): In a 1-L round-bottom flask was dissolved 7.25 g (32.5 mmol) CuBr₂ in 150 mL of dry CH₃CN and heated to 60 °C. To the warm
solution was added 4.75 mL (40 mmol) tert-butyl nitrite followed by portion wise addition of 5.9 g (25.0 mmol) of 3.17.a. The mixture was stirred at 60 °C for 1 h. The solution was cooled to room temperature and poured into 200 mL of 10% aqueous ammonia. The mixture was extracted with TBME (3 x 100 mL) and the combined organic layers were washed sequentially with 10% aqueous ammonia (100 mL), water (100 mL), brine (50 mL), and then dried over anhydrous magnesium sulfate. The solution was filtered and concentrated under reduced pressure. (75%) of 3.18.a as brown-white needles, mp = 66-68 °C. \( ^1 \)H-NMR (CDCl\(_3\)): \( \delta \) 7.64 (dd, \( J = 2.8, 7.2 \) Hz, 1 H); 7.44 (dd, \( J = 2.8, 7.2 \) Hz, 1 H). \( ^{13} \)C-NMR (CDCl\(_3\)): \( \delta \) 161.69, 159.14, 128.53 (d, \( J = 9.5 \) Hz), 124.20 (d, \( J = 24.2 \) Hz), 112.64 (d, \( J = 4.4 \) Hz), 111.90 (d, \( J = 26.3 \) Hz).

6,7-dibromo-4-fluoro-1H-indole (3.19.a): In a 250 mL flame-dried round bottom flask under argon was dissolved 0.50 g of 1,2-dibromo-5-fluoro-3-nitrobenzene 3.18.a (3.35 mmol) in THF (20 mL) and cooled to -40 °C. To this stirring solution was added vinyl magnesium bromide (1 M, 11.7 mmol) at -40 °C. The reaction was stirred at -40 °C for 1 h, then quenched with aqueous NH\(_4\)Cl (100 mL) and allowed to warm to rt. The mixture was extracted with diethyl ether (3 x 50 mL), the combined organic layers washed with water (1 x 50 mL), brine (25 mL) and dried over anhydrous magnesium sulfate. The solution was filtered and concentrated under reduced pressure. The crude mixture was purified via column chromatography on silica gel using 10% ethyl acetate in hexanes to give 150 mg of 6,7-
dibromo-4-fluoro-1H-indole 3.19.a in 31% as off-white solid, mp = 84-86 °C. $^1$H-NMR: δ 8.46 (bs, 1 H), 7.23 (m, 1 H), 7.10 (d, $J =$ 9.4 Hz, 1 H), 6.71 (dd, $J =$ 2.1, 3.3 Hz, 1 H); $^{13}$C-NMR: δ 156.26, 153.75, 125.05, 116.38, 110.43, 110.19, 102.12, 100.58.

6,7-dibromo-4-fluoro-1-methyl-1H-indole (3.20.a): In a 100 mL flame dried round bottom flask under argon was added 125 mg (0.43 mmol) of 6,7-dibromo-4-fluoro-1H-indole 3.19.a. This was dissolved in 10 mL of dry THF and to this solution was added 21 mg (0.86 mmol) of dry sodium hydride. The solution was stirred at room temperature for 30 min, and then 55 µL (0.86 mmol) of iodomethane was added via syringe. The resulting solution was stirred for 1 h, and then quenched by dropwise addition of aq. NH$_4$Cl (20 mL). The aqueous mixture was extracted with diethyl ether (3 x 25 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified via flash column chromatography on silica gel using 20% TBME in hexanes as eluent to give 268 mg (86%) of 6,7-dibromo-4-fluoro-1-methyl-1H-indole 3.20.a as a brown solid, mp = 69-71 °C. $^1$H-NMR: δ 7.07 (d, $J =$ 9.0 Hz, 1 H); 6.95 (d, $J =$ 3.1 Hz, 1H); 6.51 (d, $J =$ 3.1 Hz, 1H); 4.15 (s, 1H). $^{13}$C-NMR: δ 156.03, 153.54, 132.30, 119.43(d, $J =$ 23.4 Hz), 118.17(d, $J =$ 9.5 Hz), 110.10 (d, $J =$ 23.4 Hz), 101.73, 97.37, 37.59.
4-iodo-2-nitroaniline (3.16.b): See 4-fluoro-2-nitroaniline (3.15.a). A yellow/brown solid, mp = 120-122 °C whose physical properties were identical to that of the commercially available compound.

2-bromo-4-iodo-6-nitroaniline (3.17.b): See 2-bromo-4-fluoro-6-nitroaniline (3.17.a). A yellow solid, mp = 101-104 °C whose physical properties were identical to that of the commercially available compound.

1,2-dibromo-5-iodo-3-nitrobenzene (3.18.b): See 1,2-dibromo-5-fluoro-3-nitrobenzene (3.18.a). A brown solid, mp = 82-84 °C. $^1$H-NMR: δ 8.63 (d, $J = 2.5$ Hz, 1 H); 8.45 (d, $J = 2.5$ Hz, 1 H).
6,7-dibromo-4-iodo-1H-indole (3.19.b): See 6,7-dibromo-4-fluoro-1H-indole (3.19.a).
Purple solid, mp = 91-93 °C. $^1$H-NMR: δ 8.50 (bs, 1 H); 7.55 (s, 1 H); 7.30 (dd, $J = 2.5$, 3.3 Hz, 1 H); 6.66 (dd, $J = 2.3$, 3.3 Hz, 1 H); $^{13}$C-NMR: δ 135.36, 128.69, 126.69, 125.76, 117.16, 114.08, 106.46, 104.70.

6,7-dibromo-4-iodo-1-methyl-1H-indole (3.20.b): See 6,7-dibromo-4-fluoro-1-methyl-1H-indole (3.20.a). A purple amorphous solid. $^1$H-NMR: δ 7.51 (s, 1 H); 7.03 (d, $J = 3.3$ Hz, 1H); 6.48 (d, $J = 3.3$ Hz, 1H); 4.15 (s, 1H); $^{13}$C-NMR: δ 134.07, 133.00, 130.56, 126.68, 119.11, 114.33, 106.10, 101.94, 37.98.


6,7-dibromo-4-ethyl-1-methyl-1H-indole (3.20.d): See 6,7-dibromo-4-fluoro-1-methyl-1H-indole (3.20.a). Yield. 0.14 g (89%). Yellow oil. $^1$H-NMR: δ 7.21 (s, 1 H); 6.96 (d, $J = 3.1$ Hz, 1H); 4.62 (q, $J = 7.1$ Hz, 2H); 1.49 (t, $J = 7.1$ Hz, 3H); 1.15 (s, 3H); 1.10 (s, 3H); $^{13}$C-NMR: δ 140.90, 130.57, 126.68, 125.34, 119.10, 115.30, 114.32, 106.09, 101.93, 37.98, 31.54, 22.57, 21.63, 14.02.
Hz, 1 H); 6.44 (d, J = 3.1 Hz, 1 H); 4.14 (s, 1 H); 2.83 (q, J = 7.6 Hz, 2 H). 1.31 (t, J = 7.6 Hz, 3 H); $^{13}$C-NMR: $\delta$ 136.85, 132.05, 131.79, 129.37, 123.10, 119.44, 103.81, 99.39, 37.71, 25.51, 14.35.

4,6,7-tribromo-3-phenyl-1H-indole (3.24): See 6,7-dibromo-3-(4-methoxyphenyl)-1H-indole (3.14.b): Yellow oil. $^1$H-NMR: $\delta$ 8.56 (bs, 1 H); 7.56 (s, 1 H); 7.47-7.43 (m, 2 H); 7.42-7.37 (m, 3 H); 7.23 (m, 1 H); $^{13}$C-NMR: $\delta$ 136.18, 133.54, 131.35, 128.34, 127.38, 127.15, 125.36, 124.36, 121.37, 117.41, 113.96, 106.84

4,6,7-tribromo-1-methyl-3-phenyl-1H-indole (3.25): See 6,7-dibromo-4-fluoro-1-methyl-1H-indole (3.20.a). $^1$H-NMR: $\delta$ 7.54 (s, 1 H); 7.41–7.26 (m, 5 H); 6.99 (s, 1 H); 4.20 (s, 3 H); $^{13}$C-NMR: $\delta$ 134.75, 133.69, 133.06, 131.45, 130.03, 128.41, 127.22, 126.97, 119.46, 118.12, 114.01, 106.26, 38.22.
9-(tert-butyl)-3-(4-methoxyphenyl)-1-methyl-6,9-dihydro-1H-6,9-epoxybenzo[g]indole (3.27.2): A flame dried 50 mL round bottom flask was charged with 10 mL of dry toluene, 50 mg of 6,7-dibromo-3-(4-methoxyphenyl)-1-methyl-1H-indole (0.13 mmol) and 90 µL (0.65 mmol) of 2-tert-butyl furan under an atmosphere of argon, and the resulting mixture was cooled to -78 °C. To this cold solution was added 100 µL (2.6 M, 0.26 mmol) of n-butyllithium in toluene dropwise, and the solution was stirred at -78 °C for 30 min. The cold bath was removed and the solution was allowed to warm slowly to room temperature over 1 h. The reaction was quenched with aq. NH₄Cl (10 mL). The aqueous layer was extracted with diethyl ether (3 x 25 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified via flash column chromatography on silica gel using 10% CH₂Cl₂ in hexanes as eluent to give 34 mg (76%) of 9-(tert-butyl)-3-(4-methoxyphenyl)-1-methyl-6,9-dihydro-1H-6,9-epoxybenzo[g]indole as an off-white solid, mp = 133-135 °C; ¹H-NMR: δ 7.50–7.47 (m, 4 H), 7.15 (dd, J = 2.2, 5.5 Hz, 2 H), 7.05 (d, J = 5.5 Hz, 1 H), δ 7.00 (m, 1 H), 6.97 (d, J = 2.2 Hz, 1 H), 5.72 (d, J = 1.8 Hz, 1 H), 4.00 (s, 3 H), 3.86 (s, 3 H), 1.47 (s, 9 H); ¹³C-NMR: δ 158.11, 148.32, 146.01, 142.62, 134.61, 134.32, 130.41, 129.31, 129.10, 127.57, 117.58, 116.64, 114.08, 113.52, 104.66, 81.84, 55.31, 39.71, 33.39, 29.46. HRMS (EI): m/z calcd for C₂₄H₂₅NO: 359.1887; found: 359.1880.
9-(tert-Butyl)-3-(4-fluorophenyl)-1-methyl-6,9-dihydro-1H-6,9-epoxybenzo[g]indole

(3.27.3): See 9-(tert-butyl)-3-(4-methoxyphenyl)-1-methyl-6,9-dihydro-1H-6,9-epoxybenzo[g]indole (3.27.2): Yield: 21 mg (42%); pale yellow oil. \(^1\)H NMR: \(\delta = 7.53–7.47 \text{ (m, 3 H)}, 7.19–7.11 \text{ (m, 4 H)}, 7.07 \text{ (d, } J = 5.6 \text{ Hz, 1 H)}, 7.00 \text{ (s, 1 H)}, 5.75 \text{ (d, } J = 1.8 \text{ Hz, 1 H)}, 4.01 \text{ (s, 3 H)}, 1.48 \text{ (s, 9 H)}; ^{13}C\text{ NMR: } \delta = 162.73, 160.30, 148.58, 146.04, 142.59, 134.56 \text{ (d, } J = 5.9 \text{ Hz)}, 131.08 \text{ (d, } J = 3.7 \text{ Hz)}, 130.74, 129.42 \text{ (d, } J = 8.1 \text{ Hz)}, 129.044, 116.98, 116.43, 115.48 \text{ (d, } J = 21.4 \text{ Hz)}, 113.72, 104.71, 81.83, 39.73, 33.39, 29.47.

HRMS (EI): \(m/z\) calcd for C\textsubscript{23}H\textsubscript{22}FNO: 347.1687; found: 347.1680.

6-(tert-Butyl)-3-(4-fluorophenyl)-1-methyl-6,9-dihydro-1H-6,9-epoxybenzo[g]indole

(3.28.3): See 9-(tert-butyl)-3-(4-methoxyphenyl)-1-methyl-6,9-dihydro-1H-6,9-epoxybenzo[g]indole (3.27.2): Yield: 3 mg (3%); green oil. \(^1\)H NMR: \(\delta = 8.04 \text{ (d, } J = 8.2 \text{ Hz, 1 H)}, 7.82 \text{ (d, } J = 8.2 \text{ Hz, 1 H)}, 7.56 \text{ (m, 3 H)}, 7.32 \text{ (m, 1 H)}, 7.22-7.14 \text{ (m, 3 H)}, 6.42 \text{ (d, } J = 9.4 \text{ Hz, 1 H)}, 3.89 \text{ (s, 3 H)}, 1.35 \text{ (s, 9 H)}; ^{13}C\text{ NMR: } \delta = 162.54, 149.22, 145.10, 142.11, 136.63, 136.50, 131.11, 130.32, 127.65, 126.64, 126.30, 117.88, 117.86, 116.10, 104.89, 80.71, 37.02, 37.11, 26.67.

HRMS (EI): \(m/z\) calcd for C\textsubscript{23}H\textsubscript{22}FNO: 347.1687; found: 347.1685.

3-Benzyl-9-(tert-butyl)-1-methyl-6,9-dihydro-1H-6,9-epoxybenzo[g]indole (3.27.4): See 9-(tert-butyl)-3-(4-methoxyphenyl)-1-methyl-6,9-dihydro-1H-6,9-epoxybenzo[g]indole (3.27.2): Yield: 48 mg (53%); pink oil. \(^1\)H NMR: \(\delta = 7.28 \text{ (m, 5 H)}, 7.17 \text{ (d, } J = 7.4 \text{ Hz, 1 H)}, 6.78 \text{ (d, } J = 7.4 \text{ Hz, 1 H)}, 2.66 \text{ (s, 3 H)}, 1.49 \text{ (s, 9 H)}; ^{13}C\text{ NMR: } \delta = 162.73, 160.30, 148.58, 146.04, 142.59, 134.56 \text{ (d, } J = 5.9 \text{ Hz)}, 131.08 \text{ (d, } J = 3.7 \text{ Hz)}, 130.74, 129.42 \text{ (d, } J = 8.1 \text{ Hz)}, 129.044, 116.98, 116.43, 115.48 \text{ (d, } J = 21.4 \text{ Hz)}, 113.72, 104.71, 81.83, 39.73, 33.39, 29.47.
H), 7.12 (dd, \( J = 1.9, 5.9 \text{ Hz}, 1 \text{ H} \)), 7.07 (d, \( J = 7.4 \text{ Hz}, 1 \text{ H} \)), 7.01 (d, \( J = 5.9 \text{ Hz}, 1 \text{ H} \)), 6.54 (s, 1 H), 5.69 (d, \( J = 2.0 \text{ Hz}, 1 \text{ H} \)), 4.01 (s, 2 H), 3.86 (s, 3 H), 1.43 (s, 9 H): ¹³C NMR: \( \delta = 148.07, 145.92, 142.56, 140.67, 134.62, 133.95, 131.53, 130.72, 128.70, 128.30, 125.88, 115.92, 115.39, 112.83, 104.49, 81.89, 39.49, 33.34, 31.45, 29.44 \).

HRMS (EI): \( m/z \) calcd for C₂₄H₂₅NO: 343.1938; found: 343.1944.

3-Benzyl-6-(tert-butyl)-1-methyl-6,9-dihydro-1\( H \)-6,9-epoxybenzo[g]indole (3.28.4): See 9-(tert-butyl)-3-(4-methoxyphenyl)-1-methyl-6,9-dihydro-1\( H \)-6,9-epoxybenzo[g]indole (3.27.2): Yield: 5 mg (6%); pink oil. ¹H NMR: \( \delta = 7.26 \) (m, 5 H), 7.09 (m, 4 H), 6.56 (s, 1 H), 6.20 (d, \( J = 1.6 \text{ Hz}, 1 \text{ H} \)), 4.02 (s, 2 H), 3.83 (s, 3 H), 1.32 (s, 9 H): ¹³C NMR: \( \delta = 144.54, 144.27, 143.85, 141.13, 134.28, 132.01, 128.68, 128.41, 128.30, 127.60, 125.81, 114.65, 114.52, 114.15, 99.97, 79.86, 34.68, 32.55, 31.58, 26.79 \).

HRMS (EI): \( m/z \) calcd for C₂₄H₂₅NO: 343.1938; found: 343.1937.

![Diagram](image)

9-(tert-Butyl)-3-ethyl-1-methyl-6,9-dihydro-1\( H \)-6,9-epoxybenzo[g]indole (3.27.5): See 9-(tert-butyl)-3-(4-methoxyphenyl)-1-methyl-6,9-dihydro-1\( H \)-6,9-epoxybenzo[g]indole (3.27.2): Yield: 53 mg (55%); yellow oil. ¹H NMR: \( \delta = 7.30 \) (d, \( J = 7.4 \text{ Hz}, 1 \text{ H} \)), 7.19 (m, 2 H), 7.10 (d, \( J = 5.5 \text{ Hz}, 1 \text{ H} \)), 6.75 (s, 1 H), 5.79 (d, \( J = 1.5 \text{ Hz}, 1 \text{ H} \)), 3.94 (s, 3 H), 2.78 (q, \( J = 7.8 \text{ Hz}, 2 \text{ H} \)), 1.53 (s, 9 H), 1.38 (t, \( J = 7.8 \text{ Hz}, 3 \text{ H} \)): ¹³C NMR: \( \delta = 147.83, 145.80, 142.62, 134.66, 133.93, 130.75, 129.74, 118.16, 115.55, 112.66, 104.41, 81.83, 39.41, 33.33, 29.43, 18.14, 13.94 \).
6-(tert-Butyl)-3-ethyl-1-methyl-6,9-dihydro-1H-6,9-epoxybenzo[g]indole (3.28.5): See 9-(tert-butyl)-3-(4-methoxyphenyl)-1-methyl-6,9-dihydro-1H-6,9-epoxybenzo[g]indole (3.27.2): Yield: 9 mg (9%); yellow oil. \( ^1H \) NMR: \( \delta = 7.29 \text{ (d, } J = 7.9 \text{ Hz, } 1 \text{ H}), 7.18 \text{ (d, } J = 7.9 \text{ Hz, } 1 \text{ H}), 7.08 \text{ (m, } 2 \text{ H}), 6.71 \text{ (s, } 1 \text{ H}), 6.21 \text{ (d, } J = 1.6 \text{ Hz, } 1 \text{ H}), 3.84 \text{ (s, } 3 \text{ H}), 2.71 \text{ (q, } J = 7.5 \text{ Hz, } 2 \text{ H}), 1.34 \text{ (s, } 9 \text{ H}), 1.28 \text{ (t, } J = 7.5 \text{ Hz, } 3 \text{ H}): ^{13}C \) NMR: \( \delta = 144.53, 144.31, 143.67, 134.28, 131.94, 127.67, 126.91, 117.49, 114.45, 113.84, 100.02, 79.82, 34.55, 32.58, 26.81, 18.30, 14.50. 

HRMS (EI): \( m/z \) calcd for C\textsubscript{19}H\textsubscript{23}NO: 281.1781; found: 281.1788.

9-(tert-Butyl)-1-methyl-6,9-dihydro-1H-6,9-epoxybenzo[g]indole (3.27.6): See 9-(tert-butyl)-3-(4-methoxyphenyl)-1-methyl-6,9-dihydro-1H-6,9-epoxybenzo[g]indole (3.27.2):

Yield: 39 mg (45%); yellow oil. \( ^1H \) NMR: \( \delta = 7.28 \text{ (d, } J = 2.9 \text{ Hz, } 1 \text{ H}), 7.15 \text{ (dd, } J = 1.8, 5.6 \text{ Hz, } 1 \text{ H}), 7.11 \text{ (d, } J = 7.3 \text{ Hz, } 1 \text{ H}), 7.04 \text{ (d, } J = 5.6 \text{ Hz, } 1 \text{ H}), 6.91 \text{ (d, } J = 3.1 \text{ Hz, } 1 \text{ H}), 6.48 \text{ (d, } J = 3.1 \text{ Hz, } 1 \text{ H}), 5.71 \text{ (d, } J = 1.5 \text{ Hz, } 1 \text{ H}), 3.97 \text{ (s, } 3 \text{ H}), 1.46 \text{ (s, } 9 \text{ H}): ^{13}C \) NMR (CD\textsubscript{3}CN): \( \delta = 149.54, 147.00, 143.74, 135.41, 134.99, 134.34, 118.44, 118.38, 114.18, 105.59, 103.16, 82.65, 40.24, 34.17, 29.80. 

HRMS (EI): \( m/z \) calcd for C\textsubscript{17}H\textsubscript{19}NO: 253.1468; found: 253.1466.

6-(tert-Butyl)-1-methyl-6,9-dihydro-1H-6,9-epoxybenzo[g]indole (3.28.6): See 9-(tert-butyl)-3-(4-methoxyphenyl)-1-methyl-6,9-dihydro-1H-6,9-epoxybenzo[g]indole (3.27.2):
Yield: 14 mg (16%); yellow oil. $^1$H NMR: $\delta = 7.31$ (d, $J = 7.9$ Hz, 1 H), 7.21 (d, $J = 7.9$ Hz, 1 H), 7.09 (d, $J = 5.6$ Hz, 1 H), 7.07 (dd, $J = 1.8$, 5.6 Hz, 1 H), 6.93 (d, $J = 3.2$ Hz, 1 H), 6.39 (d, $J = 3.2$ Hz, 1 H), 6.22 (d, $J = 1.8$ Hz, 1 H), 3.90 (s, 3 H), 1.34 (s, 9 H): $^{13}$C NMR: $\delta =$ 144.53, 144.41, 143.80, 134.40, 131.52, 130.42, 128.11, 116.30, 114.65, 101.17, 100.05, 79.89, 34.92, 32.56, 26.79.

HRMS (EI): $m/z$ calcd for C$_{17}$H$_{19}$NO: 253.1468; found: 253.1470.

9-(tert-Butyl)-1-methyl-2-phenyl-6,9-dihydro-1$H$-6,9-epoxybenzo[g]indole (3.30.2): See 9-(tert-butyl)-3-(4-methoxyphenyl)-1-methyl-6,9-dihydro-1$H$-6,9-epoxybenzo[g]indole (3.27.2): Yield: 37 mg (55%); pale yellow foam. $^1$H NMR: $\delta =$ 7.56–7.08 (m, 9 H), 6.62 (s, 1 H), 5.71 (d, $J = 1.6$ Hz, 3 H), 3.56 (s, 3 H), 1.45 (s, 9 H): $^{13}$C NMR: $\delta =$ 147.97, 147.46, 146.19, 142.01, 139.72, 135.66, 132.61, 130.96, 128.80, 128.55, 127.91, 117.12, 114.33, 104.68, 103.79, 81.45, 39.55, 33.97, 29.14.

HRMS (EI): $m/z$ calcd for C$_{23}$H$_{23}$NO: 329.1781; found: 329.1788.

6-(tert-Butyl)-1-methyl-2-phenyl-6,9-dihydro-1$H$-6,9-epoxybenzo[g]indole (3.31.2): See 9-(tert-butyl)-3-(4-methoxyphenyl)-1-methyl-6,9-dihydro-1$H$-6,9-epoxybenzo[g]indole (3.27.2): Yield: 4 mg (6%); pale yellow foam. $^1$H NMR: $\delta =$ 8.09–7.22 (m, 9 H), 6.49 (s, 1 H), 6.31 (d, $J = 0.8$ Hz, 1 H), 3.84 (s, 3 H), 1.36 (s, 9 H): $^{13}$C NMR: $\delta =$ 147.87, 144.54, 144.32, 142.94, 136.13, 128.79, 128.75, 128.45, 127.44, 125.63, 121.34, 115.92, 115.13, 102.09, 100.40, 80.07, 39.13, 33.10, 32.14, 39.55.
HRMS (EI): $m/z$ calcd for C$_{23}$H$_{23}$NO: 329.1781; found: 329.1789.

9-\((\text{tert-Butyl})\)-1-methyl-2,3-diphenyl-6,9-dihydro-1$H$-6,9-epoxybenzo[g]indole (3.30.3):

See 9-(tert-butyl)-3-(4-methoxyphenyl)-1-methyl-6,9-dihydro-1$H$-6,9-epoxybenzo[g]indole (3.27.2): Yield: 54 mg (53%); yellow foam. $^1$H NMR: $\delta = 7.33$–7.27 (m, 11 H), 7.15 (m, 2 H), 7.07 (d, $J = 5.5$ Hz, 1 H), 5.71 (d, $J = 1.6$, 1 H), 3.53 (s, 3 H), 1.46 (s, 9 H); $^{13}$C NMR: $\delta = 148.43$, 146.22, 142.95, 142.18, 138.24, 135.69, 135.07, 131.80, 130.94, 130.74, 130.02, 128.29, 128.21, 127.80, 125.98, 117.78, 116.29, 114.28, 104.03, 81.46, 39.25, 34.04, 29.28.

HRMS (EI): $m/z$ calcd for C$_{29}$H$_{27}$NO: 405.2094; found: 405.2099.

6-\((\text{tert-Butyl})\)-1-methyl-2,3-diphenyl-6,9-dihydro-1$H$-6,9-epoxybenzo[g]indole (3.31.3):

See 9-(tert-butyl)-3-(4-methoxyphenyl)-1-methyl-6,9-dihydro-1$H$-6,9-epoxybenzo[g]indole (3.27.2): Yield: 9 mg (9%); yellow foam. $^1$H NMR: $\delta = 7.31$ (m, 2 H), 7.23–7.17 (m, 10 H), 7.09 (m, 2 H), 6.32 (d, $J = 0.9$ Hz, 1 H), 3.77 (s, 3 H), 1.37 (s, 9 H); $^{13}$C NMR: $\delta = 144.70$, 146.56, 142.32, 139.02, 135.14, 134.67, 132.36, 131.54, 131.10, 129.84, 128.38, 128.11, 126.51, 125.56, 117.84, 115.29, 115.15, 100.33, 100.06, 80.25, 32.83, 32.56, 29.66.

HRMS (EI): $m/z$ calcd for C$_{29}$H$_{27}$NO: 405.2094; found: 405.2090.
4-bromo-9-(tert-butyl)-1-methyl-6,9-dihydro-1H-6,9-epoxybenzo[g]indole (3.32.1): See 9-(tert-butyl)-3-(4-methoxyphenyl)-1-methyl-6,9-dihydro-1H-6,9-epoxybenzo[g]indole (3.27.2): Yellow oil. Yield: 37 mg (59%). $^1$H-NMR: $\delta$ 7.27 (s, 1H); 7.10 (dd, $J = 1.8$, 5.5 Hz, 1 H), 7.01 (d, $J = 5.5$ Hz, 1 H), 6.96 (d, $J = 3.5$ Hz, 1 H), 6.54 (d, $J = 3.5$ Hz, 1 H), 5.66 (d, $J = 1.8$ Hz, 1 H), 3.96 (s, 3H), 1.42 (s, 9H); $^{13}$C-NMR: $\delta$ 149.63, 145.81, 142.66, 133.84, 133.42, 130.60, 116.63, 111.13, 104.99, 104.69, 103.02, 81.57, 39.80, 33.26, 29.38.

HRMS (EI): $m/z$ calcld for C$_{17}$H$_{18}$BrNO: 331.0572; found: 331.0575.

4-bromo-6-(tert-butyl)-1-methyl-6,9-dihydro-1H-6,9-epoxybenzo[g]indole (3.34.1): See 9-(tert-butyl)-3-(4-methoxyphenyl)-1-methyl-6,9-dihydro-1H-6,9-epoxybenzo[g]indole (3.27.2): Yellow oil. Yield: 11 mg (17%); $^1$H-NMR: $\delta$ 7.46 (s, 1H), 7.07 (m, 2 H), 6.95 (d, $J = 3.1$ Hz, 1 H), 6.42 (d, $J = 3.1$ Hz, 1 H), 6.18 (m, 1 H), 3.98 (s, 3 H), 1.30 (s, 9 H); $^{13}$C-NMR: $\delta$ 145.60, 144.61, 144.23, 134.17, 131.00, 128.17, 122.95, 117.93, 109.88, 101.66, 100.07, 79.77, 35.14, 29.72, 26.73.

HRMS (EI): $m/z$ calcld for C$_{17}$H$_{18}$BrNO: 331.0572; found: 331.0577.

4-bromo-9-(tert-butyl)-1-methyl-3-phenyl-6,9-dihydro-1H-6,9-epoxybenzo[g]indole (3.33.2): See 9-(tert-butyl)-3-(4-methoxyphenyl)-1-methyl-6,9-dihydro-1H-6,9-epoxybenzo[g]indole (3.27.2): Off-white solid. Yield: 46 mg (62%). mp: 154-156 °C. $^1$H-NMR: $\delta$ 7.40 (m, 3 H), 7.35(m, 3 H), 7.30 (s, 1 H), 7.12 (dd, $J = 1.8$, 2.3 Hz, 1 H), 7.05(d, $J = 5.5$ Hz, 1 H), 6.99 (d, $J = 1.8$ Hz, 1 H), 6.61 (d, $J = 4.4$ Hz, 1 H), 6.18 (m, 1 H), 3.98 (s, 3 H), 3.72 (d, $J = 4.4$ Hz, 1 H), 1.30 (s, 9 H); $^{13}$C-NMR: $\delta$ 149.63, 144.61, 144.23, 134.17, 131.00, 128.17, 122.95, 117.93, 109.88, 101.66, 100.07, 79.77, 35.14, 29.72, 26.73.
Hz, 1 H), 5.67 (d, J = 1.8 Hz, 1H), 3.96 (s, 3 H), 1.45 (s, 9 H); $^{13}$C-NMR: δ 149.47, 145.78, 142.54, 135.46, 135.05, 134.22, 133.76, 131.41, 127.05, 126.62, 126.46, 119.06, 118.69, 110.77, 104.94, 81.32, 39.71, 33.60, 29.52.

HRMS (EI): m/z calcd for C$_{23}$H$_{22}$BrNO: 407.0886; found: 407.0890.

4-bromo-6-(tert-butyl)-1-methyl-3-phenyl-6,9-dihydro-1H-6,9-epoxybenzo[g]indole (3.34.2): See 9-(tert-butyl)-3-(4-methoxyphenyl)-1-methyl-6,9-dihydro-1H-6,9-epoxybenzo[g]indole (3.27.2): Off-white solid. Yield: 10 mg (14%). Mp: 185-187 °C. $^1$H-NMR: δ 7.49 (s, 1 H), 7.40 (m, 2 H), 7.35 (m, 3 H), 7.09 (m, 2 H), 6.94 (s, 1 H), 6.24 (d, J = 1.8 Hz, 1 H), 3.92 (s, 3 H), 1.33 (s, 9 H); $^{13}$C-NMR: δ 145.71, 144.66, 144.16, 134.71, 134.42, 132.34, 131.39, 131.09, 127.12, 126.52, 124.03, 119.96, 118.22, 109.74, 100.05, 79.99, 35.13, 32.52, 26.72.

HRMS (EI): m/z calcd for C$_{23}$H$_{22}$BrNO: 407.0886; found: 407.0889.

5-Bromo-9-(tert-butyl)-1-methyl-6,9-dihydro-1H-6,9-epoxybenzo[g]indole (3.36.1): See 9-(tert-butyl)-3-(4-methoxyphenyl)-1-methyl-6,9-dihydro-1H-6,9-epoxybenzo[g]indole (3.27.2): Yield: 34 mg (39%); yellow oil. $^1$H NMR: δ = 7.36 (s, 1 H), 7.19 (dd, J = 1.8, 5.5 Hz, 1 H), 7.04 (d, J = 5.5 Hz, 1 H), 6.91 (d, J = 3.3 Hz, 1 H), 6.39 (d, J = 3.3 Hz, 1 H), 5.91 (d, J = 1.9 Hz, 1 H), 3.94 (s, 3 H), 1.43 (s, 9 H); $^{13}$C NMR: δ = 147.09, 145.69, 142.95, 139.86, 136.93, 134.28, 133.31, 120.37, 107.27, 105.91, 102.05, 82.44, 39.77, 33.43, 29.41.

HRMS (EI): m/z calcd for C$_{17}$H$_{18}$BrNO: 331.0572; found: 331.0580.
5-Bromo-6-(tert-butyl)-1-methyl-6,9-dihydro-1H-6,9-epoxybenzo[g]indole (3.37.1): See 9-(tert-butyl)-3-(4-methoxyphenyl)-1-methyl-6,9-dihydro-1H-6,9-epoxybenzo[g]indole (3.27.2): Yield: 25 mg (29%); brown oil. \( ^1 \)H NMR: \( \delta = 7.43 \) (s, 1 H), 7.04 (m, 2 H), 6.94 (d, \( J = 3.1 \), 1 H), 6.31 (d, \( J = 3.3 \) Hz, 1 H), 6.24 (d, \( J = 1.6 \) Hz, 1 H), 3.88 (s, 3 H), 1.46 (s, 9 H): \( ^{13} \)C NMR: \( \delta = 144.38, 144.15, 143.61, 137.69, 132.50, 130.82, 130.59, 122.26, 106.96, 103.28, 100.11, 79.15, 35.23, 32.65, 29.81. HRMS (EI): \( m/z \) calcd for C\(_{17}\)H\(_{18}\)BrNO: 331.0572; found: 331.0579.

5-Bromo-9-(tert-butyl)-1-methyl-3-phenyl-6,9-dihydro-1H-6,9-epoxybenzo[g]indole (3.36.2): See 9-(tert-butyl)-3-(4-methoxyphenyl)-1-methyl-6,9-dihydro-1H-6,9-epoxybenzo[g]indole (3.27.2): Yield: 24 mg (36%); yellow oil. \( ^1 \)H NMR: \( \delta = 7.62 \) (s, 1 H), 7.50 (m, 2 H), 7.42 (m, 2 H), 7.29 (m, 1 H), 7.18 (dd, \( J = 1.8 \), 5.5 Hz, 1 H), 7.06 (d, \( J = 5.5 \) Hz, 1 H), 7.01 (s, 1 H), 5.93 (d, \( J = 1.8 \) Hz, 1 H), 3.99 (s, 3 H), 1.45 (s, 9 H): \( ^{13} \)C NMR: \( \delta = 145.34, 144.67, 138.60, 136.02, 135.95, 133.47, 128.50, 128.30, 127.07, 126.30, 123.65, 118.85, 117.01, 114.27, 100.76, 79.70, 39.37, 36.75, 26.67. HRMS (EI): \( m/z \) calcd for C\(_{23}\)H\(_{22}\)BrNO: 407.0886; found: 407.0895.

5-Bromo-6-(tert-butyl)-1-methyl-3-phenyl-6,9-dihydro-1H-6,9-epoxybenzo[g]indole (3.37.2): See 9-(tert-butyl)-3-(4-methoxyphenyl)-1-methyl-6,9-dihydro-1H-6,9-epoxybenzo[g]indole (3.27.2): Yield: 17 mg (26%); brown oil. \( ^1 \)H NMR: \( \delta = 7.66 \) (s, 1 H),
7.48 (m, 2 H), 7.35 (m, 2 H), 7.21 (m, 1 H), 7.04 (s, 1 H), 6.99 (m, 2 H), 6.21 (d, \(J = 1.8\) Hz, 1 H), 3.86 (s, 3 H), 1.48 (s, 9 H): \(^{13}\)C NMR: \(\delta = 146.88, 145.43, 136.78, 136.73, 134.62, 133.90, 128.50, 128.12, 127.10, 126.94, 126.30, 118.78, 116.33, 100.41, 100.34, 80.11, 37.85, 37.07, 26.82.

HRMS (EI): \(m/z\) calcd for C\(_{23}\)H\(_{22}\)BrNO: 407.0886; found: 407.0890.

9-(tert-butyl)-4-fluoro-1-methyl-6,9-dihydro-1H-6,9-epoxybenzo[g]indole (3.39.1): See

9-(tert-butyl)-3-(4-methoxyphenyl)-1-methyl-6,9-dihydro-1H-6,9-epoxybenzo[g]indole (3.27.2): Yellow oil. Yield: 39 mg (49%). \(^1\)H-NMR: \(\delta\) 7.12 (dd, \(J = 1.7, 1.7\) Hz, 1 H), 7.03 (d, \(J = 5.5\) Hz, 1 H), 6.84 (d, \(J = 3.5\) Hz, 1 H), 6.82 (d, \(J = 8.0\) Hz, 1 H), 6.52 (d, \(J = 3.3\) Hz, 1 H), 5.65 (d, \(J = 1.7\) Hz, 1 H), 3.96 (s, 3 H), 1.43 (s, 9 H); \(^{13}\)C-NMR: \(\delta\) 154.55, 152.10, 149.95, 145.66, 143.17, 132.36, 129.73, 104.62, 100.38, 99.85, 98.15, 81.86, 39.61, 33.20, 29.39.

HRMS (EI): \(m/z\) calcd for C\(_{17}\)H\(_{18}\)FNO: 271.1373; found: 271.1380.

6-(tert-butyl)-4-fluoro-1-methyl-6,9-dihydro-1H-6,9-epoxybenzo[g]indole (3.40.1): See

6-(tert-butyl)-3-(4-methoxyphenyl)-1-methyl-6,9-dihydro-1H-6,9-epoxybenzo[g]indole (3.27.2): Pale yellow solid. Yield. 17 mg (22%), mp = 118-120 °C. \(^1\)H-NMR: \(\delta\) 7.08 (d, \(J = 1.2\) Hz, 1 H), 7.03 (d, \(J = 0.6\) Hz, 1 H), 7.01 (d, \(J = 0.6\) Hz, 1 H), 6.89 (d, \(J = 3.1\) Hz, 1 H), 6.44 (d, \(J = 3.1\) Hz, 1 H), 6.19 (d, \(J = 0.8\) Hz, 1 H), 3.88 (s, 3 H), 1.31 (s, 9 H); \(^{13}\)C-
NMR: δ 154.17, 151.73, 145.55, 145.04, 144.18, 133.26, 130.02, 115.80, 101.60, 100.31, 97.35, 79.82, 34.99, 32.50, 26.67.

HRMS (EI): m/z calcd for C_{17}H_{18}FNO: 271.1373; found: 271.1372.

9-(tert-butyl)-4-iodo-1-methyl-6,9-dihydro-1H-6,9-epoxybenzo[g]indole (3.38.3): See 9-(tert-butyl)-3-(4-methoxyphenyl)-1-methyl-6,9-dihydro-1H-6,9-epoxybenzo[g]indole (3.27.2): Purple solid. Yield: 50 mg (61%), mp = 99-101 °C. \(^1\)H-NMR: δ 7.28 (s, 1 H), 7.11 (dd, J = 1.8, 5.5 Hz, 1 H), 7.01 (d, J = 5.5 Hz, 1 H), 6.96 (d, J = 3.3 Hz, 1 H), 6.54 (d, J = 3.3 Hz, 1 H), 5.66 (d, J = 1.8 Hz, 1 H), 3.96 (s, 3 H), 1.42 (s, 9 H); \(^1\)C-NMR: δ149.61, 145.80, 142.65, 133.89, 133.83, 133.42, 130.58, 116.61, 111.12, 104.68, 102.99, 81.55, 39.80, 33.25, 29.73.

HRMS (EI): m/z calcd for C_{17}H_{18}INO: 379.0434; found: 379.0444.

6-(tert-butyl)-4-iodo-1-methyl-6,9-dihydro-1H-6,9-epoxybenzo[g]indole (3.40.3): See 9-(tert-butyl)-3-(4-methoxyphenyl)-1-methyl-6,9-dihydro-1H-6,9-epoxybenzo[g]indole (3.27.2): Purple solid. Yield: 9 mg (4%), mp =136-138 °C. \(^1\)H-NMR: δ 7.46 (d, 1 H), 7.07 (m, 2 H), 6.99 (d, J = 3.3 Hz, 1 H), 6.42 (d, J = 3.3 Hz, 1 H), 6.18 (m, 1H), 3.88 (s, 3 H), 1.32 (s, 9 H); \(^1\)C-NMR: δ 145.58, 144.61, 144.21, 134.15, 131.46, 131.01, 128.15, 118.82, 117.91, 109.87, 101.65, 79.76, 35.13, 29.69, 26.72.

HRMS (EI): m/z calcd for C_{17}H_{18}INO: 379.0434; found: 379.0450.
9-(tert-butyl)-4-ethyl-1-methyl-6,9-dihydro-1H-6,9-epoxybenzo[g]indole (3.39.4): See 9-(tert-butyl)-3-(4-methoxyphenyl)-1-methyl-6,9-dihydro-1H-6,9-epoxybenzo[g]indole (3.27.2): Yellow oil. Yield: 50 mg (58%). $^1$H-NMR: $\delta$ 7.15 (dd, $J = 1.8$, 1.8 Hz, 1 H), 7.05 (d, $J = 5.7$ Hz, 1 H), 7.02 (s, 1H), 6.92(d, $J = 3.5$ Hz, 1 H), 6.53 (d, $J = 3.3$ Hz, 1 H), 5.71 (d, $J = 1.8$ Hz, 1 H), 3.97(s, 3 H), 2.89 (q, $J = 7.6$ Hz, 2 H), 1.47 (s, 9 H), 1.34 (t, $J = 7.6$ Hz, 3 H); $^{13}$C-NMR: $\delta$ 148.39, 145.76, 142.84, 133.67, 133.23, 132.17, 131.35, 129.41, 112.45, 104.54, 100.65, 81.96, 39.64, 33.27, 29.40, 25.67, 14.51.

HRMS (EI): $m/z$ calcd for C$_{19}$H$_{23}$NO: 281.1781; found: 281.1787.

6-(tert-butyl)-4-ethyl-1-methyl-6,9-dihydro-1H-6,9-epoxybenzo[g]indole (3.40.4): See 9-(tert-butyl)-3-(4-methoxyphenyl)-1-methyl-6,9-dihydro-1H-6,9-epoxybenzo[g]indole (3.27.2): Dark yellow oil. Yield: 4 mg (5%). $^1$H-NMR: $\delta$ 7.14 (s, 1 H), 7.07 (m, 1 H), 6.92 (d, $J = 3.3$ Hz, 1 H), 6.41 (d, $J = 3.3$ Hz, 1 H), 6.20 (d, $J = 1.6$ Hz, 1 H), 3.88 (s, 3 H), 2.86 (q, $J = 7.6$ Hz, 2 H), 1.34 (s, 9 H), 1.29 (t, $J = 7.6$ Hz, 3 H); $^{13}$C-NMR: $\delta$ 144.79, 144.26, 132.35, 132.02, 131.39, 129.63, 113.88, 105.00, 100.10, 99.60, 89.10, 79.90, 34.96, 32.58, 29.69, 26.69, 15.19.

HRMS (EI): $m/z$ calcd for C$_{19}$H$_{23}$NO: 281.1781; found: 281.1783.
Novel tribromoindoles

N-(m-tolyl)acetamide (4.23): In a 500 mL round bottom flask, 2.00 g (18.7 mmol) of 4.22 was dissolved in 187 mL of 1,2-dichloroethane. To this was added 19.07 (18.7 mmol) of acetic anhydride and the mixture heated to 84 °C for 1 h. The reaction mixture was poured over ice and the biphasic mixture extracted with ethyl acetate (3 x 100 mL). The combined organic layer was dried over anhydrous magnesium sulfate and then filtered. The filtrate was concentrated under reduced pressure to obtain 2.62 g (94%) of 4.23 as a white solid, mp = 65-66 °C. ¹H-NMR (CDCl₃) : δ 8.11 (bs, 1 H), 7.36 (s, 1 H), 7.30 (d, J = 7.8 Hz, 1 H), 7.17 (t, J = 7.8 Hz, 15.6, 1 H), 6.90 (d, J = 7.8 Hz, 1 H), 2.29 (s, 3 H), 2.14 (s, 3 H); ¹³C-NMR (CDCl₃) : δ 168.8, 138.7, 137.9, 128.3, 125.0, 120.7, 117.1, 24.3, 21.3.

N-(3-methyl-4-nitrophenyl)acetamide (4.24): In a 50 mL round bottom flask, 1.00 g (6.71 mmol) of 4.23 was dissolved in 7.0 mL of conc. H₂SO₄ and stirred at 0 °C. To the stirring mixture was added a mixture of conc. H₂SO₄ (1.0 mL) and conc. HNO₃ (0.3 mL) dropwise. The reaction mixture was stirred at 0 °C for 1 h and then poured over ice. The solid precipitate was filtered and dried under vacuum at 50 °C to obtain 0.98 g (75%) of 4.24 as a yellow solid, mp = 101-102 °C. ¹H-NMR (CDCl₃) : δ 8.04 (d, J = 8.9 Hz, 1 H), 7.61 (bs, 2
H), δ 7.56 (d, J = 2.2 Hz, 1 H), 7.49 (dd, J = 2.2, 8.9 Hz, 1 H), 2.62 (s, 3 H), 2.23 (s, 3 H);

$^{13}$C-NMR (CDCl$_3$): δ 168.6, 144.3, 142.2, 136.1, 126.6, 122.3, 116.9, 24.8, 21.3.

3-methyl-4-nitroaniline (4.25): In a 500 mL round bottom flask, 2.62 g (17.3 mmol) of 4.24 was dissolved in 175 mL of glyme. To this was added 5.3 mL of conc. HCl and the mixture heated to 85 °C for 3 h. The reaction mixture was poured neutralized with 1M NaOH and mixture extracted with ethyl acetate (3 x 100 mL). The combined organic layer was dried over anhydrous magnesium sulfate and then filtered. The filtrate was concentrated under reduced pressure to obtain 2.26 g (84%) of 4.25 as a yellow solid, mp = 132-133 °C.

$^1$H-NMR (CDCl$_3$): δ 8.02 (d, J = 8.9 Hz, 1 H), 6.50 (d, J = 2.7 Hz, 1 H), 6.47 (dd, J = 2.7, 8.9 Hz, 1 H), 4.26 (bs, 2 H), 2.50 (s, 3 H); $^{13}$C-NMR (CDCl$_3$): δ 151.2, 140.00, 137.7, 128.2, 116.8, 111.8, 22.1.

2,6-dibromo-3-methyl-4-nitroaniline (4.26): In 500 mL round bottom flask was dissolved 2.26 g (14.8 mmol) 4.25 in 150 mL of methanol. To the vigorously stirred solution was carefully added 7.50 mL (44.5 mmol) concentrated aqueous HBr (47% wt/wt) followed by 3.38 mL (29.7 mmol) 30% aqueous H$_2$O$_2$ dropwise over 15 minutes. The mixture was stirred at room temperature overnight. The mixture was poured into 1.0 L of 1 M NaOH and the
resulting suspension was filtered and washed with water until neutral. Dried under vacuum at 50 °C gave 4.18 g (91%) of 4.26 as a yellow solid, mp = 123-124 °C. $^1$H-NMR (CDCl$_3$): δ 8.18 (s, 1 H), 5.26 (bs, 2 H), 2.67 (s, 3 H); $^{13}$C-NMR (CDCl$_3$): δ 146.3, 140.7, 134.9, 128.7, 111.7, 103.9, 21.1.

1,2,3-tribromo-4-methyl-5-nitrobenzene (4.27): In a 500 mL round-bottom flask was dissolved 3.92 g (17.6 mmol) CuBr$_2$ in 140 mL of dry CH$_3$CN and heated to 60 °C. To the warm solution was added 2.57 mL (21.6 mmol) tert-butyl nitrite followed by portion wise addition of 4.18 g (13.5 mmol) of 4.26. The mixture was stirred at 60 °C for 1 h. The solution was cooled to room temperature and poured into 200 mL of 20% aqueous ammonia. The mixture was extracted with TBME (3 x 100 mL) and the combined organic layers were washed sequentially with 20% aqueous ammonia (100 mL), water (100 mL), brine (50 mL), and then dried over anhydrous magnesium sulfate. The solution was filtered and concentrated under reduced pressure to give 3.89 g (77%) of 4.27 as light brown solid, mp = 100-101 °C. $^1$H-NMR (CDCl$_3$): δ 8.03 (s, 1 H), 2.62 (s, 3 H); $^{13}$C-NMR (CDCl$_3$): δ 149.7, 133.7, 133.4, 131.2, 126.9, 123.16, 21.6.

4,5,6-tribromo-1H-indole (4.28): In a 50 mL round bottom flask a mixture of 3.89 g (10.4 mmol) 4.27 and 4.14 g (15.6 mmol) TPM was heated to 105 °C under vacuum (15 torr) with
vigorous stirring. After 3 h an aliquot of the mixture showed complete reaction by TLC (20% CH₂Cl₂ in hexane). Cooled to room temperature and passed through a plug of silica gel eluting with 50% TBME in hexanes and concentrated under reduced pressure to give the crude intermediate which was then suspended in 100 mL methanol in a 500 mL round bottom flask and heated to reflux. To the red solution was added 0.182 g (0.676 mmol) of FeCl₃•6H₂O and 0.412 g (34.3 mmol) activated carbon. The mixture was refluxed for 5 minutes, and then 2.03 mL (41.6 mmol) NH₂NH₂•H₂O was added via a syringe over 10 minutes and refluxed for 1 h. The mixture was cooled to room temperature and filtered through a 1 cm pad of celite, washing with methanol. The filtrate was concentrated under reduced pressure to about 5 mL, then diluted with 1M HCl (100 mL), extracted with CH₂Cl₂ (3 x 75 mL). The combined organic phases were washed with water (2 x 100 mL), brine (50 mL), and dried over anhydrous magnesium sulfate. The solution was filtered and concentrated under reduced pressure. The crude material was then purified via column chromatography on silica gel using 10% TBME in hexanes as eluent to give 1.91 g (52%) of 4.29 as a white solid, mp = 110-111 °C. ¹H-NMR (CDCl₃): δ 8.34 (bs, 1 H, NH); 7.69 (s, 1 H); 7.26 (dd, J = 3.3, 3.3 Hz, 1 H); 6.56 (dd, J = 3.3, 3.3 Hz, 1 H). ¹³C-NMR (CDCl₃): δ 134.5, 129.9, 126.3, 117.9, 117.6, 117.5, 115.1, 104.7.

4,5,6-tribromo-1-methyl-1H-indole (4.30): In a 100 mL flame dried round bottom flask under argon was added 250 mg (0.71 mmol) of 4,5,6-tribromoindole 4.29. This was
dissolved in 7.0 mL of dry THF and to this solution was added 35 mg (1.42 mmol) of dry sodium hydride. The solution was stirred at room temperature for 30 min, and then 92 µL (1.42 mmol) of iodomethane was added via syringe. The resulting solution was stirred for 1 h, and then quenched by dropwise addition of aq. NH₄Cl (20 mL). The aqueous mixture was extracted with diethyl ether (3 x 20 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified via flash column chromatography on silica gel using 10% TBME in hexanes as eluent to give 240 mg (92%) of 4,5,6-tribromo-1-methyl-1H-indole 4.30 as a white solid, mp = 97-98 °C. 

**¹H-NMR (CDCl₃):**

δ 7.61 (s, 1 H), 7.09 (d, J = 3.4 Hz, 1 H), 6.48 (d, J = 3.4 Hz, 1 H), 3.76 (s, 3 H);

**¹³C-NMR (CDCl₃):** δ 135.6, 130.9, 130.2, 117.6, 117.3, 117.0, 113.5, 103.0, 33.3.

4,6-dibromo-2-methyl-3-nitroaniline (4.31): In 500 mL round bottom flask was dissolved 2.00 g (13.2 mmol) 4.31 in 130 mL of methanol. To the vigorously stirred solution was carefully added 6.70 mL (39.6 mmol) concentrated aqueous HBr (47% wt/wt) followed by 3.00 mL (26.4 mmol) 30% aqueous H₂O₂ dropwise over 15 minutes. The mixture was stirred at room temperature overnight. The mixture was poured into 1.0 L of 1M NaOH and the resulting suspension was filtered and washed with water until neutral. Dried under vacuum at 50 °C gave 3.72 g (91%) of 4.32 as an orange solid, mp = 98-99 °C. 

**¹H-NMR (CDCl₃):**
δ 7.60 (s, 1 H), 4.37 (bs, 2 H), 2.14 (s, 3 H); $^{13}$C-NMR (CDCl$_3$): δ 142.8, 135.8, 133.5, 115.6, 110.2, 98.9, 13.7.

1,2,5-tribromo-3-methyl-4-nitrobenzene (4.33): In a 500 mL round-bottom flask was dissolved 3.47 g (15.6 mmol) CuBr$_2$ in 140 mL of dry CH$_3$CN and heated to 60 °C. To the warm solution was added 2.28 mL (19.2 mmol) tert-butyl nitrite followed by portion wise addition of 3.72 g (12.0 mmol) of 4.32. The mixture was stirred at 60 °C for 1 h. The solution was cooled to room temperature and poured into 200 mL of 20% aqueous ammonia. The mixture was extracted with TBME (3 x 100 mL) and the combined organic layers were washed sequentially with 20% aqueous ammonia (100 mL), water (100 mL), brine (50 mL), and then dried over anhydrous magnesium sulfate. The solution was filtered and concentrated under reduced pressure to give 3.49 g (78%) of 4.33 as light brown solid, mp = 83-84 °C. $^1$H-NMR (CDCl$_3$): δ 7.84 (s, 1 H), 2.47 (s, 3 H); $^{13}$C-NMR (CDCl$_3$): δ 134.8, 133.6, 133.2, 128.1, 128.0, 111.6, 20.7.

4,5,7-tribromo-1H-indole (4.35): In a 50 mL round bottom flask a mixture of 3.89 g (10.4 mmol) 4.33 and 4.14 g (15.6 mmol) TPM was heated to 105 °C under vacuum (15 torr) with vigorous stirring. After 3 h an aliquot of the mixture showed complete reaction by TLC (20%
CH₂Cl₂ in hexane). Cooled to room temperature and passed through a plug of silica gel eluting with 50% TBME in hexanes and concentrated under reduced pressure to give the crude intermediate which was then suspended in 100 mL methanol in a 500 mL round bottom flask and heated to reflux. To the red solution was added 0.182 g (0.676 mmol) of FeCl₃•6H₂O and 0.412 g (34.3 mmol) activated carbon. The mixture was refluxed for 5 minutes, and then 2.03 mL (41.6 mmol) NH₂NH₂•H₂O was added via a syringe over 10 minutes and refluxed for 1 h. The mixture was cooled to room temperature and filtered through a 1 cm pad of celite, washing with methanol. The filtrate was concentrated under reduced pressure to about 5 mL, then diluted with 1M HCl (100 mL), extracted with CH₂Cl₂ (3 x 75 mL). The combined organic phases were washed with water (2 x 100 mL), brine (50 mL), and dried over anhydrous magnesium sulfate. The solution was filtered and concentrated under reduced pressure. The crude material was then purified via column chromatography on silica gel using 10% TBME in hexanes as eluent to give 2.06 g (56%) of 4.35 as a white solid, mp = 131-132 °C. ¹H-NMR (CDCl₃): δ 8.48 (bs, 1 H, NH); 7.59 (s, 1 H); 7.32 (dd, J = 3.3, 3.3 Hz, 1 H); 6.68 (dd, J = 3.3, 3.3 Hz, 1 H). ¹³C-NMR (CDCl₃): δ 133.2, 130.7, 127.8, 126.2, 116.0, 115.4, 105.6, 104.0.

4,5,7-tribromo-1-methyl-1H-indole (4.36): In a 100 mL flame dried round bottom flask under argon was added 250 mg (0.71 mmol) of 4,5,6-tribromoindole 4.35. This was dissolved in 7.0 mL of dry THF and to this solution was added 35 mg (1.42 mmol) of dry
sodium hydride. The solution was stirred at room temperature for 30 min, and then 92 µL (1.42 mmol) of iodomethane was added via syringe. The resulting solution was stirred for 1 h, and then quenched by dropwise addition of aq. NH₄Cl (20 mL). The aqueous mixture was extracted with diethyl ether (3 x 20 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified via flash column chromatography on silica gel using 10% TBME (tert-butyl methyl ether) in hexanes as eluent to give 245 mg (94%) of 4,5,7-tribromo-1-methyl-1H-indole 4.36 as a white solid, mp = 123-124 °C. ¹H-NMR (CDCl₃): δ 7.55 (s, 1 H), 7.05 (d, J = 3.1 Hz, 1 H), 6.52 (d, J = 3.1 Hz, 1 H), 4.14 (s, 3 H); ¹³C-NMR (CDCl₃): δ 133.2, 133.0, 131.7, 129.4, 116.2, 115.0, 103.4, 103.1, 37.0.

5,6-dibromo-1-methyl-1H-indole (4.38): In a flame-dried 50 mL round bottom flask under argon was added a solution of 30 mg (0.08 mmol) 4.30 in 10 mL dry toluene and cooled to -78 °C, then 64 µL (0.16 mmol) of a 2.5 M solution of n-butyllithium in hexanes was added dropwise via syringe over 15 min. The solution was stirred at -78 °C for 30 min and quenched with water (2 mL) then allowed to slowly warm to room temperature. The reaction mixture was diluted with water (5 mL) and extracted with diethyl ether (3 x 10 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude material was then purified via column chromatography on silica gel using 10% TBME in hexanes as eluent to give 14 mg (62%) of
4.38 as a colorless oil. $^1$H-NMR (CDCl$_3$): $\delta$ 7.44 (dd, $J = 0.6$, 1.5 Hz, 1 H); 7.42 (d, $J = 1.5$ Hz, 1 H); 7.08 (d, $J = 3.2$ Hz, 1 H); 6.50 (dd, $J = 0.6$, 3.2 Hz, 1 H); 3.77 (s, 3 H); $^{13}$C-NMR (CDCl$_3$): $\delta$ 137.3, 129.9, 128.2, 124.8, 115.2, 114.6, 111.6, 101.7, 33.3.

4.5-dibromo-1-methyl-1H-indole (4.41): In a flame-dried 100 mL round bottom flask under argon was added a solution of 100 mg (0.26 mmol) 4.36 in 20 mL dry toluene and cooled to -78 °C, then 208 µL (0.52 mmol) of a 2.5 M solution of n-butyllithium in hexanes was added dropwise via syringe over 15 min. The solution was stirred at -78 °C for 30 min and quenched with water (5 mL) then allowed to slowly warm to room temperature. The reaction the mixture was diluted with water (10 mL) and extracted with diethyl ether (3 x 20 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude material was then purified via column chromatography on silica gel using 10% TBME in hexanes as eluent to give 36 mg (48%) of 4.41 as a yellow solid, mp = 61-62 °C. $^1$H-NMR (CDCl$_3$): $\delta$ 7.39 (d, $J = 8.8$ Hz, 1 H); 7.12 (dd, $J = 0.7$, 3.1 Hz, 1 H); 7.08 (d, $J = 3.1$ Hz, 1 H); 6.50 (dd, $J = 0.7$, 3.1 Hz, 1 H); 3.76 (s, 3 H); $^{13}$C-NMR (CDCl$_3$): $\delta$ 135.2, 130.8, 130.2, 125.7, 116.5, 114.9, 109.7, 102.5, 33.3.

5,7-dibromo-1-methyl-1H-indole (4.42): Yellow wax, 9 mg (12%). $^1$H-NMR (CDCl$_3$): $\delta$ 7.65 (d, $J = 1.6$ Hz, 1 H); 7.45 (d, $J = 1.6$ Hz, 1 H); 6.97 (d, $J = 3.1$ Hz, 1 H); 6.38 (d, $J = 3.1$ Hz, 1 H); $^{13}$C-NMR (CDCl$_3$): $\delta$ 132.8, 132.6, 131.9, 128.3, 122.6, 112.19, 104.3, 100.7, 36.8.
5-bromo-3-methyl-6,9-dihydro-3H-6,9-methanobenzo[e]indole (4.44): In a flame-dried 25 mL round bottom flask under argon was added a solution of 30 mg (0.08 mmol) 4.30 in 10 mL dry toluene. To this was added 135 µL (1.6 mmol) of freshly cracked cyclopentadiene. The resulting solution was cooled to -78 °C, then 64 µL (0.16 mmol) of a 2.5 M solution of n-butyllithium in hexanes was added dropwise via syringe over 15 min. The solution was stirred at -78 °C for 30 min then allowed to slowly warm to room temperature. The reaction was then quenched by addition of saturated NH₄Cl (10 mL). After stirring for 5 minutes, the mixture was diluted with water (10 mL) and extracted with diethyl ether (3 x 20 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude material was then purified via column chromatography on silica gel using 10% TBME in hexanes as eluent to give 14 mg (65%) of 4.44 as a yellow oil.

\[ \begin{align*} \end{align*} \]

\[^{1}\text{H-NMR (CDCl}_3\text{):} & \delta 7.05 (d, J = 0.8 Hz, 1 H); 6.99 (d, J = 3.3 Hz, 1 H); 6.97 (dd, J = 3.3, 5.3 Hz, 1 H); 6.90 (dd, J = 3.3, 5.3 Hz, 1 H); 6.39 (dd, J = 0.8, 3.3 Hz); 4.29 (m, 1 H); 4.22 (m, 1 H); 3.70 (s, 3 H); 2.38 (m, 2 H). \]

\[^{13}\text{C-NMR (CDCl}_3\text{):} & \delta 146.1, 144.2, 142.9, 142.1, 136.9, 130.2, 123.9, 110.6, 106.8, 97.9, 71.7, 51.2, 50.2, 33.1. \]

4-bromo-3-methyl-6,9-dihydro-3H-6,9-methanobenzo[e]indole (4.46): In a flame-dried 25 mL round bottom flask under argon was added a solution of 30 mg (0.08 mmol) 4.36 in 10 mL
mL dry toluene. To this was added 135 µL (1.6 mmol) of freshly cracked cyclopentadiene. The resulting solution was cooled to -78 °C, then 64 µL (0.16 mmol) of a 2.5 M solution of n-butyllithium in hexanes was added dropwise via syringe over 15 min. The solution was stirred at -78 °C for 30 min then allowed to slowly warm to room temperature. The reaction was then quenched by addition of saturated NH₄Cl (10 mL). After stirring for 5 minutes, the mixture was diluted with water (10 mL) and extracted with diethyl ether (3 x 20 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude material was then purified via column chromatography on silica gel using 10% TBME in hexanes as eluent to give 14 mg (64%) of 4.46 as a colorless oil. ¹H-NMR (CDCl₃): δ 7.36 (s, 1 H); 6.97 (d, J = 3.1 Hz, 1 H); 6.90 (m, 2 H); 6.42 (d, J = 3.1 Hz, 1 H); 4.20 (m, 1 H); 4.12 (s, 3 H); 3.98 (m, 1 H); 2.43 (m, 1 H); 2.35 (m, 1 H). ¹³C-NMR (CDCl₃): δ 144.3, 144.2, 143.7, 142.6, 132.7, 131.5, 127.5, 121.2, 97.9, 97.8, 71.6, 50.3, 48.8, 37.0.

5-bromo-6-(tert-butyl)-3-methyl-6,9-dihydro-3H-6,9-epoxybenzo[e]indole (4.48): A flame dried 100 mL round bottom flask was charged with 10 mL of dry toluene, 100 mg of 4.30 (0.27 mmol) and 377 µL (2.72 mmol) of 2-tert-butylfuran under an atmosphere of argon, and the resulting mixture was cooled to -78 °C. To this cold solution was added 228 µL (2.6 M, 0.59 mmol) of n-butyllithium in toluene dropwise, and the solution was stirred at -78 °C for 30 min. The cold bath was removed and the solution was allowed to warm slowly
to room temperature over 1 h. The reaction was quenched with aq. NH₄Cl (15 mL). The aqueous layer was extracted with diethyl ether (3 x 25 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified via flash column chromatography on silica gel using 10% TBME in hexanes as eluent to give 32 mg (36%) of 4.48 as a colorless oil. ¹H-NMR: δ 7.10 (s, 1 H), 6.98–6.92 (m, 3 H), 6.50 (dd, J = 0.9, 3.2 Hz, 1 H), δ 5.66 (d, J = 1.5 Hz, 1 H), 3.72 (s, 3 H), 1.45 (s, 9 H); ¹³C-NMR: δ 148.2, 143.8, 142.4, 139.9, 133.4, 128.0, 127.4, 108.0, 103.7, 102.5, 101.7, 81.2, 33.2, 32.5, 29.7.

5-bromo-9-(tert-butyl)-3-methyl-6,9-dihydro-3H-6,9-epoxybenzo[e]indole (4.49): Colorless oil, 25 mg (28%). ¹H-NMR: δ 7.12 (d, J = 0.8 Hz, 1 H), 7.06 (dd, J = 0.9, 3.1 Hz, 2 H), 6.99 (d, J = 3.1 Hz, 1 H), δ 6.35 (dd, J = 0.9, 3.1 Hz, 1 H), 5.91 (d, J = 1.5 Hz, 1 H), 3.69 (s, 3 H), 1.46 (s, 9 H); ¹³C-NMR: δ 148.1, 144.4, 143.8, 140.4, 137.2, 131.3, 122.3, 109.9, 108.8, 103.8, 97.7, 80.1, 33.1, 32.5, 29.7.

4-bromo-9-(tert-butyl)-3-methyl-6,9-dihydro-3H-6,9-epoxybenzo[e]indole (4.51): A flame dried 100 mL round bottom flask was charged with 10 mL of dry toluene, 100 mg of 4.36 (0.27 mmol) and 377 µL (2.72 mmol) of 2-tert-butylfuran under an atmosphere of argon, and the resulting mixture was cooled to -78 °C. To this cold solution was added 228 µL (2.6 M, 0.59 mmol) of n-butyllithium in toluene dropwise, and the solution was stirred at -78 °C for 30 min. The cold bath was removed and the solution was allowed to warm slowly
to room temperature over 1 h. The reaction was quenched with aq. NH₄Cl (15 mL). The aqueous layer was extracted with diethyl ether (3 x 25 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified via flash column chromatography on silica gel using 10% TBME in hexanes as eluent to give 40 mg (44%) of 4.51 as a colorless oil. 

**1H-NMR:** δ 7.32 (s, 1 H), 7.09 (dd, J = 1.8, 5.5 Hz, 1 H), 7.02 (dd, J = 3.3, 5.5 Hz, 2 H), δ 6.57 (d, J = 3.3 Hz, 1 H), 5.71 (d, J = 1.8 Hz, 1 H), 4.13 (s, 3 H), 1.39 (s, 9 H); 

**13C-NMR:** δ 146.2, 145.6, 143.4, 141.9, 133.5, 132.5, 126.5, 119.6, 102.4, 100.8, 99.2, 81.6, 37.5, 31.9, 27.3.

**5-bromo-9-(tert-butyl)-3-methyl-6,9-dihydro-3H-6,9-epoxybenzo[e]indole (4.52):**

Colorless oil, 20 mg (22%). 

**1H-NMR:** δ 7.49 (s, 1 H), 7.10 (dd, J = 1.8, 5.5 Hz, 1 H), 7.07 (d, J = 5.5 Hz, 1 H), δ 6.98 (d, J = 3.1 Hz, 1 H), 6.37 (d, J = 3.1 Hz, 1 H), 5.89 (d, J = 1.8 Hz), 4.10 (s, 3 H), 1.32 (s, 9 H); 

**13C-NMR:** δ 144.8, 144.3, 144.1, 142.0, 133.6, 131.7, 125.8, 121.3, 100.4, 98.2, 97.9, 80.5, 37.0, 32.6, 26.7.

**3,5-dimethyl-6,9-dihydro-3H-6,9-methanobenzo[e]indole (4.53):**

In a 10 mL round bottom flask under argon was added 13.4 mg (0.015 mmol) of Pd₂(dba)₃ and 10.6 mg (0.037 mmol) of tBu₃P·HBF₄ followed by 50 mg (0.184 mmol) of 4.44 in 3.0 mL of THF. To this was added 0.55 mL (0.547 mmol) of dimethylzinc (1.0 M in PhMe) and the mixture stirred at 70 °C for 3 h. After 3 h, the reaction mixture was cooled to room temperature and diluted with TBME (6.0 mL). The organic layer was washed with H₂O (3 x 5 mL) followed by brine (1 x
5 mL). The resulting organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified via flash column chromatography on silica gel using 10% TBME in hexanes as eluent to give 28 mg (72%) of 4.53 as a yellow solid, mp = 92-93 °C. $^1$H-NMR: δ 6.97 (d, $J = 3.1$ Hz, 1 H), 6.93 (m, 2 H), 6.73 (s, 1 H), 6.41 (dd, $J = 0.8, 3.1$ Hz, 1 H), 4.24 (m, 1 H), 4.15 (m, 1 H), 3.71 (s, 3 H); 2.51 (s, 3 H), 2.42 (m, 1 H), 2.33 (m, 1 H); $^{13}$C-NMR: δ 144.2, 143.7, 142.9, 141.5, 135.9, 128.9, 125.4, 122.8, 104.4, 97.5, 71.3, 49.2, 48.2, 33.0, 19.1.

5-ethyl-3-methyl-6,9-dihydro-3H-6,9-methanobenzo[e]indole (4.54): In a 10 mL round bottom flask under argon was added 13.4 mg (0.015 mmol) of Pd$_2$(dba)$_3$ and 10.6 mg (0.037 mmol) of tBu$_3$PHBF$_4$ followed by 50 mg (0.184 mmol) of 4.44 in 3.0 mL of THF. To this was added 0.55 mL (0.547 mmol) of diethylzinc (1.0 M in PhMe) and the mixture stirred at 70 °C for 3 h. After 3 h, the reaction mixture was cooled to room temperature and diluted with TBME (6.0 mL). The organic layer was washed with H$_2$O (3 x 5 mL) followed by brine (1 x 5 mL). The resulting organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified via flash column chromatography on silica gel using 10% TBME in hexanes as eluent to give 31 mg (75%) of 4.54 as a yellow solid, mp = 87-88 °C. $^1$H-NMR: δ 6.96 (d, $J = 3.1$ Hz, 1 H), 6.91 (m, 2 H), 6.73 (s, 1 H), 6.40 (dd, $J = 0.8, 3.1$ Hz, 1 H), 4.23 (m, 1 H), 4.16 (m, 1 H), 3.72 (s, 3 H), 2.84 (q, $J = 7.4, 14.8$ Hz, 2 H), 2.41 (m, 1 H), 2.32 (m, 1 H), 1.29 (t, $J = 7.4, 14.8$ Hz, 3 H);
$^{13}$C-NMR: $\delta$ 144.2, 143.8, 143.0, 141.0, 135.9, 132.2, 129.0, 122.9, 103.0, 97.5, 71.1, 49.1, 48.2, 32.9, 26.9, 16.4.

3,4-dimethyl-6,9-dihydro-3H-6,9-methanobenz[e]indole (4.55): In a 10 mL round bottom flask under argon was added 13.4 mg (0.015 mmol) of Pd$_2$(dba)$_3$ and 10.6 mg (0.037 mmol) of tBu$_3$P-HBF$_4$ followed by 50 mg (0.184 mmol) of 4.46 in 3.0 mL of THF. To this was added 0.55 mL (0.547 mmol) of dimethylzinc (1.0 M in PhMe) and the mixture stirred at 70 °C for 3 h. After 3 h, the reaction mixture was cooled to room temperature and diluted with TBME (6.0 mL). The organic layer was washed with H$_2$O (3 x 5 mL) followed by brine (1 x 5 mL). The resulting organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified via flash column chromatography on silica gel using 10% TBME in hexanes as eluent to give 32 mg (82%) of 4.55 as a brown solid, mp = 115-116 °C. $^1$H-NMR: $\delta$ 6.98 (s, 1 H), 6.94 (d, $J$ = 3.1 Hz, 1 H), 6.92 (m, 2 H), 6.41 (d, $J$ = 3.1 Hz, 1 H), 4.22 (m, 1 H), 4.03 (s, 3 H), 3.99 (m, 1 H), 2.75 (s, 3 H), 2.43 (m, 1 H), 2.34 (m, 1 H); $^{13}$C-NMR: $\delta$ 144.4, 142.8, 142.6, 141.9, 133.9, 131.5, 125.7, 119.2, 115.6, 97.6, 71.7, 50.5, 48.8, 36.8, 19.7.
4-ethyl-3-methyl-6,9-dihydro-3H-6,9-methanobenzo[e]indole (4.56): In a 10 mL round bottom flask under argon was added 13.4 mg (0.015 mmol) of Pd$_2$(dba)$_3$ and 10.6 mg (0.037 mmol) of tBu$_3$PBF$_4$ followed by 50 mg (0.184 mmol) of 4.44 in 3.0 mL of THF. To this was added 0.55 mL (0.547 mmol) of diethylzinc (1.0 M in PhMe) and the mixture stirred at 70 °C for 3 h. After 3 h, the reaction mixture was cooled to room temperature and diluted with TBME (6.0 mL). The organic layer was washed with H$_2$O (3 x 5 mL) followed by brine (1 x 5 mL). The resulting organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified via flash column chromatography on silica gel using 10% TBME in hexanes as eluent to give 35 mg (86%) of 4.56 as a pink solid, mp = 110-111 °C. $^1$H-NMR: δ 7.00 (s, 1 H), 6.92 (d, J = 3.1 Hz, 1 H), 6.89 (m, 2 H), 6.40 (d, J = 3.1 Hz, 1 H), 4.19 (m, 1 H), 4.04 (m, 1 H), 3.99 (s, 3 H), 3.08 (q, J = 7.4, 14.8 Hz, 2 H), 2.39 (m, 1 H), 2.32 (m, 1 H), 1.34 (t, J = 7.4, 14.8 Hz, 3 H); $^{13}$C-NMR: δ 144.5, 142.8, 142.7, 141.6, 133.2, 131.7, 126.0, 122.4, 117.5, 97.7, 71.7, 50.6, 48.9, 36.8, 25.5, 17.1.
SPECTRA
(±)-cis-Trikentrin B
3.20.b
4.55
Chapter 6.

CONCLUSIONS

The total synthesis of (±)-cis-trikentrin B was successfully achieved by employing a strategic combination of 6,7-indole aryne cycloaddition methodology via a selective metal-halogen exchange and elimination protocol, and Pd(0)-catalyzed Stille cross-coupling reaction.

The effect of various substitution patterns at different positions on the indole on the regioselectivity of 6,7-indole aryne cycloadditions with 2-tert-butylfuran was investigated. The presence of substituents at the 3-position gave the greatest degree of regiocontrol. The effect of substitution at the 2-position on the indole ring still resulted in significant, albeit diminished regioselectivity. There was a marked decrease in the regiochemical distribution in presence of substitution at the C-4 and C-5 sites.

We have successfully synthesized two novel tribromoindoles namely, the 4,5,6- and 4,5,7-tribromoindoles using the Leimgruber-Batcho synthesis. The examination of the sites of metal-halogen exchange in these scaffolds revealed a preference for the C-7 position in the 4,5,7-tribromoindole whereas, exclusively the C-4 site in the 4,5,6-tribromoindole. The 4,5-indole aryne generated in the 4,5,6-tribromoindole exhibited virtually no regioselectivity in cycloadditions with 2-tert-butylfuran. A slight enhancement in the regiochemical distribution was observed in the 4,5-indole aryne cycloadditions. Finally, we have demonstrated that the newly synthesized tribromoindoles can be utilized for the construction of novel benzannulated indole library compounds.
REFERENCES


Alok Nerurkar was born on 14\textsuperscript{th} of December 1984 in Mumbai, India. He obtained his Bachelor’s degree in Chemistry from the University of Mumbai in 2005 and his Master’s degree in Organic Chemistry from the same institution in 2007. After graduating with Master’s degree, he worked as an analyst with Analytical Solutions in Mumbai from 2007 to 2009. Alok arrived at UMKC in the fall of 2009 to pursue doctoral studies in Chemistry and joined the Buszek research group in the Spring of 2010. During his graduate career he was involved in numerous projects which include total synthesis of indole alkaloid natural products, regiochemical studies of 6,7-indole arynes, biologically active small molecule library development and the Buszek group collaborations with Professor J.-P Perchellet (Anti-Cancer Drug Laboratory, Kansas State University) and Professor Christopher Cramer (University of Minnesota). Alok Nerurkar has already published two papers, one manuscript has already been submitted and two in preparation. On completion of doctoral studies at UMKC, Alok will join Professor Jennifer Golden’s lab at the University of Wisconsin-Madison in the School of Pharmacy as a postdoctoral research associate.
Selected Peer-reviewed publications:
