INDOLE ARYNES IN ORGANIC SYNTHESIS: DISCOVERY AND APPLICATIONS FOR THE TOTAL SYNTHESIS OF COMPLEX NATURAL PRODUCTS

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DOCTOR OF PHILOSOPHY

by
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INDOLE ARYNES IN ORGANIC SYNTHESIS: DISCOVERY AND APPLICATIONS

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Diheng Luo, Candidate for the Doctor of Philosophy Degree

University of Missouri-Kansas City, 2011

ABSTRACT

Arynes and heteroarynes are very important and useful reactive intermediates with many applications in organic synthesis, including natural products total synthesis. Although benzyne, the parent and most famous aryne, has itself been known for over 50 years, arynes derived from the ubiquitous indole nucleus were virtually unknown before our work.

The absence of these heteroarynes from the literature was surprising, given the potential utility of these reactive intermediates for an attractive entry into the indole alkaloid class of important and architecturally complex natural products. Some deceptively simple and other more unambiguously complex targets include such members as the trikentrins, herbindoles, teleocidins, nodulisporic acids, and penitrems to name just a few representative examples.

We discovered the first indole arynes, namely the 5,6- and 6,7-indole arynes (aka indolynes), and provided a vastly superior preparation of the 4,5-indole aryne as well as the

others by devising a facile metal-halogen exchange and elimination protocol with *o*-dihaloindoles.

In addition to establishing the existence of these fascinating intermediates via trapping with their furan cycloadducts, we applied them to the successful total synthesis of several important, biologically active and challenging natural products including (±)-*cis*-trikentrin A, (±)-herbindole A, and (±)-herbindole B. These studies opened a successful strategy for the construction of natural products-inspired libraries based on this methodology.

We also conducted experimental and computational studies on the indole arynes that revealed, among other things, their unique properties and reaction profiles. The versatility of the 6,7-indole aryne in particular was evident in the many regioselective cycloadditions, ring-opening reactions, and rearrangements it exhibited.

The faculty listed below, appointed by the Dean of the School of Graduate Studies, have examined a dissertation titled "Indole Arynes in Organic Synthesis: Discovery and Applications for the Total Synthesis of Complex Natural Products," presented by Diheng Luo, candidate for the Doctor of Philosophy degree, and certify that in their opinion it is worthy of acceptance.

Supervisory Committee

Keith R. Buszek, Ph.D., Committee Chairperson
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ACKNOWLEDGMENTS

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I extend thanks to all my colleagues and friends, especially Dr. Neil Brown and Dr. Baohan Xie for their enormous support and good advice. And also, my groupmates, Dr. Sampathkumar Ellappan, Mr Ge Gao.

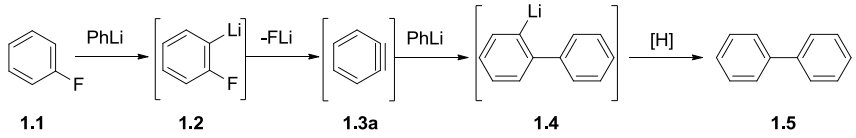
I would like to thank all the academic and technical staff of the Department of Chemistry at the University of Missouri-Kansas City.

Last, I would like to dedicate this dissertation to my parents, the two most important persons in my whole life.

CHAPTER 1. INTRODUCTION

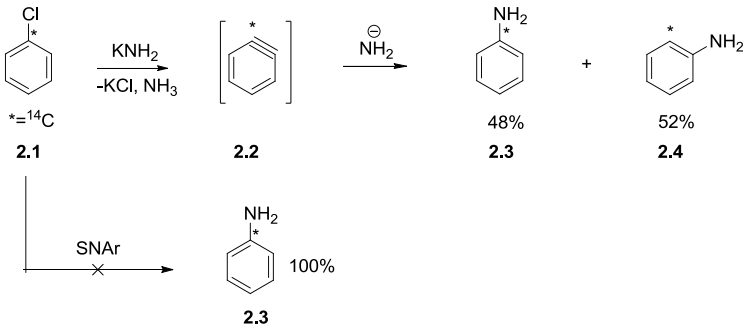
1.1 Benzynes: Preparation, Structure, and Reactivity

Benzyne is a metastable aromatic species that is commonly represented by a didehydrobenzene structure that was first postulated as a reaction intermediate by Wittig in 1942 (Scheme 1).[1]



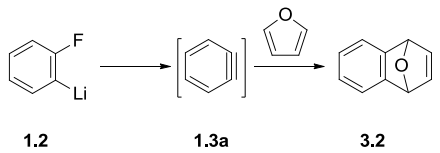
Scheme 1. Benzyne as a putative intermediate.

However, Roberts is generally credited with the first successful preparation of benzyne itself and with the establishment of the "benzyne" (or more generally, aryne) mechanism by carbon isotopic labelling experiments in 1953 (Scheme 2).[2]



Scheme 2. Roberts' benzyne preparation and labelling experiment.

Following Roberts' experiment, Wittig reported the first Diels-Alder reaction of benzyne with furan in 1955.[3] This reaction became the most important reaction type not only in application to benzynes but also as a detector of benzyne intermediates.



1.2 1.3a 3.2

Scheme 3. Diels-Alder reaction of benzynes.

Benzyne is usually represented by a benzene nucleus with a formal triple bond **1.3a**, but the alternative depiction as a cyclic cumulene structure **1.3b** is also widely used (Scheme 3).

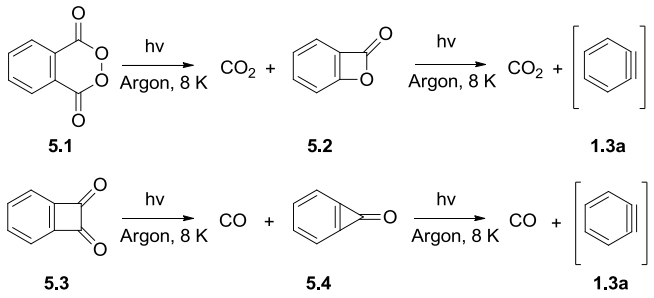
1.3a 1.3b 1.3c 1.3d 1.3e

Scheme 4. Canonical representations of benzyne.

Sometimes benzyne is drawn as a diradical canonical or resonance form **1.3e**: the pi bond is represented as having a single electron on each of two co-planar, adjacent orbitals. The most accurate electronic description (i.e., triple bond, cumulene, or diradical) is still the subject of contemporary investigations, and is influenced by specific electronic and substituent effects. The additional formal pi bond is localized and orthogonal to the other pi bonds that make up the aromatic ring. It is this additional strained formal pi bond that makes benzyne such as reactive intermediate. Unlike the ordinary pi bonds of acetylene in which the two sets of p-orbitals are parallel to each other and therefore maximize their overlap, the additional pi bond of benzyne has only partially overlapped sp^2-like orbitals (e.g., see **1.3d**, Scheme 4) that

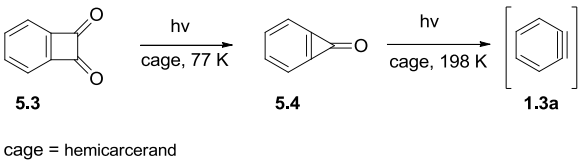
is a necessary consequence of the benzene geometry. This partial overlap creates a very weak pi bond that renders benzynes extraordinarily unstable and highly reactive, even at low temperatures (e.g., -35 °C).

The physical properties that support the structure of benzyne have been determined by numerous methods, including infrared[4-5] and nuclear magnetic resonance spectroscopy.[6] For example Chapman reported the first IR spectrum of benzyne (generated via the photochemical decomposition of either phthaloyl peroxide or of benzocyclobutenedione) in an argon matrix at 8 K (Scheme 5).[4-5]



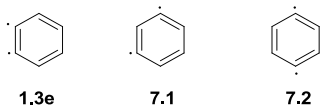
Scheme 5. Chapman's photochemical generation and trapping of benzyne in an argon matrix.

The IR study revealed that benzyne exhibited key frequencies (e.g., 1627, 1607, and 1451 cm^{-1}) that were most consistent with a localized additional pi system which suggests that the triple bond canonical form is the best representation of the benzyne electronic structure. This assignment was supported by subsequent computational studies by Berry.[7] However, subsequent low temperature solution ^{1}H and ^{13}C NMR analyses by Cram and Warmuth of benzyne in a hemicarcerand (Scheme 6) concluded that the cumulene form was in fact the dominant mesomeric structure.[6]



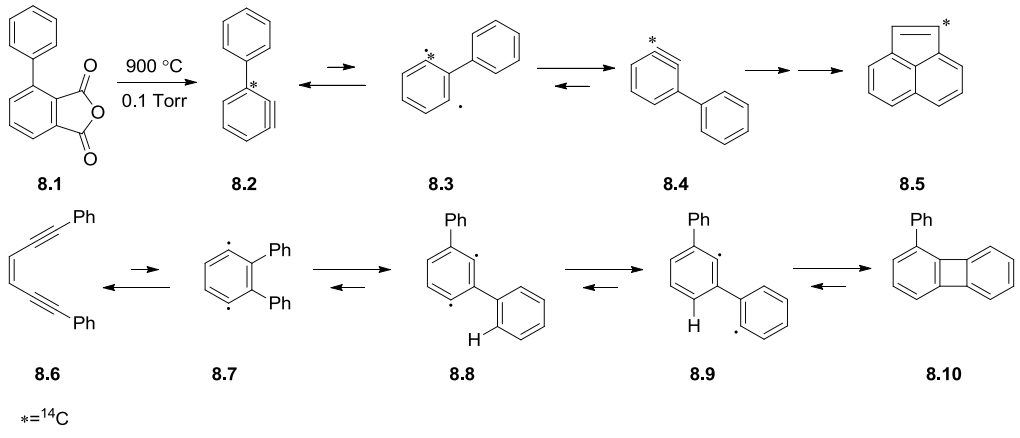
Scheme 6. Photochemical generation and trapping of benzyne in a hemicarcerand.

In addition to benzyne, or more formally *ortho*-benzyne (*o*-benzyne or 1,2-didehydrobenzene), there are two additional types of benzynes that can be formally represented by diradicals, namely, *meta*-benzyne **7.1** (*m*-benzyne or 1,3-didehydrobenzene) and *para*-benzyne **7.2** (*p*-benzyne or 1,4-didehydrobenzene) (Scheme 7).



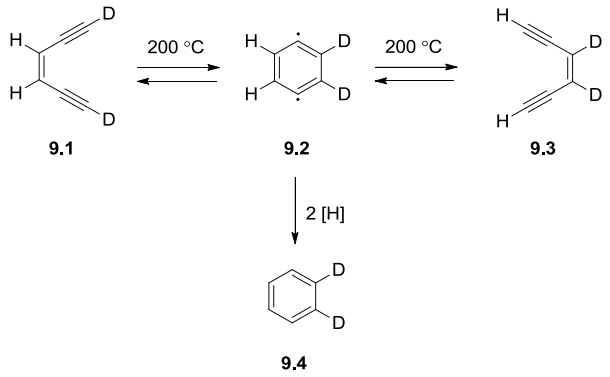
Scheme 7. Ortho-, meta-, and para-benzyne.

These other forms of benzyne have received comparatively little attention,[8] and mainly from theoretical and spectroscopic studies.[9-23] For example Jones has recently studied the interconversion of all three didehydrobenzenes (Scheme 8).[24-25]



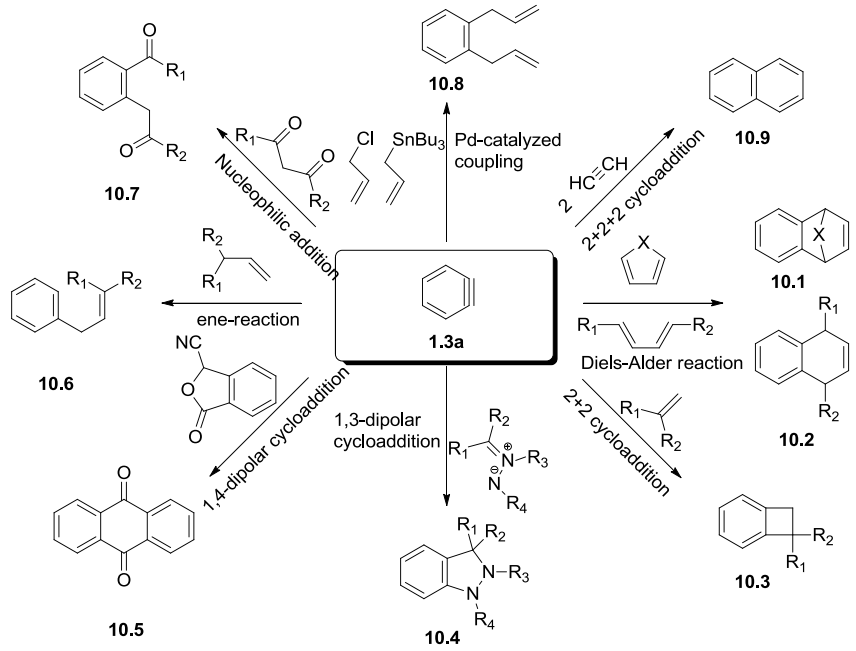
Scheme 8. Interconversion of the didehydrobenzenes.

The *p*-benzyne in particular is the putative intermediate in the Bergman cyclization of enediynes (Scheme 9).[26-27]



Scheme 9. Bergman cyclization to 1,4-didehydrobenzene (*p*-benzyne).

Ortho-benzynes, on the other hand, have been extensively studied, and have found many applications in organic synthesis since 1954.[2,28]

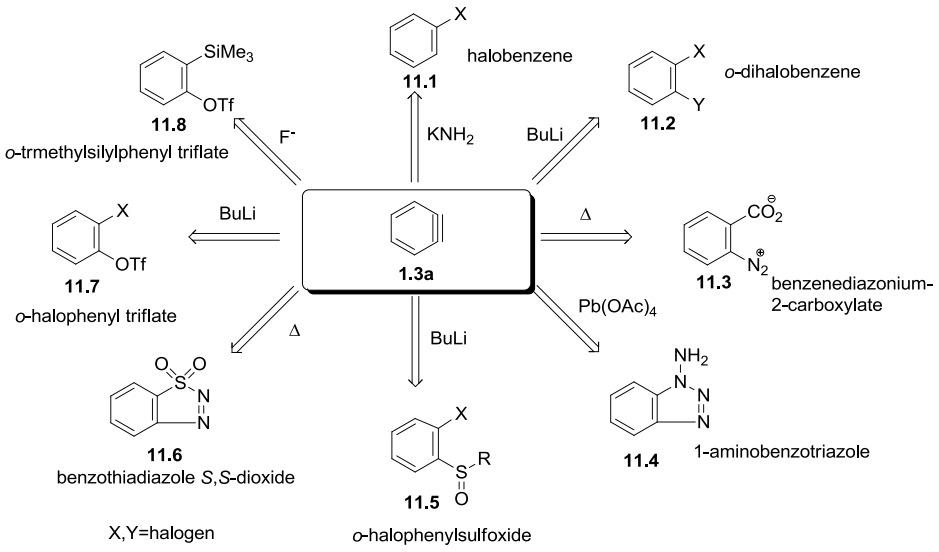


Scheme 10. Reactions using benzyne as intermediate.

For example, there are the Diels-Alder reactions with cyclic and acyclic dienes (**10.1**, **10.2**),[1] [2+2] cycloadditions (**10.3**),[29-30] 1,3 and 1,4-dipolar cycoadditions (**10.4**, **10.5**),[31-32]

ene-reaction (**10.6**),[33] nucleophilic additions (**10.7**),[34] Pd-catalyzed couplings (**10.8**)[35] and [2+2+2] cycloadditions (**10.9**).[36] The last two are three component addition reactions. The three component reactions have received more attention recently due to their high efficiency, and there are many variations of this type.

There are many methods for the generation of benzynes reported in the literature (Scheme 11).

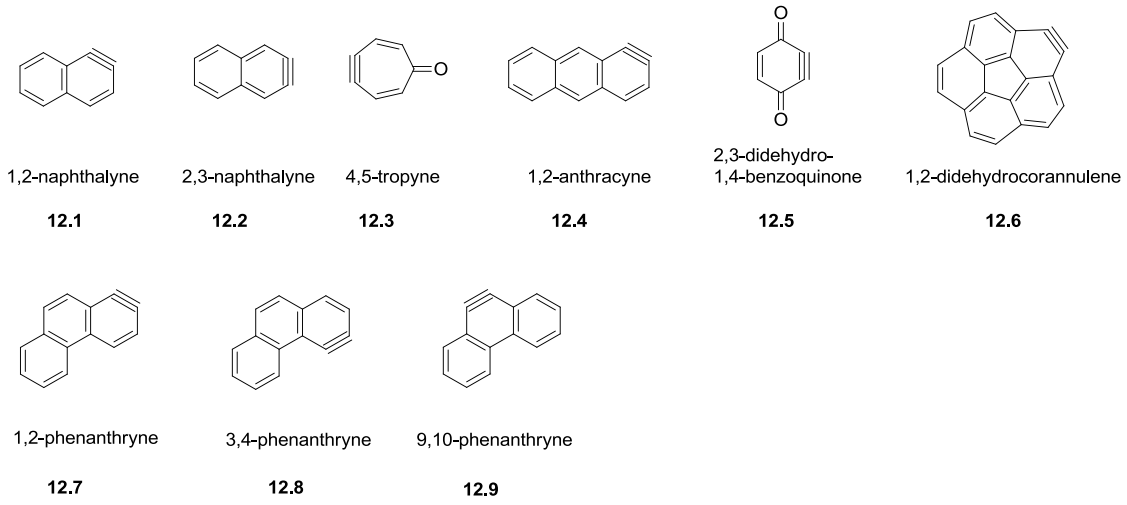


Scheme 11. Common and useful methods for generating benzynes.

The most synthetically useful methods are the dehydrohalogenation of halobenzenes **11.1**[1,37], metal-halogen exchange of *o*-dihalobenzene **11.2** and subsequent elimination,[38-40] thermal elimination of *o*-diazonium carboxylates **11.3,**[41] lead tetraacetate oxidative elimination of aminobenzotriazole **11.4**,[42] metal-halogen exchange and elimination of *o*-halophenylsulfoxide **11.5**[43] and *o*-halophenyl triflate **11.7**,[44] thermal decomposition of benzothiadiazole *S,S*-dioxide **11.6**,[45] and the fluoride induced decomposition of

o-trimethylsilylphenyl triflate **11.8**.[46-47] The last method, originally developed by Kobayashi, is the most common method for generating benzynes and other arynes under safe, mild, and economical conditions.

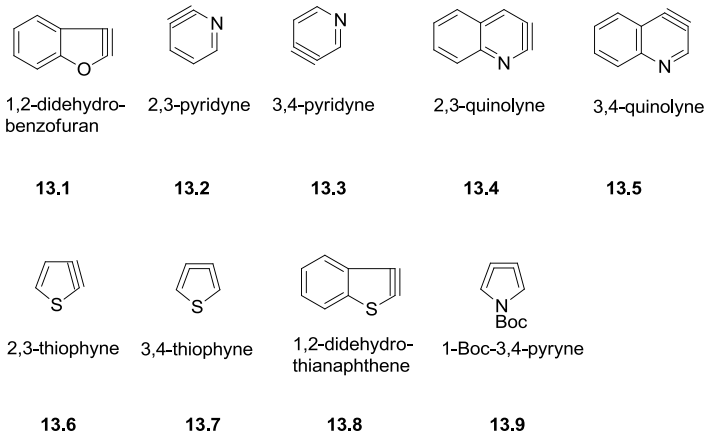
There are few other arynes (excluding heteroarynes, *vide infra*) beyond benzyne itself and substituted benzynes. These include 1,2-didehydronaphthalene (1,2-naphthalyne) **12.1**[48] and 2,3-didehydronaphthalene (2,3-naphthalyne) **12.2**[49] (Scheme 12) both of which were discovered and reported in 1958, and more recently, 4,5-tropyne **12.3**,[50] 1,2-anthracyne **12.4**,[51-52] 1,2-phenanthryne **12.7**,[36,51] 3,4-phenanthryne **12.8**,[36] 9,10-phenanthryne **12.9**,[36,51] 2,3-didehydro-1,4-benzoquinone **12.5**[53] and 1,2-didehydrocorannulene **12.6**.[54] The literature reports involving the study of these systems are fairly scarce. They have not been exploited for natural products total synthesis.



Scheme 12. Other common arynes.

1.2 Heteroarynes

Heteroarynes (also known as hetarynes) by contrast are defined as arynes with a heteroatom, usually nitrogen or oxygen, as part of the aromatic core. A few heteroarynes were known prior to this work. The oldest reference to a heteroaryne (although it was not characterized as such) was in 1902 by Stoermer and Kahlert who postulated a reactive intermediate with a formal triple bond within the furan moiety of benzofuran (**13.1** Scheme 13).[8]

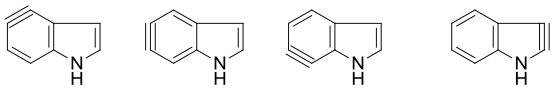


Scheme 13. Heteroarynes.

Although the existence of this intermediate has never been established, other heteroarynes based on common heteroaromatic cores have been prepared. These include the pyridynes (2,3-didehydropyridine and 3,4-didehydropyridine),[55-56] the quinolynes (2,3-didehydroquinoline and 3,4-didehydroquinoline),[57] the thiophynes (2,3-thiophyne and 3,4-thiophyne),[58-59] 1,2-didehydrothianaphthene[58] and 1-Boc-3,4-pyryne.[60] Of these classes of known heteroarynes, the pyridynes are by far more prevalent in the literature with about

200 references to date. Most of the citations involve theoretical and synthetic studies. As with the benzynes, recent experimental and theoretical studies concluded that the pyridynes also exhibit substantial triple bond and some diradical character.[61] Both types of pyridynes have found applications in natural products total synthesis by way of their Diels-Alder reactions.[28] The 3,4-pyridyne has been generated via the fluoride-induced decomposition of the correspondoing *o*-silyl triflate.[62] It has also been prepared by the lead tetraacetate oxidative elimination of 1-aminopyridinotriazole where it was used in a synthesis of isoindoles.[63] An elegant and concise total synthesis of ellipticine by Castedo made use of a 2,3-pyridyne cycloadditon as the key step.[64] Very recently Comins reported a five-step synthesis of the plant alkaloid macrostomine by a nicotine-derived 3,4-pyridyne.[65]

Suprisingly, heteroarynes derived from the ubiquitous indole nucleus have received almost no attention (Scheme 14).

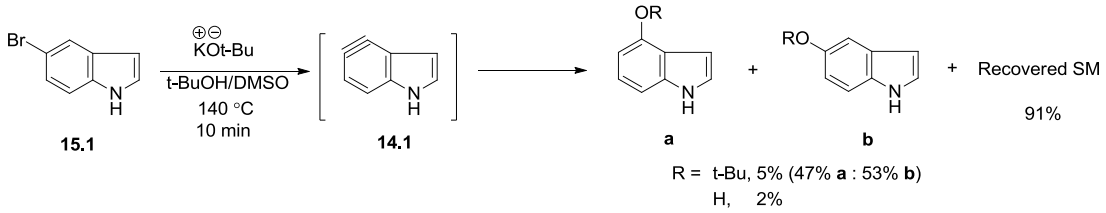


14.1 **14.2** **14.3** **14.4**

Scheme 14. The tetrad of indole arynes (indolynes).

Indoles are found in an enormous range of biologically active natural products and medicinally important agents. As such, this omission represents a major gap in the literature, and is therefore an important problem in organic chemistry. The first and only previous reports of an indole aryne (indolyne) were made by Igolen using a dehydrohalogenation method to generate presumably the 4,5 indole aryne followed by trapping with t-BuOH

(Scheme 15).[66] However, no further investigations into these indole arynes were made until the Buszek laboratory published its seminal work beginning in 2007 (vide infra).[40,67-70] Interestingly, the elusive (and presumably far more strained) 2,3-indole aryne has the been the subject of intense studies by the Gribble laboratory for decades.[71-75]



Scheme 15. Igolen's synthesis preparation of a 4,5-indole aryne.

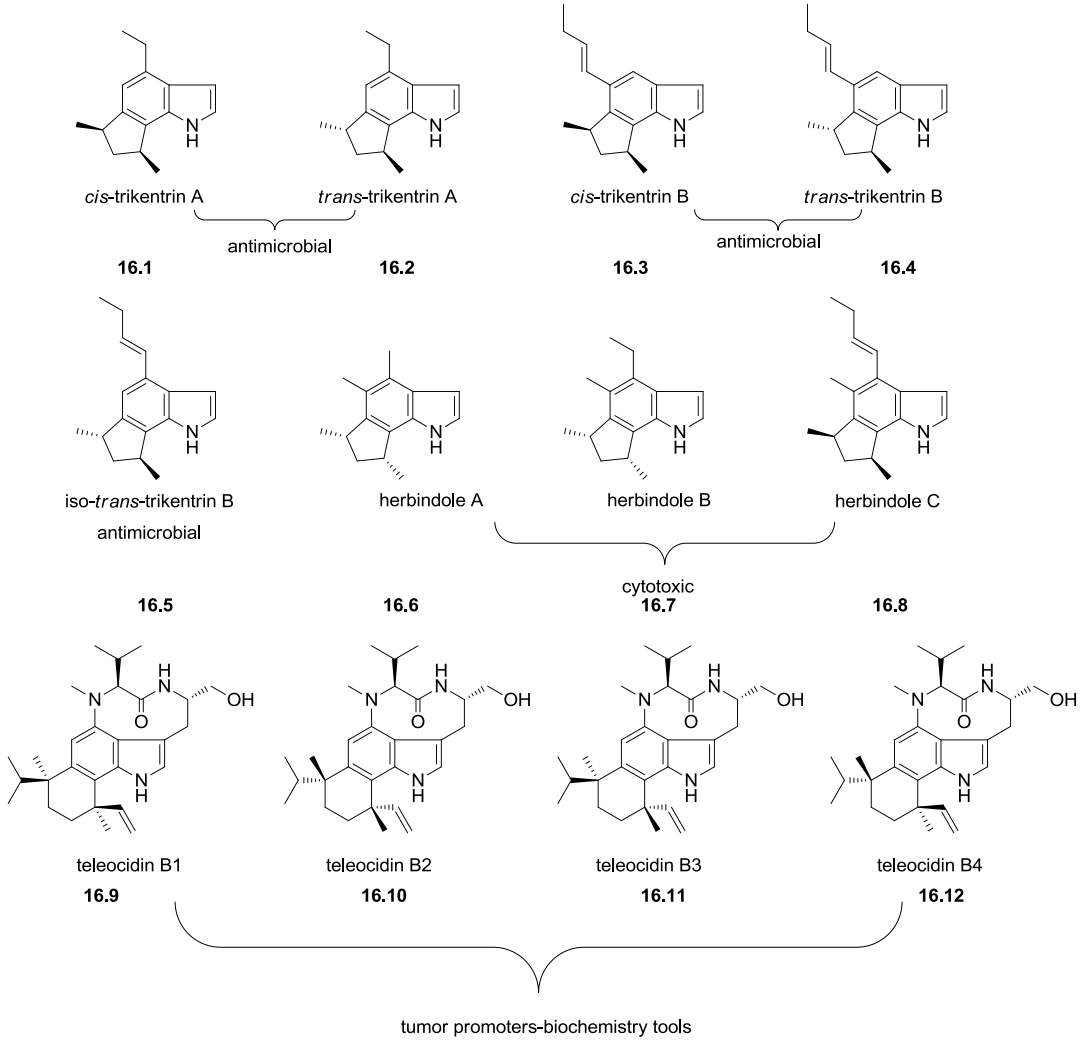
Despite extensive work by that group, no conclusive evidence for the existence of this intermediate has been presented.

The subject of the next and succeeding chapters of this dissertation will focus on the efforts to address this critical indole aryne chemistry problem. These efforts include the discovery of the heretofore unknown 5,6-, and 6,7-indole arynes, along with the development of general methods for the preparation of all of the benzenoid indole arynes (i.e., 4,5-, 5,6-, and 6,7-indolynes, but excluding the 2,3-indolyne of the pyrrole nucleus), their reactivity, theoretical and computational studies, applications for the total synthesis of complex natural products, and library development for the discovery of new bioactive compounds in medicinal chemistry.

Chapter 2. INDOLE ARYNES

2.1 Preparation, Structure, and Reactivity

Our interest in indole arynes initially grew out of a desire to use an aryne cycloaddition strategy as a means to gain rapid entry into the fascinating and important class of annulated indole alkaloid natural products such as the trikentrins, herbindoles, and teleocidins (Scheme 16).



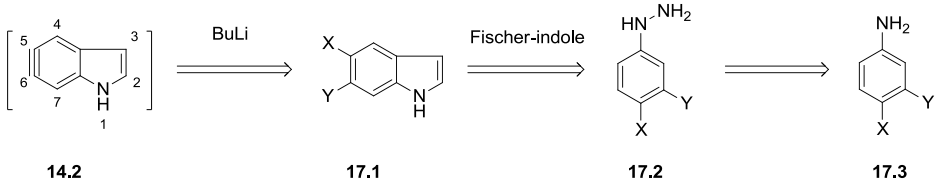
Scheme 16. Annulated indole alkaloid natural products.

The trikentrins were isolated from the marine sponge *Trikentrion flabelliforme* in 1986 and showed antibacterial activity.[76] Several years later, the structurally similar natural products, the herbindoles, were extracted from the Australian sponge *Axinella sp.*, which possessed both cytotoxic and antifeedant properties.[77] The teleocidins B families were first isolated from the Mycelia of *Streptomyces mediocidicus* by Takashima in 1962,[78-79] and were found to be potent tumor promoters.[80-81]

These deceptively simple compounds represent fantastic synthetic challenges, as evidenced by the large number of distinct approaches toward their total synthesis. We envisioned that a cycloaddition (e.g., Diels-Alder) strategy would offer the most direct method to install the annulated five- and six-membered aliphatic rings that comprise these architectures. Earlier strategies for the total synthesis of (±)-*cis*-trikentrin A relied on radical cyclization[82-84] to form the indane skeleton followed by indole ring annulation. Subsequent total synthesis efforts for the trikentrins and herbindoles involved various diverse strategies which included intramolecular allene cycloaddition,[85] heteroaromatic azadiene Diels-Alder reactions,[86] intermolecular Heck coupling,[87] intermolecular quinone monoimine Diels-Alder cyclization,[88-89] electrocyclic divinylpyrroline ring closure,[90] and ring contraction,[91] whereas the enantioselective total synthesis of trikentrins and herbindole relied on pyrrole indolization[92-95] or intramolecular allene cycloaddition strategies.[96] The (±)-teleocidins B-3 and B-4 have been synthesized by Nakatsuka in 1987[97] and Okabe in 1991,[98] via an acid-mediated Friedel–Crafts type of cyclization to form the quaternary center of the six-membered ring as the key step. However, all these approaches suffered from undesired

side reactions and low yields because of the strong acidic conditions. Very recently, Sames used Pd-catalyzed C-C bond coupling to access the stereogenic centers[99] and Resnick used an intramolecular Heck reaction of a tetrasubstituted alkene to construct the teleocidins' core.[100] However, neither of these two efforts resulted in a total synthesis of teleocidins B.

We considered many methods for generating the indole aryne, including those discussed in Scheme 11. However, we elected the use the metal-halogen exchange/elimination aryne methodology[38-39] for the indole systems because it was synthetically easier to access. The *o*-dihaloindole aryne precursors were readily prepared from commercially available *o*-dihaloanilines which would be used to synthesize the corresponding indole via the Fischer indole method (Scheme 17).

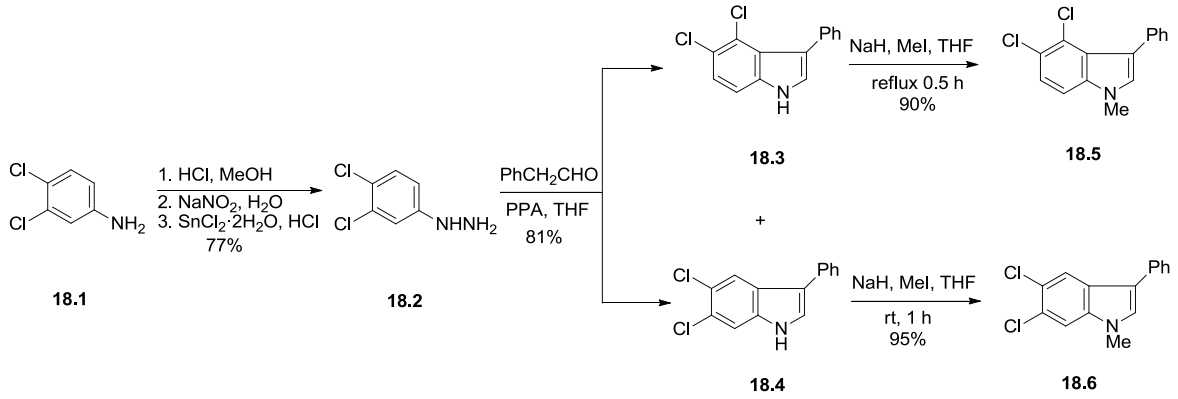


Scheme 17. Retrosynthetic analysis of a Fischer route to the indolynes.

2.2 Different *ortho*-Dihaloindoles and Their Reactions with Butyllithium

The synthesis of indolyne precursors is described below. Commercially available 3,4-dichloroaniline **18.1** was diazotized and reduced with stannous chloride in one pot to give the corresponding hydrazine in 77% yield.[101] Condensation of **18.2** with phenylacetaldehyde under Fischer conditions with polyphosphoric acid afforded the expected 5,6-dichloroindole **18.3** and 4,5-dichloroindole **18.4** as a 1:1 mixture with a total yield of 81%. After column

chromatography, methylation of the NH group gave the N-methyl indoles **18.5** and **18.6** in 90% and 95% yield, respectively. With the desired aryne precursors in hand, many protocols for generating benzynes from ortho dihalo arenes were examined.



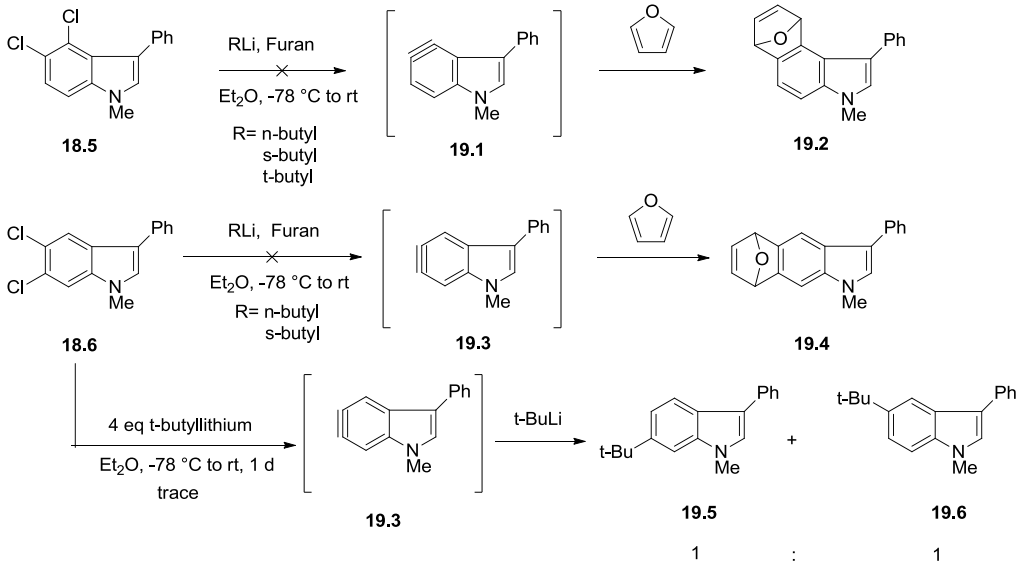
Scheme 18. Fisher-indole synthesis.

All the attempted indole aryne generation reactions were run in diethyl ether solvent since some literature references[102-103] suggested that there were dramatic solvent effects in polyhalobenzene metalation. Specifically, the diethyl ether solvent favored lithium-halogen exchange (at either halogen) while THF favored lithium-hydrogen exchange (i.e., deprotonation) adjacent to either halogen.

The original intent was to generate the indole aryne in the presence of furan, which is considered the most efficient aryne trap known. In this manner, the existence of the indole arynes **19.1** or **19.3** would be inferred by the formation of the corresponding cycloadduct (see Scheme 21 later).

Unfortunately, there was no apparent metal-halogen exchange between **18.5** and up to four equivalents of *n*-butyllithium, *sec*-butyllithium, or *t*-butyllithium even after several hours at room temperature. Surprisingly, only recovered starting materials were found in

each case. A similar observation was made with **18.6** in the case of the alkyllithiums n-BuLi and s-BuLi. However, the use of the stronger base *t*-butyllithium with **18.6** afforded a trace amount of a 1:1 mixture of the isomeric *t*-butylindoles **19.5** and **19.6** after one day, presumably via the 5,6-indole aryne. There is apparently no preference for nucleophilic attack at either position. It is still not clear whether the aryne formation was preceded by metal-halogen exchange at either C5 or C6. The same indolyne would be formed in either case.

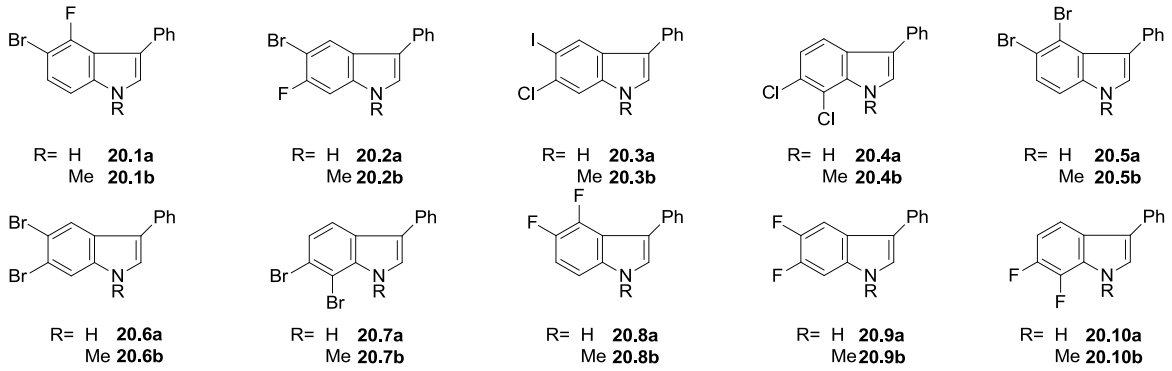


Scheme 19. First evidence for indolyne.

A search of the literature revealed that there were only a few examples of *o*-dichlorobenzenes used as precursors to benzynes. Hales[104] reported an interesting case in which hexachlorobenzene was used to generate, via metal-halogen exchange, the 3,4,5,6-tetrachlorobenzyne which was in turn reacted with benzene itself to give tetrachlorobenzobarrelene. The general difficulty in obtaining indole arynes from their

o-dichloro precursors may be due to the low metal-halogen exchange rate which generally follows the order I > Br > H > Cl > F. [103,105]

Based on this trend, our next efforts at generating the required indole arynes involved the synthesis of other *o*-dihaloindole precursors such as those shown below via the same Fischer indole sequence shown earlier and using the commercially available *o*-dihalo anilines as starting material (Scheme 20).

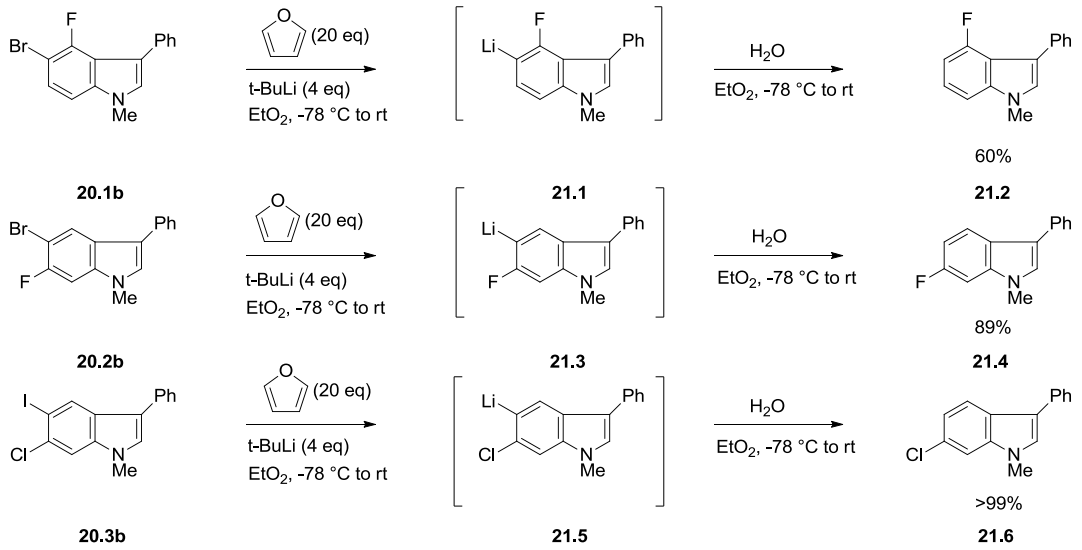


Scheme 20. Different *o*-dihaloindoles.

Mixed *o*-dihalo arenes such as F and Br, or Cl and I are much more common aryne precursors.[39,103,106-107] Similarly, dihalo arenes containing only fluorine or bromine are also found frequently in the literature.[39,105,107]

With the desired compounds in hand, reaction of **20.1b** under the previously described metal-halogen exchange conditions using t-BuLi in the presence of an excess of furan gave only the monofluoro indole **21.2** in 60% yield (Scheme 21). An analogous result was obtained in 89% yield with compound **21.4**. In both cases, lithium-bromine exchange apparently occurred preferentially, but was not followed by elimination to form the

corresponding indole aryne. The observation stands in contrast to what is known in simple benzene systems in which aryne formation occurs readily.[38,107]

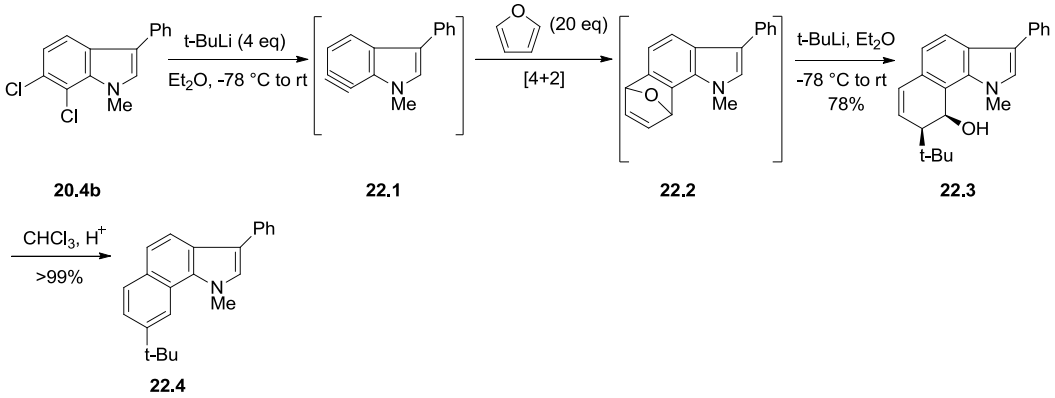


Scheme 21. Attempts at indolyne formation.

While this outcome can be ascribed to the relatively poor leaving group ability of fluoride, the same trend was also seen with compound **20.3b**. Although chloride was expected to be a better leaving group, only protonation of the lithio indole **21.5** was found in nearly quantitative yield. It is not possible to say with certaintly that this trend would stand with all possible *o*-FBr and *o*-ICl isomers since all of the needed *o*-dihalo aniline precursors were either not commercially available, or unknown in the literature. This remains an aspect of the indole aryne chemistry that requires further investigation. Even so, it is interesting to note that the trend of *o*-halolithium elimination (-LiX) in benzene is LiI < LiBr < LiCl < LiF.[108] However, a systematic study of the influence of other substituents in the benzene cases, has never been reported. It appears that the 4,5- and 5,6-dihaloindoles exhibit similar reactivity to

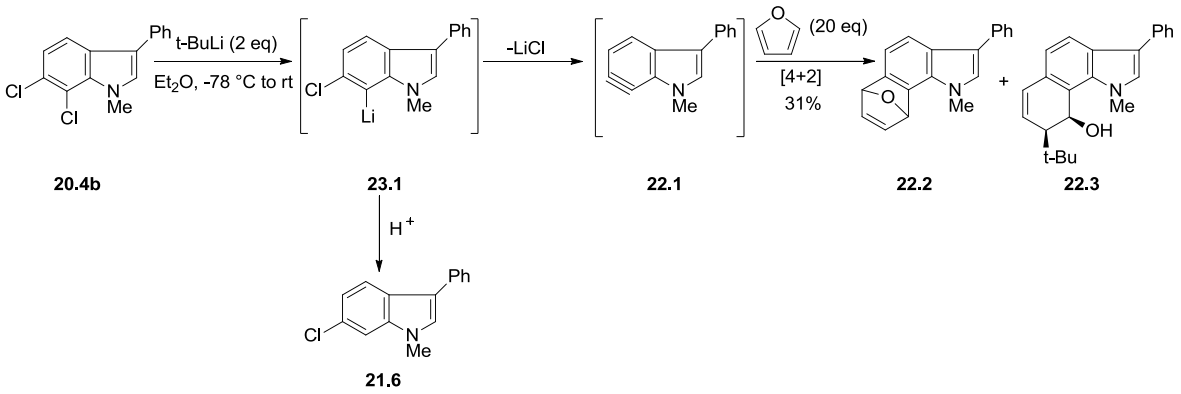
those of benzene. However, based on the data in hand, we decided to investigate the reactivity of *o*-dibromoindoles in all positions (the precursors for the *o*-diiodo cases are not known in the literature), and other readily available 6,7-dihaloindoles.

Gratifyingly, evidence for the first successful indole aryne generation at the 6,7-position came from 6,7-dichloroindole **20.4b** (Scheme 22). This compound was reacted with four equivalents of *t*-butyllithium to generate presumably the aryne **22.1**, which underwent cycloaddition in the presence of an excess of furan to give the cycloadduct **22.2**. However, this product was not stable to an excess of the alkyllithium reagent and experienced completely exo selective and regioselective S_N2' nucleophilic attack and ring opening to afford the observed product **22.3** as a single regioisomer in 78% yield. This process has ample precedent with many different nucleophiles, including hindered alkyllithiums.[109-110] The identity of compound **22.3** was confirmed unequivocally by 2D NMR analysis including COSY, NOESY, HMBC, and HSQC methods. Aromatization was induced by stirring in chloroform for several hours to give quantitatively the benzannulated derivative **22.4**.



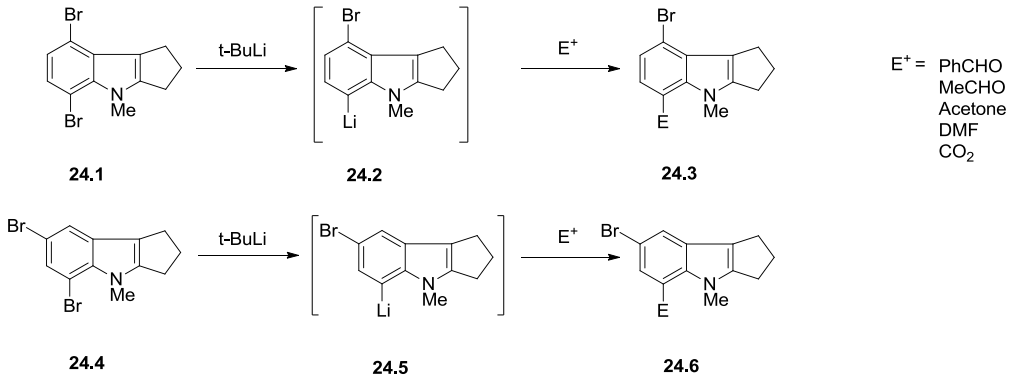
Scheme 22. First successful generation of indolynes.

Repeating this sequence of reactions with only two equivalents of t-BuLi allowed for the isolation of the furan cycloadduct **22.2** in 31% yield (Scheme 23).



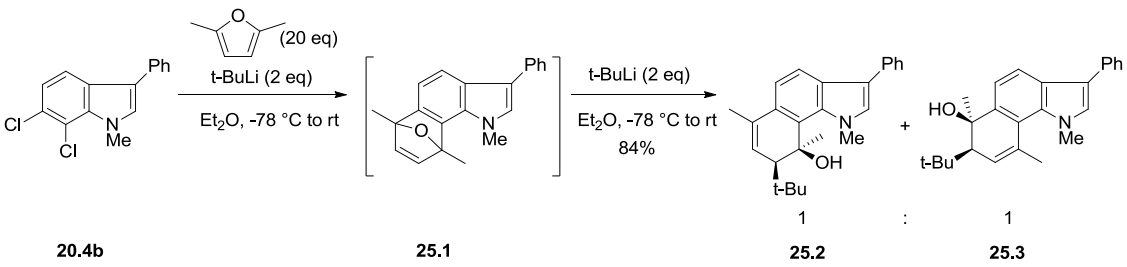
Scheme 23. Isolation of 6,7-indole aryne cycloadduct with furan.

Significantly, under these same conditions, a trace amount of the 6-chloroindole **21.6** was identified. Furthermore, no evidence for the formation of the 7-chloroindole was found. Together, these observations suggest that it is the 7-chloro position that undergoes completely selective lithium halogen exchange. Support for this claim is found in a recent literature case in which a pair of dibromoindoles, namely the 4,7- and 5,7-dibromoindoles, were found in each case to undergo lithium bromine exchange only at C7, followed by trapping with various electrophiles (Scheme 24).[111-112]



Scheme 24. Selective lithium-bromine exchange.

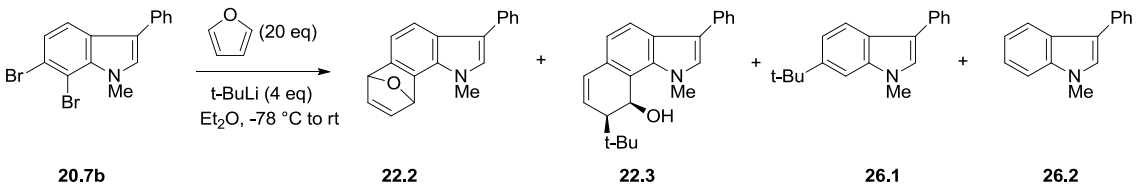
Finally, the putative 6,7-indole aryne (6,7-indolyne) also reacted with 2,5-dimethylfuran to give the corresponding cycloadduct **25.1** (Scheme 25). [111]



Scheme 25. 6,7-Indole aryne reaction with 2,5-dimethylfuran and subsequent ring opening.

This compound similarly reacted with an excess of t-BuLi, but now with an approximately equal mixture of regioisomers **25.2** and **25.3** being formed in a combined 84% yield. The difference in regiochemical outcome for these two reactions (e.g., Scheme 25) can perhaps be rationalized on the basis of ground-state destabilization. The opening of the furan cycloadduct **22.2** from the opposite side of the olefin would experience greater torsional strain thereby leading only to the observed product. This strain is significantly less pronounced from either direction with **25.1**, owing to the presence of the larger methyl groups, and a statistical distribution of products is found instead. The issue of regiocontrol in these systems remains the subject of further investigation.

Although only the 6,7-indole aryne could be prepared within the *o*-dichloroindole series, we were gratified to discover that all three benzenoid indolynes could be generated easily and trapped as their Diels-Alder cycloadducts in good yields from the *o*-dibromoindole precursors. Our first attempt paralleled that of the 6,7-dichloroindole work (Scheme 26).

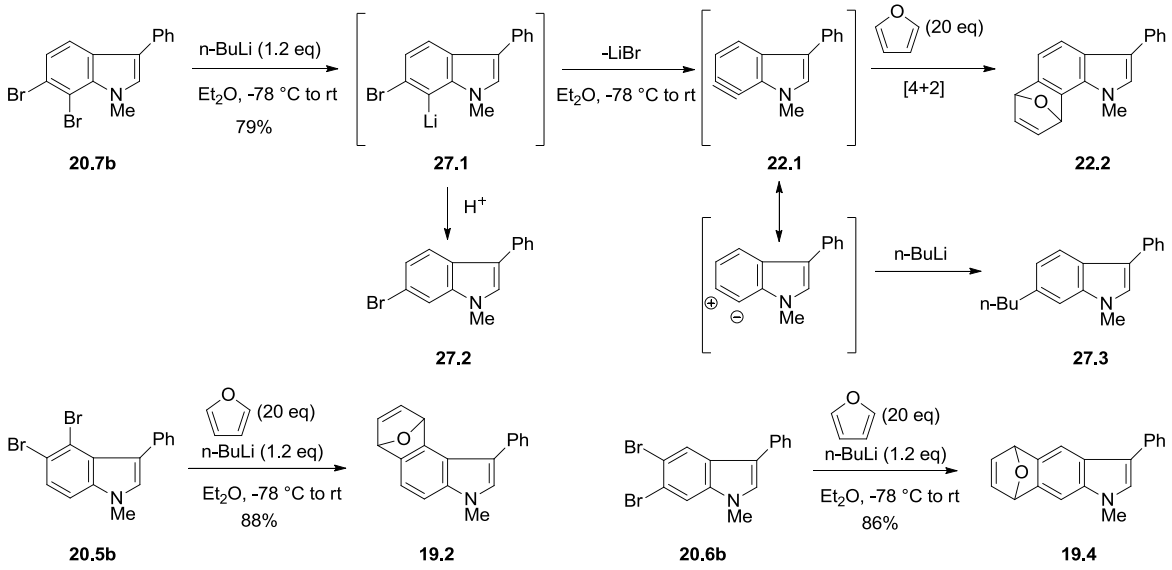


Scheme 26. General route to all three benzenoid indole arynes.

Thus, the aryne precursor **20.7b** was treated with four equivalents of t-BuLi in ether in the presence of an excess of furan to give a complex mixture of products **22.2** – **26.2**. The cycloadduct **22.2** was a minor component of this mixture for reasons that are analogous to the 6,7-dichloroindole case. The excess t-BuLi attacks the cycloadduct in the same exoselective and regioselective fashion to afford **22.3** as the major product. In addition, the t-butylated indole **26.1** likely arises from the regioselective nucleophilic attack at the 6-position on the 6,7-indolyne. Finally, the trace amount of **26.2** can be rationalized by the sequential lithiation-protonation of the 6,7-dibromoindole.

The use of *n*-butyllithium in place of the more reactive and nucleophilic *t*-butyllithium reagent during the indole aryne generation step permitted the isolation of all the furan cycloadducts (Scheme 27). In fact, it was found that only a slight excess of n-BuLi in ether was necessary to effect these transformations. The process can be envisioned as follows. Selective lithium-bromine exchange of the 6,7-dibromoindole **20.7b** gives the intermediate **27.1** which upon warming undergoes elimination to generate the 6,7-indole aryne **22.1**. Subsequent cycloaddition with furan readily affords the corresponding cycloadduct in good yield. Support for this view is provided by the minor amounts of compound **27.2** which clearly reveals an intial exchange at C7, and **27.3** which in turn suggests that the 6,7-indolyne

is a highly polarized aryne that directs nucleophiles such as n-BuLi to the more electropositive 6-position exclusively.

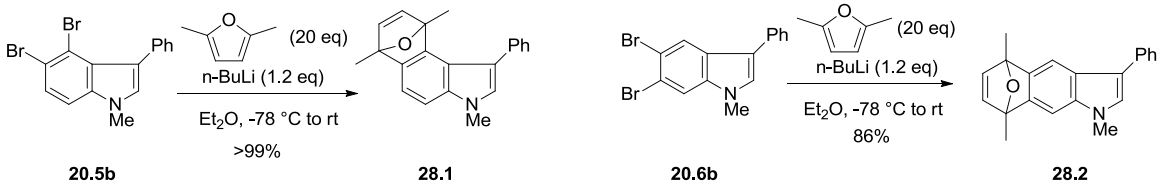


20.7b **27.1** **22.1** **22.2** **27.2** **27.3** **20.5b** **19.2** **20.6b** **19.4**

Scheme 27. General method for generating 4,5-, 5,6-, and 6,7-indole arynes.

In a similar manner, the 4,5- and 5,6-indole arynes were generated from their corresponding *o*-dibromo precursors and trapped with furan to afford the respective cycloadducts is excellent yield. With these latter two cases, no evidence of the n-butylated indoles was found.

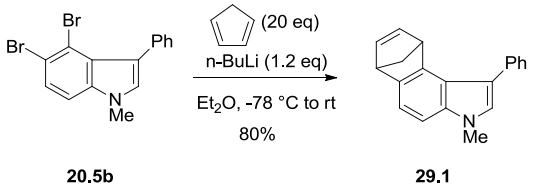
Reaction of the 4,5- and 5,6-indole arynes with 2,5-dimethylfuran gave excellent yields of the corresponding cycloadducts (Scheme 28).



20.5b **28.1** **20.6b** **28.2**

Scheme 28. Reaction of 4,5- and 5,6-indole arynes with 2,5-dimethyl furan.

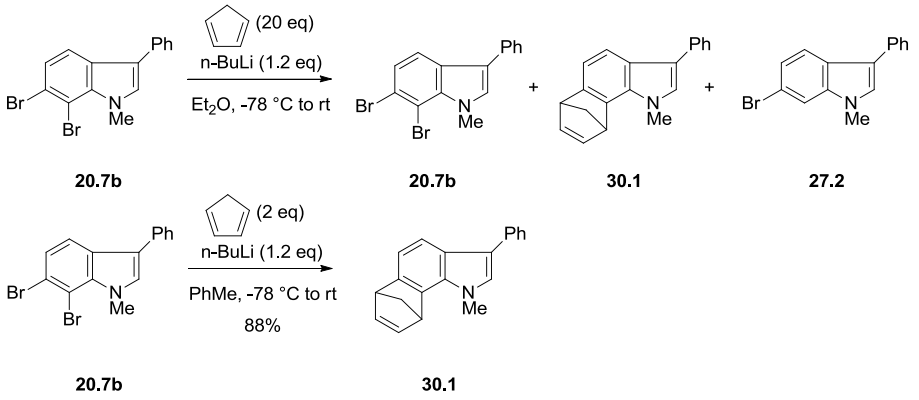
Finally, it was found that reaction of the 4,5-indole aryne with cyclopentadiene also occurs readily to give the cycloadduct in very good yield (Scheme 29).



20.5b **29.1**

Scheme 29. Reaction of a 4,5-indole aryne with cyclopentadiene.

By contrast, the corresponding reaction with the 6,7-indole aryne produced very little of the desired cycloadduct (Scheme 30). Again, it is tempting to speculate that the proposed polarized structure of the 6,7-indolyne might cause deprotonation of cyclopentadiene by the C7 carbon of the aryne. The fact that this was not observed with the 4,5-indole aryne suggests that it behaves more like benzynes and that this reactive intermediate has in fact more triple bond or diradical character. However, changing the solvent from diethyl ether to toluene allowed the 6,7-indole aryne reaction with cyclopentadiene to proceed normally.



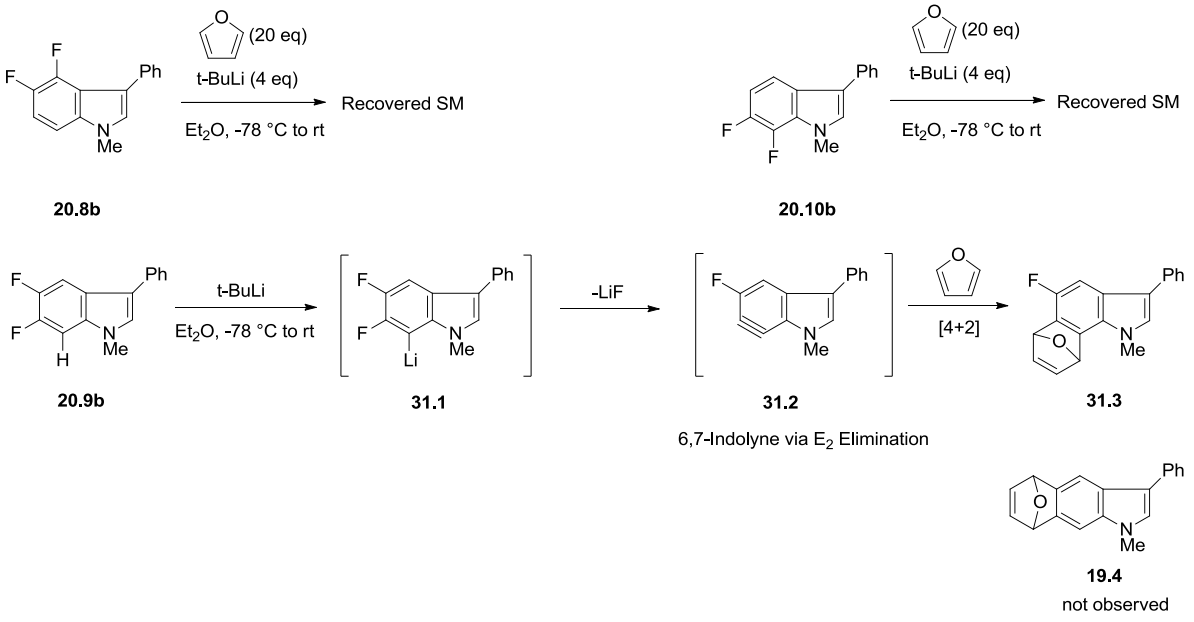
20.7b **20.7b** **30.1** **27.2**

20.7b **30.1**

Scheme 30. Reactions of indole arynes with cyclopentadiene.

Coe reports that the less polar hydrocarbon solvent promotes metal-halogen exchange and suppresses the undesired acid-base reaction. [113]

Finally, we observed that ortho difluoroindoles exhibit anomalous behavior upon treatment with *t*-butyllithiums (Scheme 31). It is known that the more electropositive halogens undergo the most rapid metal-halogen exchange, and this was indeed found to be the case with the bromo indole series. In the fluorine system, the isomeric 4,5- and 6,7-difluoroindoles gave only recovered starting material under these same conditions. The reaction of 5,6-difluoroindole **20.9b** with n-BuLi, however, gave exclusively the cycloadduct **31.3** in 80% yield.



Scheme 31. Indolyne generated from t-BuLi and difluoro-indole.

Initial deprotonation of the thermodynamically more acidic C7 hydrogen as a result of the inductive electron withdrawing effect of the adjacent nitrogen as well as the electronegative

fluorine atoms leads to aryne formation. This assumption is also consistent with well-documented observation that the rate of transmetallation of fluorine is slow compared with deprotonation at the ortho position.[102-103,111,114-117] Trapping and cycloaddition with furan thus gave the observed cycloaddduct, and ^{19}F NMR revealed one remaining fluorine at the C5 position.

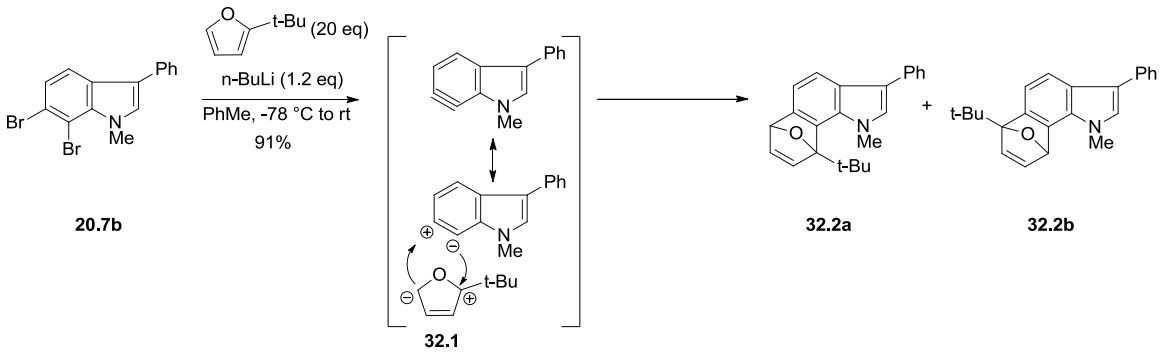
In conclusion we have provided the first evidence for the existence of all three isomeric indole arynes in the benzenoid core using a practical and general method. The facile generation of aryne indoles from dibromoindoles in particular is noteworthy for its synthetic simplicity and good yields. This discovery adds indoles to the suite of aromatic systems from which arynes can be easily and readily generated.

Bromine is a better exchanging and leaving group for indolyne, no matter where the position is. Chlorine and fluorine are usually not active enough to form indolyne, but may do the job with some particular positions. The 6,7- bond in the indole ring has a very unique property, which can assist in indolyne generation. *t*-butyllithium is a stronger base for our reaction, but *n*-butylithium gave us cleaner and more reproducible results.

CHAPTER 3. INDOLE ARYNE PROPERTIES AND REACTIONS

3.1 Regioselective Diels-Alder Cycloaddition of Indolyne

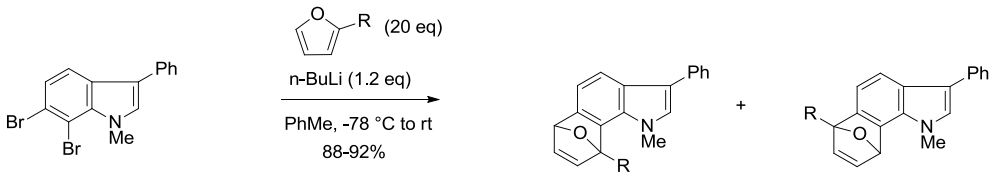
During the course of the indole aryne investigations, several interesting and surprising phenomena came to our attention. The first one involved an unexpected and highly regioselective Diels-Alder cycloaddition with the 6,7-indole arynes and 2-*t*-butylfurans (Scheme 32).



Scheme 32. The 6,7-indole aryne regioselective cycloadditions.

Thus, it was found that reaction of the 6,7-indole aryne derived from the dibromoindole **20.7b** with 2-*t*-butylfuran gave mainly a single regioisomer along with a minor product. NMR analysis of the separable mixture revealed a surprising outcome in which the more sterically crowded regioisomer, (i.e., the contrasteric product), **32.2a** was identified as the *major* isomer. This phenomenon was observed with other 2-substituted furans with somewhat diminishing levels of regiocontrol through the series i-propyl, ethyl, and methyl. This trend correlates regioselectivity with the degree of branching at the point of substitution (Table 1).

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



20.7b **a** **b**

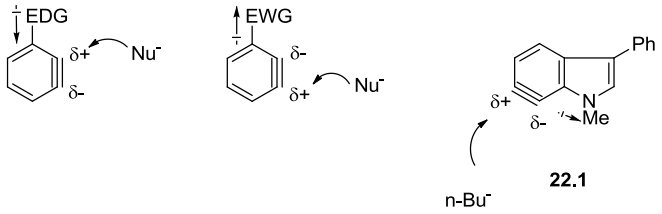
R= Me, Et, i-Pr, t-Bu, Ph, SO_2Ph

R= Me **1-1**, Et **1-2**, i-Pr **1-3**, t-Bu **32.2**, Ph **1-4**, SO_2Ph **1-5**

entry	R	Yield (%)	Ratio (**a:b**)
1	Me	89	80:20
2	Et	90	84:16
3	i-Pr	88	94:6
4	t-Bu	91	98:2
5	Ph	92	>99:1
6	SO_2Ph	83	<1:99

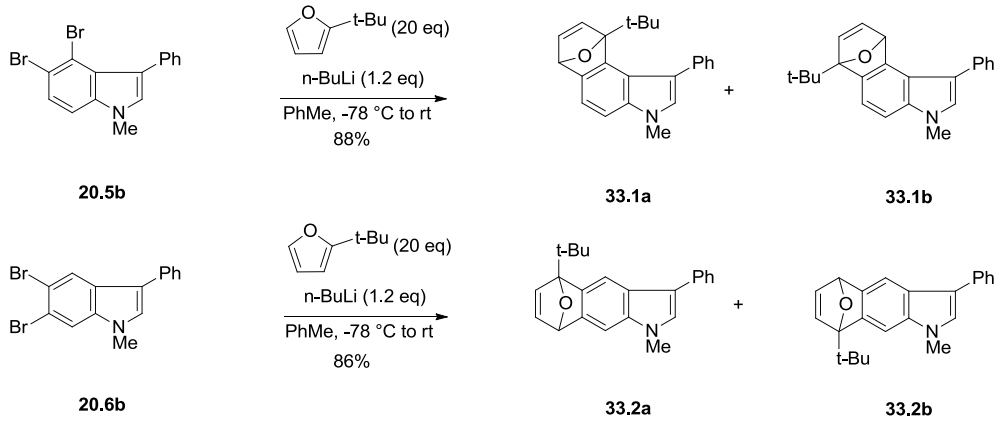
Additionally, there was virtually complete regiocontrol in the case of 2-phenylfuran. A simple first-order resonance structure analysis rationalizes this behavior in terms of a polarized 6,7-indole aryne combining with the furan in such a way that the more highly stabilized cation in **32.7** preferentially bonds to C7 (Scheme 32). The more highly branched substituent is more electron rich and therefore better able to stablize by induction an adjacent positive charge. The virtually complete regiocontrol with the 2-phenylfuran can clearly be

understood in these terms. This analysis predicts that electron withdrawing substituents at the 2-position in the furan should give the opposite regiochemistry. Indeed, this was found to be the case (entry 6, Table 1). Thus, the 2-phenylsulfonylfuran gave a >99:1 ratio of isomers favoring the reverse regiochemistry. In earlier studies by other laboratories involving the reaction of monosubstituted 3-benzynes with 2-substituted furans (Me, Et, i-Pr, and t-Bu),[117-119] regioselectivity correlated well with the strength of inductively electron-withdrawing groups such as F and OMe on the benzyne to favor the contrasteric products. It was reversed with inductively electron-donating groups such as Me (Scheme 33).



Scheme 33. Polarization effects and regioselectivity.

This regiocontrol however was specific to the 6,7-indole arynes. The corresponding 4,5- and 5,6-indolynes showed no regioselectivity with 2-*t*-butylfuran, giving a 1:1 mixture in each case.



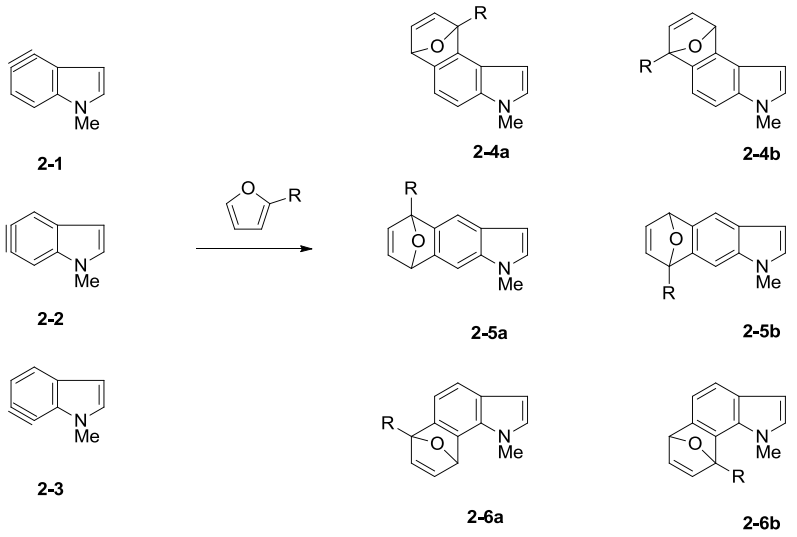
Scheme 34. The 4,5 and 5,6-indole aryne cycloadditions with 2-*t*-butylfurans.

To characterize this phenomenon in additional detail, electronic structure calculations were undertaken in collaboration with Professor Christopher Cramer and his research group (Department of Chemistry and Supercomputing Institute, University of Minnesota) to predict the structures and reactivities of the *N*-methyl-4,5-, 5.6-, and 6,7-indolynes with furan and 2-alkylfurans.[40] With respect to the methodology, all of the structures were optimized using the M06-2X density functional[120] and 6-311+G(2df,p) basis set[121] as implemented in MN-GFM,[122] a locally modified version of the Gaussian03 software package.[123] Analytical frequency calculations were employed to characterize the nature of all gas-phase structures as minima or transition states. In select instances, the effects of diethyl ether solvation were taken into account using the SMD[124-125] implicit solvation model.

The calculations support the view that the 6,7-indolyne (but not the 4,5- and 5,6-indolynes) is highly polarized in the manner previously shown (Scheme 27). The fact that the C6 position is substantially more electrophilic than the C7 position comes from inspection of atomic polar tensor partial charges and the molecular geometry. Thus, C6 is predicted to have a charge 0.26 au more positive than C7, and the C5-C6-C7 bond angle is predicted at the M06-2X level to be 135.3° while the C6-C7-C7a angle is predicted to be 117.2°. The former value is more consistent with carbocationic character, while the latter is more consisten with carbanionic character. Thus, the C6-C7 bond is strongly polarized in the expected direction by the nearby C7a-N bond dipole.

Table 2 lists the activation free energies computed for the reaction of the *N*-methylindolynes with the furans.

Table 2. $\Delta G^{\ddagger}$ values in kcal/mol for the reaction of indolynes with substituted furans.



entry	aryne	furan, R	$\Delta G^{\ddagger}$ (a)	$\Delta G^{\ddagger}$ (b)
1	**2-1**	H	10.5	
2	**2-2**	H	10.0	
3	**2-3**	H	8.7 (8.4)[a]	
4	**2-1**	t-Bu	6.3	7.3
5	**2-2**	t-Bu	6.9	6.1
6	**2-3**	t-Bu	7.0 (8.0)	[b]
7	**2-3**	Me	9.2 (9.4)	7.5 (7.8)
8	**2-3**	Et	9.0 (9.4)	7.8 (8.2)
9	**2-3**	i-Pr	9.7 (10.3)	7.6 (8.2)

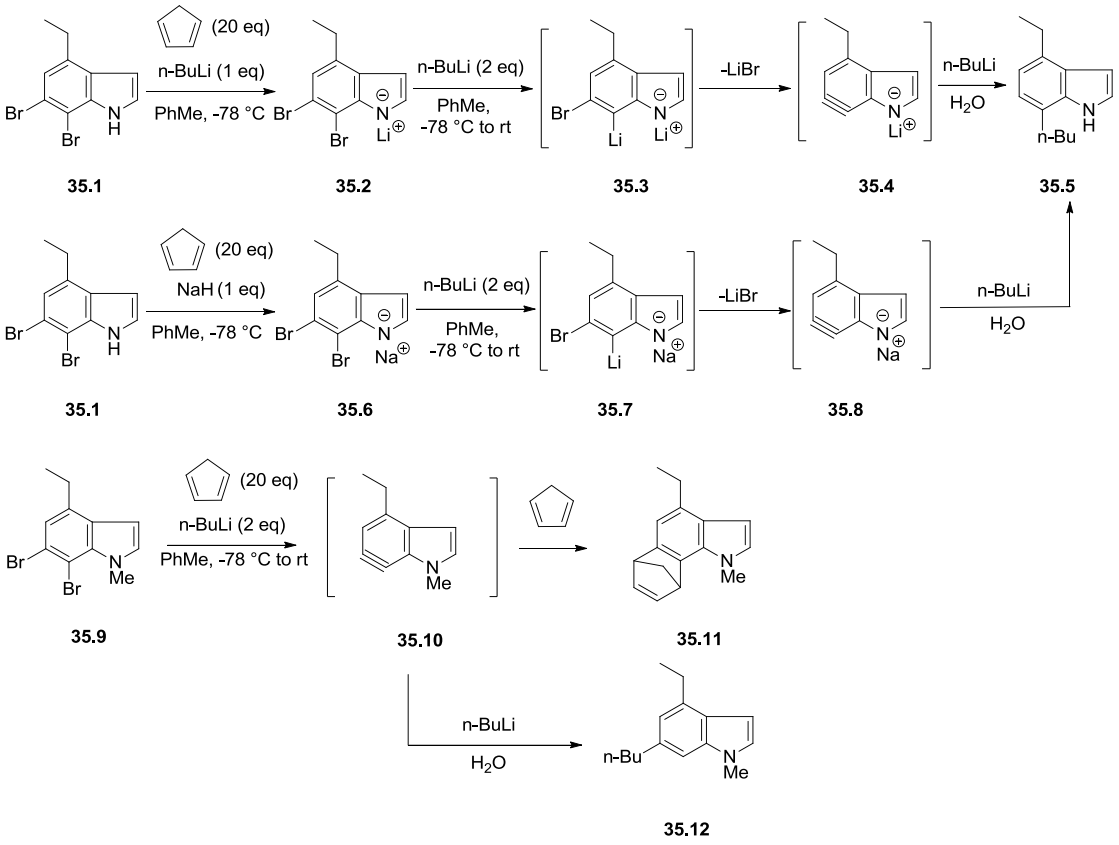
[a] Values in parentheses include continuum ethereal solvation effects.
[b] No barrier to reaction is predicted in the gas phase or continuum solution.

With unsubstituted furan, DG is similar for the 4,5- and 5,6-indolyne isomers, and slightly smaller for the 6,7-isomer. Considering 2-*t*-butylfuran, the predicted free energies of

activation are reduced by 3-4 kcal/mol compared to the reaction with furan itself in the 4,5- and 5,6-indolyne cases. Regioselection becomes possible upon 2-substitution of the furan, and the differential free energies of activation in these two instances are predicted to be 1 kcal/mol or less. In the 6,7-indolyne case, by constrast, a free energy of activation similar to those for 4,5 and 5,6 is predicted for the formation of **2-6a**, but no transition-state (TS) structure for the formation of **2-6b** could be located. The approach of the furan to the indolyne led smoothly and without barrier to the final tertacyclic product every time.

Thus, the electron-poor indolyne attacks the 2-substituited furan to generate the more stable 2-alkyldihydrofurylcarbenium ion. As the 2-substituent is varied from Me to Et to i-Pr, the increased stabilization provided by the larger alkyl groups leads to increased regioselection and increased electrophilic substitution character so that bond formation becomes decreasingly synchronous. It appears in the case of R = t-Bu the combination of unavoidably increased sterics and enhanced carbenium ion stabilization switches the mechanisms for a highly asynchronous but still concerted cycloaddition (e.g., Diels-Alder) to a stepwise electrophilic substitution and subsequent ring closure. The term “stepwise” is used with a degree of caution in this context since no TS structures or intermediates were located in either the gas phase or ethereal continuum solution for this process. To the extent that the reaction has an actual free energy of activation, it is likely associated with the displacement of discrete solvent molecules between the indolyne and furan reaction partners that was not included in the computational models used for this analysis.

A very interesting observation was made when we examined the Diels-Alder reaction of the unprotected indolyne **35.1** and cyclopentadiene. We found in this case that the 7-butylindole **35.3** was the major product (Scheme 35).



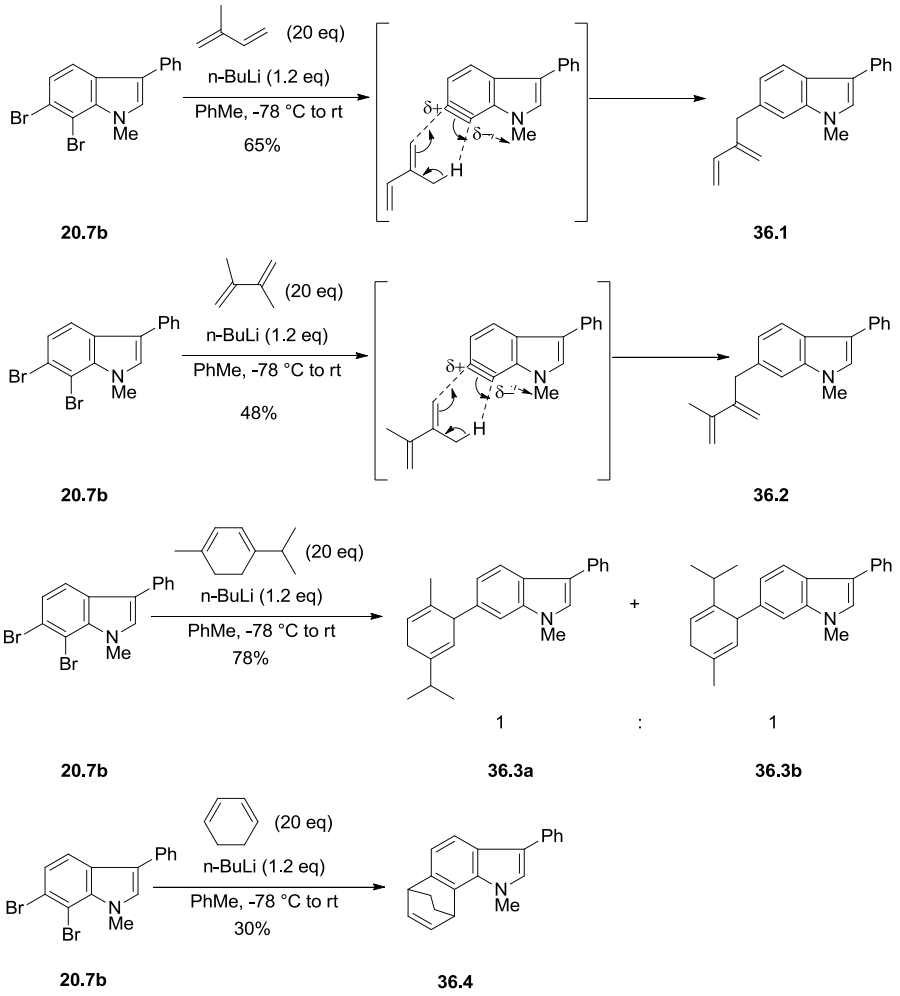
Scheme 35. Different regioselective products.

The same outcome was observed whether an excess amount of n-BuLi was used to deprotonate the indole N-H group, or whether the anion was preformed with NaH, followed by metal-halogen exchange. This results stands in contrast to the observation that 6-butylindole **33.1** was usually the only byproduct when *N*-methylindole **34.6** was the substrate. This interesting observation suggested that the regioselective reaction of 6,7-indolyne and nucleophilic compound could be reversed by the electronic properties of the

nitrogen atom in the indole aromatic ring system. A computational analysis of this phenomenon is underway.

3.2 6,7-Indole Aryne Ene Reaction

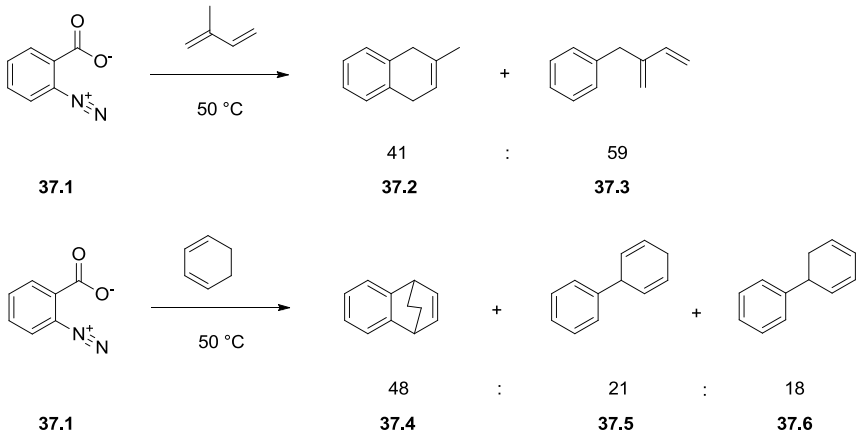
In connection with several other planned total synthesis objectives (e.g., teleocidins), we were interested in examining the behavior of 6,7-indole arynes with acyclic dienes. These cycloaddition partners are known to give different products with benzynes depending on a number of parameters,[33,126] but their reaction with indolynes was clearly not investigated. When we examined the scope of the Diels-Alder reaction between various dienes such as isoprene, 2,3-dimethyl-1,3-butadiene, and α-terpinene and the 6,7-indolyne, we also obtained unexpected results. While we were anticipating the formation of some [4+2] product, it turned out that dienes that possess allylic hydrogens gave only the corresponding ene products as the major component of the complex mixture (Scheme 36). Despite the generally good yields obtained in each case, no Diels-Alder products were identified in these examples. Interestingly we actually obtained about 30% of the Diels-Alder product when we used 1,3-cyclohexadiene instead of α-terpinene.



Scheme 36. Ene reactions between dienes and indolynes.

The reaction between α-terpinene and 6,7-indolyne is especially noteworthy. Although the ene reaction was a fairly common by-product in many Diels-Alder reactions between dienes and benzyne, it always appeared as a minor product when the diene was cyclic.[33,126] Only when allylic olefins are used instead of dienes does the ene reaction with benzyne become a synthetically useful process. There is much literature to support the concerted mechanism for the benzyne ene reaction,[33,127] but there is still no completely satisfactory explanation for the competition between the [4+2] and ene reaction.

Crews reported the cycloaddition of benzyne with isoprene and 1,3-cyclohexadiene (Scheme 37). [33,126]

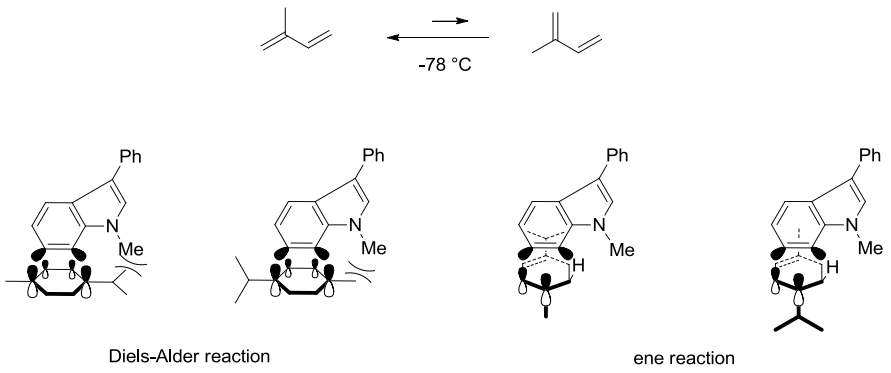


Scheme 37. Crews' results.

This method for benzyne generation required elevated temperatures to decompose the *o*-diazonium carboxylate, and in these cases there was a high percentage of [4+2] products found. Comparing these results to our work in which the indolyne was generated at low temperature (typically aryne formation occurs at approximately -35 °C), we believe that temperature played a important role in the competition between [4+2] and ene reaction. It is well known that the s-trans-butadiene is the much more stable of the two rotamers of 1,3-butadiene, but s-cis butadiene is the one that participates in Diels-Alder reaction. At room temperature, these two isomers will interconvert very rapid, but at -78 ºC, the equilibrium clearly favors the s-trans population. For isoprene, the Crews experiment was conducted at 50 ºC which would give more s-cis diene for Diels-Alder reaction, while our reaction was run at -78 ºC which would favor the ene reaction. For α-terpinene, the ene reaction would let the

diene approach to indolyne from a less stereo chemically hindered position, thus 1,3-cyclohexadiene would favor the Diels-Alder reaction while α-terpinene would favor the ene reaction (Scheme 38).

The regioselectivity in all of the 6,7-indole aryne ene reactions can be rationalized by polarization as shown in Scheme 36.

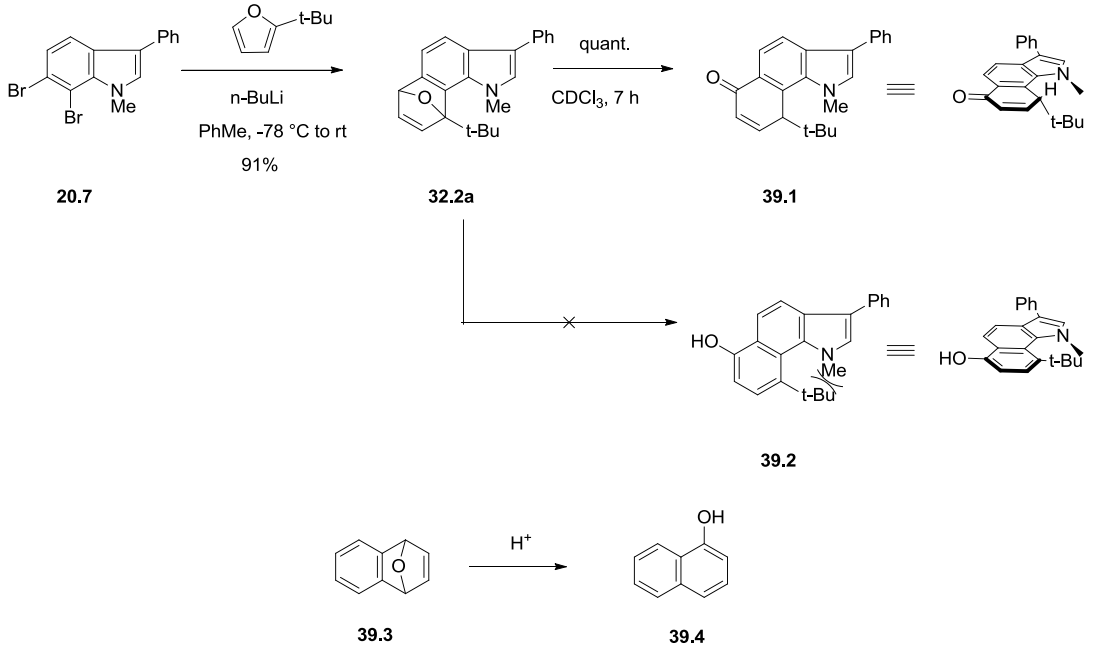


Scheme 38. Proposed explanation for ene vs Diels-Alder.

3.3 Selective Ring Opening Reaction

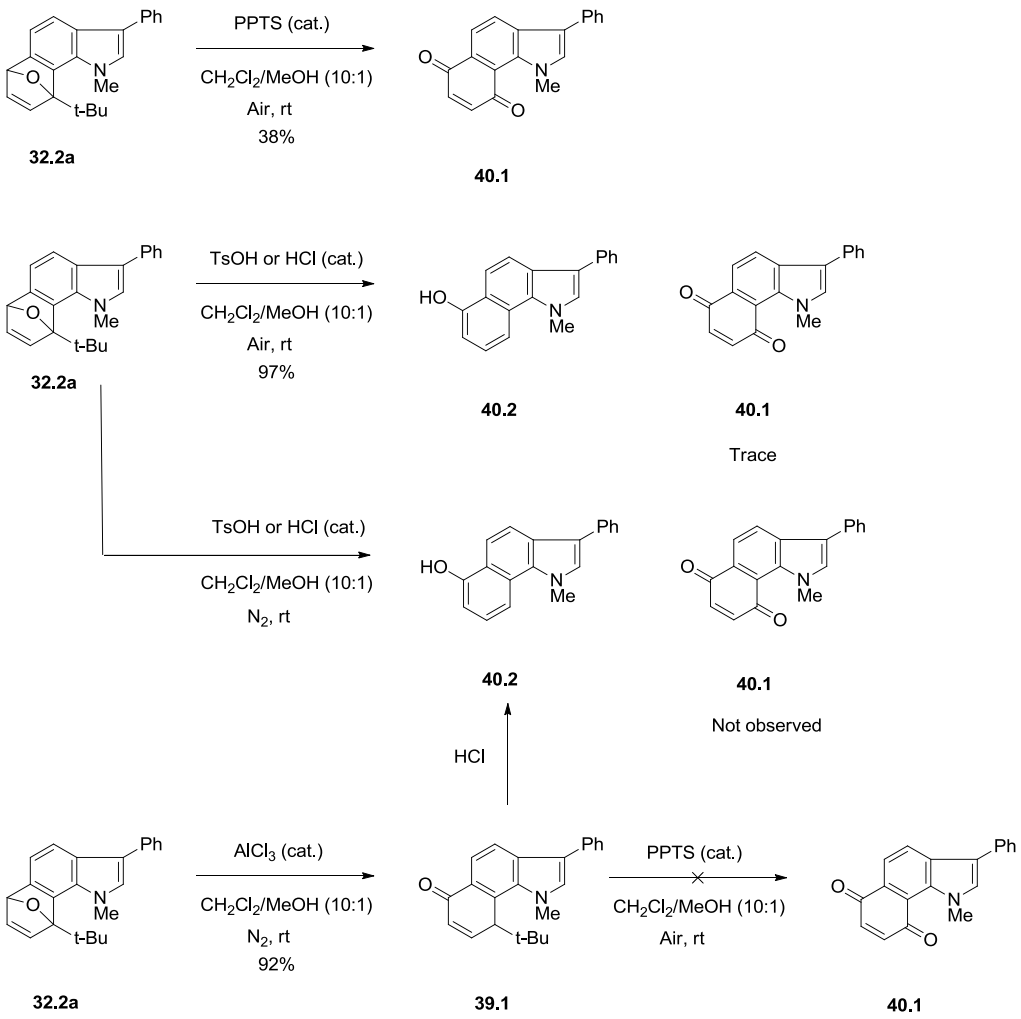
During the research into the Diels-Alder reaction with indolynes, we also found several interesting and potentially useful ring opening and rearrangement reactions with the initial cycloadducts. These phenomena were observed mainly with the products obtained from the 6,7-indole aryne cycloadditions. The first observation came from the 2-*t*-butylfuran cycloadduct **32.2a**. After purification via column chromatography and confirmation of its

identity by NMR, we noticed this compound began to rearrange slowly upon standing in $CDCl_3$. After just ten minutes, a new component was present, which increased in proportion over time. After seven hours compound **32.2a** disappeared and was replaced by a new single compound which was established unequivocally to be the ring opened annulated enone **39.1**.



Scheme 39 Ring opening reaction.

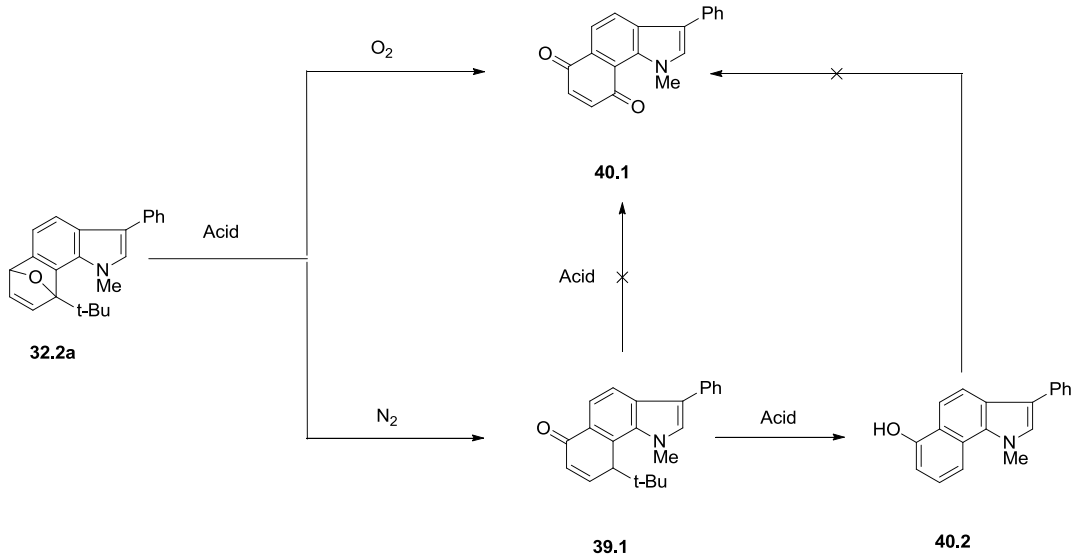
The appearance of **39.1** was unexpected, since the literature regarding the acid catalyzed ring opening of furan Diels-Alder products shows that they normally result in benzannulation to afford naphthalenols **39.4**.[118] In an effort to better understand the mechanism of this process, compound **32.2a** was reacted with various acids under different conditions. The results are summarized in Scheme 40.



Scheme 40. Different ring opening products from different acidic catalysts.

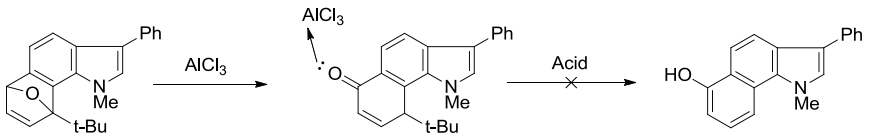
With strong acids such as TsOH or 3M ethereal HCl to open the ring, the initial product was again **39.1** but it reacted further under these conditions and rearranged to the phenol product **40.2**. Giles reported that naphthalenes containing isopropyl and t-butyl substituents in a peri relationship to another substituent are prone to undergo ready protodealkylation.[118] In our case, because of the steric hindrance between the t-butyl group and the N-methyl group, this protodealkylation became even more facile. The appearance of the naphthoquinone byproduct **40.1** was also unexpected, but it can also be explained in terms of

the release of strain with the N-methyl substituent caused by the t-butyl group. Compound **40.1** was only found when the reaction was run in air, and was totally absent when the same experiment was conducted under an inert atmosphere such as nitrogen or argon. Moreover, **40.1** was the only product when PPTS was used as the catalyst but it could not be generated from **39.1** by further acidic catalysis (Scheme 40). Together these data indicate that compounds **40.1** and **40.2** arise from different mechanisms from **32.2a**, and that neither compound **39.1** or **40.2** is intermediate in the pathway that leads to the formation of the naphthquinone (Scheme 41).



Scheme 41. Reaction direction between different products.

Aluminum chloride was an effective catalyst for effecting the transformation of **32.2a** to **39.1** without further rearrangement. Although the reason for this is not fully understood at present, we believe that the coordination of the C=O group to the Lewis acid aluminum chloride somehow prevents further aromatization.



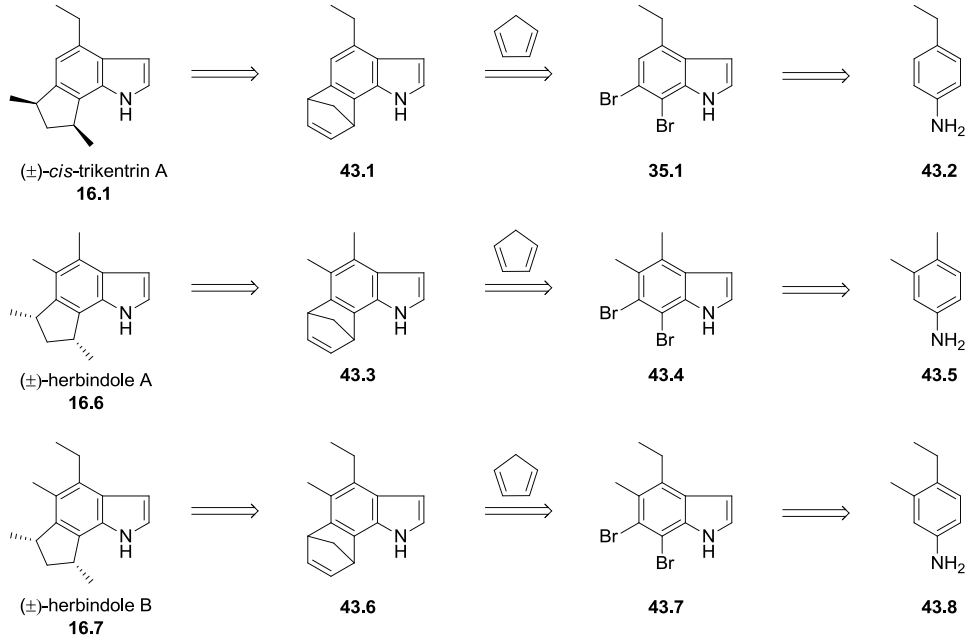
32.2a **39.1** **40.2**

Scheme 42. Coordination between C=O and $AlCl_3$.

CHAPTER 4. APPLICATIONS OF INDOLE ARYNES

4.1 Retrosynthesis and Preliminary Experiments of (±)-*cis*-Trikentrin A and (±)-Herbindole A and B

Since we discovered the new class of aryne derived from all three benzenoid positions of the indole nucleus and obtained their cycloadducts with furan successfully, we wanted to adapt this approach to the synthesis of complex natural products. The annulated indole alkaloid natural products should be especially amenable to this strategy. An intermolecular indolyne cycloaddition approach should provide a rapid entry into annulated indole natural products including *cis*-trikentrin A, herbindole A and herbindole B. The retrosynthetic analyses of these three natural products are very straight forward (Scheme 43).



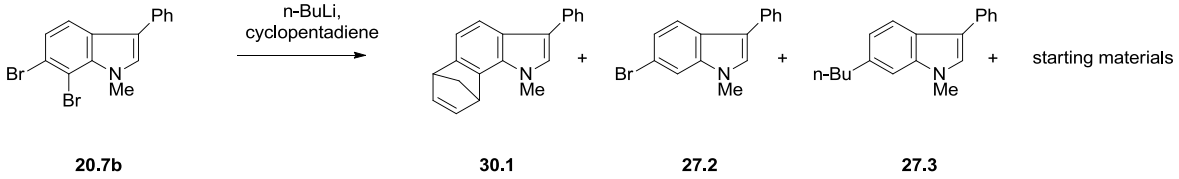
Scheme 43. Retrosynthetic analysis of the (±)-*cis*-trikentrin A, (±)-herbindole A, and (±)-herbindole B.

The annulated *cis*-disubstituted cyclopentane would be installed via the Diels-Alder reaction of cyclopentadiene and 6,7-indole aryne. The aryne precursor, namely, 6,7-dibromoindole, was synthesized via the Bartoli reaction starting from the commercially available aniline.

Before the total syntheses of these natural products were undertaken, a Diels-Alder reaction of the 6,7-indolyne and cyclopentadiene (Cp) was run to optimize this key step. In this preliminary experiment, 6,7-dibromo-1-methyl-3-phenyl-1*H*-indole **20.7b** was chosen as the starting material, and the standard reaction conditions were adopted as before: Thus, the 6,7-dibromoindole was dissolved in ether with 20 eq Cp, cooled to -78 ºC, then treated with 1.1 eq n-BuLi, and the mixture raised to room temperature over 1 h. The first run gave a complex mixture, including 13% cycloadduct **30.1**, 26% of the 6-bromoindole **27.2**, and the remainder mostly starting material.

This result could be rationalized by the competition from acid-base reaction of cyclopentadiene and n-BuLi as Coe found in trihalobenzenes.[113] This acid-base reaction would deprotonate cyclopentadiene leading to the stable aromatic anion, thus suppressing its [4+2] cycloaddition with 6,7-indole arynes. Some improvement was obtained when the concentration of Cp was reduced to 2 eq in order to limit the otherwise favorable kinetics of the acid-base reaction (Table 3, entry 3). Interestingly, it was found that when n-BuLi was added first and allowed to mix with the dibromoindole for 10 minutes prior to Cp addition, almost no cycloadduct was detected, and much more 6-bromoindole was obtained (Table 3**,** entry 2).

Table 3. The yields of cyclopentadiene addition to 6,7-indole aryne under different conditions.[a]



20.7b **30.1** **27.2** **27.3**

Entry	Cp (eq)	n-BuLi (eq)	Solvent	T (ºC)	Yield (%)	Products distribution			
					30.1	**30.1**	**27.2**	**27.3**	**20.7b**
1	20	1.1	Et_2O	-78 to rt	13	13	26	0	61
2	20	1.1	Et_2O	-78 to rt	0 [b]	0	34	0	52
3	2	2	Et_2O	-78 to rt	19	23	49	0	28
4	1.5	1.5	Et_2O	0 to rt	20	12	6	6	48
5	1	1	PhMe	0 to rt	20	46	0	13	41
6	2	2	PhMe	0 to rt	70	70	5	25	0
7	2	2	Petroleum ether	0 to rt	20	58	0	27	14
8	2	2	PhMe	-78 to rt	88	88	0	12	0

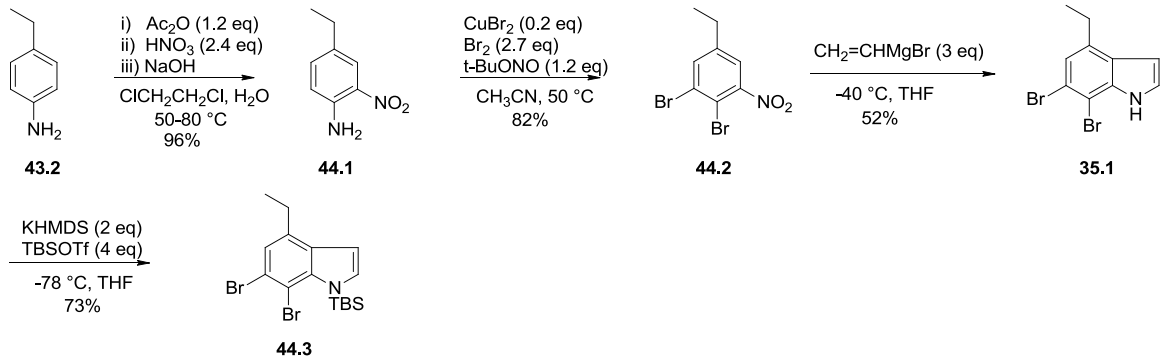
[a] General procedure: The 6,7-dibromoindole and cyclopentadiene (Cp) were dissolved in the indicated solvent, and the temperature lowered to -78ºC in a cold bath (dry ice/acetone), then n-BuLi was added into the mixture and stirred for 30 minutes. The cold bath was removed and the reaction mixture raised to room temperature over 1 h, followed by a standard organic work up. [b] n-BuLi was added at -78ºC, stirred for 10 min, then cyclopentadiene was introduced to the mixture and reacted as usual.

Decreasing the temperature at which the reaction was started reduced the byproduct 6-butylindole **27.3** by generating indole arynes at a lower rate (Table 3, entry 6 and entry 8). The most important factor for this reaction was solvent. After we changed the solvent from diethyl ether to toluene, the yield of cycloadduct increased from 20% to 70% dramatically. Protonation was suppressed in toluene, and the result was a corresponding higher yield of the desired cycloadduct as reported by Coe with simple benzynes. The best yield (88% isolated yield) of **30.1** was obtained with 2 eq cyclopentadiene and 2 eq n-BuLi at -78ºC to rt with toluene as the solvent.

4.2 Synthesis of (±)-*cis*-Trikentrin A

With the key cycloaddition step optimized in a model system, we embarked on the synthesis of (±)-*cis*-trikentrin A. The first objective was the to make the 6,7-dibromoindole precursor. We originally prepared dihaloindoles from the *o*-dihalohydrazines via Fischer indole chemistry. However, repeated efforts to synthesize *o*-dihaloindoles unsubstituted at the 2- and 3-position via Fischer chemistry gave disappointing results. Our revised plan was influenced by Bartoli's observation that such unsubstituted indoles can be obtained in good yields from the reaction of nitrobenzenes and vinyl Grignard reagents.[128-131] The synthesis of trikentrin A thus began with commercially available 4-ethylaniline **43.2** (Scheme 45). Nitration was accomplished in 96% yield in one pot by a literature procedure.[132] Diazotization with t-BuONO followed by bromination catalyzed by $CuBr_2$ was carried out in

82% yield to afford the *o*-dibromide **45.2**.[133] Application of the Bartoli indole synthesis ($CH_2CHMgBr$, 3 equiv; THF, -40 °C) proceeded uneventfully and gave the desired indole **35.1** in 52% yield.

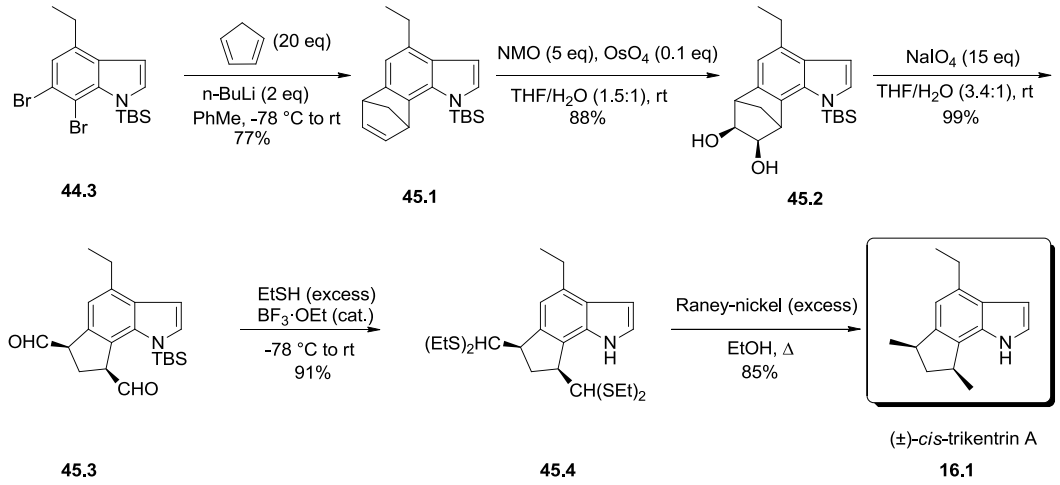


Scheme 44. *cis*-Trikentrin A: Bartoli indole synthesis.

In other cases reported by Bartoli, highly variable yields were found only with *o*-substituted nitrobenzenes. We were able to find only a few other examples of trisubstutited nitrobenzenes and no examples of 2,3-dihalo nitrobenzenes used in this procedure.[128] By comparison, the best indole synthesis yield reported by Bartoli is 67% with 2-methyl nitrobenzene.[131] The N-H group of the indole was then protected as its TBS group (KHMDS, TBSOTf, THF, -78°C) in 73% yield. Attempts to carry out the cycloaddition with the unprotected indole N-H or its anion with various simple counterions (Li^+, Na^+) met with failure.

The Diels-Alder reaction between the N-protected indolyne precursor **45.3** with Cp under the optimized reaction conditions in toluene smoothly and cleanly gave the desired cycloadduct **46.1** in 77% isolated yield. Osmylation of **46.1** (cat. OsO_4/NMO, THF/H_2O, 9:1) followed by oxidative cleavage of the diol **46.2** ($NaIO_4$, THF/H_2O (3:1)) afforded the

dialdehyde **46.3** in 87% yield for the two steps. Several methods were attempted for converting the dialdehyde into the required cis dimethyl groups, including Wolff-Kishner reduction, without success. Finally, **46.3** was converted into its corresponding dithioacetal **46.4** (excess EtSH, $BF_3 \cdot OEt_2$, -78 °C) with concomitant desilylation in 91% yield. Raney nickel reduction afforded in nine steps synthetic (±)-*cis*-trikentrin A, which was identical in all respects to the physical data reported for this racemic compound.[76]

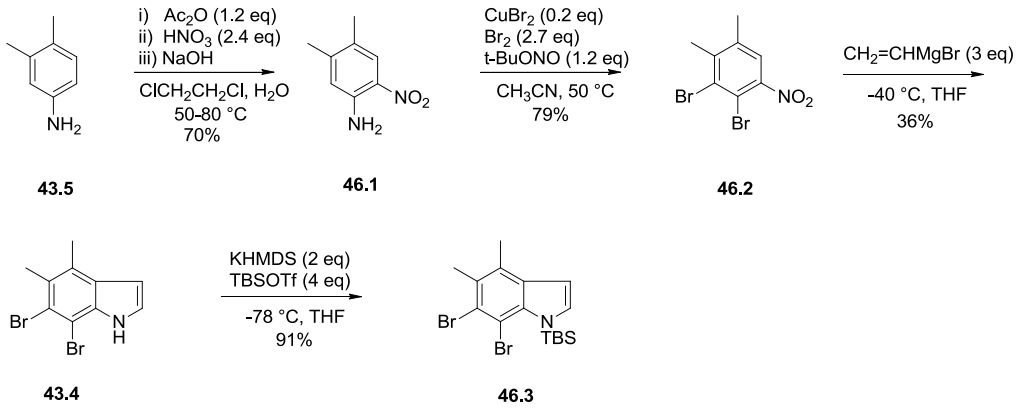


Scheme 45. *cis*-Trikentrin A: 6,7-indolyne tactic.

4.3 Synthesis of (±)-Herbindole A

Encouraged by the success with the trikentrin synthesis, we turned our attention to the total synthesis of the structurally related herbindole A (Scheme 46). The synthesis of herbindole A entirely parallels that of of *cis*-trikentrin A. The intriguing issue presented by

this synthesis was whether for electronic and steric reasons the required tetrasubstituted nitrobenzene would be viable as a substrate in the key Bartoli step.



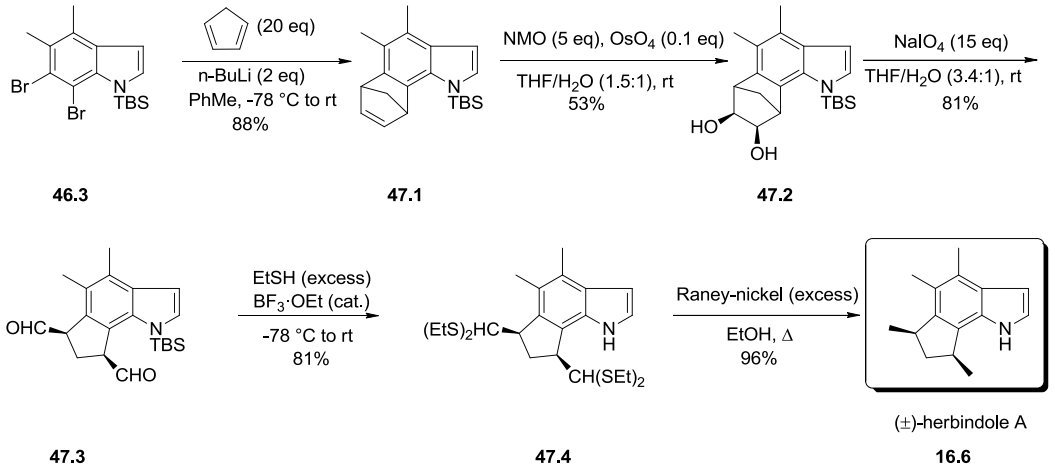
Scheme 46. Herbindole A: Bartoli indole synthesis.

Starting this time with commercially available 3,4-dimethylaniline **43.5**, a highly regioselective nitration procedure as described above gave the desired compound **46.1** in 70% yield, with the remaining material consisting mainly of the other easily separated nitroaniline isomer. Diazotization and bromination as before gave the *o*-dibromide **46.2** in 79% yield. Gratifyingly, the Bartoli protocol afforded the desired indole **43.4** albeit in a modest 36% yield. Although this example gave a lower yield than with trikentrin A (36% vs 52%), we ascribe this observation to the greater substitution of the nitrobenzene. Although generalizations are not possible with the Bartoli chemistry it is known that this process is highly sensitive to substitution patterns and substituent effects. Accordingly, yields with various substitution patterns as reported by that investigator occur over a wide range, and in most cases are well below 40%. Electron donating groups (i.e., alkyl) appear to exacerbate this effect. The remaining steps have mostly comparable yields to the trikentrin A effort.

Although attempts to improve the yield by modifying the reaction conditions proved

ineffective, it is important to note that there is only one other report in the literature of polysubstituted nitrobenzenes participating in this reaction, with much lower yields.[87] The presence of the bromine substitutents in our case appears to attenuate the apparently adverse electronic effects due to the remaining meta and para methyl substituents. N-silylation as shown above gave the desired TBS-protected 6,7-indolyne precursor **46.3** in 91% yield.

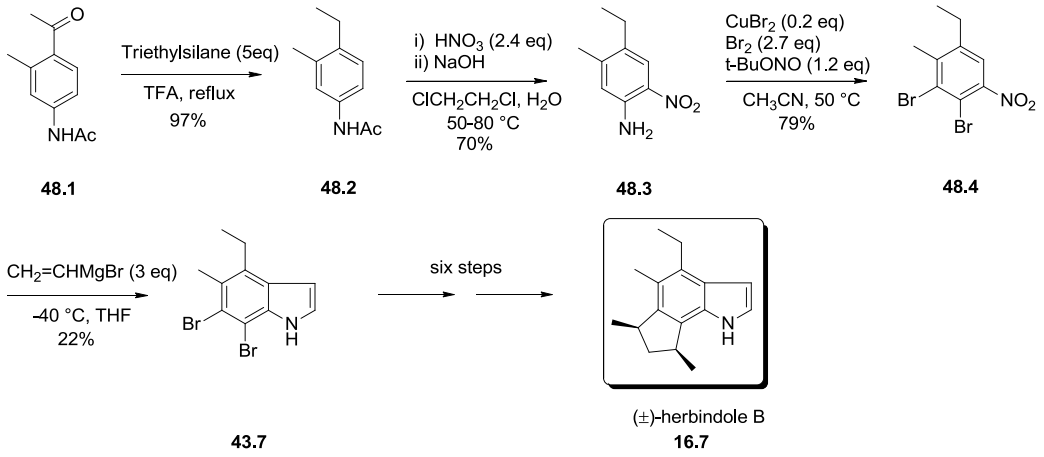
With the desired aryne precursor in hand, generation of the 6,7-indolyne followed by the Diels-Alder reaction gave the cycloadduct **47.1** in an even higher 88% yield than observed with trikentrin (Scheme 47). Compound **47.1** was carried through to the target as described above. Thus oxidative cleavage (43%, two steps), thioacetalization (81%), and Raney nickel reduction (96%) afforded racemic herbindole A in nine steps from the aniline **43.5**. Herbindole A also exhibited the same physical and spectroscopic data (except for optical rotation) as that reported for the authentic samples.



Scheme 47. Herbindole A: 6,7-indolyne tactic.

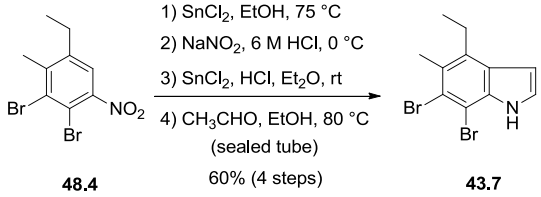
4.4 Attempted Synthesis of (±)-Herbindole B

Finally, we observed in the case of herbindole B that increasing the electron density of the aromatic ring still further results in an even lower yield of the Bartoli indole product (Scheme 48).



Scheme 48. Attempt for herbindole B synthesis.

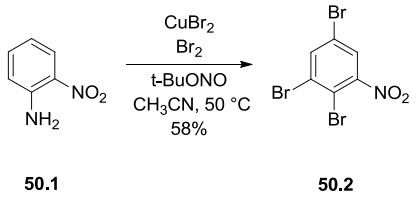
As noted above multiple electron-donating groups appear to exacerbate this effect to an even greater extent. It has been observed by Blechert that the application of the Bartoli protocol to highly substituted alkyl nitrobenzenes gives very low yields of the desired indole system and thus appears to represent a limitation of the use of this methodology.[87] However, by carrying **48.4** through an alternate Fischer indole regime (Scheme 49), the overall yield of the desired indole **43.7** is improved to 60% for the four synthetic operations.



Scheme 49. Fischer indole synthesis.

4.5 Second-Generation Synthesis of (±)-*cis*-Trikentrin A and Applications to Library Development

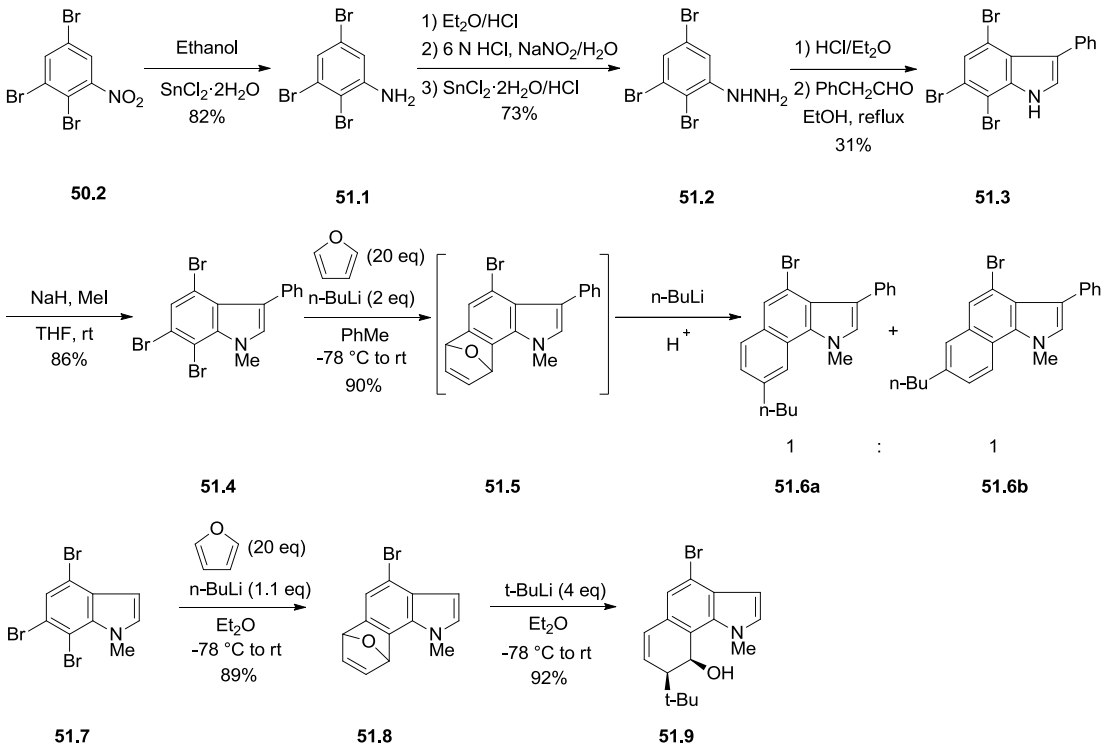
During the course of our investigations toward the total synthesis of (±)-*cis*-trikentrin A, the 1,2,5-tribromo-3-nitrobenzene **50.2** was incidentally found in a one pot reaction with good yield (Scheme 50). It occurred to us that it might be possible in this system to generate selectively the 6,7-indole aryne via metal-halogen exchange while leaving the 4-bromo position intact. That position in turn could be used to effect a Negishi cross-coupling reaction to install the required ethyl group thereby providing an alternate and shorter route to the trikentrins. More generally, this approach could be used with other metal-catalyzed cross-coupling reactions (e.g., Suzuki-Miyaura and Buchwald-Hartwig) to create a library of trikentrin analogues that would be subjected to biological evaluation.



Scheme 50. Tribromonitrobenzene formation.

As a test of these strategies, the tribromonitrobenzene **50.2** was converted to the 4,6,7-tribromoindole (Scheme 51). Thus, **50.2** was first reduced to the tribromonoaniline **51.1** (EtOH, $SnCl_2$ dihydrate, 5 eq, 70 °C, 82%) followed by conversion to the hydrazine **51.2** (10 eq ethereal HCl; 1.1 eq $NaNO_2$, 6 N HCl; $SnCl_2$ dihydrate, 3 eq, conc. HCl, 0 °C; 73% for three steps). Application of the Fischer-indole synthesis to **51.2** (protonation with ethereal

HCl; $PhCH_2CHO$, 2 eq, refluxing EtOH, 2 h) gave the desired indole, but in only 31% yield. Finally, the indole nitrogen was protected as its N-methyl group (86%).



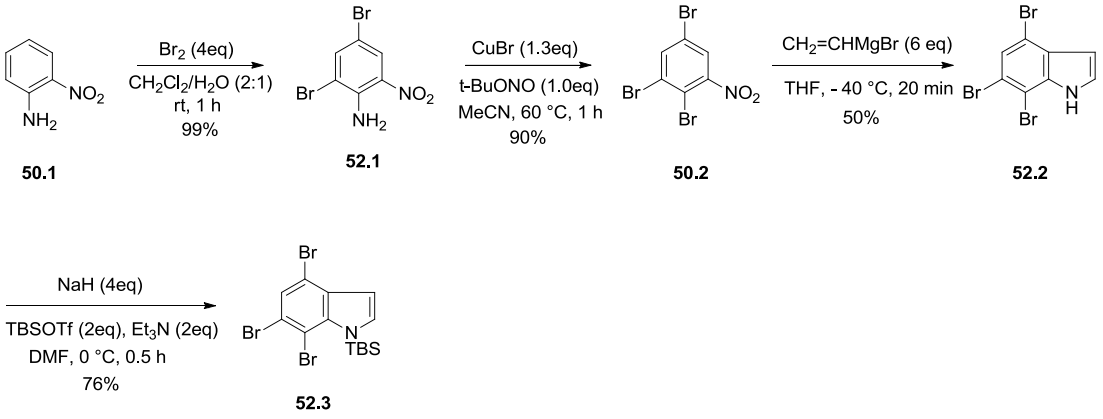
Scheme 51. Regioselective Li-Bromo exchange and indolyne formation.

We were delighted to find that the 4,6,7-tribromo-1-methyl-3-phenyl-1*H*-indole **51.4** reacted with n-BuLi and furan to generate cycloadduct **51.5**, and without any apparent evidence of metal-halogen exchange at C4. Compound **51.5** was not stable to the reaction conditions, and was readily attacked by excess n-BuLi, and after aromatization by the addition of a trace of acid, produced the ring opened products **51.6a** and **51.6b** in a 1:1 ratio in a combined 90% yield. From these data, we can see that the 6,7-indolyne can be generated exclusively with the 4-bromo position untouched. This is a previously unknown phenomenon in these systems.

A more gratifying result was observed when we subjected **51.7** to our indolyne-forming

conditions with only 1.1 eq n-BuLi. The corresponding cycloadduct **51.8** was cleanly formed and isolated in 89% yield, again with no evidence of additional metal–halogen exchange occurring at C-4. Indeed, efforts to force metal–halogen exchange at the 4-bromoindole position with an excess of t-BuLi gave only the ring-opened product **51.9** in excellent yield via regio and exoselective attack by the alkyllithium.

Application of this chemistry led to a second-generation synthesis to trikentrin A, and offers a highly flexible approach to potential trikentrin libraries.[69] Thus inexpensive *o*-nitroaniline **50.1** was brominated [Br_2 (4 eq), CH_2Cl_2/MeOH (2:1), rt, 1 h] in nearly quantitative yield to give 4,6-dibromo-2-nitroaniline **52.1**. Subsequent diazotization of this aniline with a stoichiometric amount of cupric bromide [$CuBr_2$ (1.3 eq), t-BuONO (1.0 eq), MeCN, 60 ºC, 1 h] afforded the 2,3,5-tribromonitrobenzene **50.2** in 90% yield consistently on a multi-gram (5-10 g) scale.

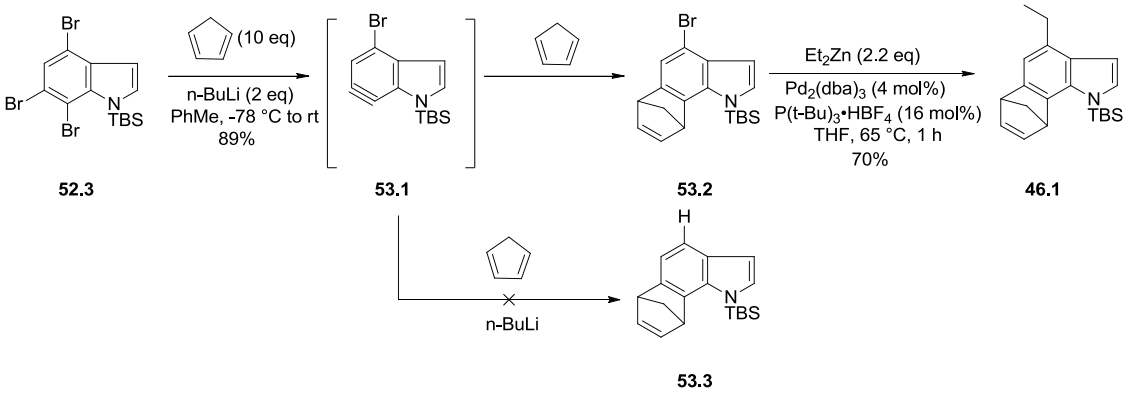


Scheme 52. Synthesis of the 4,6,7-tribromoindole scaffold.

Application of the Bartoli indole synthesis to **50.2** (vinyl Grignard, 6 eq; THF, -40 ºC, 20 min) on a 5-gram scale gave cleanly a very respectable 50% yield of the desired

4,6,7-tribromoindole **52.2**. Finally, protection of the indole N–H group as its TBS ether **52.3** was accomplished in 78% yield with NaH (4.0 eq), TBSOTf (2.0 eq), and Et_3N (2.0 eq) in DMF at 0 ºC for 0.5 h.

As noted earlier, reaction of **52.3** with n-BuLi in PhMe at -78 ºC presumably resulted in selective metal–halogen exchange at C-7 and elimination to give the 4-bromo-6,7-indolyne **53.1**, which was trapped with cyclopentadiene to afford the desired 4-bromoindole **53.2** in 89% yield.

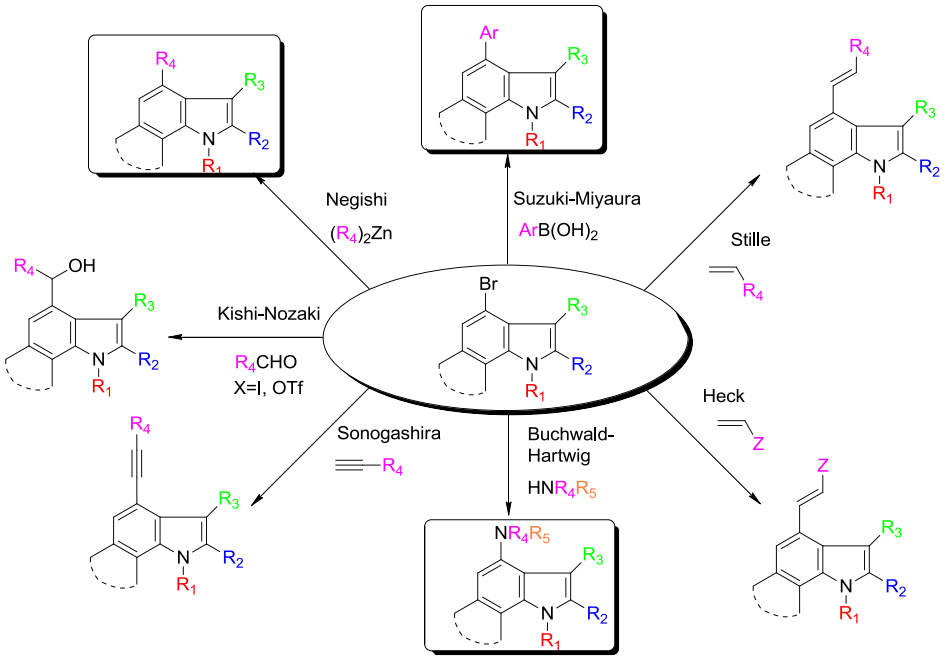


Scheme 53. Tandem 6,7-indolyne cycloaddition/Negishi cross-coupling.

Although the possibility of some metal–halogen exchange occurring at the 4-bromo position cannot be rigorously excluded at this time, it is important to note that no evidence for the formation of compound **53.3** has been found thus far. Application of the Negishi cross-coupling [Et_2Zn, 2.2 eq; $Pd_2(dba)_3$ (4 mol %); $P(t\text{-}Bu)_3 \cdot HBF_4$ (16 mol %); THF, 60 ºC, 1 h] afforded the desired product **46.1** in 70% yield. The use of the somewhat more exotic Fu catalyst/ligand combination[134-136] was found to be the best conditions in this case to achieve the optimal yield of the 4-ethylindole. This intermediate is identical in all respects to that

synthesized by our first-generation method beginning with 4-ethylaniline, and thus constitutes a formal total synthesis of (±)-*cis*-trikentrin A, as well as the shortest route to this target reported to date.

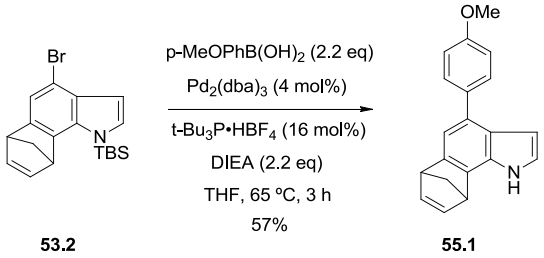
The ability to exploit this reaction orthogonality in the 4,6,7-tribromoindole system makes it a potentially valuable scaffold for the construction of trikentrin libraries using a general tandem 6,7-indolyne cycloaddition/cross-coupling strategy as depicted in Scheme 54.



Scheme 54. Cross-coupling manifolds in the 4-bromoindole scaffold.

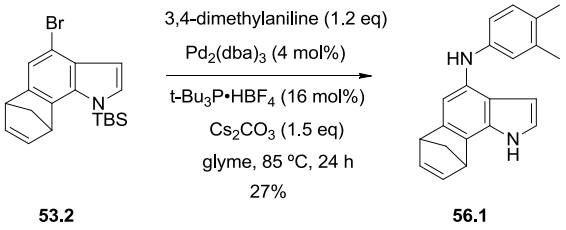
Thus it should be possible to effect a tandem cycloaddition/cross-coupling sequence with a variety of dienes and electrophiles for the subsequent transition metal-catalyzed cross-coupling reactions. The range of useful reactions include the Negishi as noted above, Suzuki-Miyaura (with boronic acids), Stille (vinyl tin), Heck (vinyl), Buchwald-Hartwig (amines), and Sonogashira (terminal alkynes). If either I or OTf is substituted for Br, then the

Nozaki-Hiyama-Kishi (NHK) reaction (aldehydes) becomes an additional possibility. We have already provided a proof-of-concept for two other manifolds in addition to the Negishi reaction. For example, coupling a boronic acid to **53.2** in the Suzuki–Miyaura reaction gave a good yield of the desired product **55.1** (Scheme 55), while the use of an aniline afforded the corresponding Buchwald–Hartwig coupled product **56.1**, albeit in modest yield (Scheme 56).



53.2 **55.1**

Scheme 55. Suzuki–Miyaura coupling with 4-bromoindoles.



53.2 **56.1**

Scheme 56. Buchwald–Hartwig coupling of anilines with 4-bromoindoles.

In both cases, the cross-coupling event proceeded with concomitant loss the N-silyl protecting group. This unexpected outcome is advantageous in that it saves a deprotection step, and allows for the subsequent introduction of further diversity elements, for example, by way of N-alkylation or N-acylation. The yields of each reaction deserve comment. While the yield of product for the Negishi reaction is certainly respectable, the first attempts at the Suzuki–Miyaura and Buchwald–Hartwig cases gave disappointing results. Both are much

lower than would be expected for simple cross-coupling reactions with an aryl bromide. This observation required us, after much experimentation, to finally adopt the less conventional catalyst and ligand combinations to achieve even the stated yields. Although cross-coupling reactions with haloindoles are certainly precedented,[137] their yields, along with other heteroarenes, tend to be highly variable, and usually low.[138] In our systems, annulation leads to a more electron-rich bromoarene, and this factor is also known to suppress yields in many cases.

The reaction conditions for the Suzuki-Miyaura and Buchwald-Hartwig reactions have since been improved. The same catalyst is employed in each case, but the use of new ligand and base combinations gave superior yields in both cross-coupling manifolds. This development recently led to the production of a 93-member annulated indole library based on this methodology.[139]

CHAPTER 5. CONCLUSIONS

In conclusion, we discovered a new class of aryne based on the ubiquitous indole nucleus. The unique properties and reaction profiles of the indole arynes (aka indolynes), and of the 6,7-indole aryne in particular, have been used to great advantage in both natural products total synthesis and natural products-inspired library development, among other things. This work has resulted in several important "firsts" for the field of organic chemistry. We provided the first evidence for the existence of all three isomeric indole arynes in the benzenoid core using a practical and general method for their synthesis via metal-halogen exchange with n-BuLi in the corresponding *o*-dibromides, followed by elimination. The facile generation of aryne indoles from *o*-dibromoindoles is noteworthy for its synthetic simplicity and high yields. We found that the 5,6- and 6,7-indole arynes can also be easily and selectively generated from the same 5,6-difluoroindole depending on the solvent and choice of base. These discoveries alone suggest that indoles can now be considered important and versatile members of the suite of aromatic systems from which arynes can be easily generated.

We provided the first examples of the completely regio- and exoselective ring opening of the furan cycloadducts from 6,7-indolynes with alkyllithium reagents. We also provided the first experimental evidence that the 6,7-indole aryne, but not the 4,5- and 5,6-indolynes, undergoes highly regioselective, contrasteric Diels-Alder cycloaddition reactions with 2-substituted furans. We found that the 6,7-indolyne/furan cycloadducts can

be induced to undergo various rearrangement reactions to afford several additionally useful compounds such as annulated enones, indolobenzoquinones, and benzannulated phenols. We also demonstrated that 6,7-indole arynes react with allylic acyclic dienes to give predictably either predominantly ene products, or regioselective contrasteric Diels-Alder products, depending on the position of the allylic substituent.

We conducted in collaboration with the University of Minnesota the first theoretical and computational study of the indole arynes which revealed that the 6,7-indolyne in particular is a highly polarized system that reacts in a concerted manner but with substantially electrophilic substitution character.

We provided the first natural products total synthesis application of the indole arynes by completing concise total syntheses of the deceptively simple, biologically important indole alkaloids (±)-*cis*-trikentrin A, and (±)-herbindole A and B. This work demonstrated the power and synthetic utility of the indole aryne cyloaddition reaction to readily access annulated indole natural products. This approach combined with the Bartoli indole synthesis provides for an especially efficient synthesis of the trikentrins and herbindoles.

Finally, we were the first to demonstrate a useful and practical reaction orthogonality regime in arynes derived from tribromoindoles. In this manner we established that 6,7-indole arynes can be generated selectively from 4,6,7-tribromoindoles, followed by cycloaddition, leaving the unreacted 4-bromo position available for subsequent reactions such as cross-coupling. This work led to a shorter and more efficient second-generation synthesis of cis-trikentrin A. More significantly, it opened the door for the design and synthesis of natural

product-like libraries using this strategy. This heretofore unrecognized reaction orthogonality renders the 4,6,7-tribromoindole a versatile platform for the total synthesis of natural products, and holds enormous potential for the construction of diverse small-molecule libraries for use in drug discovery.

CHAPTER 6. EXPERIMENTAL SECTION

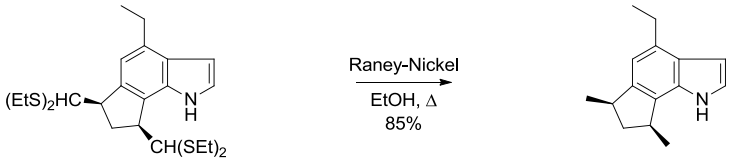
6.1 General Details

^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded with a Varian Nova-400 spectrometer, with the samples in $CDCl_3$ unless otherwise noted, with reference to residual solvent at δ 7.24 ppm and 77.0 ppm, respectively.

Melting Points reported are uncorrected.

Unless otherwise noted, all commercially obtained starting materials were used as received. Dichloromethane and toluene were distilled from calcium hydride under nitrogen prior to use. THF and diethyl ether were distilled from sodium benzophenone ketyl under nitrogen prior to use.

6.2 Experiment Procedures



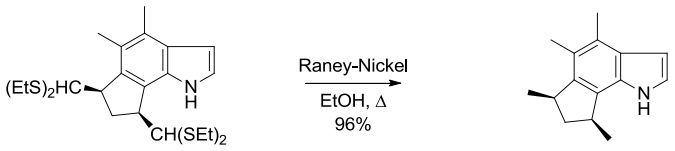
(±)-*cis*-trikentrin A

45.4 **16.1**

(±)-*cis*-trikentrin A (16.1): In a 100 mL round-bottom flask was added a solution of 88 mg (0.19 mmol) of (±)-6,8-bis(bis(ethylthio)methyl)-4-ethyl-1,6,7,8-tetrahydrocyclopenta-[*g*]indole **45.4** in 40 mL ethanol. To the stirring solution was added 2 g of Raney-Nickel (2800, Aldrich). The resulting suspension was heated to reflux and monitored by TLC. After 20 min, TLC analysis showed complete conversion and the mixture was cooled to room temperature and filtered through a pad of celite. The residue was washed with methanol (3 x 30 mL) and diethyl ether (1 x 50 mL). The combined filtrate was concentrated under reduced pressure, and the crude material was purified by passing through a plug of silica gel and eluting with 40% ethyl acetate in hexanes to give 35 mg (85%) of the title compound as a slowly darkening oil.

^{1}H-NMR and ^{13}C-NMR match those reported in the literature.

HRMS (EI) *m/e* calcd for $C_{15}H_{19}N$ 213.1519, found 213.1518.



47.4 (±)-herbindole A 16.6

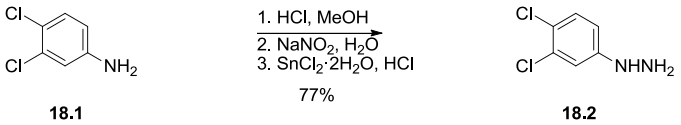
(±)-Herbindole A (16.6): See (±)-*cis*-trikentrin A **(16.1)**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (bs, 1H), 7.13-7.11 (m, 1H), 6.55-6.54 (m, 1H), 3.48-3.38 (m, 2H), 2.73-2.62 (m, 2H), 2.46 (s, 3H), 2.32 (s, 3H), 1.44 (d, *J*= 7.2 Hz, 3H), 1.34 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0, 130.4, 127.7, 126.6, 126.4, 123.2, 122.8, 101.6, 41.8, 39.1, 37.1, 23.8, 22.8, 15.5, 15.3.

HRMS (EI) m/e calcd for $C_{15}H_{19}N$ 213.1519, found 213.1519.

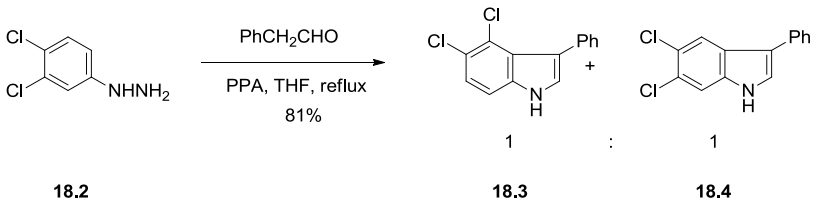
Mp = 88-91 °C.



18.1 18.2

3,4-Dichlorophenylhydrazine (18.2): In a 50 mL round-bottom flask was added 1 g (6.16 mmol) of 3,4-dicholoroaniline. This was dissolved in 15 mL of methanol with stirring. To the stirring solution was carefully added 8 mL (12 N, 96 mmol) of concentrated hydrochloric acid. The solution was then evaporated under reduced pressure to give a white powder. To the white powder was added dropwise a solution of 460 mg (6.66 mmol, 1.1 eq) $NaNO_2$ in 4 mL water at 0 ^oC. The solution was stirred for 20 min at this temperature, and then a solution of 4.3 g (19.02 mmol, 3 eq) stannous chloride dihydrate in 10 mL concentrated hydrochloric acid was added dropwise. The resulting mixture was left to stand in the refrigerator (ca. 4 ^oC) for 6 h, after which time the white precipitate was filtered and washed with three 50 mL portions of 20% ether in hexanes. The solid was added to 200 mL of 10% aqueous NaOH and 133 mL ether. The biphasic mixture was stirred for 1 h after which time the phases were separated and the aqueous layer washed with another two 50 mL portions of ether. The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure to give 842 mg (77%) of the title compound as a yellow solid.

^1H NMR (400 MHz, $CDCl_3$) δ 7.36-7.11 (m, 1H), 6.93 (s, 1H), 6.61 (d, J = 7.2 Hz, 1H), 5.21(bs, 1H), 3.55 (bs, 2H).



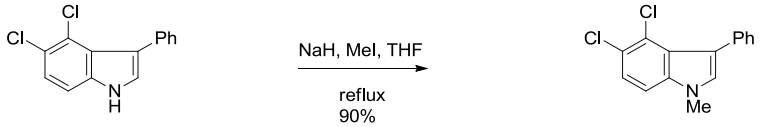
18.2 **18.3** **18.4**

4,5-Dichloro-3-phenyl-1*H*-indole (18.3): In a 50 mL round-bottom flask under nitrogen was added 50 mg (0.28 mmol) of 3,4-dichlorophenylhydrazine. This was dissolved in 5 mL dry THF. To the stirring solution was added 31 μL (0.28 mmol, 1 eq) of phenylacetaldehyde and 1 g polyphosphoric acid. The mixture was heated to reflux under nitrogen atmosphere for 2 h, then concentrated under reduced pressure and immediately separated via column chromatography on silica gel using 15% ethyl acetate/hexanes as the eluent to give 30.1 mg (40%) of the title compound as a yellow solid and 30.1 mg (40%) of 5,6-dichloro-3-phenyl-1*H*-indole as well.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (bs, 1H), 7.50-7.43 (m, 2H), 7.41-7.31 (m, 3H), 7.30-7.25 (m, 2H), 7.18 (d, J = 2.5 Hz, 1H).

5,6-Dichloro-3-phenyl-1*H*-indole (18.4):

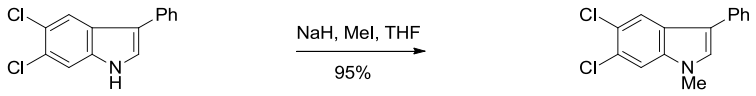
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (bs, 1H), 7.84 (s, 1H), 7.45 (apparent d, J = 7.2 Hz, 2H), 7.39 (s, 1H), 7.32 (apparent t, J = 7.7 Hz, 2H), 7.21-7.15 (m, 1H), 7.12 (s, 1H).



18.3 18.5

4,5-Dichloro-1-methyl-3-phenyl-1*H*-indole (18.5): In a 25 mL flame-dried round-bottom flask under nitrogen was added 135 mg (0.51 mmol) of 4,5-dichloro-3-phenyl-1*H*-indole. This was dissolved in 2 mL dry THF and to the solution was added 14.7 mg (0.61 mmol, 1.2 eq) of dry sodium hydride. The solution was stirred at room temperature for 30 min, and then 63 μL (1.02 mmol, 2.0 eq) of iodomethane was added via syringe. The resulting solution was stirred for 2 h and refluxed for another 30 min, and then quenched by dropwise addition of 10 mL water. The aqueous mixture was extracted with three portions of 25 mL diethyl ether. The combined organic layers were washed with brine (10 mL), dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was then purified via column chromatography on silica gel using 20% ethyl acetate/hexanes as eluent to give 126 mg (90%) of the title compound as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.42 (m, 2H), 7.40-7.28 (m, 4H), 7.18 (d, J = 8.7 Hz, 1H), 7.04 (s, 1H), 3.80 (s, 3H).

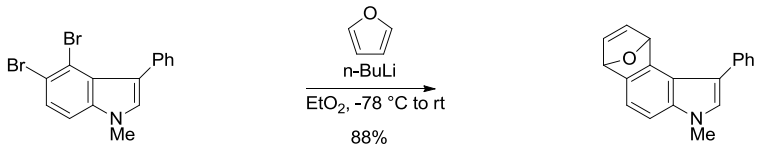


18.4 18.6

5,6-Dichloro-1-methyl-3-phenyl-1*H*-indole (18.6): In a 25 mL flame-dried round-bottom flask under nitrogen was added 65.2 mg (0.25 mmol) of 5,6-dichloro-3-phenyl-1*H*-indole. This was dissolved in 2 mL dry THF and to the solution was added 7.2 mg (0.3 mmol, 1.2 eq) of dry sodium hydride. The solution was stirred at room temperature for 30 min, then 31 μL (0.5 mmol, 2.0 eq) of iodomethane was added via syringe. The resulting solution was stirred for 2 h, and then quenched by dropwise addition of 10 mL water. The aqueous mixture was extracted with three portions of 25 mL diethyl ether. The combined organic layers were washed with brine (10 mL), dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was then purified via column chromatography on silica gel using 20% ethyl acetate/hexanes as eluent to give 65.8 mg (95%) of the title compound as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.58-7.52 (m, 2H), 7.45-7.40 (m, 3H), 7.32 -7.25 (m, 1H), 7.21 (s, 1H), 3.78 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 136.40, 134.56, 129.09, 128.32, 127.33, 126.43, 125.88, 125.86, 124.10, 121.01, 116.62, 111.20, 33.24.



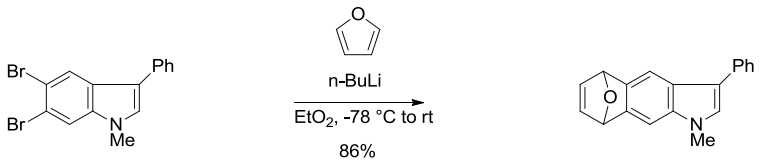
20.5 **19.2**

3-methyl-1-phenyl-6,9-dihydro-3*H*-6,9-epoxybenzo[*e*]indole (19.2):

See 1-methyl-3-phenyl-6,9-dihydro-1*H*-6,9-epoxybenzo[*g*]indole (**22.2**)

^{1}H NMR (400 MHz, CD_3CN) δ 7.46-7.51 (m, 4 H), 7.24-7.34 (m, 4 H), 7.18 (dd, *J* = 1.6 Hz and 5.6 Hz, 1 H), 7.00 (d, *J* =8.0 Hz, 1 H), 5.87 (bs, 1 H), 5.76 (s, 1 H), 3.77 (s, 3 H)

HRMS (EI) m/e calcd for $C_{19}H_{15}NO$ 273.1154, found 273.1159.



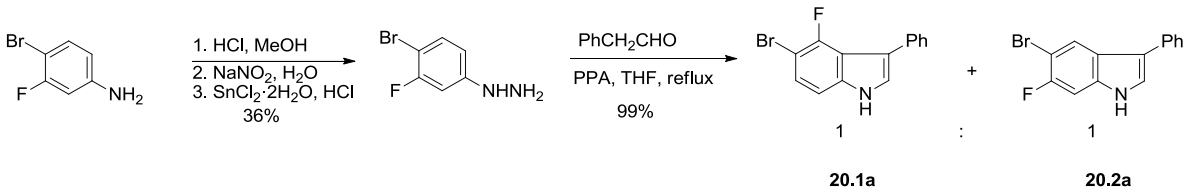
20.6 **19.4**

1-methyl-3-phenyl-5,8-dihydro-1*H*-5,8-epoxybenzo[*f*]indole (19.4):

See 1-methyl-3-phenyl-6,9-dihydro-1*H*-6,9-epoxybenzo[*g*]indole (**22.2**).

^{1}H NMR (400 MHz, CD_3CN) δ 7.72(s, 1H), 7.61 (d, J = 7.6 Hz, 2 H), 7.42 (t, J = 8.0 Hz, 2 H), 7.34 (m, 2 H), 7.24 (apparent t, J = 7.6 Hz, 1 H), 7.01 (s, 2 H), 5.73 (s, 1 H), 5.70 (s, 1 H), 3.78 (s, 3 H)

HRMS (EI) m/e calcd for $C_{19}H_{15}NO$ 273.1154, found 273.1157.



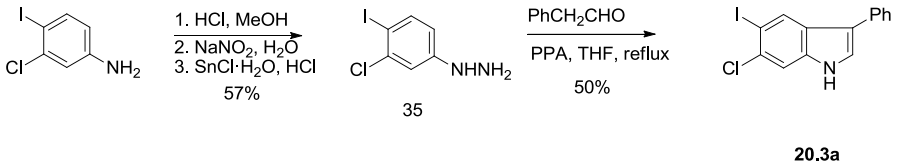
5-bromo-4-fluoro-3-phenyl-*1H*-indole (20.1a):

See 5,6-Dichloro-3-phenyl-1*H*-indole (**18.4)**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (bs, 1H), 7.62-7.56 (m, 2H), 7.47-7.21 (m, 5H), 7.10 (dd, J = 8.6, 3.4 Hz, 1H).

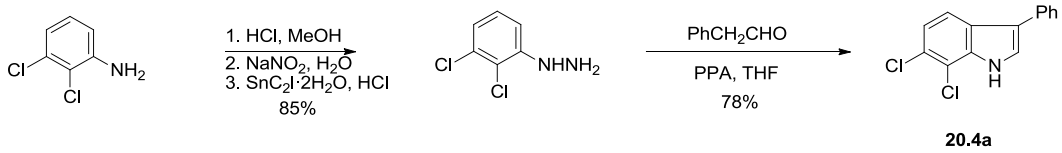
5-bromo-6-fluoro-3-phenyl-*1H*-indole (20.2a):

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (bs, 1H), 8.03 (d, J = 6.7 Hz, 1H), 7.62-7.54 (m, 2H), 7.49-7.40 (m, 2H), 7.37-7.27 (m, 2H), 7.19 (dd, J = 8.9, 0.8 Hz, 1H).



6-chloro-5-iodo-3-phenyl-1*H*-indole (20.3a): See 5,6-Dichloro-3-phenyl-1*H*-indole (**18.4)**.

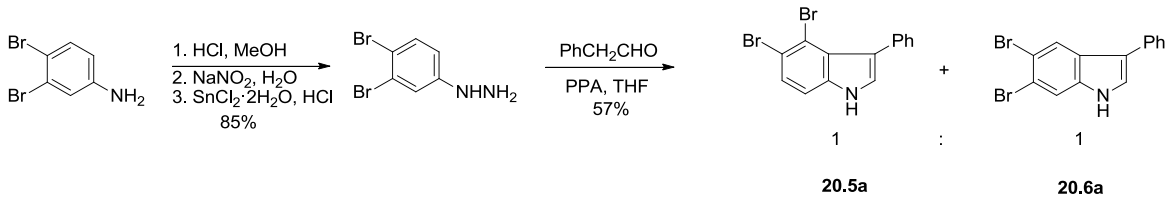
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (bs, 1H), 7.64 (d, J = 8.6 Hz, 1H), 7.48-7.41 (m, 2H), 7.40-7.32 (m, 3H), 7.14 (s, 1H), 7.09 (d, J = 8.6 Hz, 1H).



20.4a

6,7-dichloro-3-phenyl-*1H*-indole (20.4a): See 5,6-Dichloro-3-phenyl-1*H*-indole (**18.4)**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (bs, 1H), 7.72 (d, J = 8.6 Hz, 1H), 7.62-7.57 (m, 2H), 7.48-7.42 (m, 2H), 7.38 (s, 1H), 7.32 (t, J = 7.4 Hz, 1H), 7.23 (d, J = 8.6 Hz, 1H)

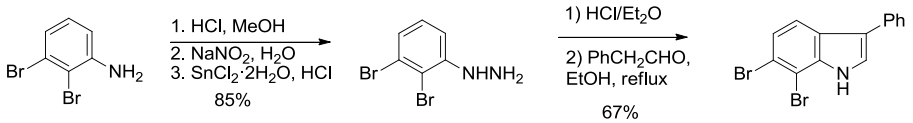


4,5-dibromo-3-phenyl-*1H*-indole (20.5a): See 5,6-Dichloro-3-phenyl-1*H*-indole (**18.4)**. The starting material (3,4-dibromophenyl)hydrazine was made from 3,4-dibromoaniline[140] as the same procedure as 3,4-Dichlorophenylhydrazine (**18.2**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (bs, 1H), 7.34-7.30 (m, 3H), 7.26-7.22 (m, 3H), 7.08 (d, J = 8.6 Hz, 1H), 7.01 (d, J = 2.5 Hz, 1H).

5,6-dibromo-3-phenyl-*1H*-indole (20.6a):

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (bs, 1H), 8.07 (s, 1H), 7.60 (s, 1H), 7.53-7.47 (m, 2H), 7.42-7.35 (m, 2H), 7.28-7.21 (m, 2H).



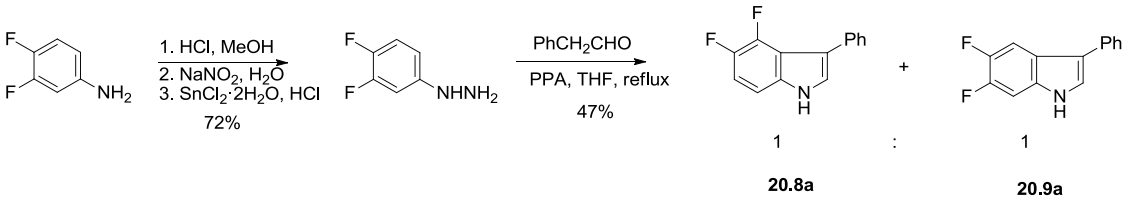
20.7a

6,7-dibromo-3-phenyl-*1H*-indole (20.7a):

The starting material 1,2-dibromophenylhydrazine was made from 1,2-dibromoaniline[140] using the same procedure as 3,4-Dichlorophenylhydrazine (**18.2**).

Dissolved 1.09 g (4.10 mmol) 1,2-dibromophenylhydrazin in a small amount of Et_2O, then added 2.05 mL 2 M HCl (1 eq) into the solution dropwise. Filtered the mixture and got white salts, washed the salts with Et_2O thoroughly, then dried it under vacuum. Then in a 100 mL round-bottom flask was added the dried salts, 478 µL phenylacetaldehyde (1 eq), and 30 mL EtOH, this was refluxed under N_2 atmosphere for 3 hours, then quenched with $NaHCO_3$ saturated solution and extracted with Et_2O. The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was then purified via column chromatography on silica gel using 20% ethyl acetate/hexanes as eluent to give 963.3 mg (67%) of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (bs, 1H), 7.70 (dd, J = 8.5, 0.7 Hz, 1H), 7.61-7.56 (m, 2H), 7.47-7.41 (m, 2H), 7.38 (dd, J = 5.5, 3.0 Hz, 2H), 7.34-7.28 (m, 1H).

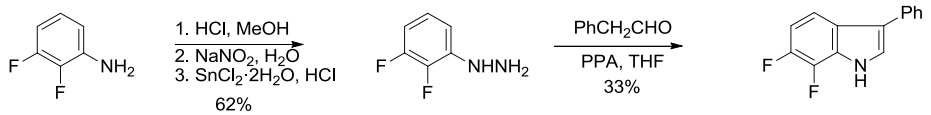


4,5-difluoro-3-phenyl-*1H*-indole (20.8a): See 5,6-Dichloro-3-phenyl-1*H*-indole (**18.4)**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (bs, 1H), 7.62-7.57 (m, 2H), 7.44-7.38 (m, 2H), 7.33 -7.28 (m, 1H), 7.25 (d, *J* = 2.5 Hz, 1H), 7.07-7.04 (m, 2H).

5,6-difluoro-3-phenyl-*1H*-indole (20.9a):

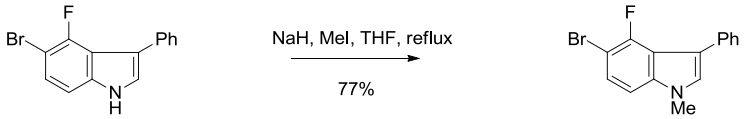
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (bs, 1H), 7.63 (dd, *J* = 11.1, 7.8 Hz, 1H), 7.60-7.55 (m, 2H), 7.47-7.42 (m, 2H), 7.35 (d, *J* = 2.5 Hz, 1H), 7.33-7.27 (m, 1H), 7.18 (dd, *J* = 10.4, 6.7 Hz, 1H).



20.10a

6,7-difluoro-3-phenyl-*1H*-indole (20.10a): See 5,6-Dichloro-3-phenyl-1*H*-indole (**18.4**).

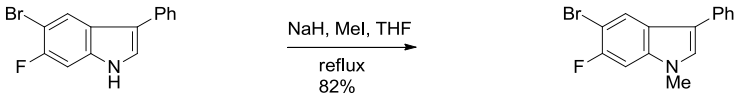
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 7.61-7.05 (m, 8H).



20.1a **20.1b**

5-bromo-4-fluoro-1-methyl-3-phenyl-1H-indole (20.1b): See 4,5-Dichloro-1-methyl-3-phenyl-1*H*-indole (**18.5**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58-7.53 (m, 2H), 7.38 (t, *J* = 7.8 Hz, 2H), 7.32 (dd, *J* = 8.7, 6.2 Hz, 1H), 7.30-7.25 (m, 1H), 7.08 (s, 1H), 7.00 (d, *J* = 8.7 Hz, 1H), 3.80 (s, 3H).

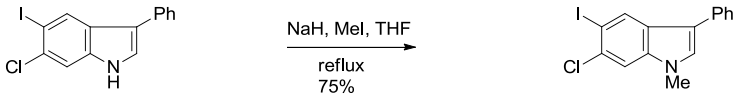


20.2a **20.2b**

5-bromo-6-fluoro-1-methyl-3-phenyl-*1H*-indole (20.2b):

See 4,5-Dichloro-1-methyl-3-phenyl-1*H*-indole (**18.5**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 6.7 Hz, 1H), 7.58-7.53 (m, 2H), 7.46-7.40 (m, 2H), 7.32-7.25 (m, 1H), 7.18 (s, 1H), 7.09 (d, *J* = 9.2 Hz, 1H), 3.76 (s, 3H).

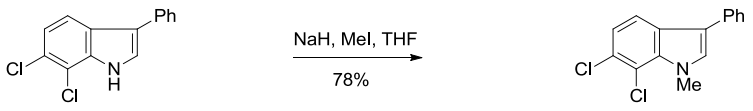


20.3a **20.3b**

6-chloro-5-iodo-1-methyl-3-phenyl-1*H*-indole (20.3b):

See 4,5-Dichloro-1-methyl-3-phenyl-1*H*-indole (**18.5**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.57-7.52 (m, 2H), 7.48 (s, 1H), 7.46-7.40 (m, 2H), 7.31-7.26 (m, 1H), 7.17 (s, 1H), 3.77 (s, 3H).



20.4a **20.4b**

6,7-dichloro-1-methyl-3-phenyl-1*H*-indole (20.4b):

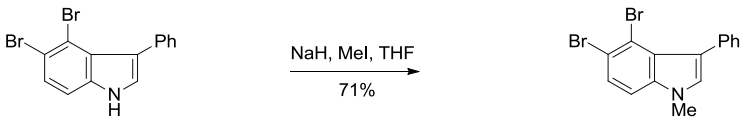
See 5,6-Dichloro-1-methyl-3-phenyl-1*H*-indole (**18.6**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (dd, *J* = 8.6, 0.6 Hz, 1H), 7.56-7.51 (m, 2H), 7.46-7.39 (m, 2H), 7.32-7.26 (m, 1H), 7.19 (dd, *J* = 8.6, 0.6 Hz, 1H), 7.11 (s, 1H), 4.18 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 134.42, 129.96, 128.95, 128.71, 128.57, 127.63, 127.03, 126.42, 121.98, 118.88, 116.91, 115.74, 37.28.

HRMS (EI) m/e calcd for $C_{15}H_{11}Cl_2N$ 275.0270, found 275.0271.

Mp = 104-105 °C.



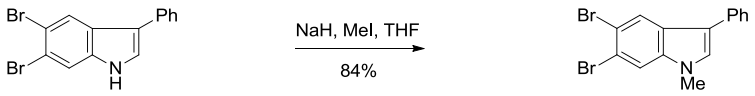
20.5a **20.5b**

4,5-dibromo-1-methyl-3-phenyl-1*H*-indole (20.5b):

See 5,6-Dichloro-1-methyl-3-phenyl-1*H*-indole (**18.6**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.47 (m, 3 H), 7.34-7.36 (m, 3 H), 7.18 (d, J = 8.8 Hz, 1 H), 7.03 (s, 1 H), 3.79 (s, 3 H).

HRMS (EI) m/e calcd for $C_{15}H_{11}Br_2N$ 362.9258, found 362.9260.



20.6a **20.6b**

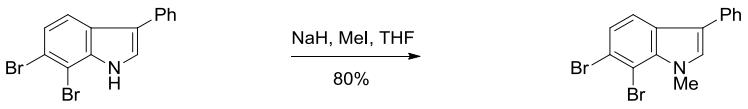
5,6-dibromo-1-methyl-3-phenyl-1*H*-indole (20.6b):

See 5,6-Dichloro-1-methyl-3-phenyl-1*H*-indole (**18.6**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1 H), 7.60 (s, 1 H), 7.53 (d, J = 7.6 Hz, 2 H), 7.28 (apparent t, J = 7.6 Hz, 1 H), 7.24 (apparent t, J = 7.6 Hz, 2 H), 3.75 (s, 3 H), 7.16 (s, 1 H).

HRMS (EI) m/e calcd for $C_{15}H_{11}Br_2N$ 362.9258, found 362.9261.

Mp = 112-113 °C.



20.7a **20.7b**

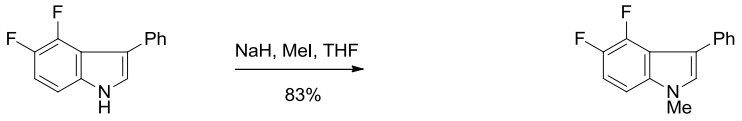
6,7-dibromo-1-methyl-3-phenyl-1*H*-indole (20.7b):

See 5, 6-Dichloro-1-methyl-3-phenyl-1*H*-indole (**18.6**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 8.5 Hz, 1H), 7.55-7.50 (m, 2H), 7.46-7.40 (m, 2H), 7.36 (d, J = 8.5 Hz, 1H), 7.33-7.27 (m, 1H), 7.10 (s, 1H), 4.18 (s, 3H).

HRMS (EI) m/e calcd for $C_{15}H_{11}Br_2N$ 362.9258, found 362.9259.

Mp = 101-102 °C.

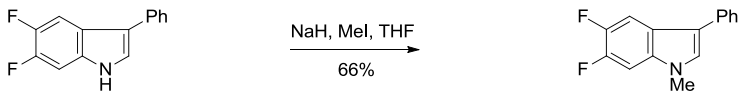


20.8a **20.8b**

4,5-difluoro-1-methyl-3-phenyl-1*H*-indole (20.8b):

See 5,6-Dichloro-1-methyl-3-phenyl-1*H*-indole (**18.6**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62-7.55 (m, 2H), 7.43-7.37 (m, 2H), 7.31-7.25 (m, 1H), 7.12 (s, 1H), 7.07 (ddd, J = 10.5, 8.9, 7.1 Hz, 1H), 6.99 (ddd, J = 8.9, 3.5, 1.0 Hz, 1H), 3.79 (s, 3H).



20.9a **20.9b**

5,6-difluoro-1-methyl-3-phenyl-1*H*-indole (20.9b):

See 5,6-Dichloro-1-methyl-3-phenyl-1*H*-indole (**18.6**).

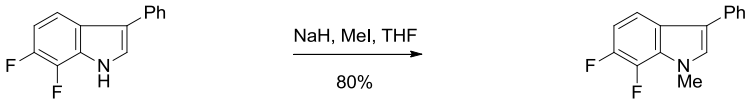
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (dd, *J* = 11.2, 7.8 Hz, 1H), 7.62-7.55 (m, 2H), 7.53-7.42 (m, 2H), 7.36-7.29 (m, 1H), 7.21 (s, 1H), 7.10 (dd, *J* = 10.6, 6.7 Hz, 1H), 3.74 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 149.36, 149.20, 148.16, 148.01, 146.96, 146.80, 145.80, 145.65, 134.96, 132.91, 132.81, 129.07, 127.76, 127.72, 127.19, 126.27, 121.41, 121.33, 117.00, 116.95, 106.77, 106.58, 97.75, 97.53, 33.29.

^{19}F NMR (376 MHz, $CDCl_3$) δ -143.43--143.82 (m, 1F), -147.69--148.10 (m, 1F).

HRMS (EI) m/e calcd for $C_{15}H_{11}F_2N$ 243.0860, found 243.0861.

Mp = 111-112 °C.

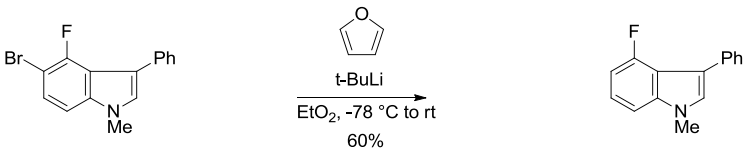


20.10a **20.10b**

6,7-difluoro-1-methyl-3-phenyl-1*H*-indole (20.10b):

See 5,6-Dichloro-1-methyl-3-phenyl-1*H*-indole (**18.6**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58-7.54 (m, 2H), 7.50 (ddd, J = 8.8, 4.3, 1.2 Hz, 1H), 7.45-7.39 (m, 2H), 7.32-7.25 (m, 1H), 7.11 (s, 1H), 7.00-6.90 (m, 1H), 4.01 (d, J = 1.8 Hz, 3H).

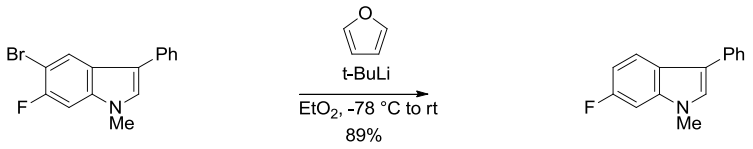


20.1b **21.2**

4-fluoro-1-methyl-3-phenyl-1*H*-indole (21.2):

See 6-fluoro-1-methyl-3-phenyl-1*H*-indole (**21.4**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63-7.56 (m, 2H), 7.43-7.35 (m, 2H), 7.29-7.24 (m, 1H), 7.16 (dd, *J* = 7.5, 4.7 Hz, 1H), 7.13-7.09 (m, 2H), 6.82 (ddd, *J* = 11.6, 7.5, 1.1 Hz, 1H), 3.82 (s, 3H).



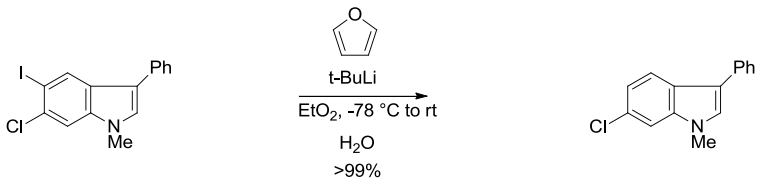
20.2b **21.4**

6-fluoro-1-methyl-3-phenyl-1*H*-indole (21.4):

In a flame-dried 5 mL round-bottom flask under nitrogen was added 14 mg (0.046 mmol) of 5-bromo-6-fluoro-1-methyl-3-phenyl-1*H*-indole (**20.2b**) and 47 µL (0.46 mmol, 10 eq) of furan; these were then dissolved in 2 mL dry diethyl ether and cooled to -78 °C. To the cold solution was added dropwise 105 µL (0.15 mmol, 3.3 eq) of a 1.45 M *t*-butyllithium in hexanes solution. The solution was stirred at -78 °C for 30 min. The cold bath was then removed and the solution was allowed to slowly warm to room temperature with stirring. After 1 h, the reaction was quenched by addition of 5 mL water. The product was extracted with 3 x 5 mL diethyl ether, and the combined organic layers were then dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified via column chromatography on silica gel using 30% ethyl acetate/hexanes as the eluent to give 9.2 mg (89%) of the title compound as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 8.7, 5.3 Hz, 1H), 7.64-7.56 (m, 2H), 7.47-7.38 (m, 2H), 7.31-7.24 (m, 1H), 7.19 (s, 1H), 7.01 (dd, *J* = 9.7, 2.2 Hz, 1H), 6.93 (ddd, *J* = 9.5, 8.8, 2.3 Hz, 1H), 3.77 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 161.36, 158.99, 137.81, 137.69, 135.41, 129.01, 127.49, 126.91, 126.87, 126.16, 122.92, 121.06, 120.96, 117.20, 108.86, 108.62, 96.21, 95.95, 33.21.



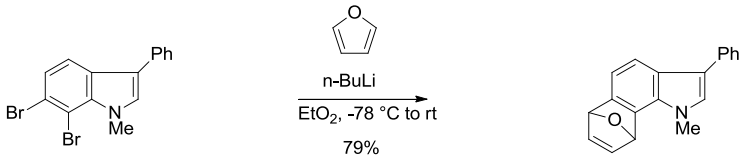
20.3b **21.6**

6-chloro-1-methyl-3-phenyl-1*H*-indole (21.6):

See 6-fluoro-1-methyl-3-phenyl-1*H*-indole (**21.4**).

Starting material 6-chloro-5-iodo-1-methyl-3-phenyl-1*H*-indole was made from 3-chloro-4-iodophenylhydrazine (**35**) as before.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.5 Hz, 1H), 7.62-7.56 (m, 2H), 7.42 (apparent t, *J* = 7.8 Hz, 3H), 7.34 (d, *J* = 1.4 Hz, 1H), 7.30-7.25 (m, 1H), 7.20 (s, 1H), 7.12 (dd, *J* = 8.5, 1.8 Hz, 1H), 3.80 (s, 3H).



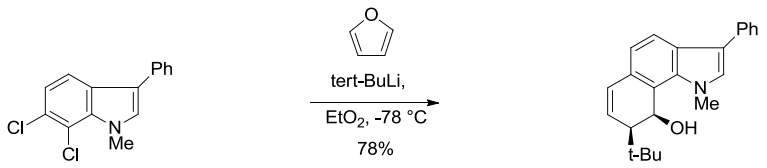
20.7b **22.2**

1-methyl-3-phenyl-6,9-dihydro-1*H*-6,9-epoxybenzo[*g*]indole (22.2): In a flame-dried 5 mL round-bottom flask under nitrogen was added 21 mg (0.059 mmol) of 6,7-dibromo-1-methyl-3-phenyl-1*H*-indole and 86 µL (1.2 mmol, 20 eq) of furan; these were then dissolved in 2 mL dry diethyl ether and cooled to -78 °C. To the cold solution was added dropwise 65 µL (0.065 mmol, 1.1 eq) of a 1.0 M *n*-butyllithium in hexanes solution. The solution was stirred at -78 °C for 30 min. The cold bath was then removed and the solution was allowed to slowly warm to room temperature with stirring. After 1 h, the reaction was quenched by addition of 5.2 mL water. The product was extracted with 3 x 5 mL diethyl ether, and the combined organic layers were then dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified via column chromatography on silica gel using 20% ethyl acetate/hexanes as the eluent to give 13 mg (79%) of the title compound as a white solid.

^{1}H NMR (400 MHz, CD_3CN) δ 7.63 (d, J = 6.4 Hz, 2 H), 7.51 (d, J = 8.0 Hz, 1 H), 7.42 (apparent t, J = 7.8 Hz, 2 H), 7.34 (s, 1 H), 7.25 (apparent t, J = 7.6 Hz, 1 H), 7.14-7.21 (m, 3 H), 6.33 (s, 1 H), 5.82 (s, 1 H), 3.95 (s, 3 H).

HRMS (EI) m/e calcd for $C_{19}H_{15}NO$ 273.1154, found 273.1155.

Mp= 158-159 °C.

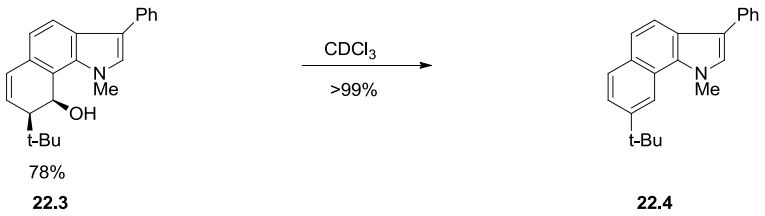


20.4b **22.3**

(±)-8-(*tert*-butyl)-1-methyl-3-phenyl-8,9-dihydro-1*H*-benzo[*g*]indol-9-ol (22.3): See 5-fluoro-1-methyl-3-phenyl-6,9-dihydro-1*H*-6,9-epoxybenzo[*g*]indole (**31.3**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.0 Hz, 1 H), 7.60 (d, *J* =7.2 Hz, 2 H), 7.43 (apparent t, *J* = 8.0 Hz, 2 H), 7.26 (apparent t, *J* = 7.2 Hz, 1H), 7.15 (s, 1 H), 6.98 (d, *J* = 8.0 Hz, 1 H), 6.76 (dd, *J* = 3.2 Hz and 10 Hz, 1 H), 6.00 (d, *J* = 10 Hz, 1 H), 5.59 (d, *J* = 5.2 Hz, 1 H), 4.17 (s, 3 H), 2.29 (q, *J* = 3.2 Hz, 1 H), 1.23 (s, 9 H).

HRMS (EI) m/e calcd for $C_{19}H_{25}NO$ 283.1937, found 283.1939.



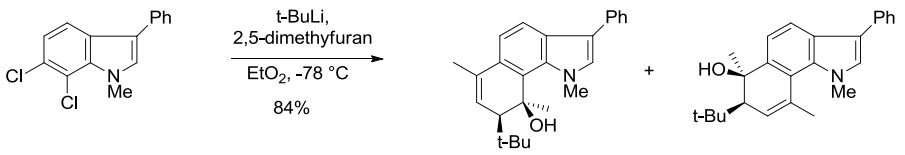
8-(*tert*-butyl)-1-methyl-3-phenyl-1*H*-benzo[*g*]indole (22.4):

Dissolved **22.3** in chloroform-D, and sat at room temperature for 7 hours. All starting material **22.3** was aromatized to product **22.4**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, J = 2 Hz, 1 H), 7.90 (apparent t, J = 8.4 Hz, 2 H), 7.65-7.67 (m, 2 H), 7.50-7.54 (m, 2 H), 7.45 (apparent t, J = 5.2 Hz, 2 H), 7.28 (apparent t, J = 7.2 Hz, 1 H), 7.19 (s, 1 H), 4.36 (s, 3 H), 1.46 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 148.1, 135.8, 131.2, 129.6, 129.0, 128.9, 128.1, 127.1, 126.1, 123.6, 123.5, 122.3, 121.1, 119.2, 118.0, 116.3, 39.0, 35.3, 31.7.

HRMS (EI) m/e calcd for $C_{19}H_{23}N$ 265.1831, found 265.1832.



20.4b 1 : 1 25.2 25.3

(±)-8-(*tert*-butyl)-1,6,9-trimethyl-3-phenyl-8,9-dihydro-1*H*-benzo[*g*]indol-9-ol (25.2):

See 5-fluoro-1-methyl-3-phenyl-6,9-dihydro-1*H*-6,9-epoxybenzo[*g*]indole (**31.3**).

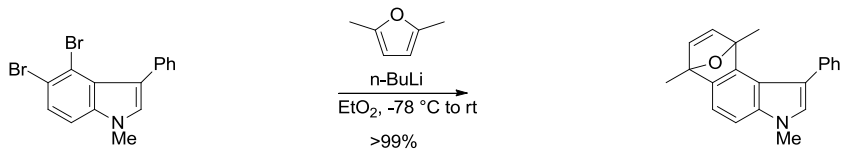
^{1}H NMR (400 MHz, CD_3CN) δ 7.70 (d, *J* = 8.4 Hz, 1 H), 7.65 (d, *J* = 8.4 Hz, 2 H), 7.44 (apparent t, *J* = 7.4 Hz, 2 H), 7.35 (d, *J* = 8.4 Hz, 1 H), 7.30 (s, 1 H) , 7.28 (t, *J* = 7.6 Hz, 1H), 6.03 (dd, *J* = 1.6 and 8.0 Hz, 1 H), 3.79 (s, 3 H), 2.96 (s, 1 H), 2.20 (s, 3 H), 1.49 (s, 3 H), 0.86 (s, 9 H)

HRMS (EI) m/e calcd for $C_{25}H_{29}NO$ 359.2250, found 359.2252.

(±)-7-(*tert*-butyl)-1,6,9-trimethyl-3-phenyl-6,7-dihydro-1*H*-benzo[*g*]indol-6-ol (25.3):

^{1}H NMR (400 MHz, CD_3CN) δ 7.72 (d, *J* = 8.4 Hz, 1 H), 7.62 (d, *J* = 5.2 Hz, 2 H), 7.44 (apparent t, *J* = 8.0 Hz, 2 H), 7.34 (s, 1 H), 7.27 (apparent t, *J* = 7.6 Hz, 1H), 7.09 (d, *J* = 8.4 Hz, 1 H), 2.95 (s, 1 H), 5.84 (dd, *J* = 1.2 and 6.8 Hz, 1 H), 4.13 (s, 3 H), 2.11 (s, 3 H), 1.75 (s, 3 H), 0.81 (s, 9 H)

HRMS (EI) m/e calcd for $C_{25}H_{29}NO$ 359.2250, found 359.2250.

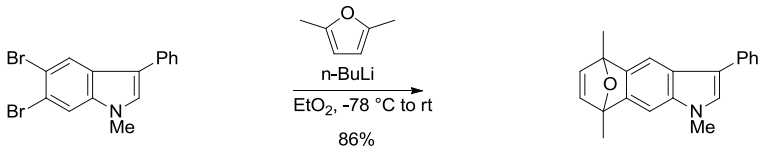


20.5b **28.1**

3,6,9-trimethyl-1-phenyl-6,9-dihydro-3*H*-6,9-epoxybenzo[*e*]indole (28.1):

See 1-methyl-3-phenyl-6,9-dihydro-1*H*-6,9-epoxybenzo[*g*]indole (**22.2**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.31 (m, 5H), 7.15 (d, J = 8.0 Hz, 1H), 6.98 (d, J = 3.6 Hz, 1H), 6.94 (dt, J = 9.6, 5.6 Hz, 3H), 3.75 (s, 3H), 1.95 (s, 3H), 1.21 (s, 3H).



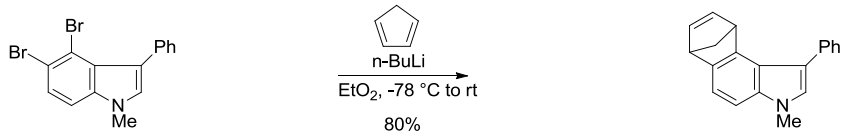
20.6b **28.2**

1,5,8-trimethyl-3-phenyl-5,8-dihydro-1*H*-5,8-epoxybenzo[*f*]indole (28.2):

See 1-methyl-3-phenyl-6,9-dihydro-1*H*-6,9-epoxybenzo[*g*]indole (**22.2**), except for using 2,5-dimethylfuran instead of furan.

^{1}H NMR (400 MHz, CD_3CN) δ 7.62 (d, J = 8.0 Hz, 2H), 7.57 (s, 1 H), 7.42 (apparent t, J = 8.0 Hz, 2 H), 7.33 (s, 1 H), 7.23-7.26 (m, 2 H), 6.78 (s, 2 H), 3.79 (s, 3 H), 1.87 (s, 3 H), 1.85 (s, 3 H).

HRMS (EI) m/e calcd for $C_{21}H_{19}NO$ 301.1467, found 301.1462.

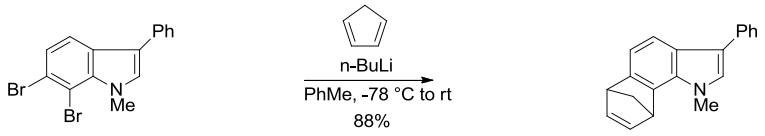


20.5b **29.1**

3-methyl-1-phenyl-6,9-dihydro-3*H*-6,9-methanobenzo[*e*]indole (29.1):

See 1-methyl-3-phenyl-6,9-dihydro-1*H*-6,9-epoxybenzo[*g*]indole (**22.2**), except for using cyclopentadiene instead of furan.

^{1}H NMR (400 MHz, CD_3CN) δ 7.58-7.50 (m, 2H), 7.50-7.40 (m, 2H), 7.35-7.26 (m, 1H), 7.24-7.17 (m, 2H), 6.94 (d, J = 7.1 Hz, 3H), 4.17 (s, 1H), 3.96 (s, 1H), 3.74 (s, 3H), 2.24 (d, J = 6.5 Hz, 1H), 2.13 (d, J = 6.5 Hz, 1H).

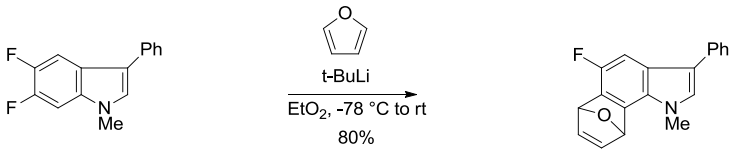


20.7b **30.1**

1-methyl-3-phenyl-6,9-dihydro-1*H*-6,9-methanobenzo[*g*]indole (30.1):

In a flame-dried 25 mL round-bottom flask was added a solution of 20 mg (0.055 mmol) 6,7-dibromo-1-methyl-3-phenyl-1*H*-indole **20.7b** in 2 mL dry toluene. To this was added 7.4 mg (0.11 mmol) of freshly cracked cyclopentadiene. The resulting solution was cooled to -78 °C, then 93 μL (0.11 mmol) of a 1.2 M solution of *n*-butyllithium in hexanes was added dropwise via syring 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 10 mL saturated ammonium chloride. After stirring for 5 min, the mixture was diluted with 10 mL water and extracted with 3 x 10 mL dichloromethane. 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 5% dichloromethane in hexanes as eluent to give 13.1 mg (88%) of the title compound as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61-7.57 (m, 2H), 7.50 (d, J = 7.8 Hz, 1H), 7.42-7.36 (m, 2H), 7.25-7.20 (m, 1H), 7.17 (d, J = 7.8 Hz, 1H), 7.05 (s, 1H), 6.92 (dd, J = 5.3, 3.0 Hz, 1H), 6.86 (dd, J = 5.2, 3.0 Hz, 1H), 4.54 (s, 1H), 4.03 (s, 1H), 3.99 (s, 3H), 2.46-2.34 (m, 2H).



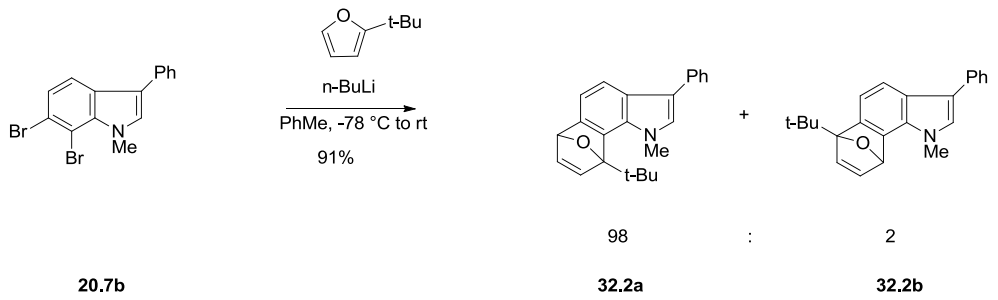
20.9b **31.3**

5-fluoro-1-methyl-3-phenyl-6,9-dihydro-1*H*-6,9-epoxybenzo[*g*]indole (31.3): In a flame-dried 5 mL round-bottom flask under nitrogen was added 20 mg (0.08 mmol) of 5,6-difluoro-1-methyl-3-phenyl-1*H*-indole (**20.9b**) and 116 μL (1.6 mmol, 20 eq) of furan; these were then dissolved in 2 mL dry diethyl ether and cooled to -78 °C. To the cold solution was added dropwise 108 μL (0.35 mmol, 4.4 eq) of a 1.7 M *t*-butyllithium in hexanes solution. The solution was stirred at -78 °C for 30 min. The cold bath was then removed and the solution was allowed to slowly warm to room temperature with stirring. After 1 h, the reaction was quenched by addition of 5 mL water. The product was extracted with 3 x 5 mL diethyl ether, and the combined organic layers were then dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified via column chromatography on silica gel using 20% ethyl acetate/hexanes as the eluent to give 18.6 mg (80%) of the title compound as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J*= 8.0 Hz, 2 H), 7.40 (apparent t, *J* = 7.6 Hz, 2 H), 7.25 (apparent t, *J* = 7.0 Hz, 1 H), 7.18-7.20 (m, 2 H), 7.11-7.14 (m, 2 H), 6.28 (s, 1 H), 6.10 (s, 1 H), 3.93 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 151.7, 144.5, 143.4, 135.2, 130.8, 130.5, 129.7, 129.1, 128.1, 127.4, 126.3, 117.3, 102.8, 102.6, 81.7, 80.3, 35.3.

HRMS (EI) *m/e* calcd for $C_{19}H_{14}FNO$ 291.1060, found 291.1058.



9-(*tert*-butyl)-1-methyl-3-phenyl-6,9-dihydro-1*H*-6,9-epoxybenzo[*g*]indole (32.2a):

See 1-methyl-3,9-diphenyl-6,9-dihydro-1*H*-6,9-epoxybenzo[*g*]indole **(1-4a)**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56-7.51 (m, 3H), 7.43-7.38 (m, 2H), 7.29-7.24 (m, 1H), 7.16-7.12 (m, 2H), 7.03 (d, *J* = 5.5 Hz, 1H), 7.01(s, 1H), 5.17 (d, *J* = 1.8 Hz, 1H), 3.99 (s, 3H), 1.45 (s, 9H).

^{13}C NMR (100 MHz, C_6D_6) δ 29.6, 33.7, 39.1, 82.2, 104.6, 114.1, 116.9, 118.5, 126.4, 128.4, 129.0, 129.7, 131.0, 135.2, 135.6, 136.0, 142.6, 146.4, 149.3.

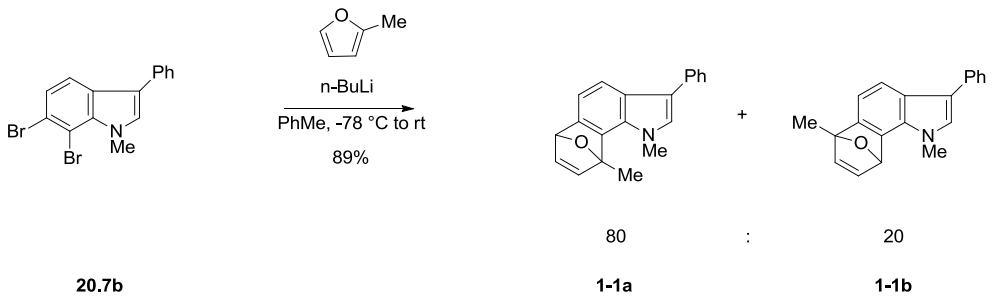
HRMS (EI) m/e calcd for $C_{23}H_{23}NO$ 329.1781, found 329.1779.

6-(*tert*-butyl)-1-methyl-3-phenyl-6,9-dihydro-1*H*-6,9-epoxybenzo[*g*]indole (32.2b):

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61-7.57 (m, 2H), 7.52 (d, *J* = 8.1 Hz, 1H), 7.43-7.38 (m, 2H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.28-7.23 (m, 1H), 7.12-7.07 (m, 3H), 6.24 (d, *J* = 1.5 Hz, 1H), 3.93 (s, 3H), 1.35 (s, 9H).

^{13}C NMR (100 MHz, THF-d_8) δ 27.13, 30.63, 34.91, 80.79, 100.45, 115.47, 115.52, 117.32, 126.05, 127.75, 129.15, 129.01, 129.27, 133.61, 136.57, 137.02, 144.72, 145.55, 145.68.

HRMS (EI) m/e calcd for $C_{23}H_{23}NO$ 329.1781, found 329.1782.



1,9-dimethyl-3-phenyl-6,9-dihydro-1*H*-6,9-epoxybenzo[*g*]indole (1-1a): See 1-methyl-3,9-diphenyl-6,9-dihydro-1*H*-6,9-epoxybenzo[*g*]indole **(1-4a)**.

^{1}H NMR (400 MHz, CD_3CN) δ 7.62-7.58 (m, 2H), 7.49 (d, *J* = 7.8 Hz, 1H), 7.44-7.39 (m, 2H), 7.27 (s, 1H), 7.27-7.22 (m, 1H), 7.15-7.11 (m, 2H), 6.94 (d, *J* = 5.4 Hz, 1H), 5.68 (d, *J* = 1.9 Hz, 1H), 3.96 (s, 3H), 2.14 (s, 3H).

^{13}C NMR (100 MHz, CD_3CN) δ 20.76, 38.16, 82.97, 91.72, 113.93, 116.32, 116.73, 126.59, 128.10, 128.23, 129.59, 130.67, 133.81, 135.59, 136.31, 146.74, 147.21, 148.82.

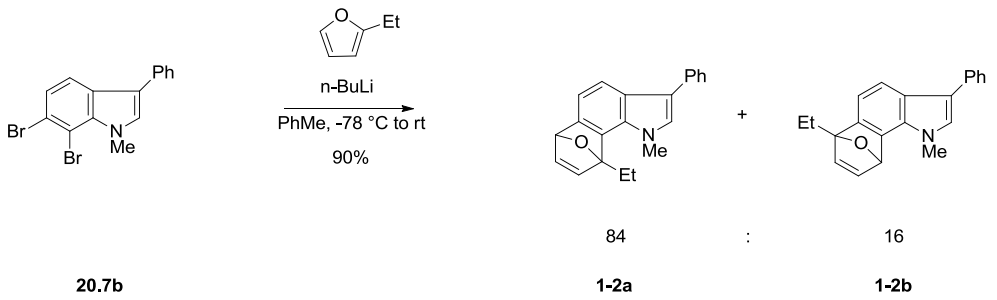
HRMS (EI) m/e calcd for $C_{20}H_{17}NO$ 287.1311, found 287.1313.

1,6-dimethyl-3-phenyl-6,9-dihydro-1*H*-6,9-epoxybenzo[*g*]indole (1-1b):

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61-7.54 (m, 3H), 7.43-7.37 (m, 2H), 7.27-7.22 (m, 1H), 7.13-7.08 (m, 3 H), 6.90 (d, *J* = 5.5 Hz, 1H), 6.20 (d, *J* = 1.8 Hz, 1H), 3.93 (s, 3H), 2.01 (s, 3H).

^{13}C NMR (100 MHz, CD_3CN) δ 15.62, 35.15, 81.20, 90.38, 112.93, 116.06, 116.70, 126.47, 126.61, 127.78, 129.61, 129.80, 133.36, 134.74, 136.49, 145.70, 147.76, 148.01.

HRMS (EI) m/e calcd for $C_{20}H_{17}NO$ 287.1311, found 287.1312.



9-ethyl-1-methyl-3-phenyl-6,9-dihydro-1*H*-6,9-epoxybenzo[*g*]indole (1-2a): See 1-methyl-3,9-diphenyl-6,9-dihydro-1*H*-6,9-epoxybenzo[*g*]indole **(1-4a)**.

^{1}H NMR (400 MHz, C_6D_6) δ 7.69-7.64 (m, 3H), 7.37-7.31 (m, 2H), 7.21-7.16 (m, 1H), 7.04 (d, *J* = 7.9 Hz, 1H), 6.83 (dd, *J* = 5.5, 1.9 Hz, 1H), 6.55 (s, 1H), 6.52 (d, *J* = 5.4 Hz, 1H), 5.56 (d, *J* = 1.8 Hz, 1H), 3.07 (s, 3H), 2.39-2.32 (m, 2H), 1.20 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (100 MHz, CD_3CN) δ 10.19, 26.60, 37.85, 82.87, 96.40, 114.15, 116.46, 116.99, 126.74, 128.27, 128.38, 129.72, 131.03, 134.29, 134.71, 136.42, 146.35, 146.96, 149.30.

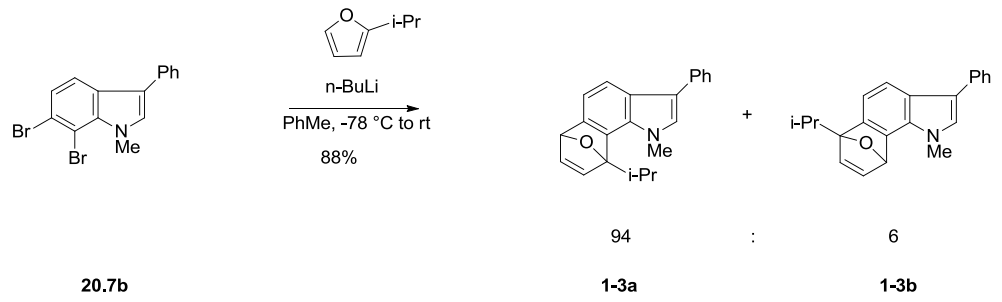
HRMS (EI) m/e calcd for $C_{21}H_{19}NO$ 301.1468, found 301.1467.

6-ethyl-1-methyl-3-phenyl-6,9-dihydro-1*H*-6,9-epoxybenzo[*g*]indole (1-2b):

^{1}H NMR (400 MHz, C_6D_6) δ 7.73-7.69 (m, 3H), 7.38-7.32 (m, 2H), 7.21-7.16 (m, 1H), 7.08 (d, *J* = 7.9 Hz, 1H), 6.77 (dd, *J* = 5.4 Hz, 1.8 Hz, 1H), 6.69 (d, *J* = 5.4 Hz 1H), 6.54 (s, 1H), 5.92 (d, *J* = 1.8 Hz, 1H), 2.84 (s, 3H), 2.35 (q, *J* = 7.5 Hz, 2H), 1.28 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (100 MHz, THF-d_8) δ 8.68, 22.40, 34.03, 80.43, 93.53, 109.99, 112.26, 115.20, 125.30, 126.27, 127.05, 128.21, 128.50, 134.61, 136.28, 136.29, 145.05, 145.83, 146.22.

HRMS (EI) m/e calcd for $C_{21}H_{19}NO$ 301.1468, found 301.1469.



9-isopropyl-1-methyl-3-phenyl-6,9-dihydro-1*H*-6,9-epoxybenzo[*g*]indole (1-3a): See 1-methyl-3,9-diphenyl-6,9-dihydro-1*H*-6,9-epoxybenzo[*g*]indole **(1-4a)**.

^{1}H NMR (400 MHz, CD_3CN) δ 7.62-7.58 (m, 2H), 7.48 (d, *J* = 7.8 Hz, 1H), 7.44-7.39 (m, 2H), 7.28-7.23 (m, 2H), 7.13 (d, *J* = 7.8 Hz, 1H), 7.09 (dd, *J* = 5.5, 1.8 Hz, 1H), 6.98 (d, *J* = 5.5 Hz, 1H), 5.72 (d, *J* = 1.8 Hz, 1H), 3.93 (s, 3H), 3.27 (septet, *J* = 6.8 Hz, 1H), 1.14 (dd, *J* = 1.8, 6.8 Hz, 6H).

^{13}C NMR (100 MHz, CD_3CN) δ 18.93, 19.06, 30.06, 37.76, 82.64, 100.26, 114.15, 116.44, 117.15, 126.77, 128.29, 128.39, 129.72, 131.29, 134.48, 134.90, 136.39, 146.12, 146.47, 149.32.

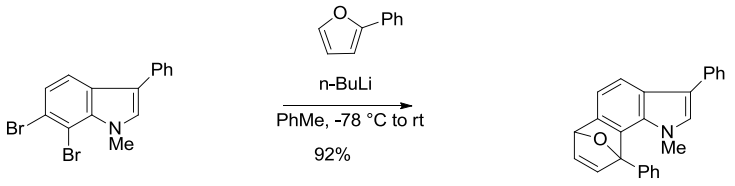
HRMS (EI) m/e calcd for $C_{22}H_{21}NO$ 315.1624, found 315.1624.

6-isopropyl-1-methyl-3-phenyl-6,9-dihydro-1*H*-6,9-epoxybenzo[*g*]indole (1-3b):

^{1}H NMR (400 MHz, C_6D_6) δ 7.73-7.68 (m, 3H), 7.38-7.32 (m, 2H), 7.21-7.17 (m, 1H), 7.12 (d, *J* = 0.5 Hz, 1H), 6.76-6.75 (m, 2H), 6.53 (s, 1H), 5.92 (s, 1H), 2.82 (s, 3H), 2.67 (septet, *J* = 6.8 Hz, 1H), 1.36 (dd, *J* = 8.7, 6.8 Hz, 6H).

^{13}C NMR (100 MHz, THF-d_8) δ 18.61, 18.76, 28.32, 35.32, 80.99, 97.93, 114.38, 116.04, 116.92, 126.58, 127.89, 129.74, 129.89, 130.07, 133.42, 135.95, 136.65, 145.72, 146.29, 146.51.

HRMS (EI) m/e calcd for $C_{22}H_{21}NO$ 315.1624, found 315.1622.



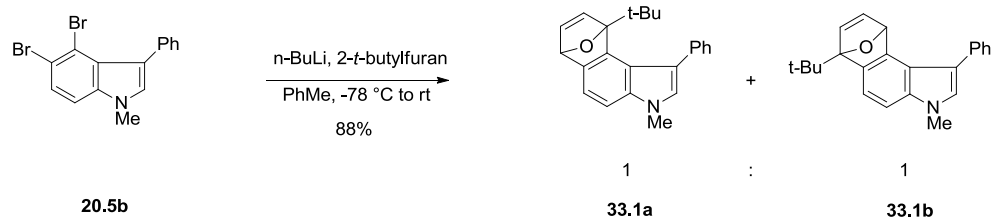
20.7b **1-4a**

1-methyl-3,9-diphenyl-6,9-dihydro-1*H*-6,9-epoxybenzo[*g*]indole (1-4a): Use the standard procedure as 1-methyl-3-phenyl-6,9-dihydro-1*H*-6,9-epoxybenzo[g]indole **(22.2)**, except for using PhMe as the solvent instead of Et_2O.

^{1}H NMR (400 MHz, C_6D_6) δ 8.03 (d, *J* = 7.9 Hz, 1H), 7.70-7.65 (m, 2H), 7.37-7.31 (m, 4H), 7.21-7.17 (m, 1H), 7.07-6.97 (br, 4H), 6.50 (s, 1H), 5.99 (dd, *J* = 3.6, 1.3 Hz, 1H), 4.57(d, *J* = 3.7 Hz, 1H), 2.60-2.53 (m, 1H), 2.52 (s, 3H).

^{13}C NMR (100 MHz, C_6D_6) δ 30.24, 83.10, 107.37, 114.23, 116.92, 117.87, 126.11, 129.32, 129.38, 129.66, 130.13, 130.45, 131.38, 131.57, 132.18, 135.61, 135.24, 135.89, 142.31, 146.20, 146.92.

HRMS (EI) m/e calcd for $C_{25}H_{19}NO$ 349.1468, found 349.1470.



20.5b **33.1a** **33.1b**

9-(*tert*-butyl)-3-methyl-1-phenyl-6,9-dihydro-3*H*-6,9-epoxybenzo[*e*]indole (33.1a):

See 1-methyl-3,9-diphenyl-6,9-dihydro-1*H*-6,9-epoxybenzo[*g*]indole **(1-4a)**.

^{1}H NMR (400 MHz, CD_3CN) δ 7.50 (d, *J* = 7.2 Hz, 1H), 7.40 (s, 1H), 7.35-7.25 (m, 2H), 7.21 (d, *J* = 7.9 Hz, 1H), 7.10 (dd, *J* = 5.5, 1.7 Hz, 1H), 7.06-7.01 (m, 3H), 6.96 (d, *J* = 5.5 Hz, 1H), 5.61 (d, *J* = 1.7 Hz, 1H), 3.73 (s, 3H), 0.73 (s, 9H).

^{13}C NMR (100 MHz, C_6D_6) δ 27.78, 33.16, 33.49, 81.82, 104.92, 106.02, 114.97, 116.32, 124.21, 127.71, 128.50, 128.81, 133.19, 138.31, 139.34, 142.68, 145.32, 145.76, 147.19.

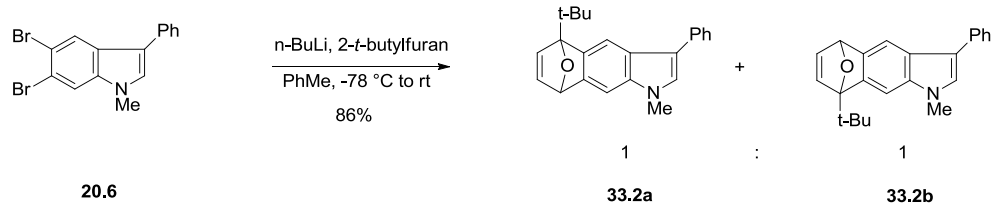
HRMS (EI) m/e calcd for $C_{23}H_{23}NO$ 329.1781, found 329.1780.

6-(*tert*-butyl)-3-methyl-1-phenyl-6,9-dihydro-3*H*-6,9-epoxybenzo[*e*]indole (33.1b):

^{1}H NMR (400 MHz, CD_3CN) δ 7.50-7.45 (m, 4H), 7.44 (d, *J* = 8.2 Hz, 1H), 7.34-7.29 (m, 1H), 7.26 (s, 1H), 7.22 (dd, *J* = 5.5, 1.8 Hz, 1H), 7.18 (d, *J* = 5.5 Hz, 1H), 6.96 (d, *J* = 8.2 Hz, 1H), 5.79 (d, *J* = 1.7 Hz, 1H), 3.76 (s, 3H), 1.27 (s, 9H).

^{13}C NMR (100 MHz, C_6D_6) δ 27.91, 33.30, 33.66, 81.75, 104.11, 108.48, 115.00, 116.78, 123.54, 127.60, 128.13, 128.81, 132.65, 133.48, 137.01, 139.6, 141.25, 145.82, 148.19.

HRMS (EI) m/e calcd for $C_{23}H_{23}NO$ 329.1781, found 329.1781.



20.6 **33.2a** **33.2b**

5-(*tert*-butyl)-1-methyl-3-phenyl-5,8-dihydro-1*H*-5,8-epoxybenzo[*f*]indole (33.2a):

See 1-methyl-3,9-diphenyl-6,9-dihydro-1*H*-6,9-epoxybenzo[*g*]indole **(1-4a)**.

^{1}H NMR (400 MHz, C_6D_6) δ 7.69 (d, *J* = 12.8 Hz, 1H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.31 (t, *J* = 7.7 Hz, 2H), 7.15 (m, 3H), 6.57 (s, 1H), 6.12 (m, 1H), 5.16 (m, 1H), 3.46 (s, 3H), 1.48 (s, 9H).

^{13}C NMR (100 MHz, C_6D_6) δ 27.01, 31.96, 33.11, 81.86, 99.34, 104.74, 110.12, 111.77, 117.67, 122.93, 125.84, 125.93, 129.06, 134.93, 136.59, 142.03, 143.80, 144.21, 144.97.

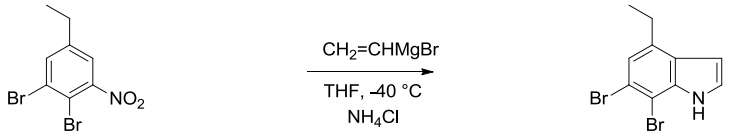
HRMS (EI) m/e calcd for $C_{23}H_{23}NO$ 329.1781, found 329.1782.

8-(*tert*-butyl)-1-methyl-3-phenyl-5,8-dihydro-1*H*-5,8-epoxybenzo[*f*]indole (33.2b):

^{1}H NMR (400 MHz, C_6D_6) δ 7.68 (d, *J* = 9.3 Hz, 1H), 7.60 (d, *J* = 7.1 Hz, 2H), 7.30 (t, *J* = 7.5 Hz, 2H), 7.15 (m, 3H), 6.62 (s, 1H), 6.27 (d, *J* = 3.7 Hz, 1H), 5.29 (m, 1H), 3.06 (s, 3 H), 1.17 (s, 9H).

^{13}C NMR (100 MHz, C_6D_6) δ 26.99, 32.08, 33.06, 81.72, 99.50, 102.78, 113.58, 118.22, 123.15, 125.69, 126.02, 128.65, 129.16, 134.68, 136.64, 141.06, 143.13, 143.83, 146.96.

HRMS (EI) m/e calcd for $C_{23}H_{23}NO$ 329.1781, found 329.1781.



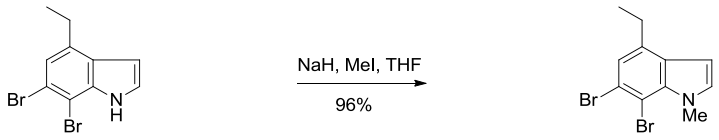
44.2 **35.1**

6,7-dibromo-4-ethyl-1*H*-indole (35.1): In a 1.0 L round-bottom flask was dissolved 9.77 g (31.6 mmol) 1,2-dibromo-5-ethyl-3-nitrobenzene (**44.2**) in 235 mL dry THF. The solution was cooled to -40 °C (dry ice/chlorobenzene) with stirring under nitrogen. To the cold solution was added 95 mL (95 mmol) of a 1.0 M solution of vinylmagnesium bromide in THF rapidly and in one portion. The mixture was stirred at -40 °C for 30 min, then 100 mL saturated ammonium chloride was added and the mixture subsequently was allowed to warm to room temperature. The mixture was then extracted with diethyl ether (3 x 100 mL), the combined organic phase was then washed with water (100 mL) and brine (50 mL), dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude material was purified via column chromatography on silica gel using 15% ethyl acetate in hexanes as eluent to give 4.98 g (52%) of the title compound as an orange oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (bs, 1H, NH), 7.21 (dd, J = 3.1, 0.8 Hz, 1H), 7.19 (s, 1H), 6.64 (dd, J = 2.1, 1.1 Hz, 1H), 2.87 (q, J = 7.6 Hz, 2H), 1.34 (t, J = 7.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 137.1, 135.3, 126.7, 124.6, 123.1, 117.3, 104.2, 102.5, 25.8, 14.5.

HRMS (EI) m/e calcd for $C_{10}H_9Br_2N$ 300.9102, found 300.9099.

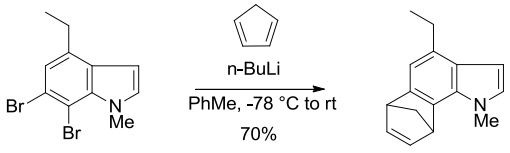


35.1 35.9

6,7-dibromo-4-ethyl-1-methyl-1*H*-indole (35.9):

See 5,6-Dichloro-1-methyl-3-phenyl-1*H*-indole (**18.6**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (s, 1H), 6.95 (d, J = 3.2 Hz, 1H), 6.43 (d, J = 3.2 Hz, 1H), 4.13 (s, 3H), 2.80 (q, J = 7.6 Hz, 2H), 1.28 (t, J = 7.6 Hz, 3H).

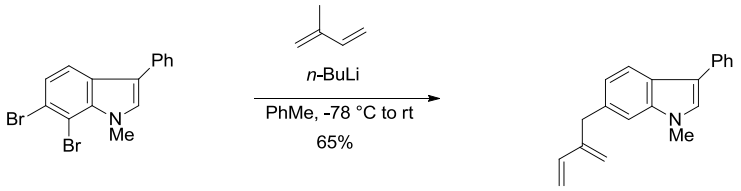


35.9 35.11

4-ethyl-1-methyl-6,9-dihydro-1*H*-6,9-methanobenzo[*g*]indole (35.11):

See (±)-1-(*tert*-butyldimethylsilyl)-4-ethyl-6,9-dihydro-1*H*-6,9-methanobenzo[*g*]indole (**45.1**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (s, 1H), 6.91-6.87 (m, 2H), 6.86-6.82 (m, 1H), 6.41 (d, *J* = 3.2 Hz, 1H), 4.49 (d, *J* = 2.3 Hz, 1H), 3.98 (s, 1H), 3.93 (s, 3H), 2.90-2.82 (m, 2H), 2.42-2.33 (m, 2H), 1.31 (t, *J* = 7.6 Hz, 3H).



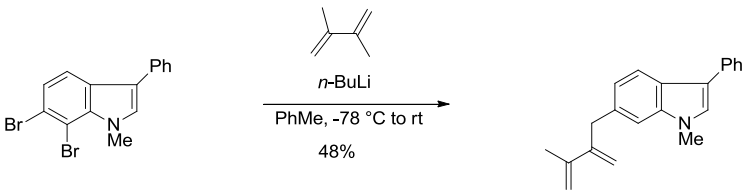
20.7b **36.1**

1-methyl-6-(2-methylenebut-3-en-1-yl)-3-phenyl-1*H*-indole (36.1):

See 1-methyl-3,9-diphenyl-6,9-dihydro-1*H*-6,9-epoxybenzo[*g*]indole **(1-4a)**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.2 Hz, 1H), 7.66-7.60 (m, 2H), 7.44-7.37 (m, 2H), 7.26-7.20 (m, 1H), 7.18-7.15 (m, 2H), 7.04 (dd, *J* = 8.2, 1.5 Hz, 1H), 6.46 (dd, *J* = 17.5, 11.2 Hz, 1H), 5.31 (d, *J* = 17.6 Hz, 1H), 5.18 (s, 1H), 5.06 (d, *J* = 10.8 Hz, 1H), 4.95 (s, 1H), 3.79 (s, 3H), 3.71 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 146.12, 138.85, 138.09, 135.98, 133.71, 128.91, 128.87, 127.43, 126.43, 125.81, 121.73, 119.88, 118.25, 114.49, 110.02, 109.69, 38.69, 33.05.

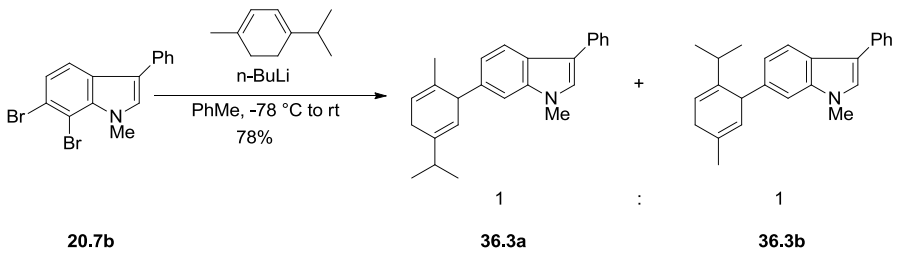


20.7b **36.2**

1-methyl-6-(3-methyl-2-methylenebut-3-en-1-yl)-3-phenyl-1*H*-indole (36.2):

See 1-methyl-3,9-diphenyl-6,9-dihydro-1*H*-6,9-epoxybenzo[*g*]indole **(1-4a)**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.2 Hz, 1H), 7.67-7.60 (m, 2H), 7.44-7.37 (m, 2H), 7.28-7.20 (m, 1H), 7.19-7.14 (m, 2H), 7.04 (dd, *J* = 8.2, 1.4 Hz, 1H), 5.29 (s, 1H), 5.19 (s, 1H), 4.98 (s, 1H), 4.94 (s, 1H), 3.79 (s, 3H), 3.78 (s, 2H), 1.95 (s, 3H).

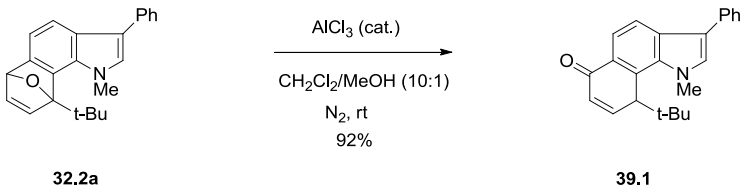


6-(5-isopropyl-2-methylcyclohexa-2,5-dien-1-yl)-1-methyl-3-phenyl-1*H*-indole (36.3a) and

6-(2-isopropyl-5-methylcyclohexa-2,5-dien-1-yl)-1-methyl-3-phenyl-1*H*-indole (36.3b):

See 1-methyl-3,9-diphenyl-6,9-dihydro-1*H*-6,9-epoxybenzo[*g*]indole **(1-4a)**. These two isomers couldn't be separated and the ratio was based on NMR analysis.

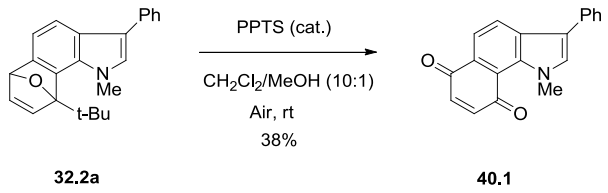
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04-7.86 (m, 1H), 7.79-7.65 (m, J = 1.3 Hz, 2H), 7.56-7.42 (m, 2H), 7.38-7.26 (m, 1H), 7.21 (s, 2H), 7.16-7.04 (m, 1H), 5.86-5.52 (m, 2H), 4.36-3.89 (m, 1H), 3.82 (s, 3H), 3.07-2.00 (m, 2H), 1.87-1.59 (m, 3H), 1.59-1.26 (m, 1H), 1.25-0.88 (m, 6H).



32.2a **39.1**

9-(*tert*-butyl)-1-methyl-3-phenyl-1*H*-benzo[*g*]indol-6(9*H*)-one (39.1): In a 50 mL round-bottom flask was added a solution of 10 mg (0.030 mmol) 9-(*tert*-butyl)-1-methyl-3-phenyl-6,9-dihydro-1*H*-6,9-epoxybenzo[*g*]indole **32.2a** in 22 mL CH_2Cl_2/MeOH (10:1). The solution was bubbled with N_2 for 30 min then lifted the needle right above the liquid surface. To the stirred solution was added one crystal of $AlCl_3$ (cat.) and kept stirring for another 3 hours. Then to the mixture was added 20 mL NaOH solution (0.5 N) and stirred for 10 min, followed by extraction with Et_2O. The organic phases were separated and washed with brine and dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel column, eluting with toluene to give 9.2 mg (92%) of the title compound as a yellow oil.

^{1}H NMR (400 MHz, C_6D_6) δ 8.57 (d, J = 8.4 Hz, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.62-7.54 (m, 2H), 7.36-7.27 (m, 2H), 7.23-7.13 (m, 1H), 6.73-6.64 (m, 2H), 6.62 (s, 1H), 3.77 (d, J = 5.2 Hz, 1H), 3.02 (s, 3H), 0.60 (s, 9H).

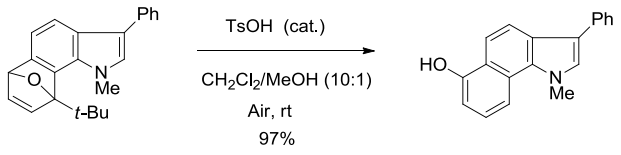


32.2a **40.1**

1-methyl-3-phenyl-1*H*-benzo[*g*]indole-6,9-dione (40.1): In a 50 mL round-bottom flask was added a solution of 10 mg (0.030 mmol) 9-(*tert*-butyl)-1-methyl-3-phenyl-6,9-dihydro-1*H*-6,9-epoxybenzo[*g*]indole **32.2a** in 22 mL CH_2Cl_2/MeOH (10:1). To the stirred solution was added one crystal of PPTS (cat.) and kept stirring for another 3 hours. Then to the mixture was added 20 mL NaOH solution (0.5 N) and stirred for 10 min, followed by extraction with Et_2O. The organic phases were separated and washed with brine and dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel column, eluting with toluene to give 3.2 mg (38%) of the title compound as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.3 Hz, 1H), 7.92 (d, *J* = 8.3 Hz, 1H), 7.58-7.52 (m, 2H), 7.49-7.42 (m, 2H), 7.38 (s, 1H), 7.36-7.30 (m, 1H), 6.89 (d, *J* = 0.8 Hz, 2H), 4.06 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 186.35, 185.86, 139.72, 137.30, 135.43, 134.37, 134.27, 133.75, 129.18, 128.91, 128.22, 127.03, 125.64, 119.89, 118.89, 118.53, 40.02.

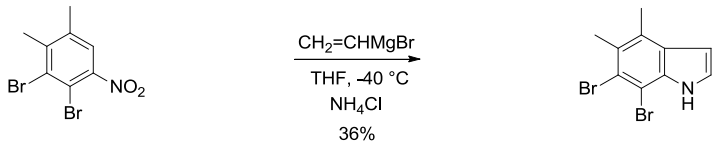


32.2a **40.2**

1-methyl-3-phenyl-1*H*-benzo[*g*]indol-6-ol (40.2):

In a 50 mL round-bottom flask was added a solution of 10 mg (0.030 mmol) 9-(*tert*-butyl)-1-methyl-3-phenyl-6,9-dihydro-1*H*-6,9-epoxybenzo[*g*]indole **32.2a** in 22 mL CH_2Cl_2/MeOH (10:1). To the stirred solution was added one crystal of TsOH (cat.) and kept stirring for another 3 hours. Then to the mixture was added 20 mL NaOH solution (0.5 N) and stirred for 10 min, followed by extraction with Et_2O. The organic phases were separated and washed with brine and dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel column, eluting with toluene to give 7.9 mg (97%) of the title compound as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 8.6 Hz, 1H), 7.98 (d, J = 9.0 Hz, 1H), 7.91 (d, J = 9.0 Hz, 1H), 7.70-7.62 (m, 2H), 7.50-7.42 (m, 2H), 7.37 (dd, J = 8.5, 7.6 Hz, 1H), 7.32-7.26 (m, 1H), 7.20 (s, 1H), 6.84 (dd, J = 7.6, 0.8 Hz, 1H), 5.42 (s, 1H), 4.31 (s, 3H).



46.2 **43.4**

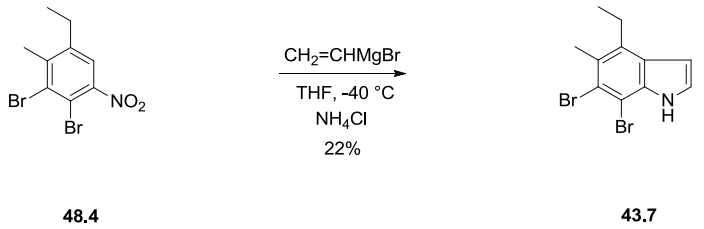
6,7-dibromo-4,5-dimethyl-1*H*-indole (43.4): See 6,7-dibromo-4-ethyl-1*H*-indole (**35.1**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.19 (dd, *J* = 2.4, 3.2 Hz, 1H), 6.57 (dd, *J* = 2.0, 3.2 Hz, 1H), 2.53 (s, 3H), 2.49 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 133.5, 128.1, 128.0, 127.9, 124.4, 121.0, 104.8, 102.4, 20.8, 17.0.

HRMS (EI) m/e calcd for $C_{10}H_9Br_2N$ 300.9102, found 300.9100.

Mp = 125-127 °C.

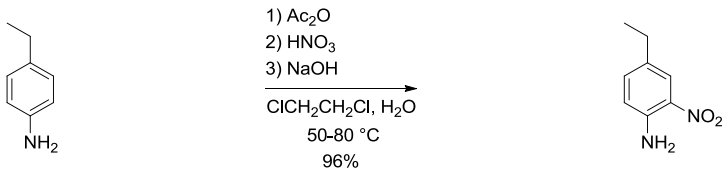


48.4 **43.7**

6,7-dibromo-4-ethyl-5-methyl-1*H*-indole (43.7): See 6,7-dibromo-4-ethyl-1*H*-indole **(35.1)**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.19 (dd, *J* = 3.2, 2.4 Hz, 1H), 6.58 (dd, *J* = 3.2, 2.2 Hz, 1H), 2.94 (q, *J* = 7.6 Hz, 2H), 2.54 (s, 3H), 1.20 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 134.73, 134.09, 127.52, 127.43, 124.73, 121.72, 105.36, 102.49, 24.75, 20.51, 14.56.



43.2 **44.1**

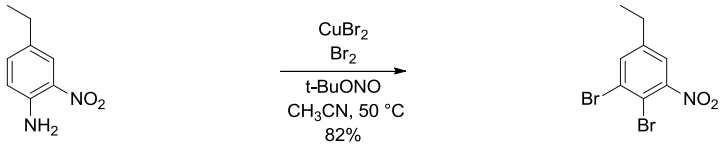
4-ethyl-2-nitroaniline (44.1): In a 250 mL round-bottom flask was added 11.73 g (115 mmol) acetic anhydride and 105 mL 1,2-dichloroethane. To this was added 12.1 g (100 mmol) 4-ethylaniline (**43.2)** and the solution was heated to 80 °C for 1 h. The solution was then cooled to 50 °C and 10.1 mL (240 mmol) of fuming nitric acid was added dropwise over 45 min. The solution was then stirred at 45-50 °C for 1 h. To the solution was then added 13 g (325 mmol) of sodium hydroxide dissolved in a minimum volume of water over a 10 min period. The temperature was raised to above 80 °C and the 1,2-dichloroethanewas distilled out of the reaction mixture, after which point the temperature was raised to between 95 and 97 °C and the reaction was monitored by TLC. After 5 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 (1 x 50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 15.85 g (96%) of the title compound as an orange crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, H), 7.18 (dd, J = 6.4, 2.1 Hz, 1H), 6.72 (d, J = 8.4 Hz, 1H), 5.96 (bs, 2H, NH2), 2.52 (q, J = 7.6 Hz, 2H), 1.17 (t, J = 7.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 142.9, 136.1, 133.0, 131.9, 124.0, 118.8, 27.4, 15.2.

HRMS (EI) m/e calcd for $C_8H_{10}N_2O_2$ 166.0742, found 166.0744.

Mp = 34-36 °C.



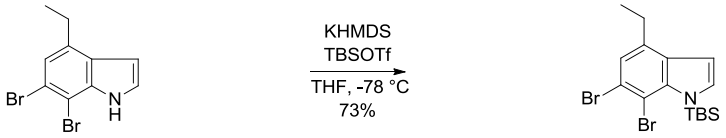
44.1 **44.2**

1,2-dibromo-5-ethyl-3-nitrobenzene (44.2): In a 500 mL three-necked round-bottom flask was added 1.881 g (8.42 mmol) $CuBr_2$. This was dissolved in 170 mL acetonitrile and the solution was heated to 50 °C. After 5 min, 18.17 g (113.7 mmol) of bromine dissolved in 42 mL acetonitrile was added to the warm solution, followed by a solution of 7.0 g (42.12 mmol) 4-ethyl-2-nitroaniline (**44.1**) in a minimum volume of acetonitrile. The mixture was stirred at 50 °C for 40 min, and then a solution of 5.21 g (50.5mmol) *tert*-butyl nitrite in 85 mL acetonitrile was added to the reaction mixture dropwise over a period of 1 h. The mixture was then stirred at 50 °C for 30 min, and then cooled to room temperature. The reaction mixture was then quenched with 150 mL saturated sodium sulfite and subsequently poured into 800 mL 3 N HCl. The aqueous mixture was extracted with 800 mL diethyl ether once and 400 mL diethyl ether once. The combined organic layer was washed with 400 mL 3 N HCl, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was then passed through a plug of silica gel, eluting with 1:1 hexane:ether to give 10.7 g (82%) of the title compound as a yellow oil which solidifies under 0 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (m, 1H), 7.45 (m, 1H), 2.66 (q, J = 7.6 Hz, 2H), 1.26 (t, J = 7.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 146.1, 136.0, 127.5, 123.0, 113.8, 27.9, 14.7.

HRMS (EI) m/e calcd for $C_8H_7Br_2NO_2$ 306.8844, found 306.8844.



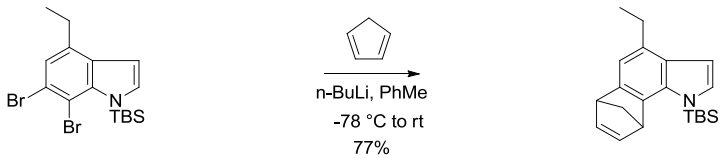
35.1 44.3

6,7-dibromo-1-(*tert*-butyldimethylsilyl)-4-ethyl-1*H*-indole (44.3): In a 500 mL three-necked round-bottom flask was dissolved 1.10 g (3.64 mmol) 6,7-dibromo-4-ethyl-1*H*-indole (**35.1**) in 100 mL dry THF under nitrogen. The solution was cooled to -78 °C and to the flask was added 1.45 g (7.28 mmol) KHMDS. The resulting dark brown solution was stirred for 5 min, then 3.2 mL (14.56 mmol) of *tert*-butyldimethylsilyl-trifluoromethanesulfonate was added dropwise over 5 min via syringe. The resulting yellow solution was stirred at -78 °C for 30 min, after which time TLC analysis showed the reaction to be complete. A solution of 10 mL triethylamine in 200 mL ether was then added and the reaction mixture was allowed to warm to room temperature. The mixture was then poured into 200 mL ether and washed with 150 mL 0.5 N HCl, 150 mL water and 100 mL brine. The ether layer was then dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude material was then purified via column chromatography on silica gel using hexanes as eluent to give 1.1 g (73%) of the title compound as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, J = 3.5 Hz, 1H), 7.27 (s, 1H), 6.66 (d, J =3.4 Hz, 1H), 2.84 (q, J = 7.6 Hz, 2H), 1.31 (t, J = 7.6 Hz, 3H), 1.00 (s, 9H), 0.72 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 140.7, 136.3, 134.2, 132.1, 124.1, 119.8, 105.7, 103.6, 27.5, 25.8, 19.9, 14.4, 2.2.

HRMS (EI) m/e calcd for $C_{16}H_{23}Br_2NSi$ 414.9967, found 414.9966.



44.3 **45.1**

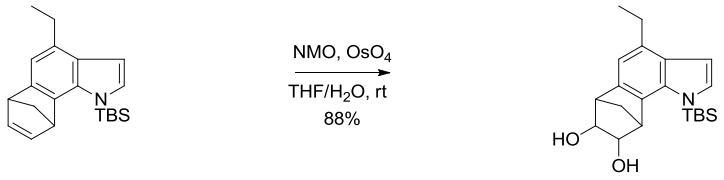
(±)-1-(*tert*-butyldimethylsilyl)-4-ethyl-6,9-dihydro-1*H*-6,9-methanobenzo[*g*]indole (45.1): In a flame-dried 500 mL three-necked round-bottom flask was added a solution of 1.84 g (4.41 mmol) 6,7-dibromo-1-(*tert*-butyldimethylsilyl)-4-ethyl-1*H*-indole **44.3** in 180 mL dry toluene. To this was added 5.83 g (88.2 mmol) of freshly cracked cyclopentadiene. The resulting solution was cooled to -78 °C, then 3.53 mL (8.82 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 was allowed to slowly warm to room temperature. The reaction was then quenched by addition of 100 mL saturated ammonium chloride. After stirring for 5 min, the mixture was diluted with 200 mL water and extracted with 3 x 150 mL dichloromethane. 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 5% dichloromethane in hexanes as eluent to give 1.1 g (77%) of the title compound as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, J = 3.4 Hz, 1H), 7.06 (s, 1H), 6.95 (dd, J = 5.2, 3.1 Hz, 1H), 6.86 (dd, J = 5.3, 2.7 Hz, 1H), 6.63 (d, J = 3.4 Hz, 1H), 4.51 (bs, 1H), 4.01 (bs, 1H), 2.90 (q, J = 7.6 Hz, 2H), 2.35 (m, 2H), 1.36 (t, J = 7.6 Hz, 3H), 1.08 (s, 9H), 0.70 (s, 3H), 0.61 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 147.3, 145.1, 142.3, 136.6, 131.9, 131.7, 131.2, 129.4, 114.3, 103.2, 70.4, 51.2, 50.7, 26.7, 26.2, 19.4, 14.7, -1.5, -1.9.

HRMS (EI) *m/e* calcd for $C_{21}H_{29}NSi$ 323.2071, found 323.2069.

Mp= 71-73 °C.



45.1 45.2

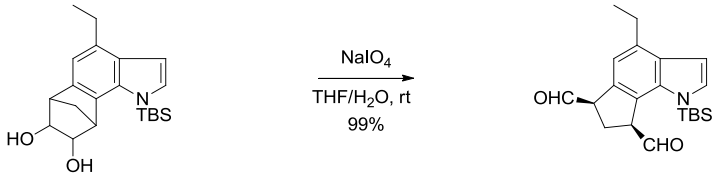
(±)-1-(*tert*-butyldimethylsilyl)-4-ethyl-6,7,8,9-tetrahydro-1*H*-6,9-methanobenzo[*g*]indole-7,8-diol (45.2): In a 20 mL vial was added 10 mg (0.031 mmol) (±)-1-(*tert*-butyldimethylsilyl)-6,9-dihydro-5-ethyl-6,9-methano-1*H*-benz[*g*]indole **45.1** and this was dissolved in 2.5 mL THF/water (1.5:1). To the solution was added 21 mg (0.155 mmol) NMO hydrate. The mixture was stirred at room temperature, and 1 drop osmium tetroxide solution (4% in water) was added and the reaction was followed by TLC. After intervals of 1 h, another 2 drops osmium tetroxide solution was added and stirring continued until 6 h, at which time TLC showed complete reaction. The reaction mixture was quenched by addition of 2 mL saturated sodium bisulfite, and the subsequent mixture was stirred rapidly for 30 min. The mixture was then extracted with ethyl acetate (3 x 15 mL), and 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 30% ethyl acetate in hexanes as eluent to give 10 mg (88%) of the title compound as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, J = 3.5 Hz, 1H), 6.92 (s, 1H), 6.65 (d, J = 3.5 Hz, 1H), 3.82 (m, 2H), 3.72 (bs, 1H), 3.27 (bs, 1H), 3.07 (bs, 1H, OH), 2.90 (q, J = 7.6 Hz, 2H), 2.81 (bs, 1H, OH), 2.23 (m, 1H), 1.93 (m, 1H), 1.33 (t, J = 7.6 Hz, 3H), 1.02 (s, 9H), 0.71 (s, 3H), 0.60 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 140.0, 135.8, 134.6, 131.4, 130.7, 125.5, 113.8, 103.3, 71.7, 71.6, 50.8, 50.4, 42.4, 26.7, 26.3, 19.5, 14.6, -1.5, -1.9.

HRMS (EI) *m/e* calcd for $C_{21}H_{31}NO_2Si$ 357.2125, found 357.2124.

Mp = 165-166 °C.



45.2 45.3

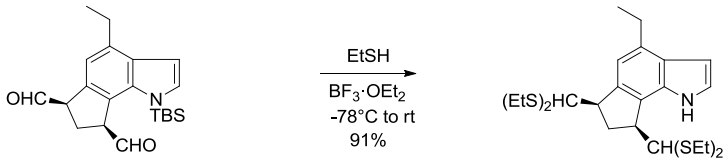
(±)-1-(*tert*-butyldimethylsilyl)-4-ethyl-1,6,7,8-tetrahydrocyclopenta[*g*]indole-6,8-dicarbaldehyde (45.3): In a 250 mL round-bottom flask was added a solution of 120 mg (0.336 mmol) (±)-1-(*tert*butyldimethylsilyl)-6,7,8,9-tetrahydro-5-ethyl-7,8-dihydroxy-6,9-methano-1*H*-benz[*g*]indole **45.2** in 24 mL THF. To the stirred solution was added 7 mL water followed by 1.078 g (5.04 mmol) sodium periodate. The mixture was stirred at room temperature until TLC analysis indicated complete reaction, about 1 h. The mixture was diluted with 150 mL ethyl acetate and 150 mL water. 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 119 mg (100%) of the title compound as a brown solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.64 (s, 1H), 9.63 (s, 1H), 7.30 (d, J = 3.4 Hz, 1H), 7.04 (s, 1H), 6.73 (d, J = 3.5 Hz, 1H), 4.52 (d, J = 9.3 Hz, 1H), 3.97 (d, J = 8.9 Hz, 1H), 3.00 (m, 1H), 2.94 (q, J =7.6 Hz, 2H), 2.58 (dt, J = 9.3, 13.6 Hz, 1H), 1.35 (t, J = 7.6 Hz, 3H), 0.77 (s, 9H), 0.63 (s, 3H), 0.62 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 201.1, 200.2, 138.8, 137.5, 134.0, 133.0, 132.9, 121.0, 116.5, 104.2, 56.9, 56.8, 29.7, 27.6, 26.3, 20.2, 14.4, -1.3, -1.4.

HRMS (EI) *m/e* calcd for $C_{21}H_{29}NO_2Si$ 355.1968, found 355.1966.

Mp = 136-138 °C.



45.3 45.4

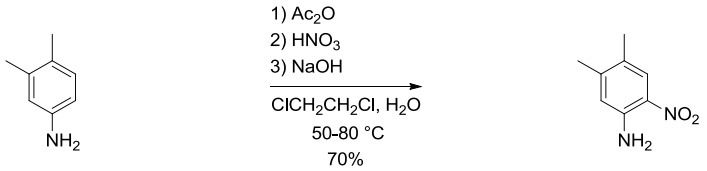
(±)-6,8-bis(bis(ethylthio)methyl)-4-ethyl-1,6,7,8-tetrahydrocyclopenta[*g*]indole (45.4):

In a 50 mL flame-dried round-bottom flask under nitrogen was added a solution of 108 mg (0.304 mmol) (±)-1-(*tert*-butyldimethylsilyl)-4-ethyl-1,6,7,8-tetrahydrocyclopenta[*g*]indole-6,8-dicarbaldehyde **45.3** in 10 mL ethanethiol. This solution was cooled to -78 °C, then 4 drops of $BF_3{\cdot}OEt_2$ was added 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% ethyl acetate in hexanes as eluent to give 98 mg (71%) of the title compound as a pale purple oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.14 (bs, 1H, NH), 7.22 (dd, *J* = 3.0, 2.6 Hz, 1H), 7.03 (s, 1H), 6.57 (dd, *J* = 3.2, 2.1 Hz, 1H), 4.53 (d, *J* = 4.7 Hz, 1H), 4.25 (d, *J* = 3.8 Hz, 1H), 3.88 (m, 1H), 3.75 (m, 1H), 2.99-2.47 (m, 12H), 1.41-1.32 (m, 9H), 1.27-1.21 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0 135.6, 132.5, 126.8, 123.0, 122.8, 114.6, 100.7, 55.1, 54.8, 49.2, 48.3, 35.7, 27.0, 26.4, 26.3, 26.12, 26.09, 14.8, 14.6, 14.52, 14.50, 14.4.

HRMS (EI) *m/e* calcd for $C_{23}H_{35}NS_4$ 453.1656, found 453.1655.



43.5 **46.1**

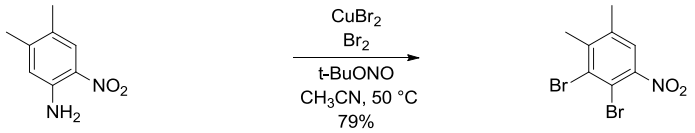
4,5-dimethyl-2-nitroaniline (46.1): See 4-ethyl-2-nitroaniline **(44.1)**. The crude material was purified via column chromatography on silica gel using 10% EA in hexanes as eluent to remove the minor isomer 3,4-dimethyl-2-nitroaniline.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 6.57 (s, 1H), 5.89 (s, 2H), 2.20 (s, 3H), 2.15 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 146.6, 143.1, 130.1, 126.0, 125.5, 119.0, 20.0, 18.5.

HRMS (EI) m/e calcd for $C_8H_{10}N_2O_2$ 166.0742, found 166.0743.

Mp = 135-137 °C.



46.1 46.2

2,3-dibromo-4,5-dimethyl-1-nitrobenzene (46.2):

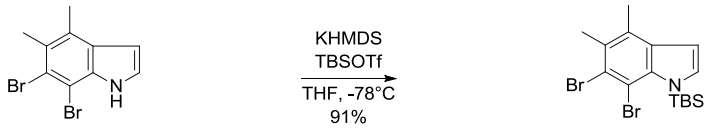
See 1,2-dibromo-5-ethyl-3-nitrobenzene **(44.2)**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (s, 1H), 2.51 (s, 3H), 2.36 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 149.3, 143.3, 138.0, 130.2, 124.4, 114.7, 22.1, 21.2.

HRMS (EI) m/e calcd for $C_8H_7Br_2NO_2$ 306.8844, found 306.8847.

Mp = 82-84 °C.



43.4 46.3

6,7-dibromo-1-(*tert*-butyldimethylsilyl)-4,5-dimethyl-1*H*-indole (46.3):

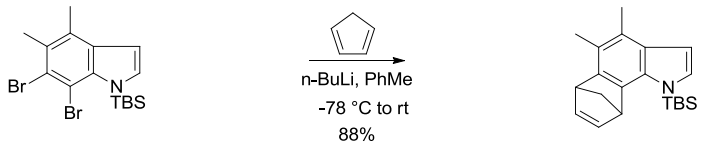
See 6,7-dibromo-1-(*tert*-butyldimethylsilyl)-4-ethyl-1*H*-indole **(44.3)**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 3.6 Hz, 1H), 6.61 (d, *J* = 3.6 Hz, 1H), 2.53 (s, 3H), 2.47 (s, 3H), 0.96 (s, 9H), 0.69 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0, 134.1, 133.1, 129.1, 127.5, 123.5, 106.5, 104.0, 27.5, 21.5, 19.9, 17.1, 2.1.

HRMS (EI) m/e calcd for $C_{16}H_{23}Br_2NSi$ 414.9967, found 414.9965.

Mp = 112-114 °C.



46.3 47.1

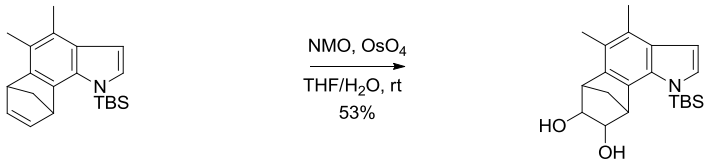
(±)-1-(*tert*-butyldimethylsilyl)-4,5-dimethyl-6,9-dihydro-1*H*-6,9-methanobenzo[*g*]indole (47.1):

See (±)-1-(*tert*-butyldimethylsilyl)-4-ethyl-6,9-dihydro-1*H*-6,9-methanobenzo[*g*]indole **(45.1)**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, J = 4.8 Hz, 1H), 6.92-6.91 (m, 1H), 6.85-6.84 (m, 1H), 6.55 (d, J = 4.4 Hz, 1H), 4.49 (s, 1H), 4.17 (s, 1H), 2.42 (s, 3H), 2.38 (s, 3H), 2.31 (d, J = 8 Hz, 1H), 2.22 (d, J = 8 Hz, 1H), 1.03 (s, 9H), 0.66 (s, 3H), 0.58 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 146.2, 144.7, 142.7, 134.9, 131.5, 131.3, 130.5, 123.3, 122.4, 103.6, 69.6, 51.0, 49.2, 26.7, 19.5, 15.6, 15.3, -1.5, -1.8.

HRMS (EI) m/e calcd for $C_{21}H_{29}NSi$ 323.2071, found 323.2070.



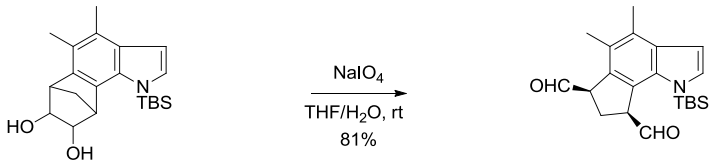
47.1 47.2

(±)-1-(*tert*-butyldimethylsilyl)-4,5-dimethyl-6,7,8,9-tetrahydro-1*H*-6,9-methanobenzo[*g*]indole-7,8-diol (47.2): See (±)-1-(*tert*-butyldimethylsilyl)-4-ethyl-6,7,8,9-tetrahydro-1*H*-6,9-methanobenzo[*g*]indole-7,8-diol **(45.2)**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, *J* = 3.6 Hz, 1H), 6.58 (d, *J* = 3.6 Hz, 1H), 3.77 (s, 2H), 3.72 (d, *J* = 1.6 Hz, 1H), 3.43 (d, *J* = 1.6 Hz, 1H), 3.20 (bs, 1H), 3.09 (bs, 1H), 2.42 (s, 3H), 2.33 (s, 3H), 2.21 (dt, *J* = 9.6, 1.2 Hz, 1H), 1.88 (dt, *J* = 9.2, 1.6 Hz, 1H), 0.99 (s, 9H), 0.69 (s, 3H), 0.58 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0, 133.9, 131.8, 131.4, 125.8, 125.1, 122.1, 103.6, 71.6, 70.9, 50.7, 48.9, 41.9, 26.7, 19.5, 15.7, 15.2, -1.5, -1.9.

HRMS (EI) m/e calcd for $C_{21}H_{31}NO_2Si$ 357.2125, found 357.2128.



47.2 47.3

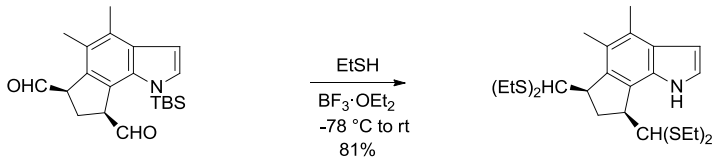
(±)-1-(*tert*-butyldimethylsilyl)-4,5-dimethyl-1,6,7,8-tetrahydrocyclopenta[*g*]indole-6, 8-dicarbaldehyde (47.3):

See (±)-1-(*tert*-butyldimethylsilyl)-4-ethyl-1,6,7,8-tetrahydrocyclopenta[*g*]indole-6,8-dicarbaldehyde **(45.3)**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (s, 1H), 9.53 (d, *J* = 2.4 Hz, 1H), 7.26 (d, *J* = 3.6 Hz, 1H), 6.67 (d, *J* = 3.6 Hz, 1H), 4.51 (d, *J* = 8.8 Hz, 1H), 4.04 (dd, *J* = 2.4, 8.8 Hz, 1H), 2.90 (d, *J* = 13.6 Hz, 1H), 2.60-2.53 (m, 1H), 2.47 (s, 3H), 2.29 (s, 3H), 0.75 (s, 9H), 0.61 (s, 3H), 0.60 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 201.1, 200.2, 137.0, 134.4, 133.7, 133.1, 128.9, 125.3, 121.0, 104.5, 57.0, 56.3, 29.7, 28.5, 26.3, 20.3, 16.0, 15.9, 1.0, -1.2, -1.5.

HRMS (EI) m/e calcd for $C_{21}H_{29}NO_2Si$ 355.1968, found 355.1968.



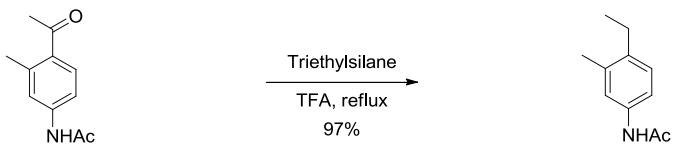
47.3 **47.4**

6,8-bis(bis(ethylthio)methyl)-4,5-dimethyl-1,6,7,8-tetrahydrocyclopenta[*g*]indole (47.4): See (±)-6,8-bis(bis(ethylthio)methyl)-4-ethyl-1,6,7,8-tetrahydrocyclopenta[*g*]indole **(45.4)**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.02 (s, 1H), 7.16 (dd, J = 2.4, 3.2 Hz, 1H), 6.49 (dd, J = 2.0, 2.8 Hz, 1H), 4.63-4.60 (m, 2H), 3.96-3.92 (m, 1H), 3.68-3.65 (m, 1H), 2.93-2.84 (m, 1H), 2.80-2.70 (m, 3H), 2.67-2.57 (m, 2H), 2.45 (s, 3H), 2.40-2.36 (m, 1H), 2.34 (s, 3H), 2.30-2.20 (m, 3H), 1.38-1.31 (m, 6H), 1.07 (t, J = 7.6 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 131.7, 128.6, 127.6, 124.2, 123.2, 123.0, 100.9, 56.3, 54.7, 50.3, 35.1, 31.6, 27.3, 26.6, 26.2, 25.5, 22.6, 16.2, 15.8, 14.8, 14.7, 14.5.

HRMS (EI) m/e calcd for $C_{23}H_{35}NS_4$ 453.1656, found 453.1654.

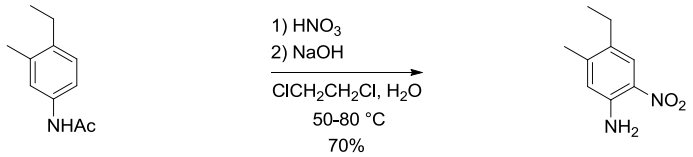


48.1 **48.2**

N-(4-ethyl-3-methylphenyl)acetamide (48.2):[141] 4.50 g **48.1** was dissolved in 18.8 mL trifluoroacetic acid and then triethylsilane was added into the solution. The mixture was refluxed for 5 hours. Then the solution was cooled down to room temperature, followed by very slow addition of $NaHCO_3$ saturation until evolution of gas had ceased and the solution remained alkaline. The mixture was then extracted with Et_2O and the combined organic phase was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure, which gave the crude product containing lots of triethylsilane. The crude material was then washed and filtered with hexane several times to give 4.04 g (90%) of the title compound as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.29-7.20 (m, 2H), 7.02 (d, J = 8.0 Hz, 1H), 2.53 (q, J = 7.5 Hz, 2H), 2.20 (s, 3H), 2.10 (s, 3H), 1.13 (t, J = 7.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.59, 138.12, 135.87, 135.70, 127.86, 122.11, 118.24, 25.45, 23.74, 18.91, 14.23.

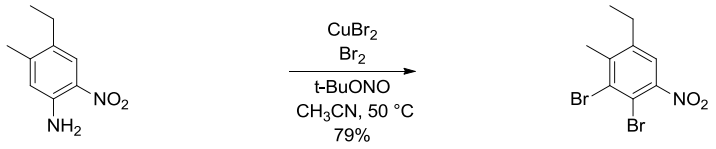


48.2 **48.3**

4-ethyl-5-methyl-2-nitroaniline (48.3): In a 100 mL round-bottom flask was added 23.4 mL 1,2-dichloroethane. To this was added 3.94 g (22.3 mmol) N-(4-ethyl-3-methylphenyl)acetamide (**48.2**) and the solution was heated to 50 °C and 2.2 mL (53.5 mmol) of fuming nitric acid was added dropwise over 1 hour. The solution was then stirred at 45-50 °C for 1 h. To the solution was then added 3.2 g (80 mmol) of sodium hydroxide dissolved in a minimum volume of water over a 10 min period. The temperature was raised to above 80 °C and the 1,2-dichloroethane was distilled out of the reaction mixture, after which point the temperature was raised to between 95 and 97 °C and the reaction was monitored by TLC. After TLC analysis showed complete hydrolysis of the intermediate amide, 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 (1 x 50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified via column chromatography on silica gel using 10% EA in hexanes as eluent to give 2.8 g (71%) of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 6.57 (s, 1H), 5.90 (s, 2H), 2.50 (q, J = 7.5 Hz, 2H), 2.23 (s, 3H), 1.18 (t, J = 7.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 146.28, 143.09, 132.24, 130.71, 124.25, 119.54, 25.13, 19.74, 14.27.



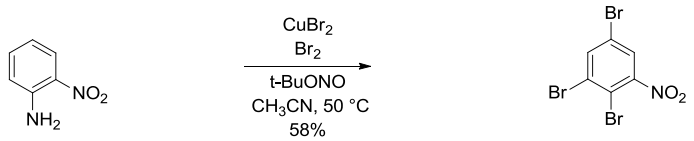
48.3 **48.4**

2,3-dibromo-5-ethyl-4-methyl-1-nitrobenzene (48.4):

See 1,2-dibromo-5-ethyl-3-nitrobenzene **(44.2)**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (s, 1H), 2.71 (q, *J* = 7.5 Hz, 2H), 2.53 (s, 3H), 1.22 (t, *J* = 7.5 Hz, 3H).

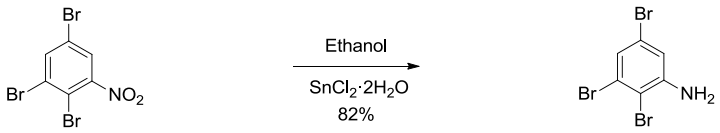
^{13}C NMR (100 MHz, $CDCl_3$) δ 144.00, 142.89, 130.91, 123.18, 114.99, 110.00, 27.82, 21.77, 14.18.



50.1 **50.2**

1,2,5-tribromo-3-nitrobenzene (50.2): In a 500 mL three-necked round-bottom flask was added 446 mg (2 mmol) $CuBr_2$. This was dissolved in 40 mL acetonitrile and the solution was heated to 50 °C. After 5 min, 2.11 mL (41 mmol) of bromine dissolved in 10 mL acetonitrile was added to the warm solution, followed by a solution of 1.38 g (10 mmol) 2-nitroaniline (**50.1**) in a minimum volume of acetonitrile. The mixture was stirred at 50 °C for 2 hours; then a solution of 1.44 mL (12 mmol) *t*-butyl nitrite in 60 mL acetonitrile was added to the reaction mixture dropwise over a period of 1 h. The mixture was then stirred at 50 °C for 1 hour; then cooled to room temperature. The reaction mixture was then quenched with 50 mL saturated sodium sulfite and subsequently poured into 300 mL 3 N HCl. The aqueous mixture was extracted with 300 mL diethyl ether once and 100 mL diethyl ether once. The combined organic layer was washed with 100 mL 3 N HCl, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was then passed through a plug of silica gel, eluting with 1:1 hexane/ether to give 2.08 g (58%) of the title compound as a brown solid.

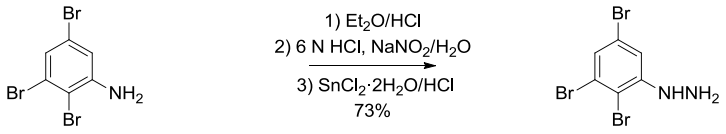
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 2.2 Hz, 1H), 7.75 (d, J = 2.2 Hz, 1H).



50.2 51.1

2,3,5-tribromoaniline (51.1): In a 50 mL round-bottom flask was added 1,2,5-tribromo-3-nitrobenzene (1 g, 2.78 mmol) in 17 mL absolute ethanol. To this solution 3.14 g $SnCl_2 \cdot 2H_2O$ (13.9 mmol, 5 eq) was added; then, the mixture was heated to 70 ºC and stirred for 1 hour at this temperature. After that, the solution was poured directly onto 111 g of ice. The aqueous phase was adjusted to pH 9 with 2 N NaOH and extracted with ether. The organic phase was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give 753 mg (82%) of the title compound as a yellow solid.

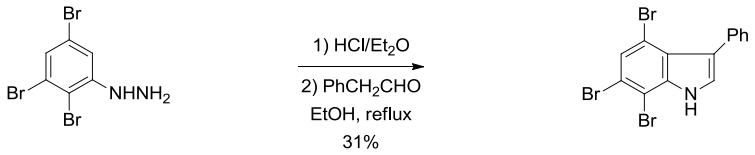
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, J = 2.1 Hz, 1H), 6.81 (d, J = 2.1 Hz, 1H).



51.1 51.2

(2,3,5-tribromophenyl)hydrazine (51.2): In a 50 mL round-bottom flask was added 2,3,5-tribromoaniline (1 g, 3.03 mmol) in small amount ether. To this solution 15 mL HCl/Et_2O (2 M, 30 mmol, 10 eq) was added and the mixture was stirred for 1 hour. Then the white salts were filtered and washed with Et_2O and dried by vacuum. Dissolved the dried white salts in 50 mL HCl (6 N) and kept it at 0 ºC. To this solution added 230 mg $NaNO_2$ (3.33 mmol, 1.1 eq) in minimum water dropwise. Kept stirring at 0 ºC for 30 min, then added 2.05 g $SnCl_2 \cdot 2H_2O$ (9.09 mmol, 3 eq) (dissolved in 12 N HCl) dropwise into the solution and kept stirring at 0 ºC for 1 hour. After that, filtered the solution and got white solid. Kept stirring the white solid with a mix solvent of 2 N NaOH solution and TBME for 30 min; then separated the organic phase and dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give 762 mg (73%) of the title compound as a yellow solid.

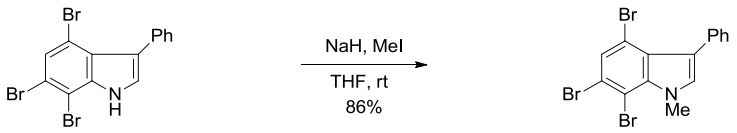
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J = 2.2 Hz, 1H), 7.17 (d, J = 2.2 Hz, 1H), 5.93 (s, 1H), 3.85 (s, 2H).



51.2 **51.3**

4,6,7-tribromo-3-phenyl-1*H*-indole (51.3): See 6,7-dibromo-3-phenyl-*1H*-indole (**20.7a**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 7.56 (s, 1H), 7.48-7.43 (m, 2H), 7.42-7.37 (m, 3H), 7.20 (d, J = 2.5 Hz, 1H).



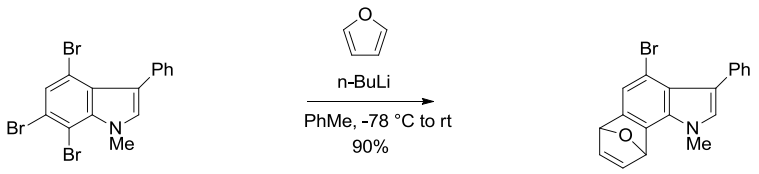
51.3 **51.4**

4,6,7-tribromo-1-methyl-3-phenyl-1*H*-indole (51.4):

See 5,6-Dichloro-1-methyl-3-phenyl-1*H*-indole **(18.6)**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (s, 1H), 7.43-7.34 (m, 5H), 6.99 (s, 1H), 4.19 (s, 3H).

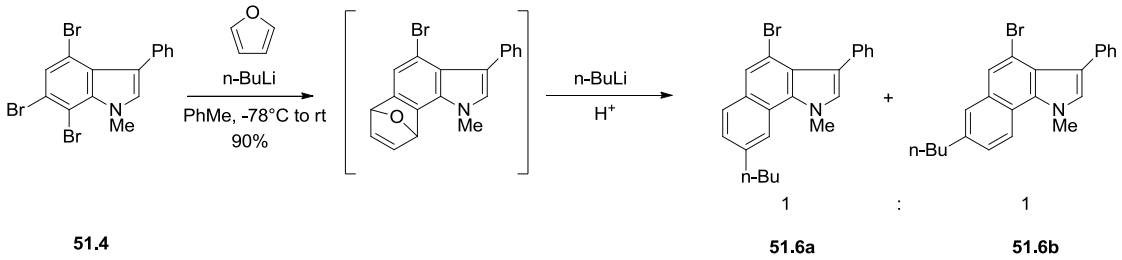
^{13}C NMR (100 MHz, $CDCl_3$) δ 134.99, 133.92, 133.27, 131.67, 128.64, 127.43, 127.18, 126.60, 119.69, 118.37, 114.24, 106.47, 38.41.



51.4 **51.5**

4-bromo-1-methyl-3-phenyl-6,9-dihydro-1*H*-6,9-epoxybenzo[*g*]indole (51.5): In a flame-dried 25 mL round-bottom flask was added a solution of 44 mg (0.099 mmol) 4,6,7-tribromo-1-methyl-3-phenyl-1*H*-indole (**51.4**) in 2 mL dry toluene. To this was added 144 μL (1.98 mmol, 20 eq) of furan. The resulting solution was cooled to -78 °C, then 40 μL (0.099 mmol 1 eq) 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 was allowed to slowly warm to room temperature. The reaction was then quenched by addition of 10 mL saturated ammonium chloride. After stirring for 5 min, the mixture was diluted with 10 mL water and extracted with 3 x 10 mL dichloromethane. 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 15% EA in hexanes as eluent to give 31 mg (90%) of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.39 (m, 2H), 7.36-7.31 (m, 4H), 7.12 (ddd, J = 11.9, 5.5, 1.7 Hz, 2H), 6.93 (s, 1H), 6.28 (s, 1H), 5.82 (s, 1H), 3.91 (s, 3H).



51.4 **51.6a** **51.6b**

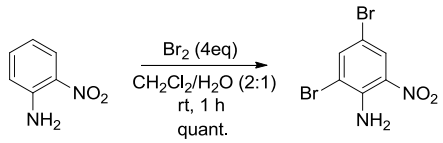
4-bromo-8-butyl-1-methyl-3-phenyl-1H-benzo[*g*]indole (51.6a):

See 4-bromo-1-methyl-3-phenyl-6,9-dihydro-1*H*-6,9-epoxybenzo[*g*]indole (**51.5**), except for using 2 eq n-BuLi instead of 1 eq n-BuLi.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, *J* = 8.7 Hz, 1H), 7.66 (s, 1H), 7.60 (s, 1H), 7.51-7.45 (m, 2H), 7.40-7.32 (m, 4H), 7.00 (s, 1H), 4.30 (s, 3H), 2.81-2.74 (m, 2H), 1.73-1.62 (m, 2H), 1.44-1.30 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H).

4-bromo-7-butyl-1-methyl-3-phenyl-1*H*-benzo[g]indole (51.6b):

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.74 (d, *J* = 8.3 Hz, 1H), 7.67 (s, 1H), 7.48 (dd, *J* = 7.8, 1.7 Hz, 2H), 7.40-7.32 (m, 3H), 7.29 (d, *J* = 8.3 Hz, 1H), 7.01 (s, 1H), 4.32 (s, 3H), 2.86-2.77 (m, 2H), 1.76-1.65 (m, 2H), 1.40 (dd, *J* = 14.9, 7.4 Hz, 2H), 0.95 (t, *J* = 7.4 Hz, 3H).



50.1 **52.1**

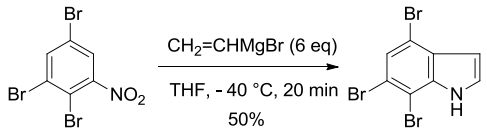
2,4-dibromo-6-nitroaniline (52.1)

In a 1.0 L round-bottom flask **50.1** (13.8 g, 100 mmol) was dissolved in 200 mL CH_2Cl_2/MeOH (2:1). To this mixture was added a solution of Br_2 (63.9 g, 4 eq) in 100 mL CH_2Cl_2 dropwise and stirred at rt for 1h. The reaction mixture was then quenched with saturated $NaHCO_3$ and $Na_2S_2O_3$. The aqueous mixture was extracted with ethyl acetate, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give 29.59 g of the title compound 4,6-dibromo-2-nitroaniline **52.1**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 6.2 Hz, 1H), 7.80 (d, *J* = 6.4 Hz, 1H), 6.60 (bs s, 2H, NH_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ 141.2, 140.8, 128.2 (2C), 112.7, 106.8.

Mp = 127.8-129.3 ºC.



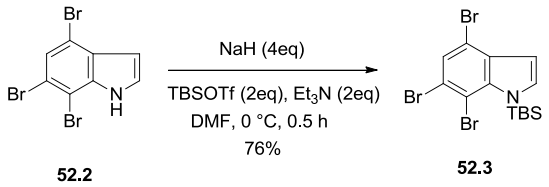
50.2 **52.2**

4,6,7-tribromo-1*H*-indole (52.2): See 6,7-dibromo-4-ethyl-1*H*-indole (**35.1**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (bs s, 1H, NH), 7.53 (s, 1H), 7.28 (m, 1H), 6.65 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 128.2, 126.7, 125.7, 117.2, 114.1, 106.5, 104.7.

Mp = 97.0-99.0 ºC.



52.2 52.3

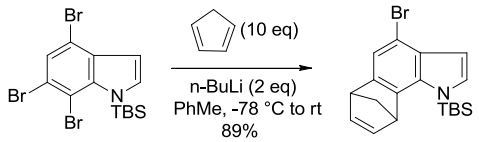
4,6,7-tribromo-1-(*tert*-butyldimethylsilyl)-1*H*-indole (52.3):

In a 100 mL three-necked round-bottom flask was added 10 mL DMF. To this was added 57.3 mg Et_3N (0.57 mmol, 2 eq) and the mixture was cooled to 0 ºC. Then 27.2 mg sodium hydride (1.13 mmol, 4 eq) was added, followed by 100 mg **52.2** (0.28 mmol). The mixture was stirred at 0 ºC for 30 min, after that, a solution of 139.4 mg TBSOTf (0.57 mmol, 2 eq) was added dropwise. The solution was strirred at 0 ºC for another 30 min. After quenched with water, the aqueous mixture was extracted with ethyl acetate, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude products were purified via column chromatography on silica gel to give 103.7 mg title compound.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.43 (d, J = 3.6 Hz, 1H), 6.71 (d, J = 3.3 Hz, 1H), 0.99 (s, 9H), 0.73 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 140.7, 135.4, 133.4, 127.6, 119.4, 113.7, 108.0, 106.2, 27.4, 19.9, 2.2.

Mp = 90.5-91.6 ºC.



52.3 53.2

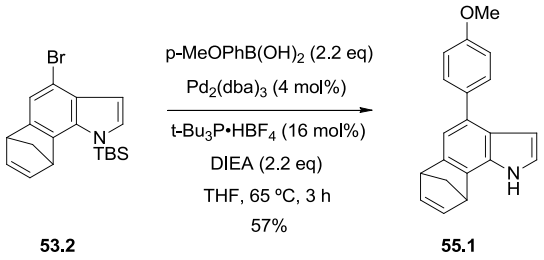
4-bromo-1-(*tert*-butyldimethylsilyl)-6,9-dihydro-1*H*-6,9-methanobenzo[*g*]indole (53.2): See

(±)-1-(*tert*-butyldimethylsilyl)-4-ethyl-6,9-dihydro-1*H*-6,9-methanobenzo[*g*]indole (**45.1**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (s, 1H), 7.22 (d, *J* = 3.3 Hz, 1H), 6.92 (m, 1H), 6.84 (m, 1H), 6.64 (d, *J* = 3.5 Hz, 1H), 4.48 (s, 1H), 3.98 (s, 1H), 2.36-2.26 (m, 2H), 1.04 (s, 9H), 0.69 (s, 3H), 0.61 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 145.0, 142.0, 136.9, 134.2, 132.4, 130.8, 118.6, 109.2, 105.4, 70.4, 51.0, 50.6, 26.6, 19.4, -1.5, -1.8.

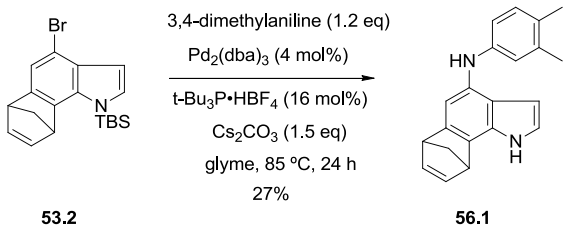
Mp = 114.1-115.2 ºC.



53.2 **55.1**

4-(4-methoxyphenyl)-6,9-dihydro-1*H*-6,9-methanobenzo[*g*]indole (55.1): A 5 mL vial was flame-dried, flowed with argon. To the vial was added $Pd_2(dba)_3$ (4.6 mg, 0.0044 mmol, 4 mol%), t-Bu_3P•HBF_4 (5.1 mg, 0.018 mmol, 16 mol%) and p-$MeOPhB(OH)_2$ (33.7 mg, 0.22 mmol, 2.2 eq). Placed the vial under vacuum and flowed with argon. To the vial was added a solution of 41.6 mg **53.2** (0.11 mmol) and DIEA (0.24 mmol, 2.2 eq) in THF. Heated the solution to 60-70 ºC and stirred for 3 h. Then cooled it to room temperature and worked up as usual. A flash column chromatography purification gave 18.2 mg (57%) title compound.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (bs, 1H), 7.30 (s, 1H), 7.20-7.14 (m, 1H), 6.91-6.72 (m, 4H), 6.56-6.50 (m, 1H), 4.13 (s, 1H), 4.00 (s, 1H), 3.75 (s, 3H), 2.42-2.36 (m, 2H), 2.35-2.30 (m, 2H).



53.2 **56.1**

N-(3,4-dimethylphenyl)-6,9-dihydro-1*H*-6,9-methanobenzo[*g*]indol-4-amine (56.1):

In a 5 mL vial was added $Pd_2(dba)_3$ (4.3 mg, 0.0042 mmol, 4 mol%), t-Bu_3P•HBF_4 (4.9 mg, 0.017 mmol, 16 mol%), Cs_2CO_3 (51.3 mg, 0.16 mmol, 1.5 eq) and 3,4-dimethylaniline (16 mg, 0.13 mmol, 1.2 eq). This vial was sealed and placed under vacuum, then flowed with argon. To the vial was added a solution of 39.4 mg **53.2** (0.11 mmol) in glyme, and then it was heated to 80-85 ºC for 24 h. The reaction was quenched with water and extracted with t-BuOMe. Organic layer was separated and dried over $MgSO_4$, filtered, concentrated under vacuum. The crude material was then purified via column chromatography on silica gel using 15% EA in hexanes as eluent to give 8.5 mg (27%) of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (bs, 1H), 7.30 (s, 1H), 7.19-7.14 (m, 1H), 7.08-6.79 (m, 6H), 6.57-6.50 (m, 1H), 4.13 (s, 1H), 3.99 (s, 1H), 2.42-2.29 (m, 2H), 2.20 (s, 6H).

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