Some Synthetic Applications of 3,4-disubstituted Indoles Generated *via* Zirconocene-Stabilized Benzyne Complexes

By John Limanto

B. S. Chemistry, University of Wisconsin at Madison, 1995

Submitted to the Department of Chemistry in
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Department of Chemistry
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Abstract

A method previously developed for the regiospecific synthesis of polysubstituted indolines and indoles has been investigated for its utility in organic synthesis. The method relies on the regiospecific generation of zirconocene-stabilized benzyne complexes from *N*-allyl-2-bromoaniline derivatives. These complexes undergo an intramolecular olefin insertion to provide 5,5,6-tricyclic indoline zirconacycles, which can be cleaved with iodine to provide regiochemically pure 3-iodomethyl-4-iodoindoline derivatives. These derivatives are then converted into 3-bromomethyl-4-iodoindoles, which have been shown to be versatile synthetic intermediates in the preparation for other polyfunctionalized indole derivatives.

Initially, we investigated the utility of 3-bromomethyl-4-iodoindole derivatives for the preparation of enantiomerically pure 4-iodotryptophan compounds. The synthesis involved asymmetric alkylation of Schöllkopf's bis-

lactim ethers, followed by hydrolysis of the alkylated product to generate the desired chiral tryptophan. In addition we also studied the synthesis of α-substituted-4-iodotryptophan derivatives *via* a double alkylation of the Schöllkopf's *t*-butyl bis-lactim ether to generate trisubstituted bis-lactim ethers. The hydrolysis of such ethers, however, proved to be problematic.

We have further applied the zirconocene-benzyne method towards the synthesis of two biologically active marine alkaloids, eudistomin D and eudistomidin D. Since these alkaloids contain a 3,4,5-trisubstituted indole fragment of their β-carboline ring systems, we anticipated to form such fragment by an electrophilic cleavage reaction of a 5,5,6-tricyclic zirconacyle intermediate, generated *via* zirconocene-benzyne complexes.

Thesis Supervisor : Stephen L. Buchwald

Title : Camille & Henry Dreyfus Professor of Chemistry

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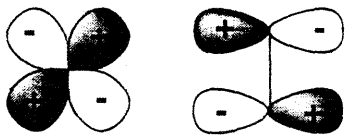
INTRODUCTION

Zirconium, relatively inexpensive and one of the most abundant elements on earth, and its complexes are of broad utility in the area of organometallic and synthetic organic chemistry.[1] Since the synthesis of the first zirconocene complex Cp_2ZrBr_2, in 1953,[2] the area of zirconocenes and their synthetic applications has rapidly developed and still expands at a considerable pace.[3]

During the past decade, a major focus of research in the Buchwald group has been the study of zirconium complexes with highly unstable unsaturated ligands, such as cycloalkynes[4] and benzynes.[5] In order to understand the chemistry of these types of complexes, one must first gain sufficient understanding of their structure and bonding.

In general, while transition metals have partially filled d orbitals and empty s and p orbitals, most organic ligands have filled sp^n hybrid orbitals, and in the case of unsaturated ligands, vacant anti-bonding π^* orbitals which share similar symmetry and energy to those of the filled d orbitals on the metals (Figure 1).[6] According to the bonding model proposed by Dewar, Chatt and Duncanson, there are two different types of interactions between the frontier molecular orbitals of the metal and the organic ligand: σ-donor and π-donor (Figure 2).[7] σ-Donor bonds are formed by the overlap of the filled π-bonding

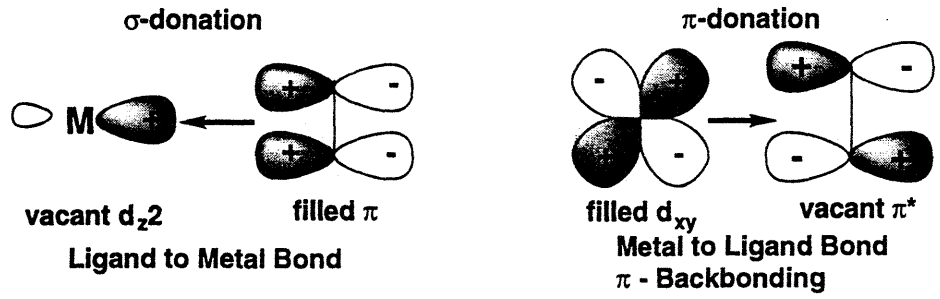
Figure 1 : Symmetry of Metal's d orbitals and ligand's π^* Orbitals



orbital of the ligand with the empty d_{z2} hybrid orbital on the metal, allowing electron density to flow from the ligand to the metal. In contrast, π-donor bonds (π-backbonds) are formed by the interaction between the filled d orbital (e.g.

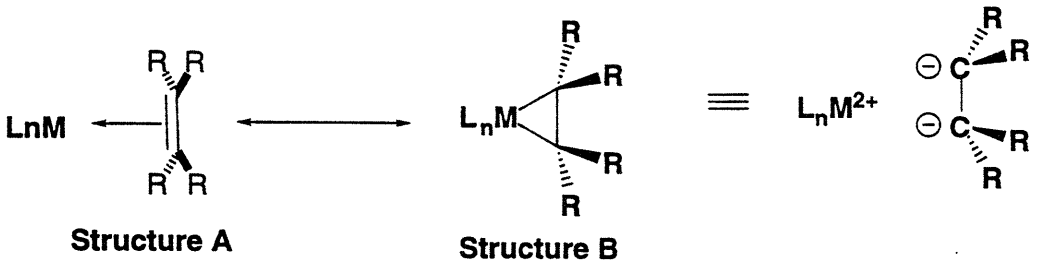
d_{xy}) of the metal with the vacant π^*-antibonding orbital of the ligand, allowing electron density to flow from the metal to the ligand. Note that π-backbonding usually occurs only if the metal is electron rich (in a low oxidation state).

Figure 2 : Dewar, Chatt, Duncanson Metal-Ligand Bond Model



Several consequences arise from these two metal-ligand interactions. As the electron density flows from an unsaturated ligand (such as an olefin) to the metal in σ-bonds, the metal becomes more electron rich and the π–bond of the ligand is weakened, causing an increase in the carbon-carbon bond length. The increase in bond length is also a result of π-backbonding; as the electron density from the metal is donated into the vacant π^* orbital, the C-C bond order is reduced. Furthermore, as π-backbonding occurs, substituents of the olefin bend out of the plane due to the change in the carbon hybridizations. This model of bonding leads to two resonance structures that need to be considered for olefin-complexes (Figure 3). Structure A represents a minimal π-backbonding between an electron-deficient metal and the olefinic ligand resulting in a similar C-C bond length to that of the uncomplexed olefin. Structure B (a metallacyclopropane) represents maximal π-backbonding between an electron-rich metal and the ligand, which results in lengthening of the C-C single bond and bond angle distortions. The actual bonding in metal-olefin complexes lies somewhere in the continuum between these two structures, as shown in Figure 3.

Figure 3.

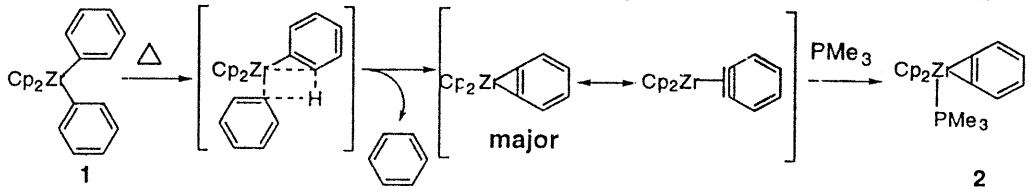


Structure A Structure B

The interaction of type B, in which there is a considerable amount of π-backbonding from the metal to the unsaturated ligand, allows the stabilization of highly reactive and strained unsaturated molecules such as cyclobutene,[8] cyclopentyne[4] and benzyne.[5] The remainder of this thesis will focus on the zirconocene stabilized benzyne complexes.

Evidence for the existence of a group 4 metallocene complex of benzyne came from the elegant mechanistic work of Erker in the late 1970s.[9] He studied the thermolysis of diaryl zirconocene **1** and obtained results that were consistent with the intermediacy of a zirconocene-benzyne complex. The formation of this intermediate was finally confirmed when Buchwald *et al* prepared and isolated the zirconocene-benzyne•PMe_3 complex **2**.[5] The X-ray crystal structure showed that the bond angles and bond lengths of the aromatic ring were approximately the same as those observed in benzene, suggesting significant π-backbonding between the metal and the ligand. Mechanistic studies on the formation of the metallocene-benzyne complexes were carried out by Erker.[10] These studies demonstrated that the reaction proceeds via a four-centered, concerted cyclometallation mechanism (Scheme 1).

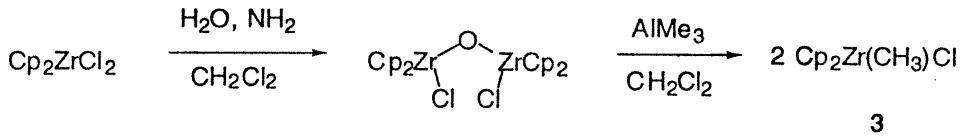
Scheme 1 : Four-centered, concerted cyclometallation mechanism



1 2

In addition to the thermolysis reaction shown above, an alternative route to Zr-benzyne complex was developed by Buchwald.[11,12] Aryl(methyl)zirconocene complex **5** was produced by a reaction between an aryllithium **4** and zirconocene(methyl) chloride **3**, prepared in two steps from the commercially available zirconocene dichloride (Scheme 2).[13] The overall reaction, as depicted in Scheme 3, generated methane gas and an ortho-

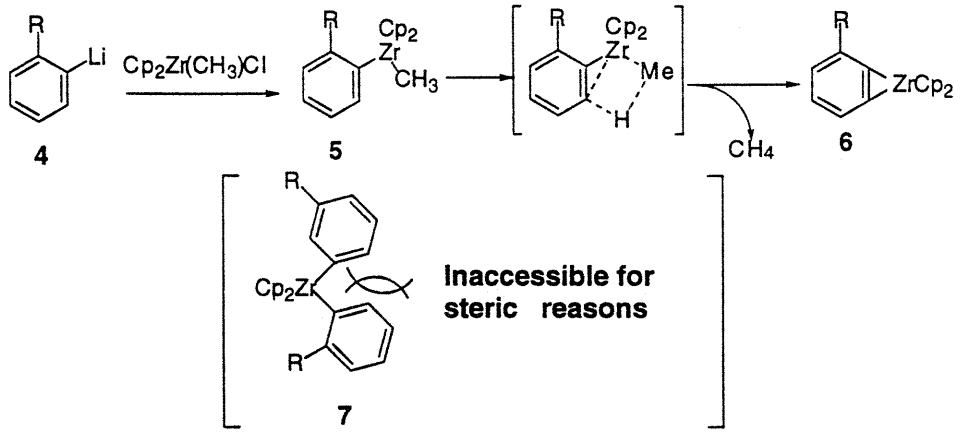
Scheme 2.



3

substituted benzyne complex **6**, which was not accessible by the original method since the required *o*-substituted diarylzirconocene **7** could not be formed for steric reasons. Furthermore, generation of the benzyne complex from an aryl(methyl)zirconocene was more efficient than the thermolysis of an *o*-substituted diarylzirconocene, since thermolysis of the latter would sacrifice one equivalent of the valuable *o*-substituted aryl moiety.

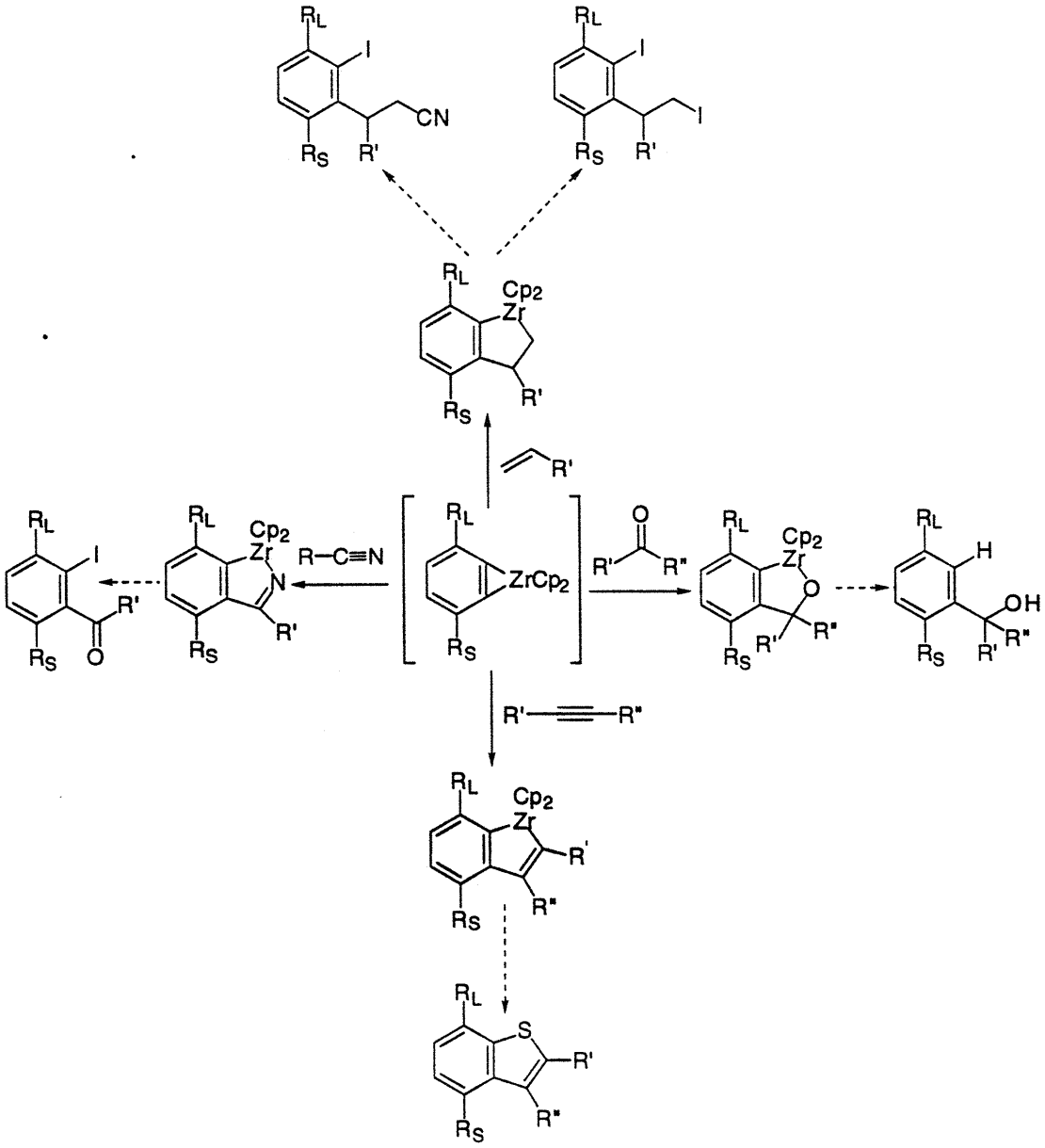
Scheme 3.



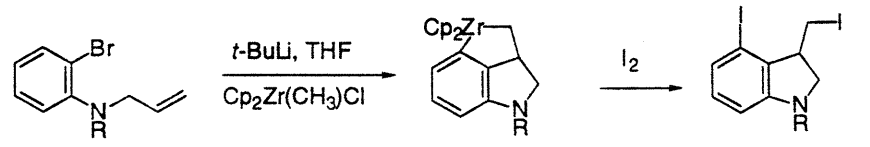
Applications of zirconocene-benzyne complexes to organic synthesis have been actively pursued in the Buchwald group. One of these applications involved a regioselective insertion reaction of unsaturated organic molecules to these complexes.[14] As depicted in Scheme 4, these insertions primarily occur from the side of the smaller substituent R_S of the aromatic ring. The resulting zirconocylopentane complexes were usually not isolated, but rather treated with various electrophiles to give a variety of highly functionalized compounds. Recently, Tidwell and Buchwald used an intramolecular version of this methodology to regiospecifically synthesize 3,4-diiodoindolines **8** (Scheme 5).[15]

The preparation and some synthetic applications of 3,4-diiodoindolines **8** and their derivatives, generated from the intramolecular olefin insertion into a zirconocene-benzyne complex followed by electrophilic cleavage, will be discussed in greater detail in the following chapters of this thesis.

Scheme 4.



Scheme 5.



R : allyl or benzyl

R : allyl or benzyl

8

References

References

1. Zirconium is ca. 10^4 times more abundant than palladium (*CRC Handbook of Chemistry and Physics*, 73rd Ed., **1992-1993**, p. **14**-7). The most readily available zirconocene, bis(cyclopentadienyl)zirconium dichloride, sells at $0.50-1.50/g.

2. Wilkinson, G.; Pauson, P. L.; Birmingham, J. M.; Cotton, F. A. *J. Am. Chem. Soc.* **1953**, *75*, 1011.

3. For an extensive overview of organozirconium chemistry, see : a) Cardin, D.J.; Lappert, M.F.; Ratson, C.L. *Chemistry of organo-zirconium and -hafnium compounds*; Wiley: New York, 1986. b) Wailes, P.C.; Coutts, R.S.P.; Weigold, H. *Organometallic chemistry of titanium, zirconium, and hafnium*; Academic Press, New York, 1974.

4. a) Buchwald, S.L.; Lum, R.T.; Fisher, R.A.; Davis, W.M. *J. Am. Chem. Soc.* **1989**, *111*, 9113. b) Buchwald, S.L.; Lum, R.T.; Dewan, J.C. *J. Am. Chem. Soc.* **1986**, *108*, 7441.

5. Buchwald, S. L.; Watson, B. T.; Huffman, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 7411.

6. For a more rigorous treatment of bonding, see : Collman, J.P.; Hegedus, L.S.; Finke, R.O.; Norton, J.R. *Principles and Applications of Organotransition Metal Chemistry.* University Science Books, Mill Valley, CA, 1987, pp. 21-56.

7. a) Chatt, J.; Duncanson, L.A. *J. Chem. Soc.* **1953**, 2939. b) Dewar, M.J.S. *Bull. Soc. Chim. Fr.* **1951**, *18*, C71.

8. Buchwald, S. L.; Fisher, R. A. *Organometallics* **1990**, 871.

9. a) Erker, G.; Albrecht, M.; Kruger, C.; Werner, S. *J. Am. Chem. Soc.* **1992**, *114*, 8531. b) Erker, G. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 396.

10. Erker, G. J. *Organometallics* **1977**, *134*, 189.

11. Buchwald, S. L.; Nielsen, R. B. *J. Am. Chem. Soc.* **1988**, *110*, 3171.

12. Buchwald, S. L.; Watson, B. T.; Lum, R. T.; Nugent, W. A. *J. Am. Chem. Soc.* **1987**, *109*, 7137.

13. Wailes, P. C.; Weigold, H.; Bell, A. P. *J. Organomet. Chem.* **1971**, *33*, 181-188.

14. a) Broene, R. D.; Buchwald, S.L. *Science* **1993**, *261*, 1696. b) Buchwald, S.L.; Fisher, R.A. *Chemica. Scr.* **1989**, *29*, 417. c) Bennett, M.A.; Schwemlein, H.P. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1296. d) Buchwald, S.L.; Nielsen, R.B. *Chem. Rev.* **1988**, *88*, 1047.

15. Tidwell, J. H; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 11797.

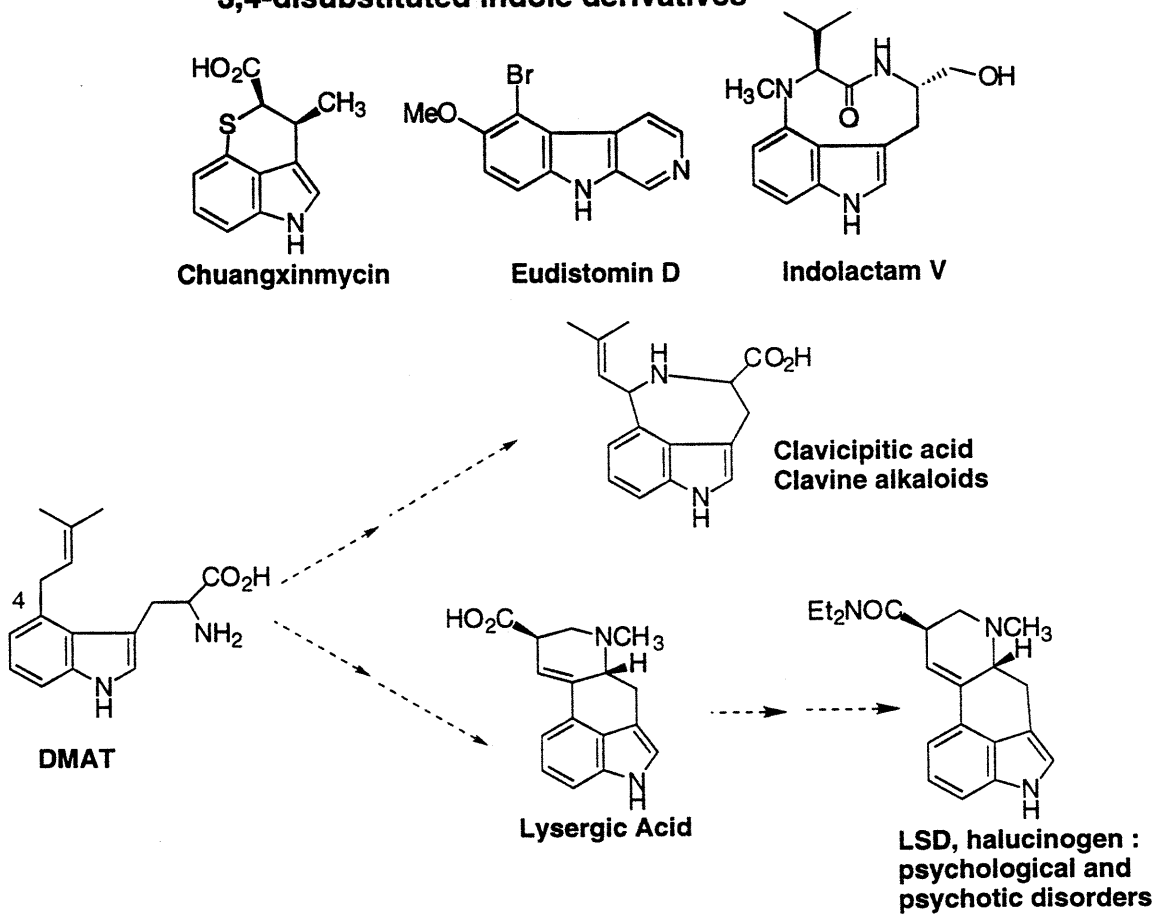
Chapter One

Efforts towards the synthesis of a chiral 4-iodotryptophan ester and α-substituted-4-iodotryptophan ester derivatives

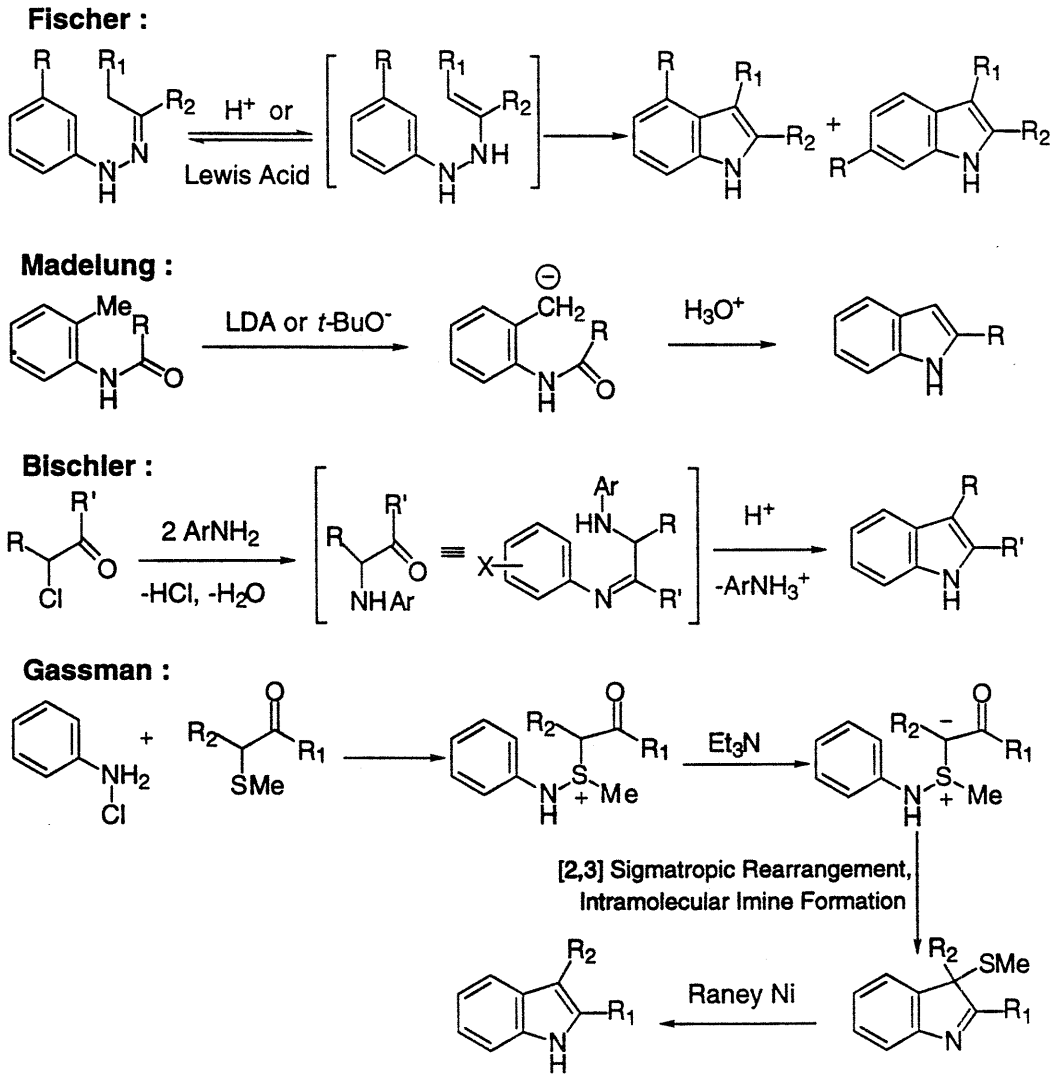
INTRODUCTION

Methods for generating 3,4-disubstituted indole ring systems are of interest as this type of structure is found in a large number of biologically active natural products,[1] including indolactam V,[2] chuangxinmycin,[3] and eudistomin D[4] (Figure 1). In addition, chiral 4-substituted tryptophan derivatives have also been found in various biologically active natural products. Dimethylallyltryptophan (DMAT), for example, has been found to be a significant intermediate for many biosynthetic pathways of clavine and ergot alkaloids.[5] Some of the final biosynthetic products generated by these alkaloids are clavicipitic acids and lysergic acid (Figure 1). The latter has been used as a

Figure 1 : Some biologically active 3,4-disubstituted indole derivatives

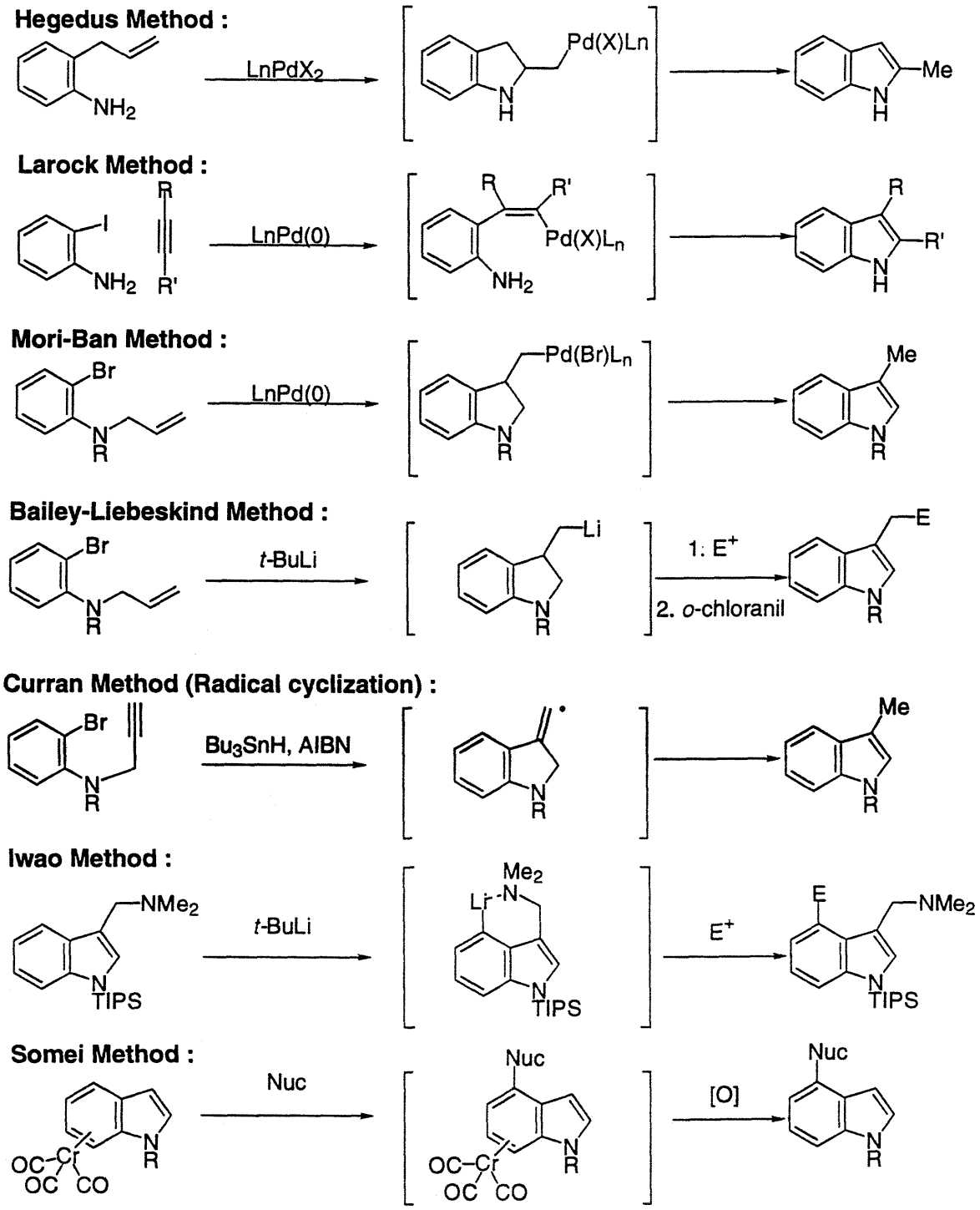


Scheme 1 : Classical Indole Syntheses

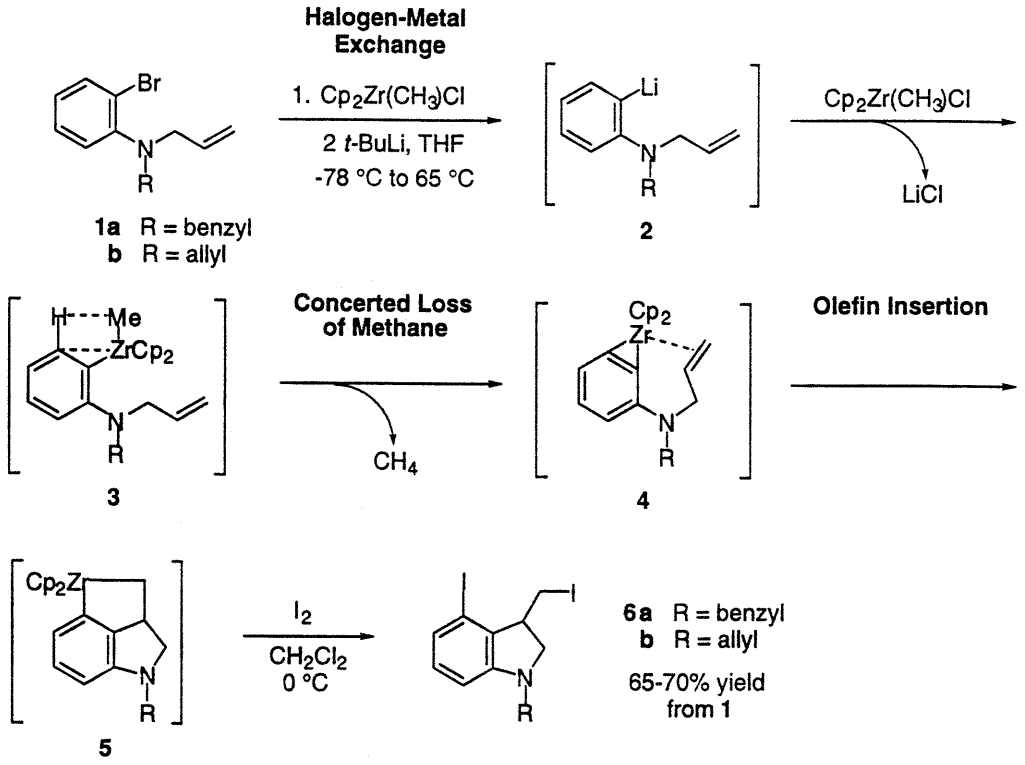


corresponding aryllithium **2**, which is then trapped with zirconocene methyl chloride to yield the aryl(methyl)zirconocene complex **3**. Upon warming, the desired zirconocene-benzyne complex **4** is generated with a concerted loss of methane. Coordination of the olefin to this benzyne complex followed by insertion, gives the 5,5,6 tricyclic zirconacycle **5**, which is cleaved by an electrophile such as iodine to yield the 3,4-diiodoindoline **6** in 65-70% yield.

Scheme 2 : Modern Indole Syntheses



Scheme 3.



During initial studies, Tidwell found that the 3,4-diiodoindoline derivative **6** was indeed a useful intermediate in the synthesis of many complex indoles. Dehydroiodination of this intermediate gave an exocyclic olefinic indoline, which upon treatment with alkenes or unsaturated electrophiles yielded various interesting ene products.[12] In addition, a diiodoindoline derivative was also used as the key intermediate in the synthesis of the pharmacophore of CC-1065 and duocarmycin A,[13] two potent antitumor antibiotics.[13,14]

Encouraged by the success of these studies, we wished to further apply our methodology to construct other interesting indoline and indole derivatives. In addition, we planned to apply the method towards synthesis of small biologically active molecules, including enantiomerically pure 4-substituted tryptophan derivatives, discussed in this chapter, and eudistomin D, discussed in a subsequent chapter.

References

1. a) *The Alkaloids*; The Chemical Society: London, 1971: Specialist Periodical Reports. b) Saxton, J.E. *Nat. Prod. Reports*, **1989**, *6*, 1. c) Hesse, M. *Alkaloid Chemistry*; WIley: New York, 1978. d) Cordell, G.A. *Introduction to Alkaloids: A Biogenetic Approach*; Wiley: New York, 1981. e) Gilchrist, T.L. *Heterocyclic Chemistry*; Pitman: London, 1981. f) Pindur, A.R. *J. Heterocyclic Chem.* **1988**, *25*, 1.

2. For lead references, see: a) Semmelhack, M.F.; Rhee, H. *Tetrahedron Lett.* **1993**, *34*, 1399. b) Kogan, T.P.; Somers, T.C.; Venuti, M.C. *Tetrahedron* **1990**, *46*, 6623.

3. a) Ishibashi, H.; Tabata, T.; Hanaoka, K.; Iriyama, H.; Akamatsu, S.; Ikeda, M.*Tetrahedron Lett.* **1993**, *34*, 489. b) Dickens, M.J.; Mowlem, T.J.; Widdowson, D.A.; Slawin, A.M.Z. *J. Chem. Soc., Perkin Trans. 1* **1992**, 323. c) Matsumoto, M.; Watanabe, N. *Heterocycles* **1987**, *26*, 1775. d) Murase, M.; Koike, T.; Moriya, Y.; Tobinaga, S. *Chem. Pharm. Bull.* **1987**, *35*, 2656. e) Kozikowski, A.P.; Greco, M.N.; Springer, J.P.; *J. Am. Chem. Soc.* **1982**, *104*, 7622.

4. Rinehart, R.L.; Kobayashi, J.; Harbour, G.C.; Gilmore, J.; Mascal, M.; Holt, T.G.; Shield, L.S.; Lafargue, F. *J. Am. Chem. Soc.* **1987**, *109*, 3378.

5. a) Plieninger, H.; Fischer, R.; Liede, V. *Ann. Chem.* **1964**, *672*, 223. b) Robbers, J.E.; Floss, H.G. *Arch. Biochem. Biophys.* **1968**, *126*, 967. c) Cheng, M.; Saini, M.S.; Anderson, J.A. *Phytochemistry* **1976**, *15*, 1497. d) Agurell, S.; Lindgren, J.-E. *Tetrahedron Lett.* **1968**, *49*, 5127.

6. Sundberg, R.J. *The Chemistry of Indoles*; Academic Press: New York, 1970.

7. Robinson, B. *The Fischer Indole Synthesis*; Wiley-Interscience: New York, 1982.

8. a) Brown, R.K. *Indoles*; Wiley-Interscience: New York, 1972. b) Houlihan, W.J.; Parrino, V.A.; Uike, Y. *J. Org. Chem.* **1981**, *46*, 4511.

9. a) Sundberg, R.J. *The Chemistry of Indoles*; Academic Press: New York, 1970, pp. 164. b) Bischler, A. *Ber.* **1893**, *26*, 1336.

10. Gassman, P.G. *J. Am. Chem. Soc.* **1974**, *96*, 5508.

11. a) Larock, R.C.; Yum, E.K.; *J. Am. Chem. Soc.* **1991**, *113*, 6689. b) Hegedus, L.S. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1113. c) Zhang, D.; Liebeskind, L.S. *J. Org. Chem.* **1996**, *61*, 2594. d) Bailey, W.F.; Jiang, X.-L. *J. Org. Chem.* **1996**, *61*, 2596. e) Iwao, M. *Heterocycles* **1993**, *36*, 29. f) Gill, U.S.; Moriarty, R.M.; Ku, Y.Y.; Butler, I.R. *J. Organometallic Chem.* **1991**, *417*, 313. g) Semmelhack, M.F.; Rhee, H. *Tetrahedron Lett.* **1993**, *34*, 1395. h) Boger, D.L. *J. Am. Chem. Soc.* **1988**, *110*, 4796.

12. a) Tidwell, J.H.; Buchwald, S.L. *J. Am. Chem. Soc.* **1994**, *116*, 11797. b) Tidwell, J.H.; Buchwald, S.L. *J. Org. Chem.* **1992**, *57*, 6380. c) Tidwell, J. H.; Senn, D.R.; Buchwald, S.L. *J. Am. Chem. Soc.* **1991**, *113*, 4685.

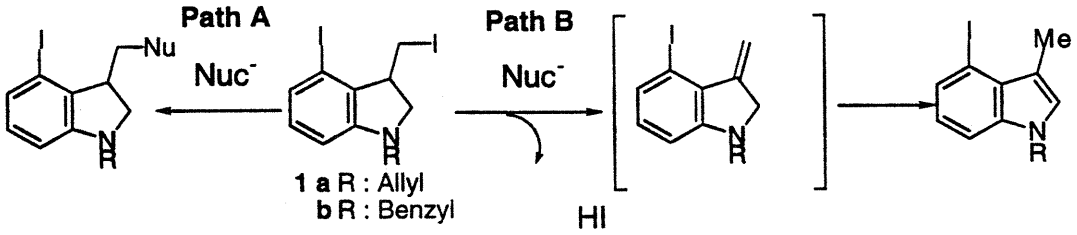
13. Tietze, L.F.; Buhr, W. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1366.

14. Boger, D.L.; Boyce, C.W.; Garbaccio, R.M.; Goldberg, J.A. *Chem. Rev.* **1997**, *97*, 787.

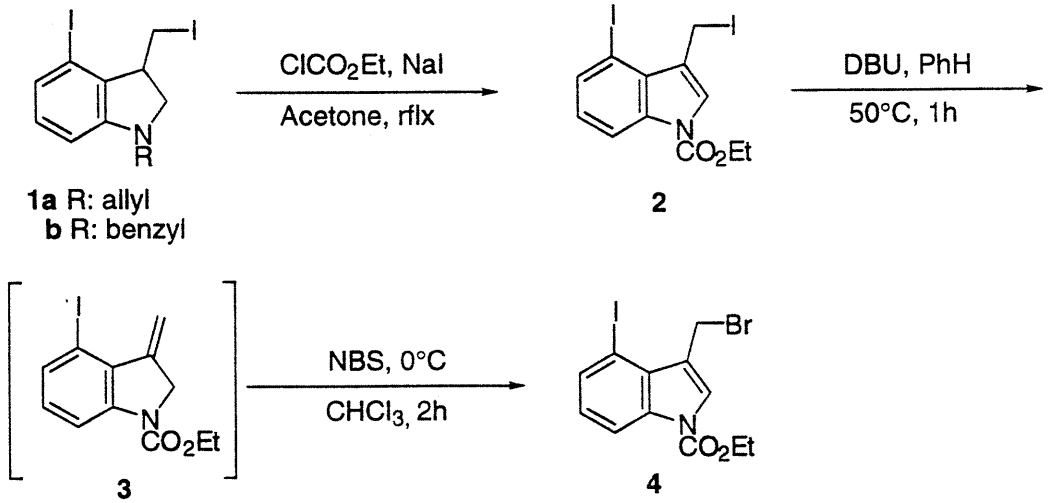
Results and Discussions

During initial investigations towards the further elaboration of the diiodoindoline derivative **1**, Tidwell and Buchwald attempted to displace the alkyl iodide with various nucleophiles (Scheme 1).[1] Unfortunately, an elimination-isomerization reaction (path B) competed favorably with the desired nucleophilic substitution reaction (path A). However, the 3-bromomethyl-4-iodoindole derivative **4**, which was synthesized as shown in Scheme 2,[2] was found to be an excellent electrophile for various nucleophilic substitution reactions.[3,4] Additionally, **4** could be transformed by employing Pd-catalyzed cross coupling reactions to further functionalize its 4-position.[1,3]

Scheme 1 : Substitution vs. Elimination Reaction



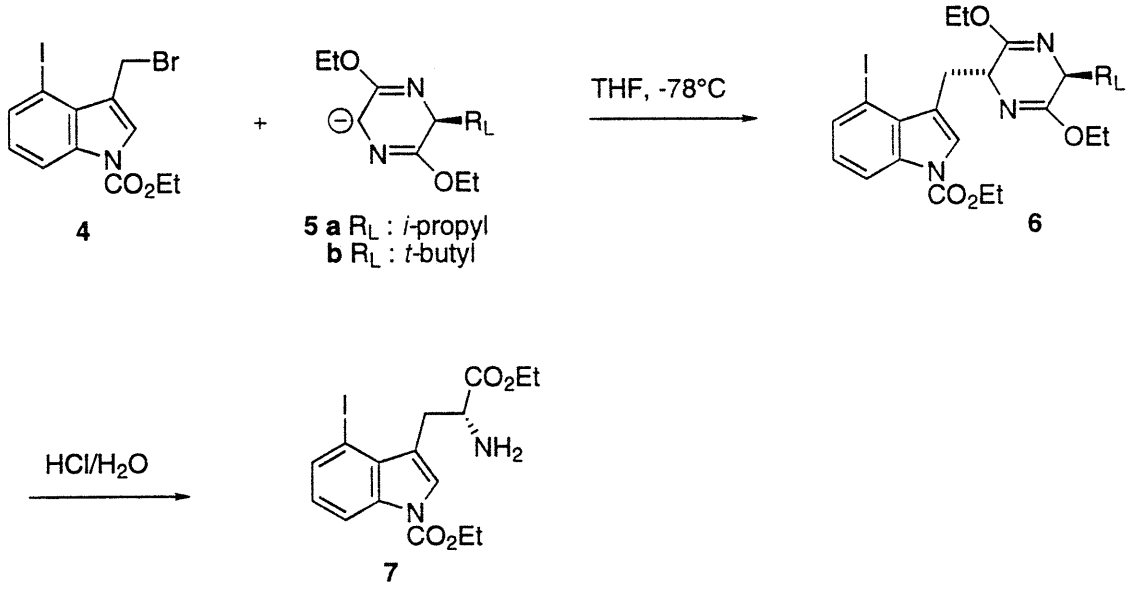
Scheme 2 : Synthesis of 3-bromomethyl-4-iodoindole derivative



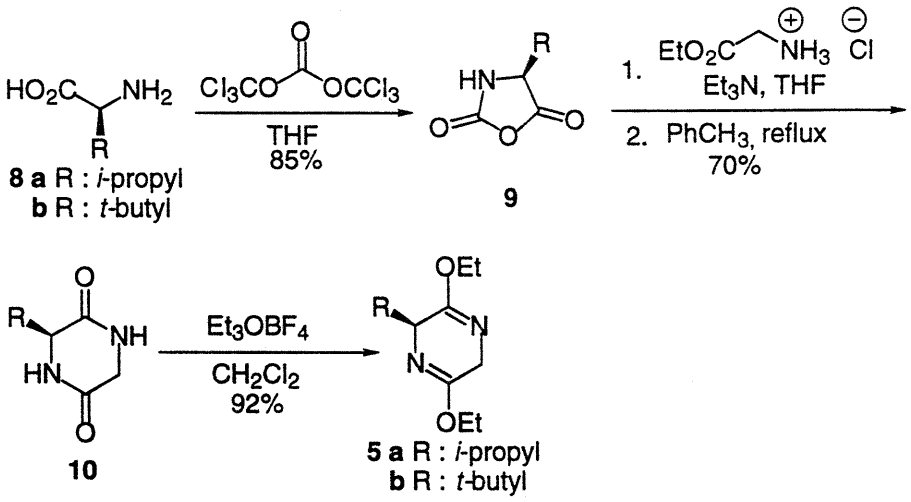
The use of **4** as an electrophile in the enantioselective alkylation of chiral bis-lactim ether anion **5** (Schöllkopf's reagent) was also investigated (Scheme 3).[5-7] The alkylation step was anticipated to yield the *trans*-diastereomer **6**, which upon acidic hydrolysis, would afford an enantiomerically pure 4-iodotryptophan ester **7**. Initial studies of this concept were begun by Tidwell[1] and Peat[3] and completed by the author.

The chiral bis-lactim ethers were synthesized from commercially available L-valine or L-tert-leucine and glycine according to Schöllkopf's procedure, as shown in Scheme 4.[5,8] Treatment of either L-valine **8a** or L-tert-leucine **8b** with triphosgene in THF provided the N-carboxyanhydride **9**, which then was reacted with glycine methyl ester to afford the diketopiperazine **10**. The desired bis-lactim ether **5** was obtained upon the reaction of **10** with triethyloxonium tetrafluoroborate, in an overall yield similar to that reported by Schöllkopf.

Scheme 3 : Asymmetric synthesis of a 4-iodotryptophan ester derivative



Scheme 4 : Synthesis of Schöllkopf's bis-lactim ethers



The desired chiral tryptophan derivatives were synthesized by a reaction sequence of alkylation and hydrolysis. Lithiation of the bis-lactim ether **5a** or **5b** with n-BuLi generated a planar dihydropyrazine anion,[9] which upon trapping with **4** gave the *trans*-diastereomer adduct in 70% yield and 88% de for R=*i*-propyl or 75% yield and 95% de for R=*t*-butyl (Scheme 5). Schöllkopf postulated that the *trans* isomer preference was primarily due to steric factors; the electrophile approaches from the opposite site of the bulky isopropyl or *tert*-butyl group (Figure 1) of the planar bis-lactim ether anion.[9] Interestingly, the diastereoselectivity was found to be dependent on the order the reagents were added. Higher diastereoselectivities (88% de) were observed when the bis-lactim ether anion was added slowly to a solution of the electrophile at -95 °C. Lower diastereoselectivities (70% de) were obtained when the order of addition was reversed.[1] Upon treatment with 2N HCl for 1-3 days, **6a** was fully hydrolyzed to form the chiral tryptophan ethyl ester **7** in 70% isolated yield and 95% ee (Scheme 6).

Scheme 5: Alkylation of the bis-lactim ether

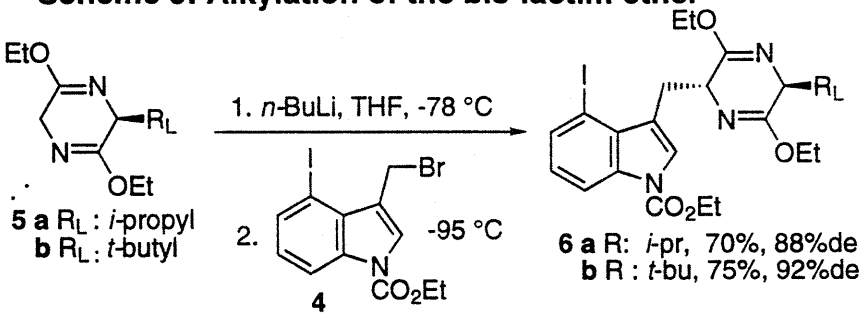
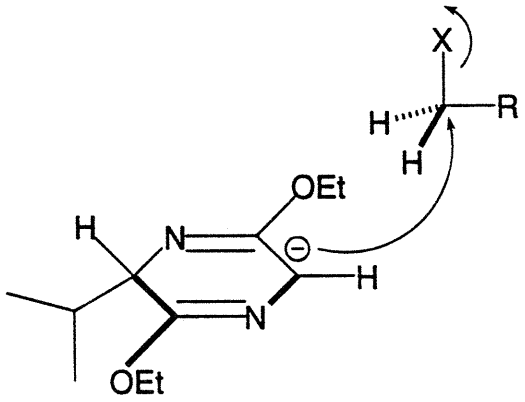
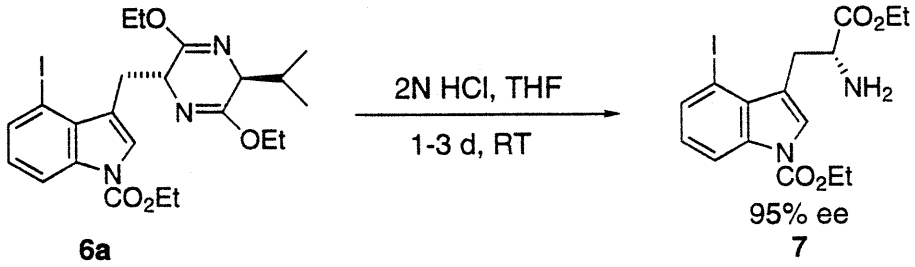


Figure 1: *Trans*-attack by the planar dihydropyrazine anion

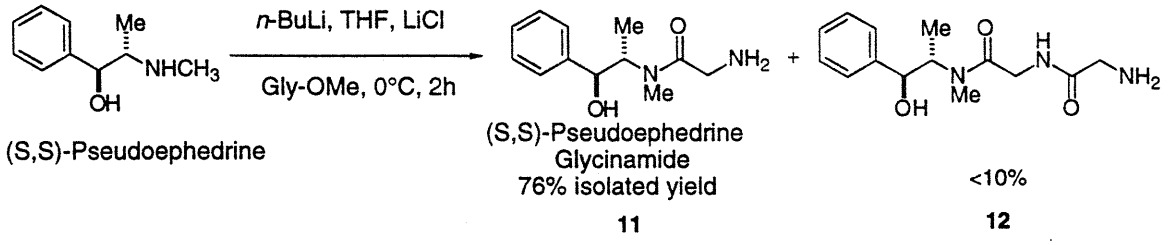


Scheme 6 : Hydrolysis of the alkylated bis-lactim ethers



In addition to Schöllkopf's chiral bis-lactim ethers, we investigated the utility of pseudoephedrine glycinamide **11** as a chiral auxiliary for the generation of enantiomerically pure 4-iodotryptophan ester **7**. The preparation and enantioselective alkylation of pseudoephedrine glycinamide was first reported by Myers and coworkers.[10,11] As depicted in Scheme 7, the synthesis

Scheme 7 : Synthesis of Pseudoephederine Glycinamide



(S,S)-Pseudoephedrine

(S,S)-Pseudoephedrine Glycinamide
76% isolated yield
11

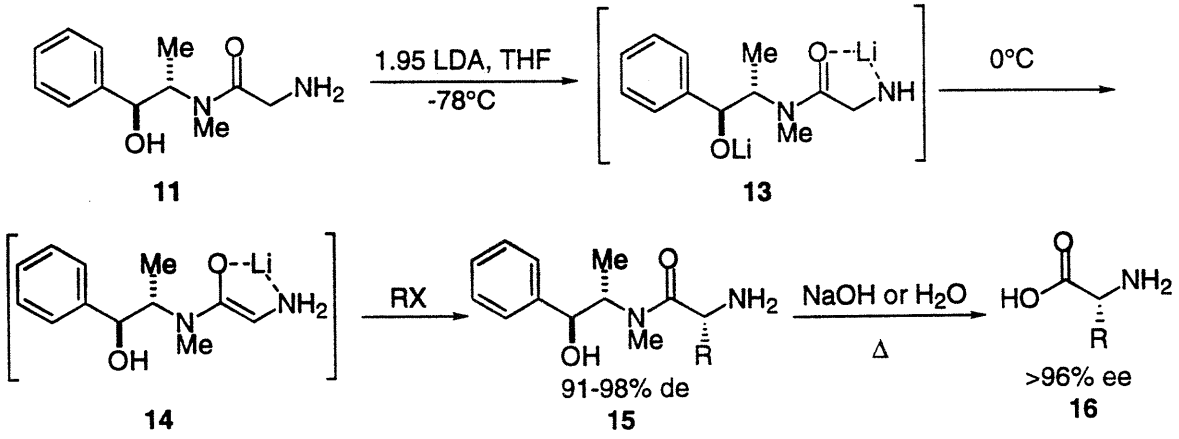
<10%
12

of **11** involved condensation of pseudoephedrine with the "free-base" form of glycine methyl ester.[12] This one-step reaction was effected by partial lithiation of pseudoephedrine (1 equiv) with a substoichiometric amount of n-BuLi (0.7-0.9 equiv) in THF at 0°C in the presence of LiCl (>2 equiv) followed by slow addition of a solution of glycine methyl ester in THF. The proposed mechanism for this reaction involves initial transesterification of the glycine methyl ester with the alkoxy group of lithiated pseudoephedrine, promoted by the presence of n-BuLi in the reaction mixture, followed by a rapid intramolecular O --> N acyl transfer to form the N-acyl product.[13] Myers also reported that the use of lithium chloride as an additive was crucial to the success of the reaction.[10] The rate acceleration observed when lithium chloride was employed as an additive has been attributed to the activation of glycine methyl ester via a bidentate coordination to the lithium cation, which increases the electrophilicity of the carbonyl group. This coordination was also believed to reduce the nucleophilicity of the amino group of glycine and the desired product **11**, thereby slowing two major processes which decrease the yield of **11**: the self-dimerization of glycine and the overglycylation of **11** to produce **12**.

Myers and coworkers reported that treatment of **11** with 1.95 equivalent of LDA at -78°C resulted in the formation of dianion **13**, which upon warming to 0 °C, equilibrated to the thermodynamically more stable (*Z*)-enolate **14** by C-to-N proton transfer (Scheme 8). Reaction of this enolate with various electrophiles

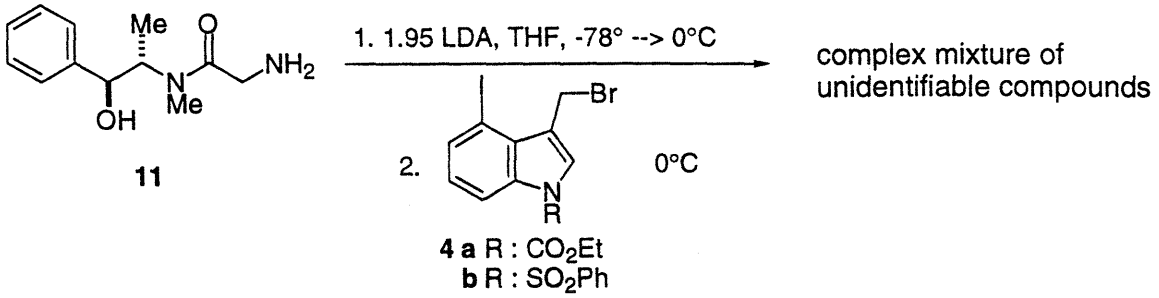
at 0°C gave the α-substituted glycinamide derivatives **15** in 91-98% de.[11] One major advantage of this methodology is the ease of hydrolysis to remove the chiral auxiliary and afford the non-proteinogenic amino acids **16** in >96% ee. Hydrolysis can either be carried out under basic condition (i.e $NaOH/H_2O$:MeOH) or neutral condition (the solutions of the alkylated products in pure water were sufficiently basic, pH~10, to promote hydrolysis without the need for external bases). The ease of this hydrolysis was believed to arise from a proximally favorable intramolecular N-->O acyl transfer step to give the corresponding ester, which hydrolyzed rapidly to liberate **16**.

Scheme 8: Enolate Alkylation of Pseudoephedrine Glycinamide



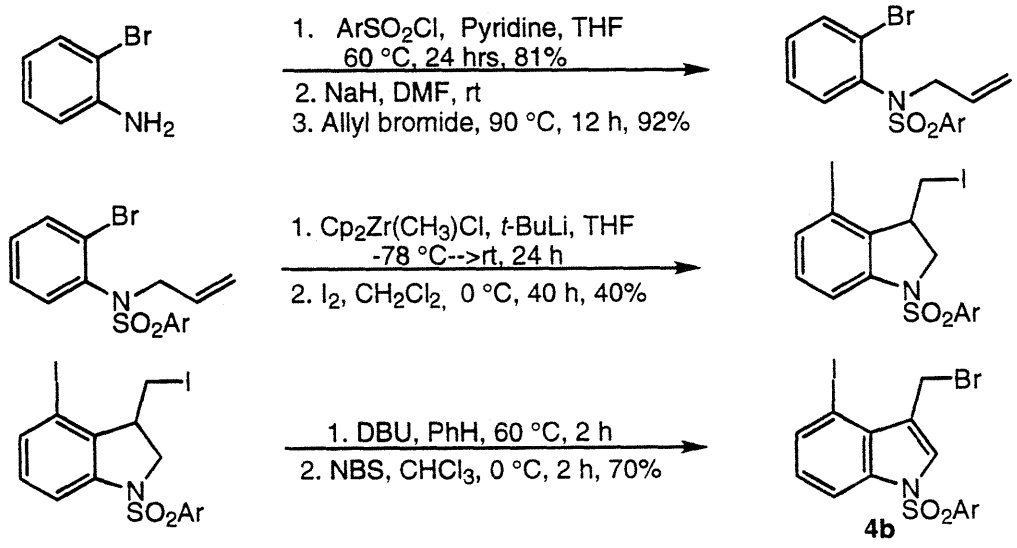
Although the preparation of pseudoephedrine glycinamide was simpler than that of Schöllkopf's bis-lactim ether, and its derivatives were more easily hydrolyzed than those of the latter, attempts to synthesize the desired chiral 4-iodotryptophan **7** using the pseudoephedrine technology were unsuccessful. When 3-bromomethyl-4-iodoindole derivatives **4a** or **4b** were used as electrophiles, no desired product was observed in either case. Moreover, TLC, GC, and ^1H NMR analysis of the crude reaction showed that complex mixtures of unidentifiable compounds were found (Scheme 9). In addition, cleavage of

Scheme 9.



the carboethoxy protecting group on the indole **4a** was observed by analysis of the ^1H NMR spectrum of the crude reaction mixture. Cleavage of the carbamate, perhaps by the alkoxide group on the chiral auxiliary, might have led to the formation of the undesired and unidentifiable products. The use of a sulfonamide protecting group in **4b** did not, however, change the outcome of the reaction. Note that the indoline ring system in **4b** was generated by our zirconocene-benzyne method (Scheme 10), which has also been used by Tietze and cowokers to generate related systems.[14]

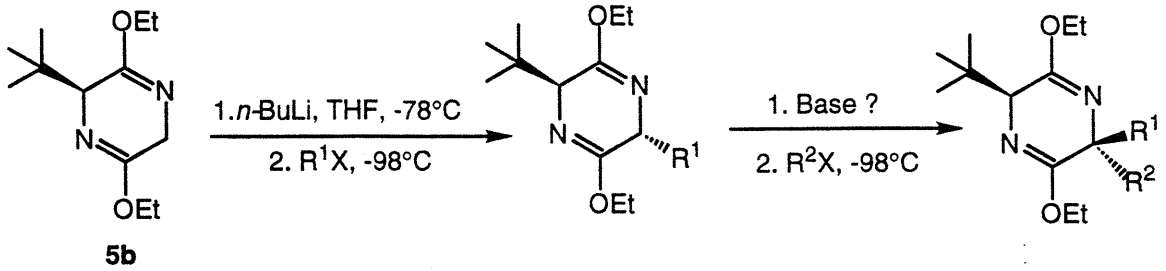
Scheme 10: Synthesis of N-Sulfonamide Bromoindole



After several unsuccessful attempts, it became apparent that pseudoephedrine glycinamide was not a compatible chiral auxiliary reagent for our electrophilic indoles. A graduate student in the Myers group has attempted to carry out the same reaction under similar conditions and also obtained disappointing results. No structural modifications of either pseudoephedrine glycinamide or the indoles have been carried out up to this point. Schöllkopf's bis-lactim ether is currently the preferred reagent for generating the desired enantiomerically pure 4-iodotryptophan.

To further extend the synthetic utility of our electrophilic indole **4**, we turned our focus to the preparation of enantiomerically pure α-substituted 4-iodotryptophan derivatives via a double alkylation of Schöllkopf's bis-lactim ether (Scheme11). Asymmetric synthesis of α-substituted tryptophan derivatives has received relatively little to no attention. To our best knowledge, only three asymmetric syntheses of L-methyltryptophan[5,15,16] and one of L-2-methylthioethyltryptophan[17] have been reported. Many of these α-substituted tryptophan derivatives exhibit significant biological activity and act as potent enzyme inhibitors as effective competitive inhibitors for 5-hydroxytryptophan decarboxylase, which degrades serotonin.[18] α-Methyltryptophan, for instance, shows antihypertensive and noradrenaline-depleting properties, and its 5-hydroxy derivative is known to be a potent inhibitor of tyrosine hydroxylase and aromatic acid decarboxylase.[19]

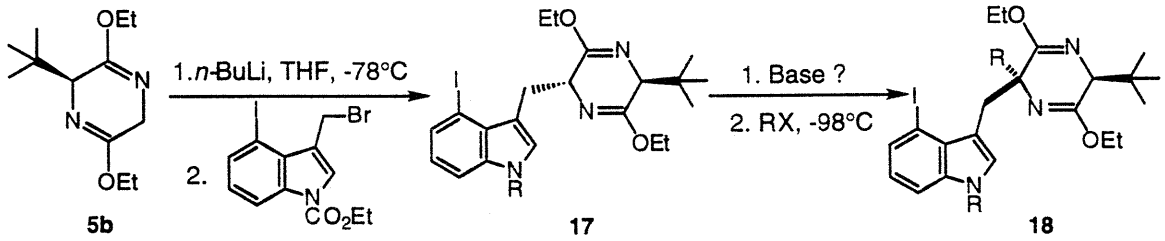
Scheme 11 : Double Alkylation of a Schöllkopf reagent



5b

In order to maximize the reaction diastereoselectivity, the *t*-butyl derivative **5b** was chosen as the chiral auxiliary for the double alkylation strategy. Initial studies were directed towards an "indole-alkyl attachment sequence" (Scheme 12), in which the indole was first attached to the chiral auxiliary followed by alkylation with another carbon electrophile. The principal questions in this approach concern the second lithiation: which base should be used and which methine carbon is deprotonated. As the pKa of either methine hydrogen in **17** lies somewhere between 25 and 30, LDA and *n*-BuLi were chosen as bases for the second lithiation. We anticipated that for steric reasons, deprotonation by such bases during the second lithiation should occur primarily at the methine carbon bearing the indole group.

Scheme 12: "Indole-Alkyl Attachment Sequence"

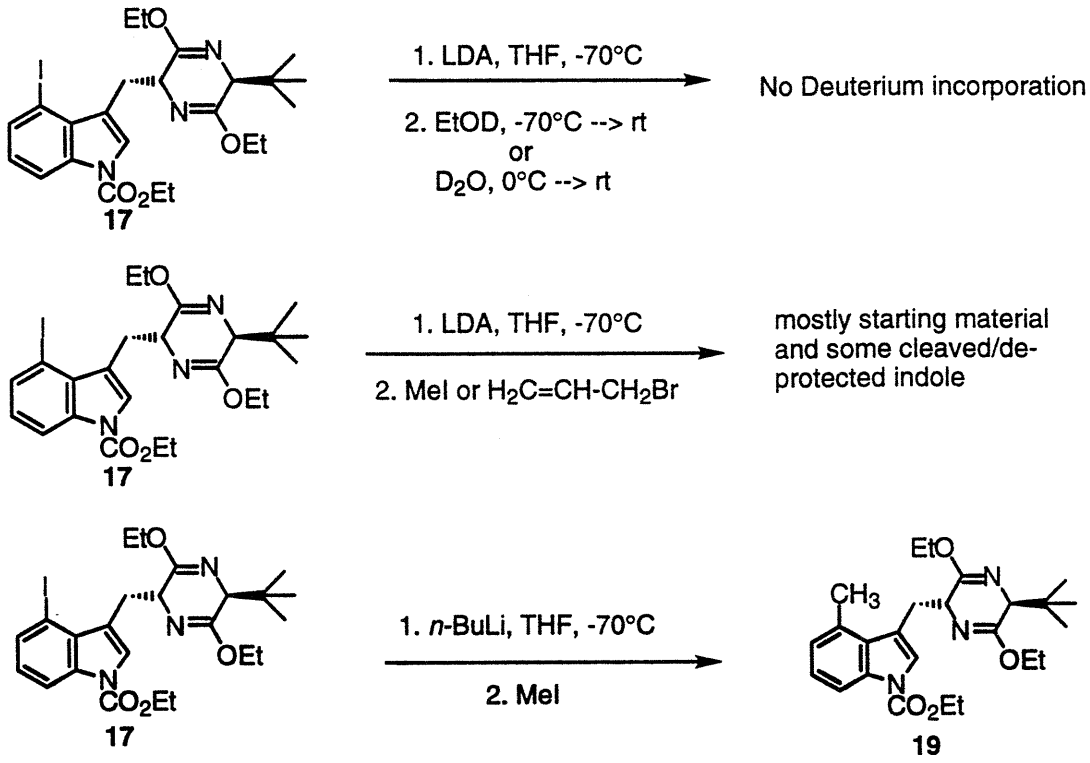


5b **17** **18**

Unfortunately, asymmetric alkylation of compound **17** via lithiation with LDA or *n*-butyllithium proved to be rather disappointing. Treatment of **17** with LDA at -78 °C to 0 °C followed by quenching with D_2O (0 °C to RT) afforded no

deuterium incorporation in the product (Scheme 13). Further investigation showed that lithiation of **17** with LDA at the same temperature followed by addition of methyl iodide or allyl bromide gave mostly starting material and

Scheme 13 : Results of Second Alkylation

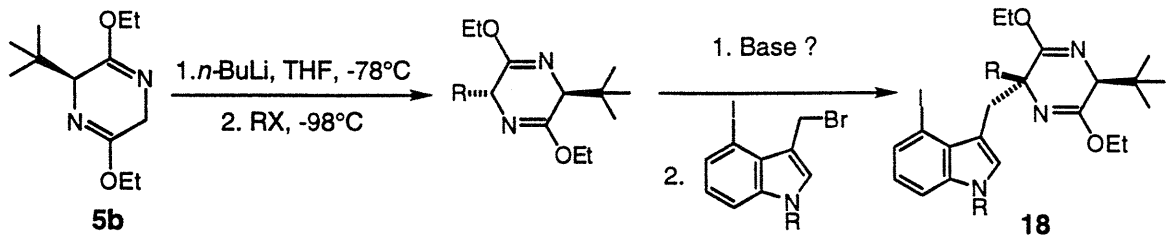


some N-deprotected product. When *n*-BuLi was used as the base and methyl iodide was used as the trapping agent, only 4-methylated product **19** was obtained, suggesting that for this specific substrate, halogen-metal exchange at the 4 position occured faster than deprotonation of a methine hydrogen.

Unsuccessful attempts to synthesize the desired chiral trisubstituted bis-lactim ether **18** using the method described above led us to look for an alternative approach. Since deprotonation of **17** appeared to be kinetically unfavorable for steric reasons, we felt that the reverse order of alkylation would

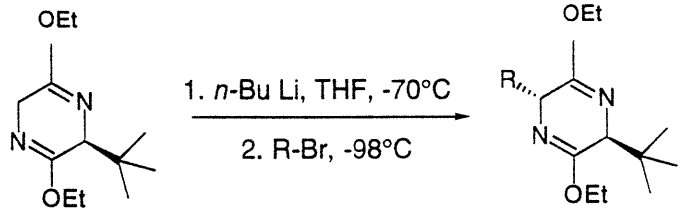
be a more promising sequence. An "alkyl-indole attachment sequence" (Scheme 14) approach was then investigated.

Scheme 14: "Alkyl-Indole Attachment Sequence"



As depicted in Scheme 15, the first alkylation with several electrophiles gave diastereoselectivities and isolated yields comparable to those obtained by Schöllkopf.[8,9] High diastereoselectivity was not strictly necessary in the first step, since this stereochemical information would be lost during the second lithiation. Deprotonation of **20a-c** with *n*-BuLi at -78°C followed by reaction with 3-bromomethyl-4-iodoindole **4a** gave the desired trisubstituted bis-lactim ethers **21** in excellent de and yields. Addition of 1,3-dimethylimidazolidinone (DMI/DMEU) as a cation-coordinating agent slightly improved the yield of the

Scheme 15 : First Lithiation-Alkyl Attachment Reaction

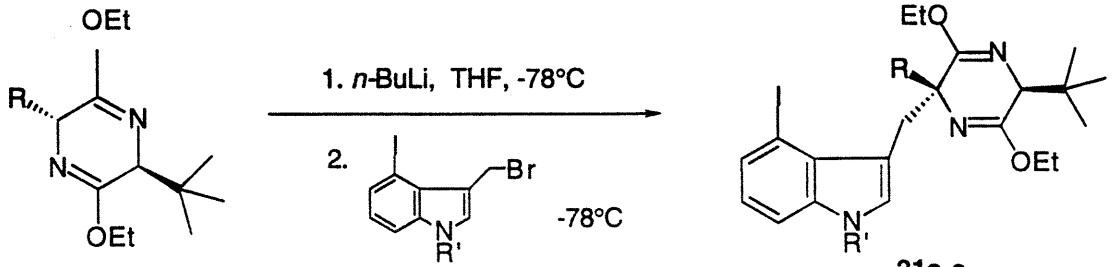


5b **20a-c**

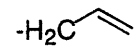
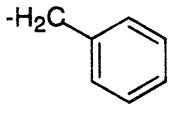
Entry	R	Yield	de
a	$-CH_3$	83%	65%
b	$-H_2C$	85%	95%
c	$-H_2C$	95%	95%

reaction as shown in Scheme 16. The relative stereochemistry of the product was established by examination of the ^{1}H-NMR spectra of starting materials **20a-c** and products **21a-c**. In the desired product, the methine hydrogen attached to the carbon adjacent to the *t*-butyl group was shifted further upfield by ~0.5-0.7 ppm than that in the starting material. These results appeared to be consistent with the proposed conformational structure, in which the desired product exhibits a "folded" conformation, leading to maximum π-stacking interactions between the π system of the indole ring and that of the bis-lactim ether (Figure 3).[5,20,21] Based on this model, the methine hydrogen next to the *t*-butyl group is located within the shielding cone of the heteroaromatic indolyl ring current, decreasing the chemical shift value of this hydrogen in the ^{1}H NMR spectrum.

Scheme 16 : Second Lithiation-Indole Attachment Reaction



20a-c **21a-c**

R	Entry	Yield[a]	Yield[b]	de[c]
-CH_3	a	60%	75%	~93%
-H_2C 	b	75%	88%	~93%
-H_2C 	c	60%	70%	~93%

[a]Without DMI/DMEU, 1,3-dimethylimidazolidinone
[b]With DMI/DMEU as a substitute for HMPA
[c]The values were assigned when only one diastereomer was observed from H-NMR spectra

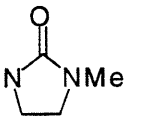
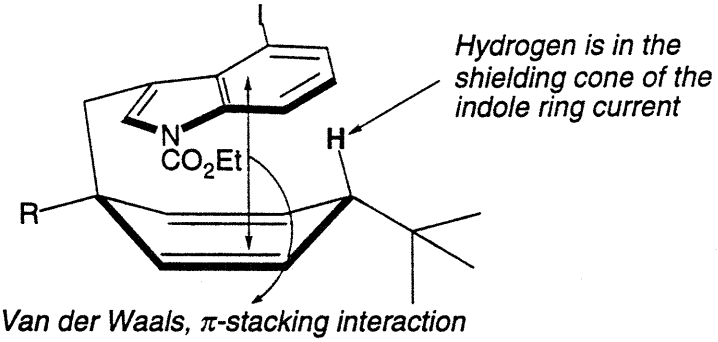
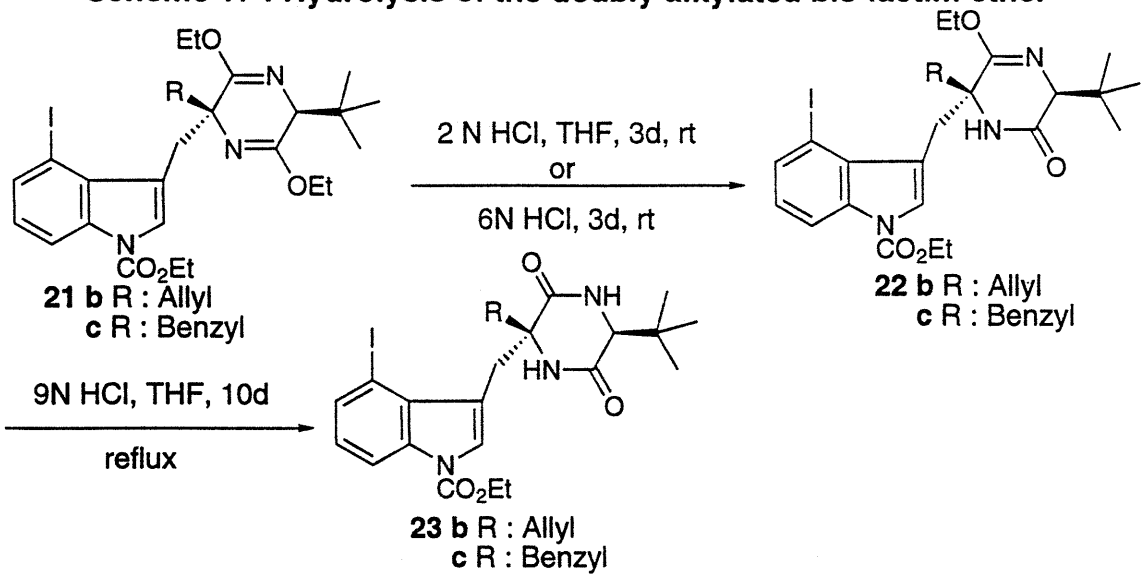
DMI/DMEU = 

Figure 3 : "Folded" conformation, π-stacking interaction, upfield methine hydrogen



Although the double alkylation of bis-lactim ether **5b** was successful, hydrolysis of **21** was found to be extremely difficult. Treatment of **21** with 2N HCl in THF at room temperature for 3 days gave only partially hydrolyzed product (Scheme 17). An increase in HCl concentration to 6 N failed to improve the outcome of the reaction. When the partially hydrolyzed compounds **22** were refluxed with 9 N HCl in THF for 10 days only the diketopiperazine **23** was obtained. The difficulty encountered during the hydrolysis reflected the great stability of the cyclic peptidic dimers **23**. Because of the difficulty in removing the chiral *t*-leucine from the desired α-substituted tryptophan, even under harsh and strongly acidic conditions, research in this area of synthesis was discontinued.

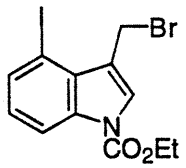
Scheme 17 : Hydrolysis of the doubly alkylated bis-lactim ether



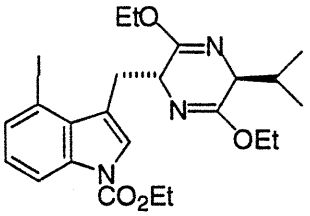
EXPERIMENTAL SECTION

All reactions involving organometallic reagents were conducted under an atmosphere of purified argon using standard Schlenk techniques or under nitrogen in a Vacuum Atmosphere Co. drybox. The argon was purified and deoxygenated by passage through a column of activated R3-11 catalyst obtained from Schweizer-Hall, Plainfield, NJ. It was then dried by passage through a column of activated 3 Å molecular sieves. All reactions were performed under an atmosphere of argon or nitrogen. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian XL-300, VXR-500 or a Bruker AC250 FT spectrometer. Infrared (IR) spectra were recorded on either a Mattson Cygnus Starlab 100 or Perkin-Elmer Series 1600 FT spectrometer. Gas chromatographic analyses were performed on a Hewlett Packard model 5890 GC with a 3392A integrator and FID detector using a 25 m capillary column with cross linked SE-30 as a stationary phase. Liquid chromatography analyses were performed on a Hewlett Packard model 1050 HPLC equipped with a Hewlett Packard model 1040A diode array detector using an Alltech 250mm x 4.6mm silica 5 μ column. Tetrahydrofuran and diethyl ether were dried and deoxygenated by continous refluxing over sodium/benzophenone ketyl under nitrogen or argon followed by distillation. Anhydrous methylene chloride, benzene, hexane, pentane, chloroform, acetonitrile and *N,N*-dimethyl formamide (DMF) were purchased from Aldrich Company Co. and were used without further purification. Cp_2ZrCl_2 was purchased from Boulder Scientific Inc., Mead, Colorado, and converted to $Cp_2Zr(Me)Cl$ by a known procedure.[22] All other reagents were either prepared according to published procedures or were available from commercial sources and used without further purification. Unless otherwise stated, preparative flash chromatography was performed on

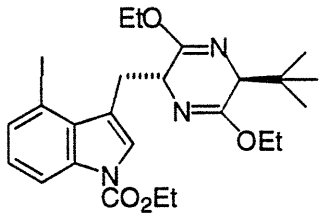
E.M. Science Kieselgel 60 (2300-400 mesh). Yields refer to isolated yields of compounds estimated to be ≥95% pure (unless otherwise noted) as determined by ^{1}H NMR, and either capillary GC, HPLC analysis, or combustion analysis. Elemental analyses were performed by Onieda Research Services, Whitesboro, NY.



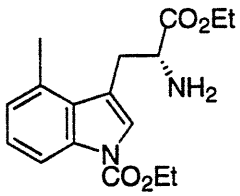
3-Bromomethyl-1-carboethoxy-4-iodoindole (4).[1] Into a flask were placed 1-carboethoxy-4-iodo-3-iodomethylindoline **1** (980 mg, 2.14 mmol), DBU (0.35 mL, 356 mg, 2.34 mmol), and benzene (5 mL). The mixture was heated to 50 °C for 1 h, then filtered and the benzene was removed using a rotary evaporator leaving a brownish solid. The solid was dissolved in $CHCl_3$ (5 mL), the solution cooled to 0 °C and NBS (402 mg, 2.26 mmol) was added as a solid in one portion. The resulting mixture was allowed to stir at 0 °C for 2h, then it was poured into a separatory funnel containing $CHCl_3$ (15 mL) and water (15 mL). The organic layer was collected and washed with water (2 x 15 mL), brine (15 mL), dried over $MgSO_4$, filtered through a plug of silica (15 cm) and the solvents were removed using a rotary evaporator to leave 700 mg (80%) of a white solid, mp 109-110 °C. An analytical sample was prepared by recrystallization from CH_3CN. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.22 (d, *J*=8.4 Hz, 1H), 7.79 (d, *J*=8.1 Hz, 1H), 7.00 (t, *J*=8.1 Hz, 1H), 4.90 (s, 2H), 4.46 (q, *J*=7.0 Hz, 2H), 1.45 (t, *J*=7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 149.7, 136.3, 135.0, 129.1, 127.8, 126.2, 118.7, 115.3, 84.2, 63.8, 25.1. Anal. Calcd for $C_{12}H_{11}BrNO_2I$: C, 35.34; H, 2.72; N, 3.43. Found: C, 35.41; H, 2.68; N, 3.64.



6a. A solution of *n*-BuLi (0.26 mL, 1.58 M in hexane, 0.44 mmol) was added dropwise to a solution of bis-lactim ether **5a** (78 mg, 0.37 mmol) in THF (3 mL) under argon at -78 °C. After 15 min, the solution was cooled to -95 °C and added dropwise via cannula to a solution of the bromoindole **4** (150 mg, 0.37 mmol) in THF (2 mL) at -95 °C under an argon atmosphere. The mixture was stirred between -95 °C and -78 °C for 24 h, then precooled MeOH (3 mL) was added at -78 °C. Upon warming to 0 °C, the mixture was poured into a separatory funnel containing H_2O (5 mL) and Et_2O (5 mL). The organic layer was washed with brine (5 mL), dried over $MgSO_4$, filtered, and the solvent was removed using a rotary evaporator. ^1H NMR analysis of the crude reaction mixture showed the desired product in 88% de. The diastereomers were separated by flash chromatography (10:1 hexane/ethyl acetate) to give 176 mg (88%) white solid, mp 75.0-76.0 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.21 (d, *J*=8.4 Hz, 1H), 7.70 (d, *J*=7.5 Hz, 1H), 7.60 (s, 1H), 6.95 (t, *J*=8.0 Hz, 1H), 4.45 (q, *J*=7.5 Hz, 2 H), 4.38-3.80 (m, 7H), 3.05 (dd, *J*=9.0 Hz, 1H), 2.25 (m, 1H), 1.45 (t, *J*=7.2 Hz, 3 H), 1.25 (t, *J*=6.9 Hz, 3 H), 1.20 (t, *J*=6.9 Hz, 3 H), 1.05 (d, *J*=6.6 Hz, 3 H), 0.72 (d, *J*=6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.5, 163.3, 150.5, 136.3, 135.1, 131.6, 126.4, 125.4, 118.9, 115.3, 85.1, 63.4, 61.1, 60.9, 60.8, 56.1, 32.1, 30.3, 19.3, 17.0, 14.6.



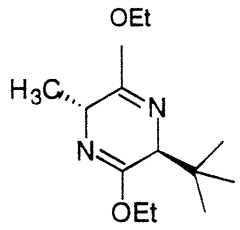
6b. The experimental procedure and workup described above was used to give 164 mg (75%) of colorless oil in 92% de. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.27 (d, 1H), 7.72 (d, 1H), 7.60 (s, 1H), 6.95 (t, 1H), 4.45 (q, 2H), 4.30-4.00 (m, 6H), 3.80 (d, 1H), 3.00 (dd, 1H), 1.43 (t. 3H), 1.30 (t, 3H), 1.25 (t. 3H), 0.98 (s, 9H).



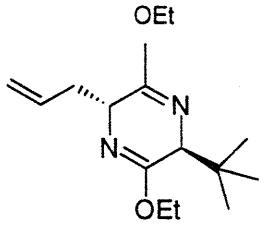
7. Into a flask were placed **6a** (38 mg, 0.07 mmol), THF (1 mL), and 2N HCl (0.142 mL) and the resulting homogenous solution was stirred at room temperature for overnight. The following day, ether (4 mL) was added to the flask and the resulting biphasic layer was separated. The aqueous phase was poured into a small beaker filled with ether (2 mL) and ice (~1 g) and neutralized to pH = 8-9 by slow addition of concentrated ammonium hydroxide. The organic layer was then separated and the aqueous layer washed with ether (3 x 5 mL). The combined ether layers were washed with brine (10 mL), dried with $MgSO_4$, filtered and the solvent was removed using a rotary evaporator to give a yellowish oil which solidified upon standing under vacuum. The crude product was purified by flash chromatography (1:2 hexane/ethyl acetate) to give 30 mg (70%) of a white solid, mp 79.0-81.0 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.30 (d, 1 H), 7.73 (d, 1 H), 7.58 (s, 1 H), 7.00 (t, 1 H), 4.46 (q, 2 H), 4.19 (dq, 2 H), 3.97 (dd, 1 H), 3.55 (dd, 1 H), 3.05 (dd, 1 H), 1.72 (b, 2 H), 1.45 (t, 3 H), 1.23

(t, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.2, 150.4, 136.7, 135.2, 131.0, 126.4, 126.0, 117.9, 115.6, 84.8, 63.7, 61.2, 55.4, 31.3, 14.6, 14.4. IR (KBr pellet, cm^{-1}) 3348, 3250, 3161, 3112, 2977, 1742, 1693, 1595, 1552, 1464, 1419, 1379, 1351, 1250, 1196, 1106, 1087, 1052, 770, 746.

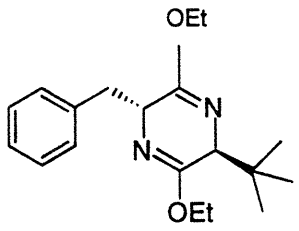
General experimental procedure for the disubstituted bis-lactim ether 20a-c. A solution of *n*-BuLi (1.1 mL, 1.65 mmol) was added dropwise to a solution of the bis-lactim ether **5b** (0.36 g, 1.6 mmol) in THF (5 mL) under argon at -78 °C. After 15 min, the solution was added dropwise via cannula to a solution of the electrophile (R-Br, 1.80 mmol) in THF (3 mL) at -78 °C under argon. The mixture was stirred for 12 h, then MeOH (3 mL) was added at -78 °C. Upon warming to 0 °C, the mixture was poured into a separatory funnel containing H_2O (10 mL) and ether (10 mL). The organic layer was washed with brine (10 mL), dried over $MgSO_4$, filtered, and the solvent was removed using a rotary evaporator. The desired product was purified by flash column chromatography (40:1 hexane/ethyl acetate).



20a. The general procedure gave 0.30 g (83%) of the desired product as a colorless oil in 60% de. ^1H NMR ($CDCl_3$, 300 MHz) δ 4.20-4.05 (m, 4H), 3.95-3.88 (m, 1H), 3.78(d, 1H), 1.19 (d, 3 H), 1.30-1.23 (2 t, 6 H), 0.98 (s, 9H).



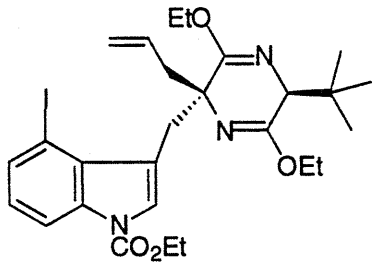
20b. The general procedure gave 0.36 g (85%) colorless oil in 95% de. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.81-5.68 (m, 1H), 5.1-4.98 (m, 2H), 4.20-4.03 (m, 4H), 3.98-3.95 (m, 1H), 3.75 (d, 1H), 2.62-2.47 (m, 2H), 1.30-1.24 (2 t, 6 H), 0.95 (s, 9H).



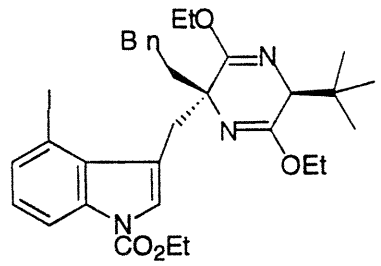
20c. The general procedure gave 0.47 g (95%) of the desired product as a colorless oil in 95%de. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30-7.20 (m, 5H), 4.3-4.1 (m, 5H), 3.58 (d, 1 H), 3.23 (dd, 1H), 3.12 (dd, 1H), 1.40 (t., 3H), 1.30 (t, 3H), 0.98 (s, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.2, 162.7, 138.6, 130.3, 127.8, 126.2, 65.2, 60.8, 60.5, 56.7, 40.0, 37.9, 27.3, 14.6, 14.5.

General experimental procedure for the trisubstituted bis-lactim ether 21b-c. A solution of *n*-BuLi (0.09 mL, 0.14 mmol) was added dropwise to a solution of the disubstituted bis-lactim ether **19** (0.13 mmol) in THF (3 mL) under argon at -78 °C. After 15 min, the solution was cooled to -95 °C and added dropwise via cannula to a solution of bromoindole **4** (53 mg, 0.13 mmol) in THF (2 mL) at -95 °C under argon. The mixture was stirred between -95 °C and -78 °C for 24 h, then MeOH (3 mL) was added. Upon warming to 0 °C, the mixture was poured into a separatory funnel containing H_2O (5 mL) and

ether (5 mL). The organic layer was washed with brine (5 mL), dried over $MgSO_4$, filtered and the solvent was removed using a rotary evaporator. The crude product was purified by flash column chromatography (40:1 hexane/ethyl acetate).



21b. The general procedure gave the desired product as white solid in 88% yield and 93% de. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.20 (d, 1H), 7.70 (d, 1H), 7.38 (s, 1H), 6.91 (t, 1H), 5.95-5.80 (m, 1H), 5.13-5.03 (m, 2H), 4.43 (q, 2H), 4.20-4.27 (m, 2H), 4.00-3.72 (m, 2H), 3.60 (d, 1H), 3.48 (d, 1H), 3.42 (s, 1H), 2.70-2.55 (m, 2H), 1.45 (t, 3H), 1.25 (t, 3H), 1.17 (t, 3H), 0.98 (s, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 207.6, 162.4, 162.0, 135.06, 135.6, 125.6, 125.3, 120.2, 118.3, 117.6, 115.3, 85.5, 64.6, 63.4, 62.5, 60.4, 45.2, 36.2, 33.8, 28.4, 14.6, 14.5.



21c. The general procedure gave the desired product as white solid in 60% yield and 93% de. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.29 (d, 1H), 7.75 (d, 1H), 7.45 (s, 1H), 7.30-7.15 (m, 5H), 6.97 (t, 1H), 4.50 (q, 2H), 4.25-3.90(m, 4H), 3.70

(dd, 1H0, 3.63 (dd, 1H), 3.40 (d, 1H), 3.32 (s, 1H), 3.15 (d, 1H), 1.50 (t, 3H), 1.4 (t, 3H), 1.2 (t, 3H), 0.58 (s, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.1, 161.6, 150.4, 137.7, 136.0, 135.6, 131.4, 127.9, 126.4, 125.8, 125.3, 118.1, 115.2, 85.5, 64.2, 63.7, 63.4, 60.4, 45.8, 36.0, 34.3, 27.7, 14.8, 14.7, 14.5.

References

1. Tidwell, J.H Ph.D. Thesis, Massachussetts Institute of Technology, 1994.

2. a) Tidwell, J.H; Buchwald, S.L. *J. Am. Chem. Soc.* **1994**, *116*, 11797. b) Tidwell, J.H; Buchwald, S.L. *J. Org. Chem.* **1992**, *57*, 6380. c) Tidwell, J. H; Senn, D.R.; Buchwald, S.L. *J. Am. Chem. Soc.* **1991**, *113*, 4685.

3. Peat, A.J. Ph.D. Thesis, Massachusetts Institute of Technology, 1997.

4. Sundberg, R.J. *The Chemistry of Indoles*; Academic Press: New York, 1970.

5. Schöllkopf, U.; Lonsky, R.; Lehr, P. *Liebigs. Ann. Chem.* **1985**, 413.

6. a) Gander-Coquoz, M.; Seebach, D. *Helv. Chim. Acta* **1988**, *71*, 224. b) Sato, M.; Kahn, M. *Tetrahedron Lett.* **1990**, *31*, 4607. c) Nagarantham, D. *J. Heterocycl. Chem.* **1992**, *29*, 953. d) Allen, M.S.; Hamaker, L.K.; LaLoggia, A.J.; Cook, J.M. *Synth. Commun* **1992**, *22*, 2077. e) Venkatachalam, T.K.; Mzengeza, S.; Diksic, M. *Org. Prep. Proc. Intl.* **1993**, *25*, 249. f) Nagarantham, D.; Johnson, M.E. *Synth. Commun.* **1993**, *23*, 2011.

7. For reactions involving asymmetric glycine equivalents, see : a) Williams, R.M. *Synthesis of Optically Active α-Amino Acids*; Pergamon Press: New York, 1989. b) Myers, A.G.; Gleason, J.L.; Yoon, T.; Kung, D.W. *J. Am. Chem. Soc.* **1997**, *119*, 656. c) Oppolzer, W.; Moretty, R.; Zhou, C. *Helv. Chim. Acta* **1994**, *77*, 2363 and references cited therein.

8. Schöllkopf, U.; Neubauer, H.-J. *Synthesis* **1982**, 861.

9. Schöllkopf, U.; Groth, U.; Deng, C. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 798.

10. Myers, A.G.; Yoon, T.; Gleason, J.L. *Tetrahedron Lett.* **1995**, *36*, 4555.

11. Myers, A.G.; Gleason, J.L.; Yoon, T. *J. Am. Chem. Soc.* **1995**, *117*, 8488.

12. a) Frankel, M.; Katchalski, E. *J. Am. Chem. Soc.* **1942**, *64*, 2264. b) Almeida, J.F.; Anaya, J.; Martin, N.; Grande, M.; Moran, J.R.; Caballero, M.C. *Tetrahedron Asymm.* **1992**, *3*, 1431.

13. a) Brenner, M.; Hubber, W. *Helv. Chim. Acta* **1953**, *36*, 1109. b) Welsh, L.H. *J. Am. Chem. Soc.* **1947**, *69*, 128.

14. Tietze, L.F.; Buhr, W. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1366.

15. Seebach, D.; Gandez-Coquez, M. *Helv. Chim. Acta* **1988**, *71*, 224.

16. Horwell, D.C.; Bourne, G.T.; Crich, D.J. *J. Chem. Soc., Perkins Trans. 1* **1991**, 1693.

17. Brana, M.F.; Garrido, H.; Lopez, M.L.; Sanz, A.M. *J. Heterocycl. Chem.* **1980**, *17*, 829.

18. Anantharamaiah, G.M.; Roeske, R.W. *Tetrahedron Lett.* **1982**, *23*, 3335.

19. Crich, D.; Davies, J.W. *J. Chem. Soc., Chem. Commun.* **1989**, 1418.

20. Schöllkopf, U.; Hartwig, W.; Groth, U.; Westphalen, K.O. *Liebigs Ann. Chem.* **1981**, 696.

21. Schöllkopf, U.; Hartwig, W. *Liebigs Ann. Chem.* **1982**, 1952.

22. Wailes, P. C.; Weigold, H.; Bell, A. P. *J. Organomet. Chem.* **1971**, *33*, 181-188.

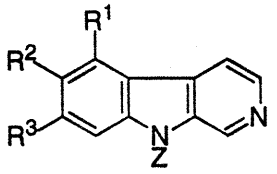
Chapter Two

Efforts toward the synthesis of eudistomin D and eudistomidin D

INTRODUCTION

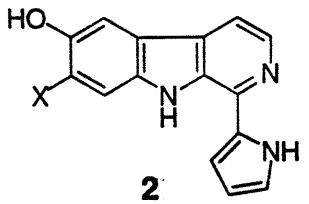
Eudistomins, originally isolated from the Carribean colonial tunicate *Eudistoma olivaceum* and studied by Rinehart *et al.*,[1] are natural marine alkaloids which show very interesting biological properties.[2] Most of them, including eudistomin D, exhibit significant antimicrobial and antiviral activities against *Herpes simplex* virus, type 1 (HSV-1). There are 4 major classes of Eudistomins: **1.** simple β-carbolines; **2.** 1-(2-pyrrolyl)-β-carbolines; **3.** 1-(1-pyrrolin-2-yl)-β-carbolines; and **4.** oxathiazepine ring fused tetrahydro-β-carbolines (Figure 1).

Figure 1 : Eudistomins Family



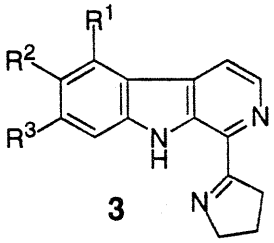
1

	Z	R^1	R^2	R^3
Eudistomin	D	H	Br	OH	H
	J	H	H	OH	Br
	N	H	H	Br	H
Eudistomidin	D	Me	Br	OH	H



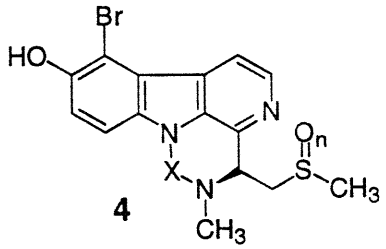
2

	X
Eudistomin A	Br
M	H



3

	R^1	R^2	R^3
Eudistomin G	H	Br	H
H	Br	H	H
I	H	H	H
P	OH	Br	H
Q	OH	H	H

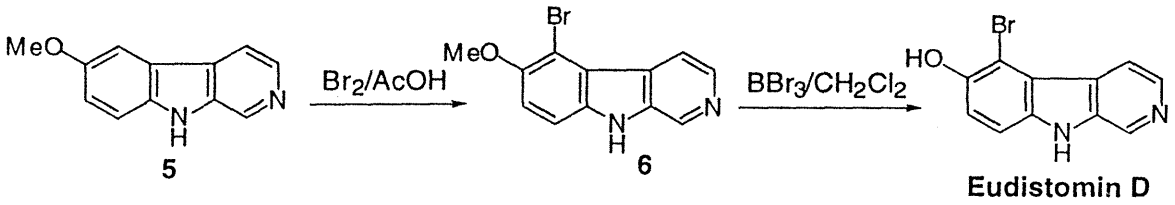


4

	X	n
Eudistomidin C	H,H	0
E	CH_2	1
F	CH_2	0

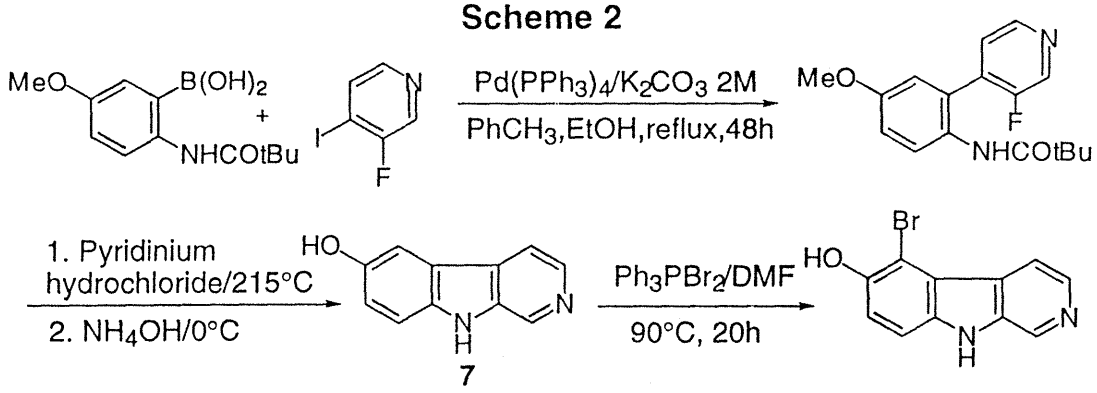
Many of these eudistomins have been previously synthesized by the groups of Rinehart,[2] Hino,[3] and Queguiner.[4] The first described synthesis of eudistomin D in 1987 by Rinehart involved bromination of 6-methoxy-β-carboline **5** (Scheme 1)[5,6] [prepared from commercially available 5-methoxytryptamine by the usual tryptamine --> β-carboline route (glyoxylic acid condensation, decarboxylation and dehydrogenation)] and subsequent demethylation of the resulting 5-bromo-6-methoxy-β-carboline **6**.[2]

Scheme 1



Eight years later, Queguiner and coworkers developed a new convergent route to β-carboline ring systems through cross-coupling and intramolecular substitution strategy (Scheme 2).[4] Deprotection and bromination of the cross-coupled product **7** afforded eudistomin D in 85% yield.

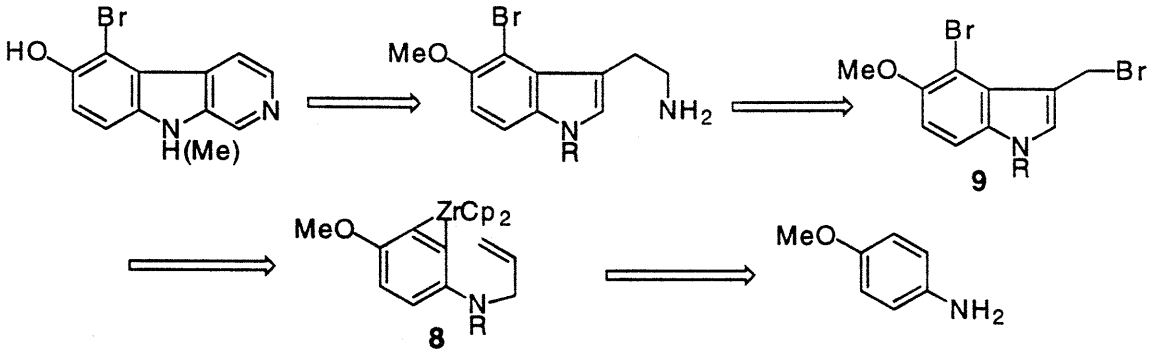
Scheme 2



The key step in our initial strategy for the synthesis of eudistomin D, depicted in Figure 2, was the intramolecular olefin insertion of the zirconocene-

stabilized benzyne complex **8** to generate the 3,4,5-trisubstituted indole derivative **9**. The pyridine ring of the β-carboline system was to be formed by Bischler-Napieralski cyclization[7,8] followed by dehydrogenation of the dihydro-β-carboline. Although our approach to Eudistomin D is longer than the previously reported syntheses, we wished to show the generality and effectiveness of our method for the construction of 3,4-disubstituted indoline derivatives.

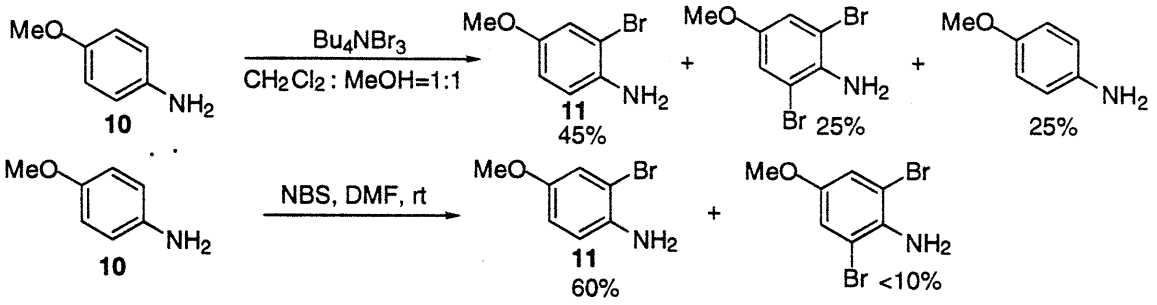
Figure 2 : Retrosynthetic Strategy



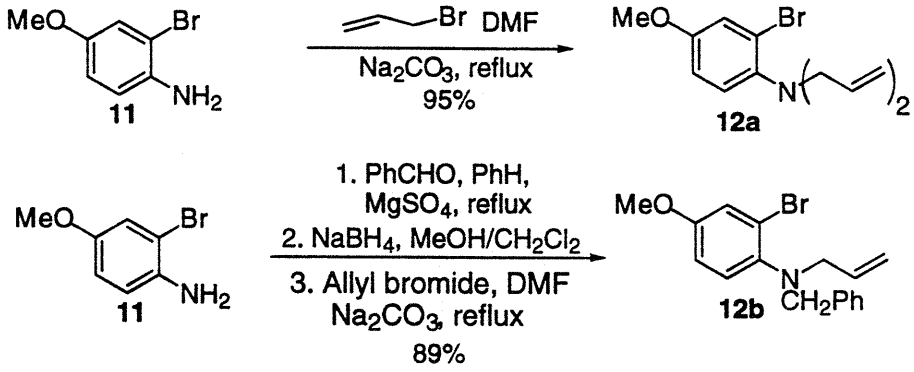
RESULTS AND DISCUSSION

To begin our synthesis of eudistomin D, we chose the inexpensive, commercially available *p*-anisidine **10** as our starting material. Monobromination of **10** was best achieved either by employing tetrabutylammonium tribromide in methanol and dichloromethane[9] or with NBS in dry DMF (Scheme 3). The resulting product **11** was either diallylated to give **12a** in 96% yield or monobenzylated and monoallylated to give **12b** in 89% yield (Scheme 4). Treatment of **12** with t-BuLi at -78°C in THF gave the aryllithium **13** which was reacted *in situ* with zirconocene methyl chloride to give aryl(methyl)zirconocene complex **14**. Upon warming to room temperature

Scheme 3

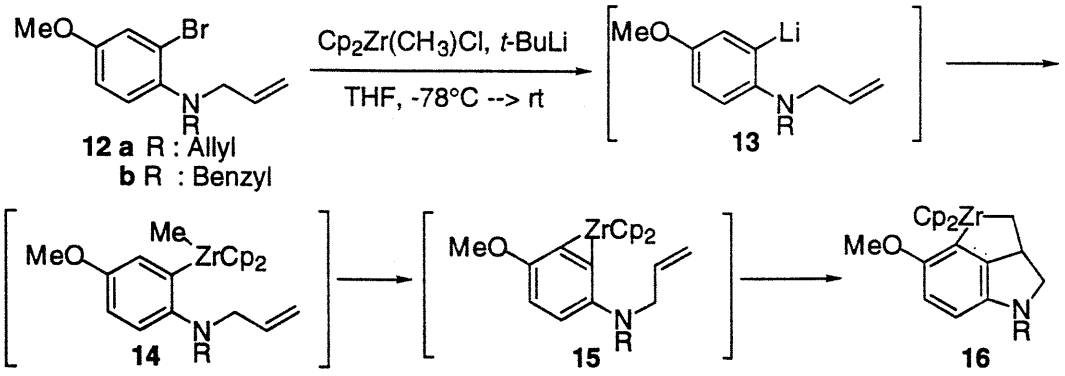


Scheme 4

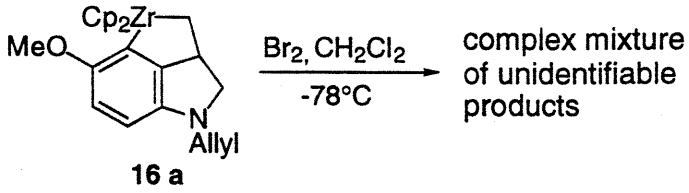


for 16 hours, the zirconocene-benzyne complex **15** was formed and underwent intramolecular olefin insertion to yield the 5,5,6-tricylic zirconacycle **16** (Scheme 5).[9] Since eudistomin D contains a bromo group at the 5-position of the β-carboline ring system, we wished to cleave the tricyclic core with bromine or its electrophilic equivalent. Quenching **16a** with 2 equivalents of Br_2 at -78°C or 0°C in dry dichloromethane, however, gave a complex mixture of compounds that could not be easily separated by column chromatography (Scheme 6). The presence of an allyl group and an electron-rich aromatic ring was believed to be responsible for the undesired outcome of the reaction, since either of these functional groups may be incompatible with the highly electrophilic bromine even at low temperature.

Scheme 5

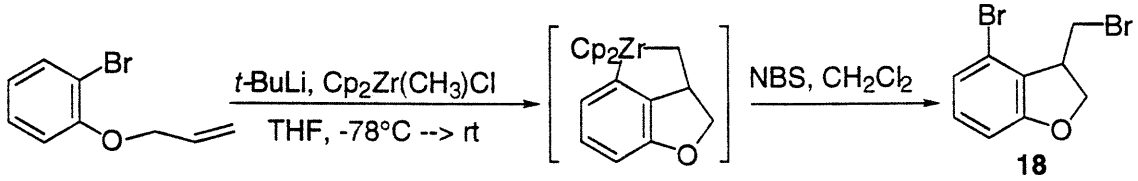


Scheme 6



The poor results obtained when using bromine as an electrophilic reagent prompted us to look for a milder, brominating agent. Buchwald and Cox have shown that the oxygen analog 5,5,6-tricyclic zirconocene complex can be cleaved cleanly at 0°C by N-bromosuccinimide to yield the dibromoindoline **18** in good yield, as shown in Scheme7.[10] Based on this result, we examined the

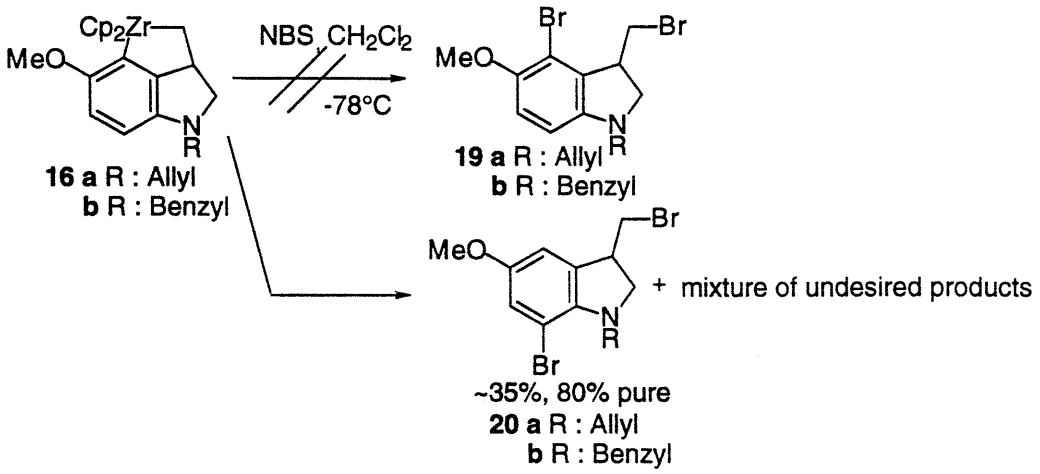
Scheme 7



reaction of NBS with the tricyclic zirconacycle **16**. Treatment of **16** with a solution of 2 equivalents of NBS in dry dichloromethane at -78°C yielded several compounds, one of which initially appeared to be the desired product **19** as judged by ^{1}H NMR and GC-MS analysis. This product was isolated in

~35% yield accompanied by some inseparable impurities (~80% pure). The other portion of the product mixture consisted of several undesired compounds, which will be discussed in greater detail later in the chapter.

Scheme 8



Repeating the exact experiment of the NBS-zirconacycle cleavage reaction and analyzing the product more carefully led us to conclude that *the major product isolated was not the desired dibromoindoline **19** but rather its regioisomer **20*** (plus some other undesired products shown in Scheme 8 and 9). The small coupling constant (~2Hz) observed for the aromatic hydrogens of the major isolated product was indicative of a *meta* coupling rather than an *ortho* coupling and suggested that **20** was the actual product obtained. Furthermore, if **19** had been the major product obtained, the coupling constant of its aromatic hydrogens should have been close to the ~8 Hz observed for the corresponding diiodoindoline **21b** (Figure 3).

To further support our interpretation of the results for the NBS-zirconacycle cleavage reaction, we synthesized the undesired dibromoindoline **20** via the procedure developed by Bailey[11] and Liebeskind.[12] When *N*-allyl-*N*-benzyl-2,6-dibromo-*p*-anisidine **22**, synthesized from *p*-anisidine as shown in

Scheme 9

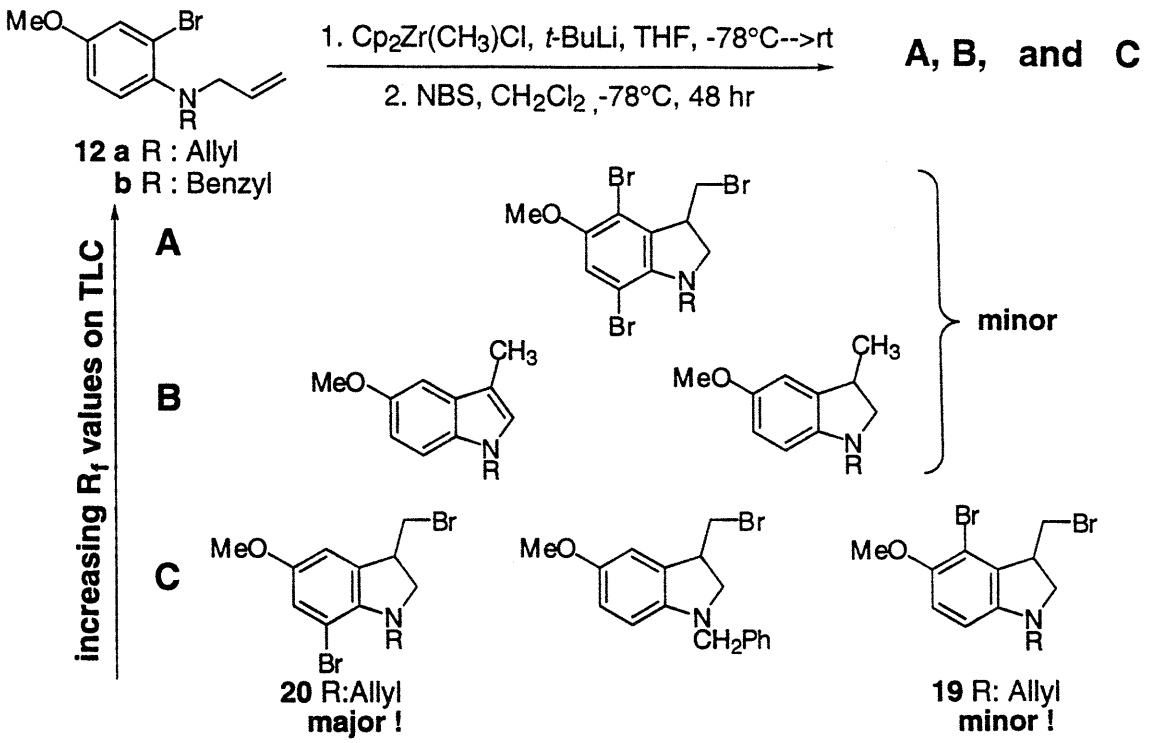
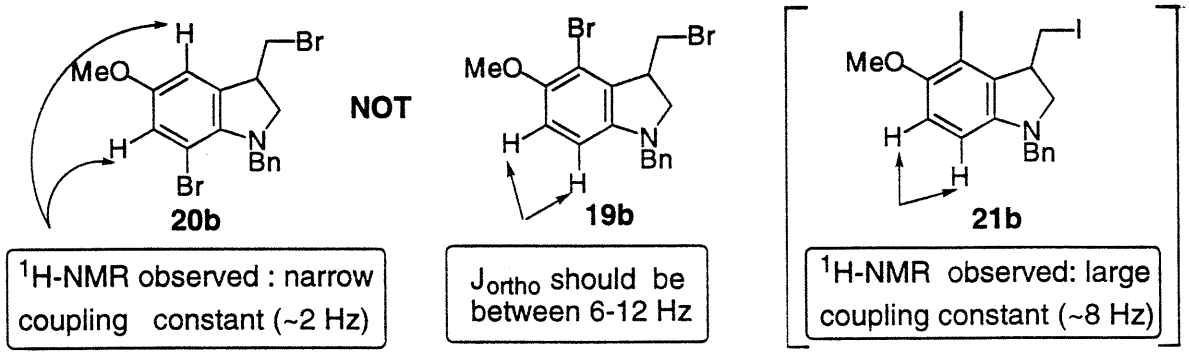
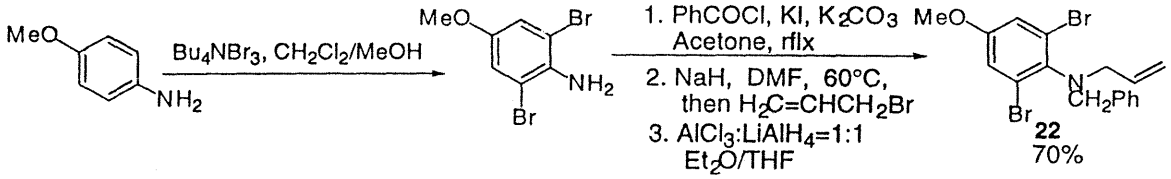


Figure 3



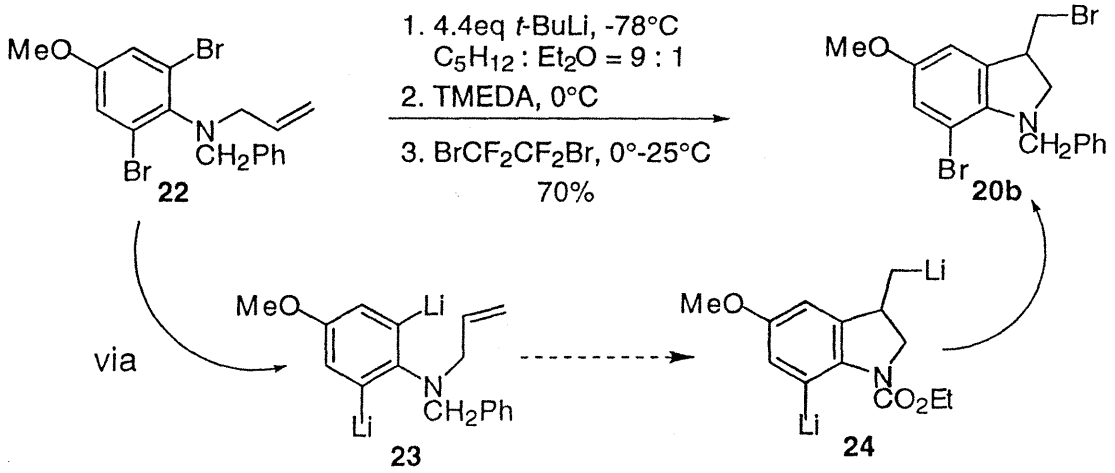
Scheme 10, was treated with 4.4 equivalents of *t*-BuLi at -78 °C in 9:1 pentane:ether, aryllithium dianion **23** was generated. Upon addition of TMEDA and warming to 0°C, π-anionic cyclization occurred to give the lithium indoline dianion derivative **24**. When this dianion was trapped with excess 1,2-dibromo-1,1,2,2-tetrafluoroethane, dibromoindoline **20** was obtained in about 70% yield

Scheme 10



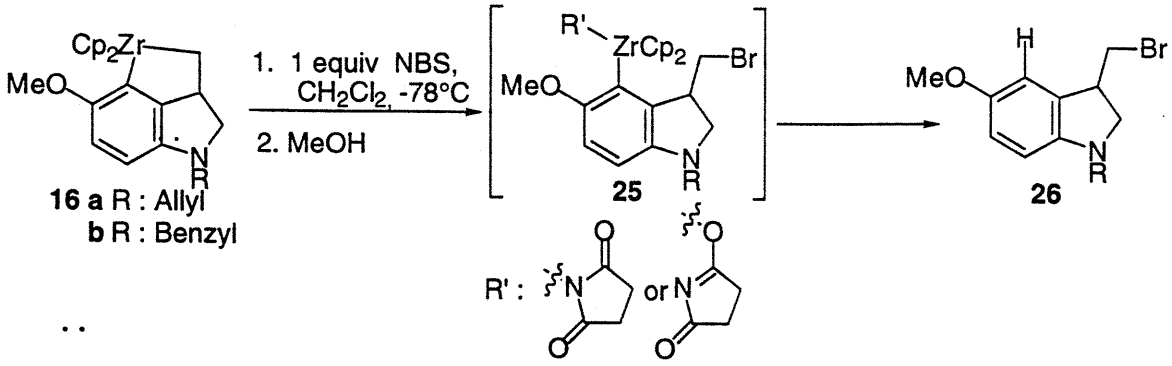
(Scheme 11). Indeed, the ^{1}H-NMR spectrum of this product matched that of the major product from the NBS-zirconacycle cleavage reaction (Scheme 9).

Scheme 11



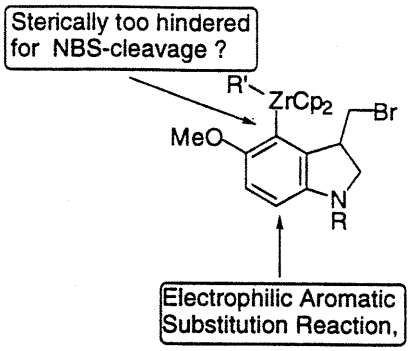
The formation of the undesired regioisomer from the NBS-zirconacycle cleavage can be explained as follows. Treatment of the 5,5,6-tricyclic zirconacycle **16** with 1 equivalent of NBS at -78 °C gives the aryl(methyl)zirconocene complex **25** which upon quenching with methanol affords the monobrominated product **26** (Scheme 12). We believe that the predominant NBS cleavage of the sp^3C-Zr bond in **16** was due to the greater nucleophilicity of sp^3 carbon and its more accessible site compared to that of the aryl sp^2 carbon. The fact that we observed the undesired regioisomer

Scheme 12

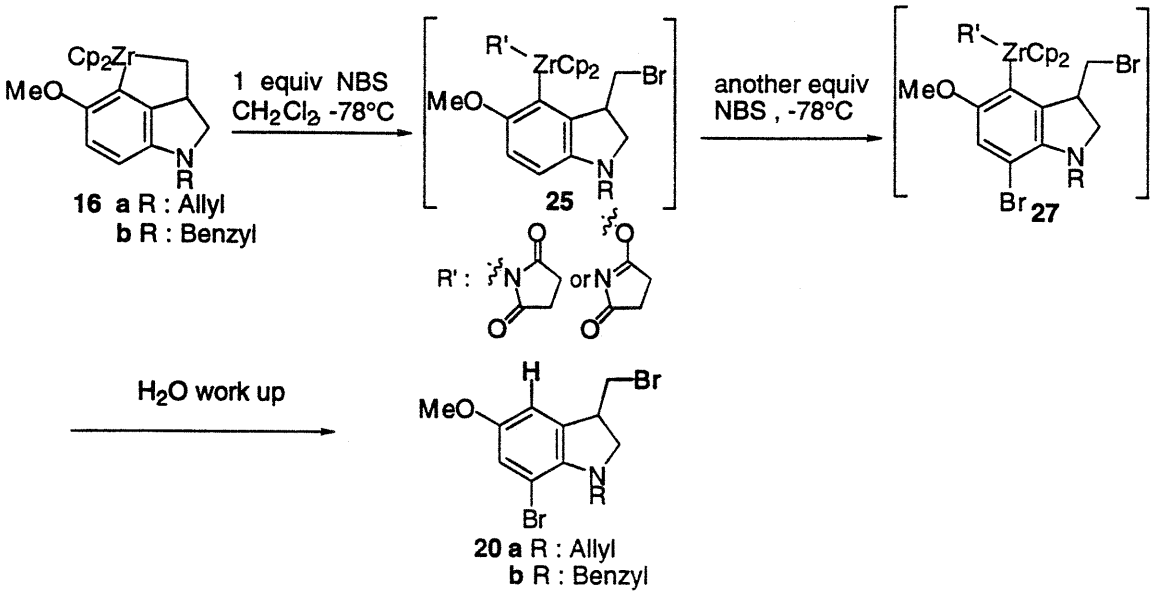


20 suggests that electrophilic aromatic substitution (EAS) reaction of the electron-rich aromatic compound **25** at the 7-position with a second equivalent of NBS occured at a faster rate than the electrophilic cleavage of the more sterically hindered aryl sp^2C-Zr bond (Figure 4). Even at -78 °C, the reaction proceeded to give the 7-brominated zirconocene complex **27**, which after aqueous work up yielded the undesired dibromoindoline **20** (Scheme 13). When the electrophilic cleavage reaction of **16** was carried out with 2 equivalents of NBS at 0 °C, the tribrominated indoline **28** was obtained as the major product in 45% yield as well as monobrominated product **29** (Scheme 14). Conducting the same reaction at -78 °C, followed by slow warming to 0 °C, afforded the tribrominated product **28** in about 35% yield, and a mixture of dibrominated product **20** and the monobrominated product **26** in about 15% combined yield (Scheme 15). Attempts to vary solvents, reagent concentrations and temperatures, as well as to recrystallize N-bromosuccinimide prior to use, gave identical results as described above.

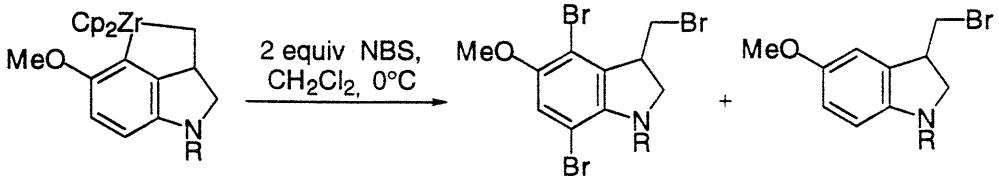
Figure 4



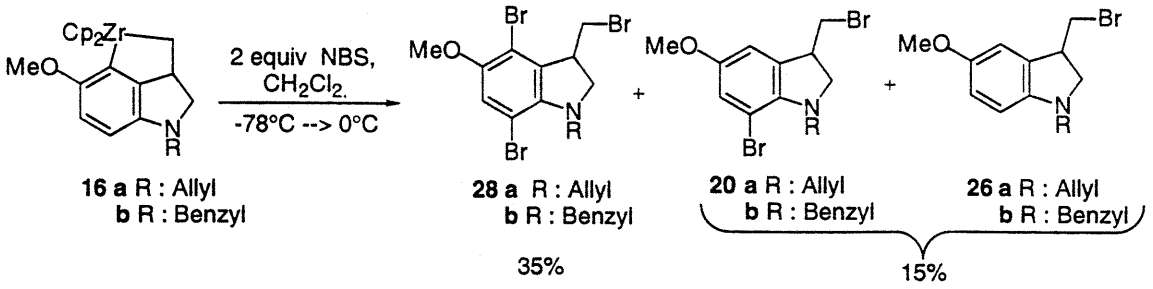
Scheme 13



Scheme 14



Scheme 15



16 a R : Allyl
b R : Benzyl

28 a R : Allyl
b R : Benzyl

35%

20 a R : Allyl
b R : Benzyl

26 a R : Allyl
b R : Benzyl

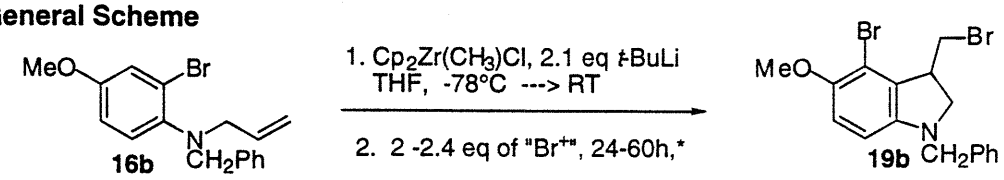
15%

The unanticipated results of the NBS-zirconacycle cleavage reaction forced us to find alternative reaction conditions. Several brominating agents were chosen and the results obtained were summarized in Table 1.

Since we believed that the second bromination favored substitution at the 7-position of **25** for steric reasons, we felt that a smaller brominating agent such as Br_2 might be able to overcome our problem. Since the reaction of the *N*-allyl-tricyclic zirconacycle **16a** with Br_2 at -78°C gave a mixture of several unidentifiable products as explained earlier in this chapter, we used the N-benzyl zirconacycle analog **16b** as a substrate for testing the bromine cleavage reaction. Not surprisingly, at 0°C, the reaction proceeded to give the tribrominated product **28b** as well as the monobrominated product **26b** (entry 2, Table 1). Performing the reaction at temperature between -78°C and 0°C, or at an initial temperature of -78°C followed by slow warming to 0°C, gave the tribrominated product **28b** in 35% yield and the undesired isomer **20b** in 10% yield. When the reaction was carried out at -78°C, we again obtained **28b** in 25% yield, the undesired regioisomer product **20b** in 25% yield, and trace amount of the aromatized product **29b** (<5% yield).

Table 1

General Scheme



*dichloromethane was used as the solvent unless otherwise noted

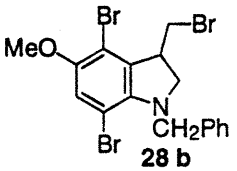
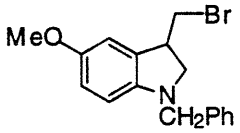
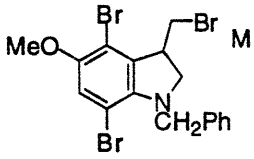
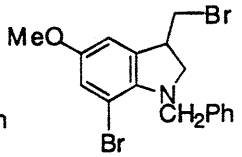
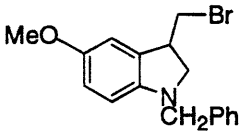
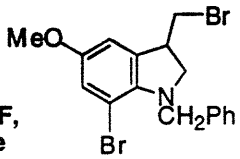
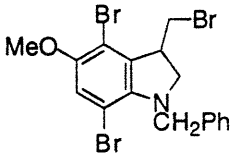
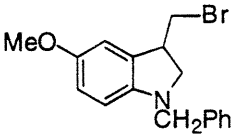
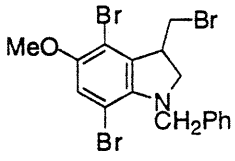
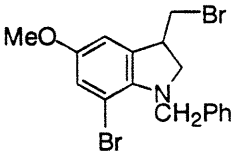
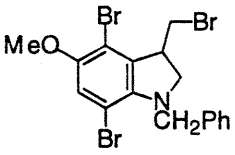
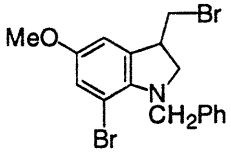
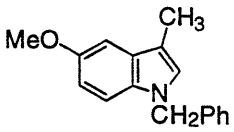
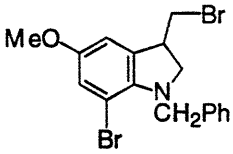
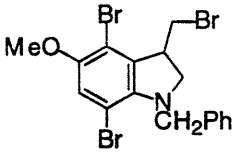
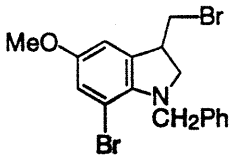
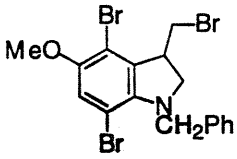
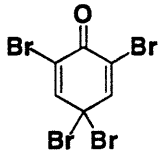
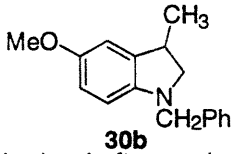
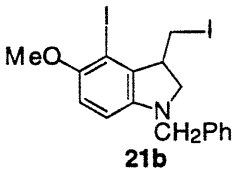
Entry	"Br^+"	eq	T(°C)	Observed product(s)
1	NBS	2.1	0°C	 **28 b** 45%  **26 b** <10%
		2.0	-78°C-->0°C	 **28 b** 35%  **20b** 15%  **26 b**
		2.0	-78°C **both in CH_2Cl_2 or THF, recrystallization gave the same results**	 **20b** 35% other products shown in Scheme 11
2	Br_2	1.95	0°C	 **28b** 50%  **26 b** <10%
		2.0	-78°C-->0°C	 **28b** 40%  **20b** <10%

Table 1 (continued)

Entry	"Br^+"	eq	T(°C)	Observed product(s)
	Br_2 both in CH_2Cl_2 or in $CHCl_3$	2.0	-78°C	 **28b** 25%  **20b** 25%  **29b** <5%
		2.0	-78°C THF	mixture of unidentifiable compounds
3	Bu_4NBr_3	2.0	-78°C	 **20b** 73%  **28b** 20%
4	$PhCH_2N(Me)_3Br_3$	2.0	-78°C	 **20b** ~70%  **28b** 20%
5		2.0	-78°C --> 0°C	mixture of unidentifiable compounds
6	$BrCF_2CF_2Br$	2.5	0°C-->rt 72-80 h	no reaction [ **30b** obtained after work-up]
7	IBr	2.0	-78°C	 **21b** 79%

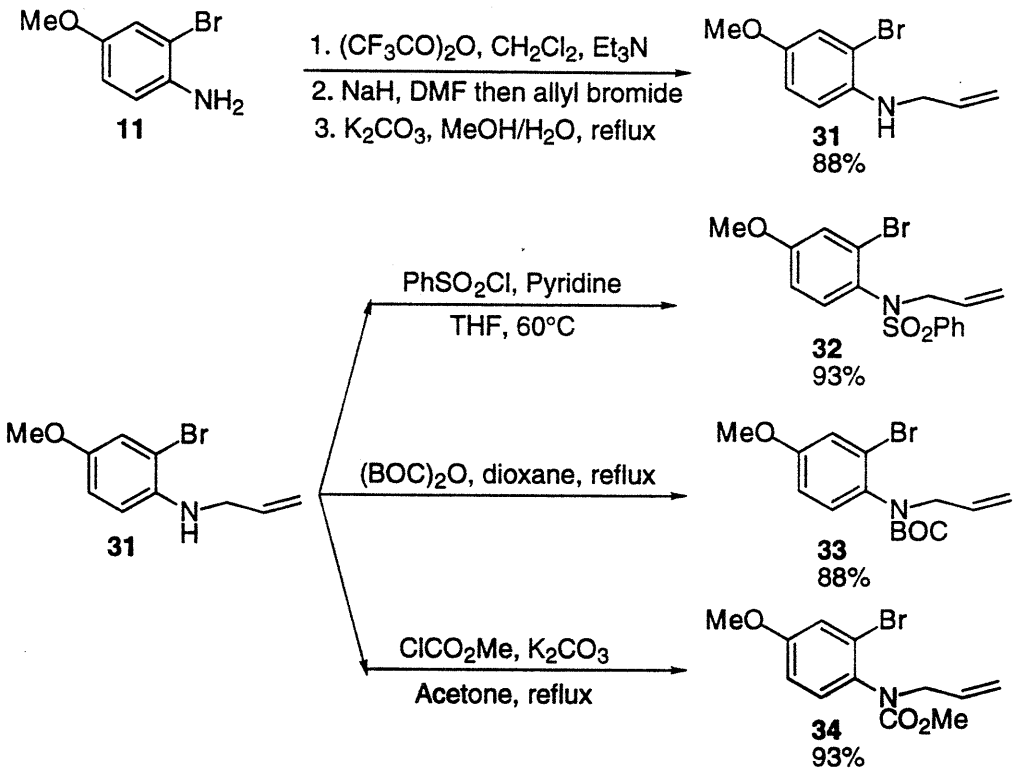
We next investigated the use of milder brominating reagents, such as tetrabutylammonium tribromide (entry 3) and benzyltrimethylammonium tribromide (entry 4). As with bromine or NBS, at -78°C in dichloromethane, 2 equivalents of either reagent gave the undesired regioisomer **20b** as the major product (70% isolated yield) and the tribrominated product **28b** as the minor one (~15% yield). Neither tetrabromocyclohexadienone (entry 5) nor dibromotetrafluoroethane (entry 6) gave detectable quantities of the desired products. While the former reagent gave a mixture of several unidentifiable compounds, the latter gave only the non-brominated indoline **30b,** even after 3 days at room temperature. This result suggested that there was no reaction between this reagent and the tricyclic zirconacycle **16b**. Treatment of **16b** with 2 equivalents of IBr at -78°C, gave only the diidoindoline product **21b** in ~79% isolated yield.

After trying a wide variety of brominating reagents and obtaining very poor results, we attempted a different approach to the problem by attaching an electron withdrawing group to the indoline nitrogen, in hopes of suppressing the facile EAS reaction. We chose *N*-sulfonamide, *N*-methylcarbamate, and *N*-BOC as the nitrogen protecting groups. Synthesis of each *N*-protected-*N*-allyl-2-bromo-*p*-anisidine derivative is shown in Scheme 16. The initial precursor, 2-bromo-*p*-anisidine, was first monoallylated in three steps to yield *N*-allyl-2-bromo-*p*-anisidine in 88% overall yield. This allylated bromoanisidine was then treated with appropriate electrophiles to yield the corresponding *N*-protected anisidine derivatives **32-34.**

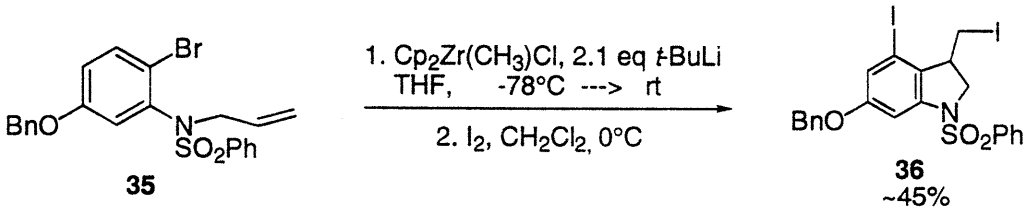
As the first substrate, we chose the *N*-allyl-*N*-benzenesulfonylbromoanisidine **32**, because Tietze and coworkers had reported that the reaction of **35** with 2.1 equiv of *t*-BuLi and zirconocene(methyl)

chloride at -78°C in THF followed by electrophilic cleavage with iodine at 0°C gave the desire diiodoindoline **36** in approximately 45% yield (Scheme 17).[13]

Scheme 16

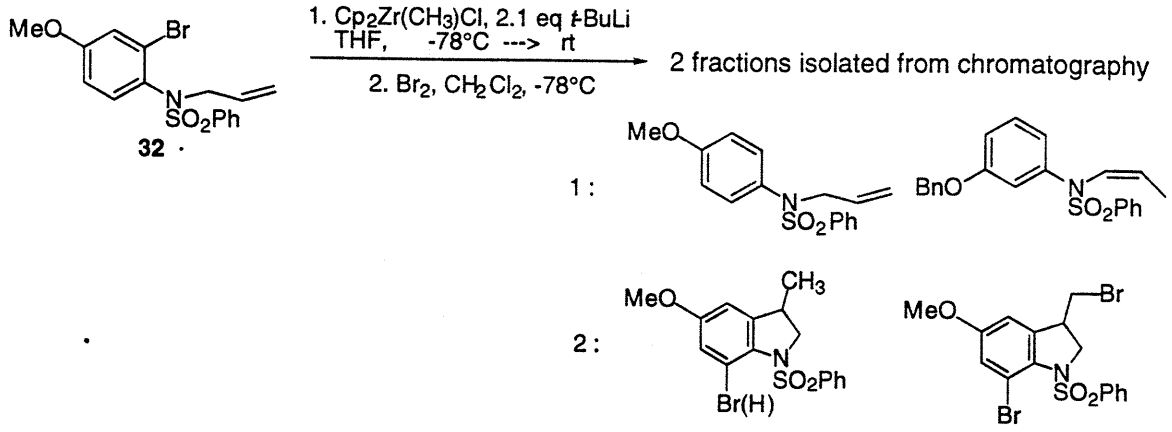


Scheme 17



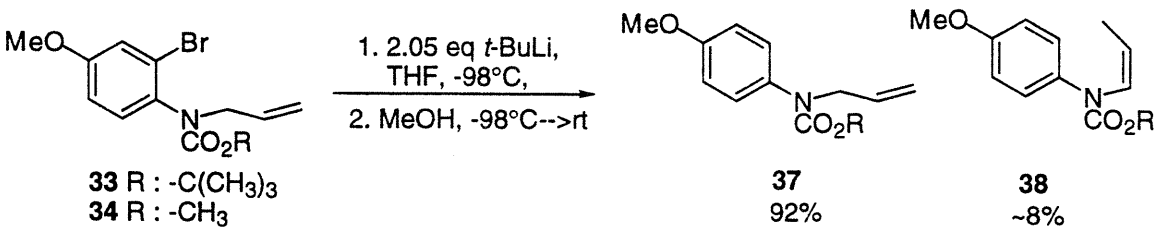
Using our substrate **32** under Tietze's conditions followed by the addition of Br_2 at -78 °C to the zirconacycle gave no desired products. The compounds, which were isolated after flash column chromatography, are shown in Scheme 18. No further investigations were carried out using **32**.

Scheme 18



We next investigated the utility of *N*-carbomethoxy and *N*-BOC protected anisidine (**33** and **34**, respectively) during our attempt to generate the desired 3,4-dibromoindoline. Prior to performing the bromination reaction, we first studied the halogen-metal exchange step as well as the iodination reaction. Upon treatment of either protected anisidine with 2.05 equivalent of t-BuLi at THF at -98°C followed by quenching with methanol, debrominated product **37** was obtained in 92% yield as well as debrominated-isomerized product **38** in about 5% yield (Scheme 19). This result suggested that the carbamate protecting groups were compatible with *tert*-butyllithium and that halogen-metal exchange occurred readily at -98°C for either substrate. We have no evidence for the mechanism of formation of the isomerized product, however we propose that the process involves deprotonation of one of the allylic hydrogens (Figure 5) by either a small excess of t-BuLi to generate the dianion **39** which upon quenching with methanol gives the isomerized product **38**, or by the *in situ* generated lithium methoxide, which then catalyzes the isomerization.

Scheme 19 : Halogen-Metal Exchange Study

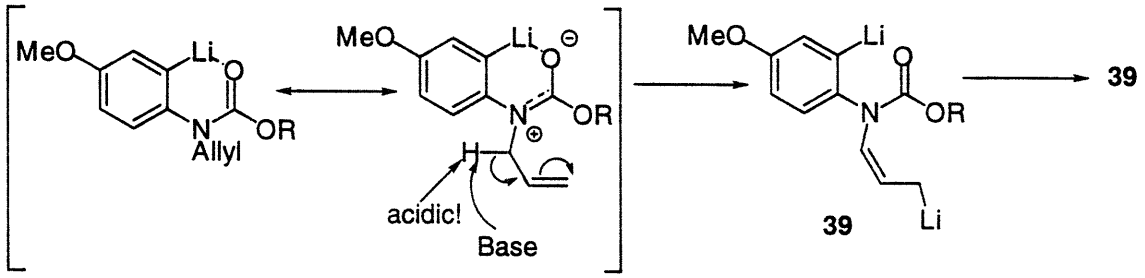


33 R : -$C(CH_3)_3$
34 R : $-CH_3$

37
92%

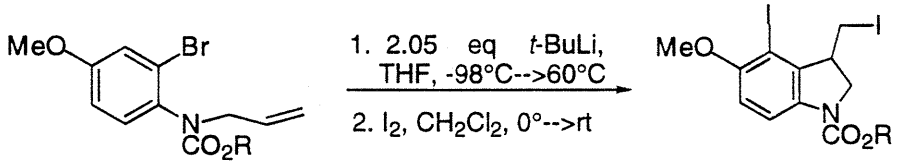
38
~8%

Figure 5



In our studies of the iodination reaction, the *N*-protected-bromoanisidines were treated with *t*-BuLi and zirconocene(methyl) chloride followed by quenching with iodine; the desired diiodoindoline **40** was obtained in less than 40% yield (Scheme 20). We found that harsher conditions (i.e. heating to 60 °C rather than at room temperature) were necessary to form the benzyne and the

Scheme 20



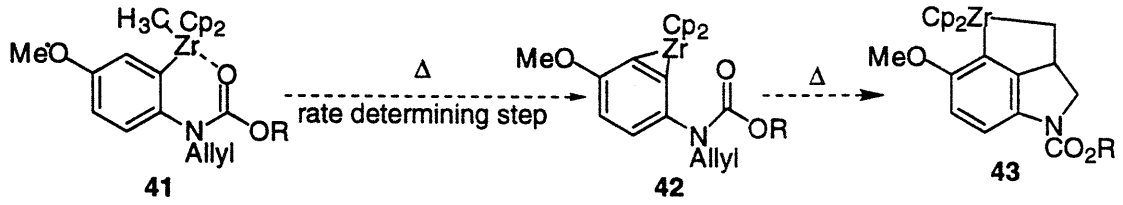
33 R : -$C(CH_3)_3$
34 R : $-CH_3$

40
<40%

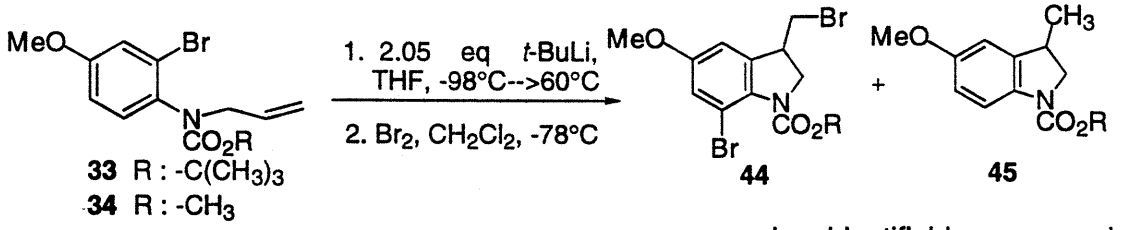
5,5,6-tricyclic zirconacycle. We believe that the low reactivity is due to the interaction of the $Cp_2Zr(Me)$- fragment with the lone pairs of the carbamate oxygen (i.e. **41** in Figure 6), as such interaction has also been observed by

Peat and Buchwald in other related systems.[14] When we attempted to use bromine to cleave the tricyclic zirconacycle **43**, only the undesired regioisomer dibromoindoline **44** was observed as the major product as well as other unidentifiable products(Scheme 21).

Figure 6



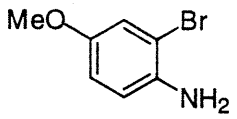
Scheme 21



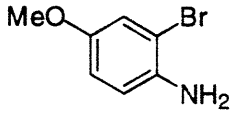
Although we did not have eudistomin D in hand as of this writing, have we had the desired regioisomer of the dibromoindoline derivative, we should be able to afford the natural product by a series of viable synthetic steps.[15] The remaining challenging task is to find the proper conditions to electrophilically cleave the 5,5,6-tricyclic zirconacyle **16** and introduce the bromo group in the desired position.

Experimental Section

All reactions involving organometallic reagents were conducted under an atmosphere of purified argon using standard Schlenk techniques or under nitrogen in a Vacuum Atmospheres Co. drybox. All reactions were performed under an atmosphere of argon or nitrogen. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian XL-300, VXR-500 or a Bruker AC250 FT spectrometer. Infrared (IR) spectra were recorded on a Perkin-Elmer Seried 1600 FT spectrometer. Gas chromatography analyses were performed on a Hewlett Packard model 5890 GC with a 3392A integrator and FID detector using a 25 m capillary column with cross linked SE-30 as a stationary phase. Tetrahydrofuran and diethyl ether were dried and deoxygenated by continuous refluxing over sodium/benzophenone ketyl under nitrogen or argon followed by distillation. Anhydrous methylene chloride, benzene, pentane, hexane, acetonitrile, dioxane, and *N,N*-dimethyl formamide (DMF) were purchased from Aldrich Chemical Co. and were used without further purification. Molecular sieves were flame dried under vacuum for 1 hour prior to use. Cp_2ZrCl_2 was purchased from Boulder Scientific Inc., Mead, Colorado, which was converted to $Cp_2Zr(Me)Cl$.[16] All other reagents were either prepared according to published procedures or were available from commercial sources and used without further purification. Unless otherwise stated, preparative flash chromatography was performed on E.M. Science Kieselgel 60 (230-400 mesh). Yields refer to isolated yields of compounds estimated to be ≥95% pure (unless otherwise noted) as determined by ^1H NMR and either capillary GC or combustion analysis. All reported yields are representative. Elemental analyses were performed by E&R Microanalytical Laboratory, Inc., Corona, N.Y.

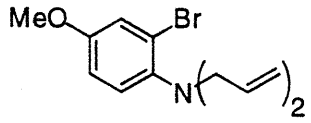


2-bromo-4-methoxyaniline (11): Method A. Into a flask were placed *p*-aniside (2.47 g, 20.05 mmol), methanol (40 mL), and CH_2Cl_2 (80 mL). To the colorless solution was added *n*-Bu_4NBr_3 (9.68 g, 20.07 mmol) in one portion, causing the reaction mixture to turn purple. The resulting mixture was allowed to stir at RT for 35 min and was then poured into a separatory funnel containing saturated aqueous Na_2SO_3 (100 mL) and ether (100 mL). The organic layer was collected and washed with water (2 x 100 mL), brine (100 mL), dried over $MgSO_4$, filtered through a short plug of silica and the solvents were removed to leave a dark, red oil. The product was isolated by flash chromatography (9:1 hexane/ethyl acetate) to yield 1.75 (45%) of a brown oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 6.98 (d, *j*= 2.4 Hz, 1H), 6.69 (m, 2H), 3.78 (br, s 2H), 3.69 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 152, 138, 117, 116, 115, 109, 56. IR (neat, cm^{-1}) 3442, 3358, 3203, 2999, 2949, 2832, 1623, 1600, 1499, 1440, 1275, 1230, 1212, 1037, 865.

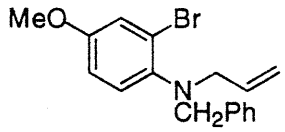


2-bromo-4-methoxyaniline (11): Method B. A solution of NBS (0.28 g, 1.57 mmol) in dry DMF (5 mL) was added to a solution of *p*-anisidine (0.19 g, 1.57 mmol) in dry DMF (3 mL) at room temperature. The resulting solution was stirred for 45 min, and slowly poured into a separatory funnel containing ether (40 mL) and water (20 mL). The organic layer was separated, washed with water (2 x 20 mL), brine (20 mL), dried over $MgSO_4$ and filtered. The solvents were removed under a rotary evaporator to give dark residue which was purified by flash column chromatography (10:1 hexane/ethyl

acetate). The desired product was isolated as a brown oil (0.17 g, 60%). Consult Method A for information on physical data.

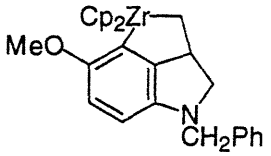


***N,N*-diallyl-2-bromo-4-methoxyaniline (12a)** To a flask were added 2-bromo-4-methoxyaniline **13** (3.75 g, 18.56 mmol), allyl bromide (4.0 mL, 5.59 g, 46.22 mmol), Na_2CO_3 (5.92 g, 55.85 mmol), and DMF (30 mL). The mixture was heated to reflux for 1 h, allowed to cool to RT and poured into a separatory funnel containing ether (50mL) and water (60mL). The organic layer was collected and washed with water (2 x 60 mL), brine (60 mL), dried over $MgSO_4$ and the solvents were removed to leave a drak, brown oil. The product was isolated by Kugelrohr distillation (T= 120-130 °C, P= 0.1 mmHg) to give 4.62 g (95%) of a yellow oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.13 (d, *J*= 3.3 Hz, 1H), 6.97 (d, *J*= 9.0 Hz, 1H), 6.77 (dd, *J*= 3.3, 9.0 Hz, 1H), 5.79 (m, 2H), 5.10 (m, 4H), 3.75 (s, 3H), 3.60 (d, *J*= 6.0 Hz, 4H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.9, 141.9, 134.9, 124.8, 122.4, 118.5, 117.3, 113.2, 56.2, 55.6. IR (neat, cm^{-1}) 3076, 3005, 2977, 2938, 2834, 1601, 1563, 1495, 1463, 1440, 1286, 1209, 1040, 992, 921, 810, 740, 675.

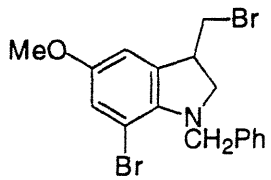


***N*-allyl-*N*-benzyl-2-bromo-4-methoxyaniline (12b).** Into a flask were added 2-bromo-4-methoxyaniline **11** (6.67 g, 33.02 mmol), activated molecular sieves (18 g), anhydrous benzene (60 mL), and freshly distilled benzaldehyde (3.52 mL, 34.67 mmol). The resulting suspension was heated to 70 °C for 24 h, allowed to cool to RT and filtered through a plug of celite to give

a yellowish solution. The solvents were removed using a rotary evaporator and the residue was dissolved in CH_2Cl_2 (30 mL) and MeOH (30 mL) to give an orange-yellowish solution, which was then slowly treated with $NaBH_4$ (5 g, 132 mmol) at 10 °C. The resulting greenish solution was stirred for 5 h and slowly poured into a separatory funnel containing CH_2Cl_2 (200 mL) and ice cold H_2O (200 mL). The organic layer was collected and the aqueous phase washed with CH_2CL_2 (2 x 150 mL). The combined organic layer was washed with brine, dried over K_2CO_3, and filtered. The solvents were removed using a rotary evaporator to give a yellowish residue, which was purified by flash column chromatography (40:1 hexane/ehter) to give 9 g of *N*-benzyl-2-bromo-4-methoxyaniline as a colorless oil. Into a flask were placed *N*-benzyl-2-bromo-4-methoxyaniline (7.3 g, 25 mmol), Na_2CO_3 (11 g, 100 mmol), allyl bromide (9 mL, 100 mmol), and anhydrous DMF (100 mL). The reaction mixture was refluxed for 5h, cooled to RT, and poured into a separatory funnel containing ether (300 mL) and water (200 mL). The organic layer was collected, washed with water (2 x 200 mL) and brine (200 mL), dried over $MgSO_4$, and filtered. The solvents were removed using a rotary evaporator to give a yellowish oil, which was purified by flash column chromatography (30:1 hexane/ethyl acetate). The desired product was obtained as a colorless oil (8.0 g, 96%). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.30-7.10 (m, 5H), 7.08 (d, 1H), 6.90 (d, 1H), 6.70 (dd, 1H), 5.86-5.74 (m, 1H), 5.14-5.05 (m, 2H), 4.12 (s, 2H), 3.83 (s, 3H), 3.53 (d, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 156.3, 142.1, 138.6, 134.9, 128.8, 128.3, 127.1, 125.1, 122.7, 118.8, 117.8, 113.5, 57.4, 56.1, 55.7. IR (neat, cm^{-1}) 3062, 3026, 2937, 2834, 1600, 1490, 1453, 1439, 1286, 1227, 1206, 1038, 921, 856, 751, 698.

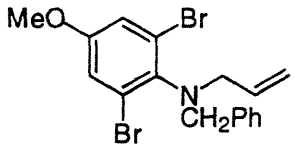


16b. Into a dry Schlenk flask were added *N*-allyl-*N*-benzyl-2-bromo-4-methoxyaniline **12b** (1.80 g, 5.43 mmol), zirconocene methyl chloride (1.55 g, 5.70 mmol) and anhydrous THF (20 mL). The resulting solution was cooled to -78 °C and slowly treated with *t*-BuLi (6.80 mL, 11.41 mmol). The reaction mixture was stirred at -78 °C for 15 min, slowly warmed to RT and stirred for overnight at this temperature. The following day, the dark brownish solution was concentrated *in vacuo* and the residue dissolved in 9:1 dry toluene:ether (18 mL:2 mL) to give a brownish suspension which was transfered via a filtered cannula to another Schlenk flask. The solvents were then concentrated *in vacuo* and the residue was brought into a glovebox, weighed (2.4 g, 93%), and used for further reactions without purification. ^{1}H NMR (C_6D_6, 300 MHz) δ 7.38 (d, 2H), 7.20-7.0 (m, 3H), 6.38 (d, 1H), 6.28 (d, 1H), 5.85 (s, 5H), 5.73 (s, 5H), 4.34 (d, 1H), 3.64-3.53 (m, 2H), 3.43 (s, 3H), 2.80-2.70 (m, 1H), 2.35 (dd, 1H), 1.15 (m, 1H), 0.86 (dd, 1H).



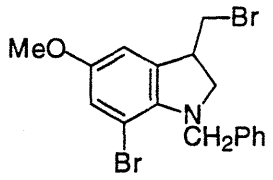
***N*-benzyl-3-bromomethyl-7-bromo-4-methoxyindole (20b) via 16b.** A precooled solution of NBS (0.23 g, 1.27 mmol) in CH_2Cl_2 (5 mL) was slowly transferred via cannula to a Schlenk flask containing a solution of **16b** (0.28 g, 0.6 mmol) in CH_2Cl_2 (5 mL) at -78 °C. The resulting brownish solution was stirred at -78 °C for 24 h and was treated with a suspension of Na_2SO_3 in MeOH. The reaction mixture was stirred at -78 °C, slowly warmed to RT, and

poured into a separatory funnel containing CH_2Cl_2 (20 mL) and H_2O (15 mL). The organic layer was separated, washed with H_2O (2 x 15 mL), brine (20 mL), dried over $MgSO_4$ and filtered. The solvents were removed using a rotary evaporator to give a brownish residue which was purified by flash column chromatography (50:1 hexane/ether). The desired product was collected as a yellowish oil (90 mg, 36%). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.40-7.25 (m, 5H), 6.92 (d, 1 H), 6.80 (d, 1H), 4.65 (s, 2H), 3.78 (s, 3H), 3.63-3.47 (m, 3H), 3.32-3.25 (m, 1H), 3.24-3.16 (m, 1H).

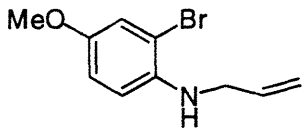


***N*-allyl-*N*-benzyl-2,6-dibromo-4-methoxyaniline (22).** Into a flask were added 2,6-dibromo-4-methoxyaniline[17] (2.27g, 8.07 mmol), benzoyl chloride (1.03 mL, 8.87 mmol), sodium iodide (3.6 g, 24.21 mmol), sodium carbonate (2.6 g, 24.21 mmol) and acetone (20 mL). The resulting suspension was refluxed overnight, cooled to RT, and poured into a separatory funnel containing ether (40 mL) and water (30 mL). The organic layer was collected, washed with H_2O (2 x 30 mL) and brine (40 mL), dried over Na_2SO_4 and filtered. The solvents were removed using a rotary evaporator to give a yellowish residue, which was recrystallized from CH_2Cl_2 to yield *N*-(2,6-dibromo-4-methoxyphenyl) benzamide as white crystals (2.15 g), used for the next step. The benzamide derivative (2.15 g, 5.58 mmol) was then dissolved in dry DMF (20 mL) and the resulting solution was transferred via cannula to a Schlenk flask containing a suspension of 95% NaH (0.270 g, 11.16 mmol) in dry DMF (20 mL). The resulting mixture was stirred for 1 h at 50 °C, then treated

with allyl bromide (1.5 mL, 16.75 mmol) and stirred for an additional 2 h at 50 °C. After cooling to room temperature, the reaction mixture was slowly poured into a separatory funnel containing ether (50 mL) and ice-cold H_2O (30 mL). The organic layer was collected, washed with H_2O (2 x 30 mL) and brine (30 mL), dried over $MgSO_4$ and filtered. The solvents were removed using a rotary evaporator to give a yellowish residue which was purified by flash column chromatography (20:1 hexane/ethyl acetate). The desired allylated benzamide was collected as a yellowish oil which solidified upon standing under vacuum (2.1 g). The material was then dissolved in dry ether (15 mL) and transferred via cannula to a precooled (0 °C) solution of $LiAlH_4$ (0.4 g, 10.28 mmol) and $AlCl_3$ (1.4 g, 10.28 mmol) in dry ether (15 mL), which had been stirred together for 15 min. The resulting clear solution was stirred at 0 °C for 3 h and any excess of hydride was quenched by slow addition of ice-cold H_2O at 0 °C. The reaction mixture was then poured into a separatory funnel containing ether (20 mL) and water (20 mL). The organic layer was separated and collected, washed with H_2O (2 x 30 mL) and brine (30 mL), dried over $MgSO_4$ and filtered. The solvents were removed using a rotary evaporator to give a yellowish residue which was purified by flash column chromatography (24:1 hexane/ether) to give a pale yellowish oil (1.8 g, 90%). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.67 (d, 2H), 7.51-7.40 (m, 3H), 7.27 (s, 2H), 6.20-6.07 (m, 1H), 5.30 (dd, 1H), 5.20 (dd, 1H), 4.50 (s, 2H), 3.93 (s, 3H), 3.90 (d, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.5, 140.0, 139.2, 136.2, 129.5, 128.2, 127.4, 127.1, 118.6, 117.1, 57.1, 55.9, 55.5. IR (neat, cm^{-1}) 3075, 3027, 2936, 2837, 1641, 1589, 1537, 1470, 1433, 1265, 1210, 1174, 1041, 992, 921, 879, 857, 836, 744, 698.



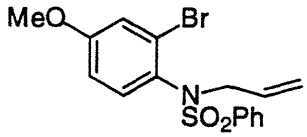
***N*-benzyl-3-bromomethyl-7-bromo-4-methoxyindole (20b) via 22.** A solution of *t*-BuLi (2.0 mL, 3.30 mmol) was slowly added to a solution of **22** (0.32 g, 0.75 mmol) in 9:1 mixture of dry pentane:ether (9 mL:1 mL) at -78 °C. The resulting solution was stirred at -78 °C for 15 min, treated with freshly distilled TMEDA (0.50 mL, 3.30 mmol), stirred for another 5 min, slowly warmed to 0 °C and stirred for 45 min. The orange-colored suspension was recooled to -78 °C and treated with precooled 1,2-dibromo-1,1,2,2-tetrafluoroethane (0.5 mL, 3.75 mmol). The resulting mixture was stirred for 30 min at -78 °C, another 30 min at RT, quenched with saturated NH_4Cl, and then was poured into a separatory funnel containing ether (20 mL) and water (15 mL). The organic layer was collected, washed with water (2 x 15 mL) and brine (20 mL), dried over $MgSO_4$ and filtered. The solvents were removed using a rotary evaporator to give a brownish oil, which was purified by flash column chromatography (39:1 hexane/ether) to give the desired product as a yellowish oil (0.25 g, 70%). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.33-7.25 (m, 5H), 6.82 (d, 1H), 6.70 (d, 1H), 5.74 (s, 2H), 3.75 (s, 3H), 3.62-3.46 (m, 3H), 3.32-3.24 (m, 1H), 3.24-3.16 (m, 1H).



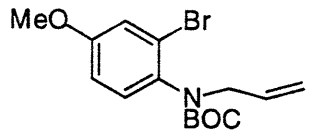
***N*-allyl-2-bromo-4-methoxyaniline (31).** Into a flask were added 2-bromo-4-methoxyaniline **11** (4 g, 19.8 mmol), Et_3N (11 mL, 79,2 mmol), trifluoroacetic anhydride (5.6 mL, 39.6 mmol), and dry CH_2Cl_2 (50 mL). The

resulting solution was stirred for 10 min at 0 °C ,1 h at RT, treated with phosphate buffer (pH =7) followed by MeOH (20 mL). The biphasic mixture was stirred for 10 min and concentrated *in vacuo* to remove any volatile compounds. It was then poured into a separatory funnel containing 1:1 ether/ethyl acetate (30:30 mL) and H_2O (30 mL). The organic layer was collected, washed with H_2O (2 x 20 mL) and brine (20 mL), dried over $MgSO_4$ and filtered. The solvents were removed using a rotary evaporator to give a reddish-brown solid which was recrystallized from hexane to give 4.9 g of *N*-(2-bromo-4-methoxyphenyl) trifluoroacetamide as white fluffy crystals, which were used for the next step. The trifluoroacetamide derivative (4.6 g, 15.44 mmol) were then dissolved in dry DMF (20 mL) and transferred via cannula to a Schlenk flask containing a suspension of 95% NaH (0.41 g, 16.98 mmol) in dry DMF (25 mL). The resulting mixture was heated to 60 °C for 30 min, treated with allyl bromide (2.67 mL, 30.87 mmol), and stirred for 2 h at 90 °C. The reaction mixture was cooled to RT, and poured into a separatory funnel containing ether (30 mL) and water (20 mL). The organic layer was collected, washed with water (1 x 20 mL), and the solvents were removed using a rotary evaporator to give a yellowish residue which was dissolved in 5:2 MeOH:H_2O (25 mL:10 mL). Lithium methoxide (10g) was then added and the reaction mixture was stirred at 60 °C for 16 h, cooled to room temperature and poured into a separatory funnel containing ether (50 mL) and water (25 mL). The organic layer was collected, washed with H_2O (2 x 25 mL) and brine (25 mL), dried over $MgSO_4$ and filtered. The solvents were removed using a rotary evaporator to give a yellowish residue which was purified by flash column chromatography (50:1 hexane/ether). The desired product was obtained as a colorless oil (3.5 g, 95%). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.08 (d, 1H), 6.80 (dd, 1H), 6.60 (d, 1H), 6.02-5.90 (m, 1H), 5.32-5.18 (m, 2H), 4.13 (b, 1H), 3.79 (m, 2H), 3.70 (s, 3H).

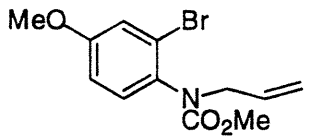
^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.8, 139.4, 135.2, 118.4, 116.4, 114.6, 112.5, 110.0, 56.1, 47.1. IR (neat, cm^{-1}) 3405, 3078, 2999, 2932, 2831, 2069, 1644, 1614, 1572, 1510, 1463, 1438, 1402, 1309, 1281, 1241, 1213, 1181, 1041, 995, 920, 857, 795, 745, 676.



***N*-allyl-*N*-benzenesulfonyl-2-bromo-4-methoxyaniline (32).** Into a flask were added *N*-allyl-2-bromo-4-methoxyaniline **32** (1.93 g, 7.98 mmol), benzene sulfonyl chloride (1.83 mL, 14.36 mmol), and deoxygenated THF (25 mL). The resulting solution was heated to 60 °C at which pyridine (2.6 mL, 31.90 mmol) was added and the reaction mixture stirred for 15 h. After cooling to room temperature, the reaction mixture was then poured into a separatory funnel containing ether (30 mL) and 2N HCl (20 mL). The organic layer was collected, washed with water (2 x 20 mL), brine (20 mL), dried over $MgSO_4$ and filtered. The solvents were removed using a rotary evaporator to give purplish residue which was purified by flash column chromatography (9:2 hexane/ethyl acetate) to give the titled compound as white needle-like crystals (2.85 g, 93%), mp= 67-68 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.77 (d, 2 H), 7.57 (t, 1H), 7.48 (t, 2H), 7.10 (d, 1H), 6.96 (d, 1H), 6.76 (dd, 1H), 5.90-5.75 (m, 1H), 5.10-4.95 (m, 2H), 4.23 (dd, 1H), 4.13 (dd, 1H), 3.80 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 185.1, 159.9, 140.0, 133.0, 132.9, 132.8, 130.1, 129.1, 128.0, 126.4, 119.6, 118.9, 113.8, 55.9, 54.3. IR (neat, cm^{-1}) 3094, 3026, 2937, 2836, 1644, 1597, 1571, 1489, 1446, 1420, 1402, 1351, 1286, 1248, 1213, 1162, 1089, 1037, 999, 937, 922, 873, 834, 724, 689, 621, 575, 536.

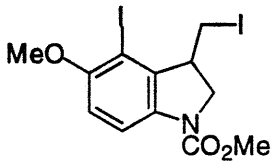


***N*-allyl-*N*-(*tert*-butoxy)carbonyl-2-bromo-4-methoxyaniline (33).** Into a flask were added *N*-allyl-2-bromo-4-methoxyaniline **32** (0.52 g, 2.15 mmol), di-*t*-butyl-dicarbonate (0.52 g, 2.36 mmol) and dry dioxane (10 mL). The resulting solution was refluxed for 24 h, cooled to room temperature, and poured into a separatory funnel containing ether (40 mL) and water (40 mL). The organic layer was collected, washed with water (2 x 40 mL) and brine (40 mL), dried over $MgSO_4$ and filtered. The solvents were removed using a rotary evaporator to give a yellowish residue which was purified by flash column chromatography (10:1 hexane/ether). The desired product was isolated as a colorless oil (0.6 g, 88%). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.15 (d, 1H), 7.05 (d, 1H), 6.80 (dd, 1H), 5.97-5.83 (m, 1H), 5.10-5.03 (m, 1H), 4.50-4.33 (m, 1H), 3.82-3.73 (m, 4H), 1.35 (s, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz) d 184.9, 158.7, 154.4, 134.1, 134.0, 133.8, 131.2, 130.8, 124.3, 124.1, 118.4, 117.9, 117.6, 117.1, 113.9, 113.4, 80.5, 80.0, 55.7, 55.6, 53.3, 52.1, 28.2. IR (KBr pellet, cm^{-1}) 3080, 2977, 2931, 2839, 1708, 1601, 1568, 1494, 1441, 1382, 1287, 1270, 1224, 1151, 1038, 1004, 924, 859, 766, 607.



***N*-allyl-*N*-carbomethoxy-2-bromo-4-methoxyaniline (34).** Into a flask were added *N*-allyl-2-bromo-4-methoxyaniline **32** (1.01 g, 4.17 mmol), methyl chloroformate (0.65 mL, 8.35 mmol), K_2CO_3 (2.30 g, 16.70 mmol),

acetone (20 mL). The resulting suspension was refluxed for 20 h, cooled to room temperature, and poured into a separatory funnel containing ether (40 mL) and water (40 mL). The organic layer was separated, washed with water (2 x 30 mL) and brine (1 x 40 mL), dried over $MgSO_4$ and filtered. The solvents were removed using a rotary evaporator to give a yellow oil, which was purified by flash column chromatography (9:1 hexane:ethyl acetate). The desired product was obtained as a colorless oil (1.15 g, 94%) ^1H NMR ($CDCl_3$, 300 MHz) δ 7.15 (d, 1H), 7.08 (d, 1H), 6.82 (dd, 1H), 6.0-5.83 (m, 1H), 5.15-5.05 (m, 2H), 4.53-4.46 (dd, 1H), 3.85-3.80 (m, 4H), 3.65 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 185.0, 159.2, 156.0, 133.5, 133.3, 133.1, 131.3, 130.9, 124.3, 118.3, 118.2, 117.7, 114.0, 113.8, 55.7, 53.2, 53.0. IR (neat, cm^{-1}) 3080, 2953, 2839, 2060, 1720, 1601, 1567, 1500, 1445, 1379, 1345, 1286, 1224, 1193, 1151, 1036, 1007, 927, 856, 770, 736, 676, 602.



N-carbomethoxy-3-iodomethyl-4-iodo-5-methoxyindoline (40). A solution of *tert*-butyllithium (0.95 mL, 1.68 M in pentane, 1.61 mmol) was slowly added to a solution of **34** (0.23 g, 0.77 mmol) and zirconocene(methyl) chloride (0.23 g, 0.84 mmol) in dry THF (8 mL) at -95 °C. The resulting mixture was stirred at this temperature for 15 min, slowly warmed to RT and heated to 60 °C for 12 h. After cooling to RT, the solution was concentrated in vacuo to remove all the solvents. The residue was dissolved in dry dichloromethane (8 mL) to give a brownish solution, which was then cooled to 0 °C and treated with a solution of I_2 (0.51 g, 1.99 mmol) in dry CH_2Cl_2 (10 mL). The resulting mixture

was stirred for 4 h at 0 °C and for additional 10 h at RT. The solution was then poured into a separatory funnel containing ether (75 mL) and saturated Na_2SO_3 solution (50 mL). The organic layer was separated and collected, washed with water (2 x 50 mL), brine (50 mL), dried over $MgSO_4$ and filtered. The solvents were then removed using a rotary evaporator to give a dark residue which was purified by flash column chromatography (15:1 hexane/ethyl acetate) to yield a yellowish oil, which solidified upon standing under vacuum (0.15 g, 40%), mp 152-153 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.80 (b, 1H), 6.70 (d, 1H), 4.20-3.90 (m, 5H), 3.85 (s, 3H), 3.70-3.50 (m, 2H), 3.15 (t, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 185.0, 154.2, 137.6, 136.7, 61.8, 57.2, 53.8, 47.0. IR (KBr pellet, cm^{-1}) 3034, 2976, 2828, 1640, 1593, 1575, 1462, 1396, 1308, 1263, 1172, 1152, 1091, 1048, 814, 760, 584.

References

1. Rinehart, K. L.; Kobayashi, J.; Harbour, G. C.; Hughes, R. G.; Mizsak, S. A.; Scahill, T. A. *J. Am. Chem. Soc.* **1984**, *106*, 1524.

2. Rinehart, R. L.; Kobayashi, J.; Harbour, G. C.; Gilmore, J.; Mascal, M.; Holt, T. G.; Shield, L. S.; Lafargue, F. *J. Am. Chem. Soc.* **1987**, *109*, 3378.

3. Hino, T.; Lai, Z.; Seki, H.; Hara, R.; Kuramochi, T.; Nakagawa, M. *Chem. Pharm. Bull.* **1989**, *37*, 2596.

4. Rocca, P.; Marsais, F.; Godard, A.; Quéguiner, G. *Tetrahedron Lett.* **1995**, *36*, 7085.

5. Ho, B. T.; McIsaac, W. M.; Walker, K. E.; Estevez, V. *J. Pharm. Sci.* **1968**, *57*, 269.

6. Ho, B. T.; Li, K.-C.; Walker, K. E.; Tansey, L. W.; Kralik, P. M.; McIsaac, W. M. *J. Pharm. Sci.* **1970**, *59*, 1445.

7. Abramovitch, R. A.; Spenser, I. D. *Advances in Heterocyclic Chemistry*; Academic Press: New York, 1964; Vol. 3.

8. Whaley, W. M.; Govindachari, T. R. *Org. React*. **1951**, *6*, 74.

9. Tidwell, J. H Ph.D. Thesis, Massachusetts Institute of Technology, 1994.

10.Cox, D.I.; Buchwald, S.L. unpublished results.

11. Bailey, W. F.; Jiang, X.-L. *J. Org. Chem.* **1996**, *61*, 2596.

12. Zhang, D.; Liebeskind, L. S. *J. Org. Chem.* **1996**, *61*, 2594.

13. Tietze, L. F.; Buhr, W. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1366.

14. Peat, A.J. Ph.D. Thesis, Massachusetts Institute of Technology, 1997.

15. The initial plan was to construct the pyridine ring of the β-carboline ring system from the correct dibromoindoline regioisomer by a series of the following chemical transformations : *N*-dealkylation-*N*-carbamate formation --> oxidation of the dibromoindoline to dibromoindole --> bromide displacement by cyanide anion --> cyanide reduction followed by the formation of a formamide derivative --> Bischler-Napieralski cyclization and dehydrogenation --> demethylation. For the use of haloformates in the dealkylation of tertiary amines, see: a) Olofson, R.A. *Pure Appl. Chem.* **1988**, *60*, 1715. b) Olofson, R. A.; Abbott, D.E. *J. Org. Chem.* **1984**, *49*, 2795. c) Olofson, R.A.; Martz, J.T.; Senet, J.P.; Piteau, M.; Malfroot, T. *J. Org. Chem.* **1984**, *49*, 2081. For reviews on Bischler-Napieralski reactions, see: a) Abramovitch, R. A.; Spenser, I. D. *Advances in Heterocyclic Chemistry*; Academic Press: New York, 1964; Vol. 3. b) Whaley, W. M.; Govindachari, T. R. *Org. React.* **1951**, *6*, 74. For reviews on dehydrogenation

reagents, see: a) Murakami, Y.; Takahasi, H.; Nakazawa, Y.; Koshimizu, M.; Watanabe, T.; Yokoyama, Y. *Tetrahedron Lett.* **1989**, *30*, 2099. b) Reddy, M.S.; Cook, J. M. *Tetrahedron Lett.* **1994**, *35*, 5413. c) Still, I.W.J.; McNulty, J. *Heterocycles* **1989**, *29*, 2057.

16. Wailes, P. C.; Weigold, H.; Bell, A. P. *J. Organomet. Chem.* **1971**, *33*, 181-188.

17. This compound was obtained as the side product of monobromination reaction of *p*-anisidine with tetrabutylammonium tribromide in methanol and dichloromethane (Scheme 3).