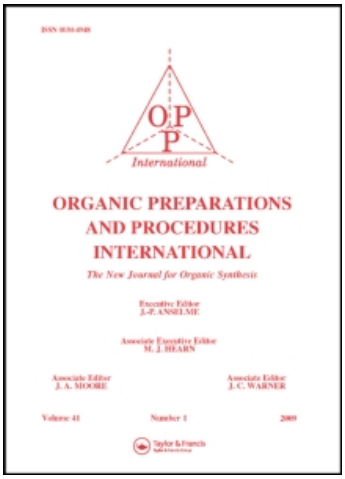

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

TURNING THE CORNER: RECENT ADVANCES IN THE SYNTHESIS OF THE WELWITINDOLINONES

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To cite this Article Brown, Lauren E. and Konopelski, Joseph P.(2008) 'TURNING THE CORNER: RECENT ADVANCES IN THE SYNTHESIS OF THE WELWITINDOLINONES', Organic Preparations and Procedures International, 40: 5, 411 — 445
To link to this Article: DOI: 10.1080/00304940809458104
URL: http://dx.doi.org/10.1080/00304940809458104

ORGANIC PREPARATIONS AND PROCEDURES INT., 40 (5), 411-445 (2008)

TURNING THE CORNER: RECENT ADVANCES IN THE SYNTHESIS OF THE WELWITINDOLINONES

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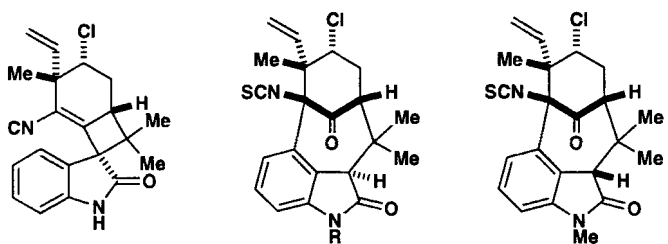
INTRODUCTION

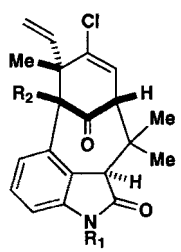
In 1994, seven compounds of the unique welwitindolinone family (**1-7**) were isolated by the research group of Moore from the antifungal and multidrug resistance (MDR)-reversing lipophilic extract of *Hapalosiphon welwitschii*.[1] Two additional oxidized welwitindolinones (**8** and **9**) were discovered in 1999 (*Fig. 1*).[2] In addition to the welwitindolinones, compounds **10-17**,



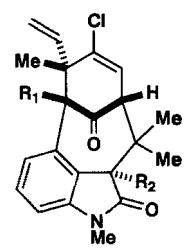
1

2 R = H
3 R = CH_3

4



5 R_1 = H, R_2 = NCS
6 R_1 = CH_3, R_2 = NC
7 R_1 = CH_3, R_2 = NCS

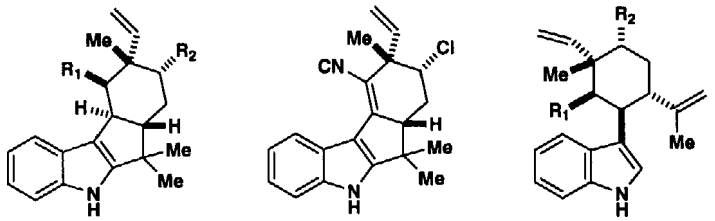


8 R_1 = NC, R_2 = OH
9 R_1 = NCS, R_2 = OH

The Welwitindolinones

Fig 1

members of the structurally related fischerindole (**10-13**) and hapalindole (**14-17**) alkaloid families, were isolated and identified in the original extract (*Fig. 2*).



10 R_1 = NC, R_2 = Cl
11 R_1 = NC, R_2 = H
12 R_1 = NCS, R_2 = H

13

14 R_1 = NC, R_2 = Cl
15 R_1 = NC, R_2 = H
16 R_1 = NCS, R_2 = Cl
17 R_1 = NCS, R_2 = H

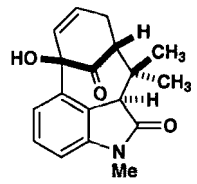
The 12-*epi*-Fischerindoles **10-13** and the 12-*epi*-Hapalindoles **14-17**

Fig 2

Since their isolation, synthetic efforts towards the welwitindolinones have focused on *N*-methylwelwitindolinone C isothiocyanate (**7**), also known as "welwistatin," its des-methyl analog welwitindolinone C isothiocyanate (**5**) and welwitindolinone A isonitrile (**1**), due to the pronounced biological activity of the three. Compound **1** has been credited as the fungicidal component of *H. welwitschii*'s extracts, and is also proposed by Moore to be a biogenetic precursor to the rest of the welwitindolinone family. Compounds **5** and **7**, in contrast, initially demonstrated an ability to reverse P-glycoprotein mediated MDR in a vinblastine-resistant subline of a human ovarian cancer cell line. The cytotoxicity was demonstrated in tests on less-resistant breast carcinoma cells, where cytotoxicity was shown to occur at the micromolar level for **7**, and nanomolar level for **5**.[3]

While compound **1** shares a large amount of functionality with the B, C, and D classes of welwitindolinones, the most notable difference is in their carbon framework. Welwitindolinone A isonitrile differs from the other eight welwitindolinone congeners in that it is the only compound that lacks the 3,4-bridged oxindole core. In its place, a spirooxindole-fused cyclobutane joins the upper cyclohexyl and lower indole portions of the molecule. In the decade following Moore's isolation, much synthetic attention was directed toward developing methods for the synthesis of the welwistatin architecture, including, but not limited to, the bicyclo[4.3.1]decane fragment and the fused cycloheptaindole.[4]

The clear standout in early welwistatin chemistry was the synthesis of the fully assembled tetracycle **18** by Wood *et al.* in 2004 (*Fig. 3*).[5] This chemistry, as well as synthetic efforts toward the aforementioned structural motifs present in both welwistatin and other natural products, was reviewed thoroughly by Avendaño and Menendez the same year.[6] Unfortunately, a number of the initial promising strategies for the assembly of these challenging motifs have proven to be synthetic dead ends thus far.



18

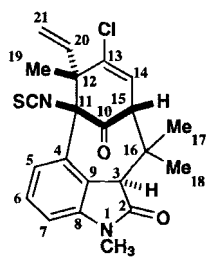
Wood's Completed Tetracycle

Fig 3

Despite these frustrations, the years 2005-2006 saw a sudden upsurge of monumental achievements in the realm of welwitindolinone synthesis. Wood's first assembly of the completed tetracycle was followed by four additional syntheses of the welwistatin core by Simpkins,[7] Rawal,[8] Funk[9] and Shea,[10] each employing a markedly different synthetic strategy. In addition, Baran and coworkers achieved the first total synthesis of both **1** and its potential biosynthetic precursors, fischerindoles **10** and **13**.[11] This groundbreaking accomplishment was followed by Wood's synthesis of (±)-**1** in the subsequent year.[12] These syntheses, as well as additional synthetic studies on the two target compounds, will be reviewed herein.

I. RECENT ADVANCES IN THE SYNTHESIS OF WELWITINDOLINONE C ISOTHIOCYANATE

N-Methylwelwitindolinone C isothiocyanate (**7**) poses a clear synthetic challenge due to a number of unique structural motifs (*Fig. 4*). The C11-C12-C13 array, with contiguous chiral centers followed by a vinyl chloride functionality are the first of such challenges. Assembly of



7

N-Methylwelwitindolinone C Isothiocyanate Numbering

Fig 4

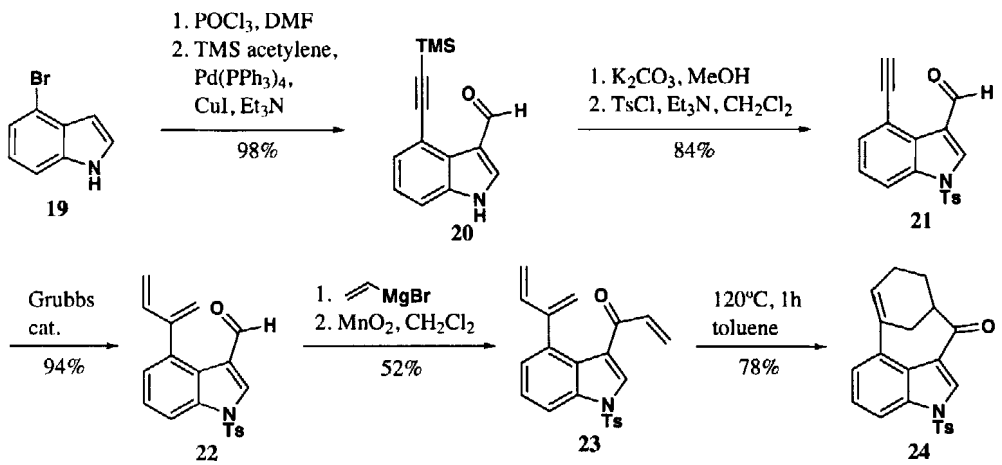
the tetracycle has been shown to prohibit attempts at substituting C12, making further elaboration of Wood's unfunctionalized tetracycle incomplete as of yet. In addition, results from the Konopelski laboratory indicated that full substitution at C12 presents enough steric hindrance to shut down a lead-mediated cyclohexanone-indole coupling that had been successfully performed on the C12-unsubstitued analogous compound.[13]

The four most recent successful efforts toward the total synthesis of welwistatin can be first divided into three general approaches. The first invokes the strategy of building the tetracyclic core around a preexisting indole scaffold. The second entails late closure of the lower heptacycle after coupling of a cyclohexyl and indole unit. Lastly, the synthesis of welwistatin can also be envisioned by late assembly of the indole portion of the molecule, starting from a functionalized bicyclo[4.3.1]decane unit.

1. Building the Skeleton From an Indole Scaffold (Shea's Approach)

Some as-yet unsuccessful attempts to build the welwitindolinone C isothiocyanate skeleton from an indole scaffold have been reported[14, 15] and reviewed[6] in earlier publications. In 2006, Lauchli and Shea reported the first successful tetracycle synthesis employing this strategy.[10] The synthesis hinged on a type-2 intramolecular Diels-Alder (T2IMDA) reaction[16] to concomitantly assemble the bicyclo[4.3.1]decane unit onto an indole tether.

The synthesis commenced with 4-bromoindole **19**,[17] which was formylated[18] and coupled to TMS acetylene under Sonogashira conditions to give **20** (*Scheme 1*). This was followed by TMS-deprotection and tosylation of the indole nitrogen to give compound **21**. The



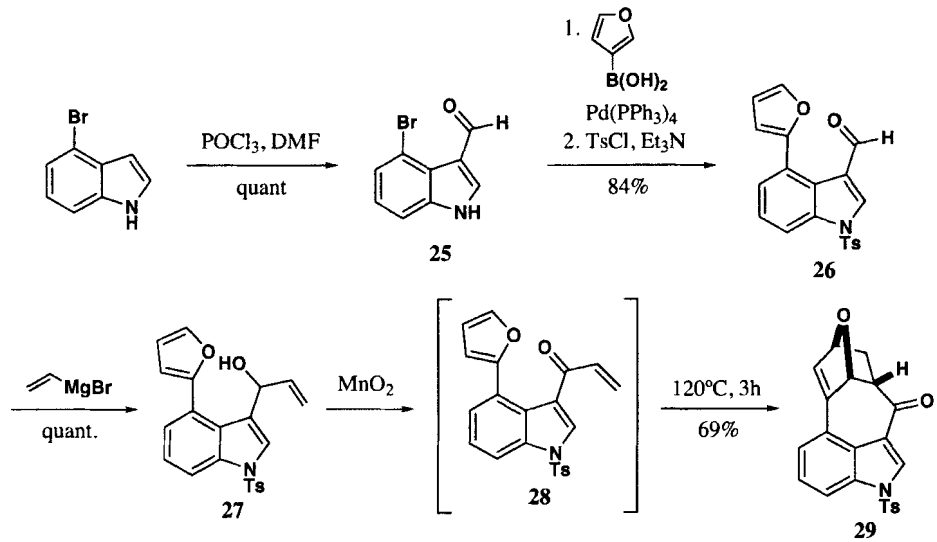
Completed Tetracycle *via* a Type-2 Intramolecular Diels-Alder Reaction

Scheme 1

requisite diene of compound **22** was then incorporated via an ene-yne metathesis reaction employing Grubbs catalyst and ethylene.[19] The dienophile portion was then constructed by vinyl Grignard attack of the aldehyde and MnO_2-oxidation to give Diels-Alder precursor **23**.

It was hoped that a reduction in conformational freedom caused by the indole tether would enhance the T2IMDA reaction under milder conditions than those required for the analogous reaction of simpler alkyl compounds, which have shown to necessitate temperatures of over 200°C for cyclization.[20] This turned out to be the case, as the cycloaddition proceeded at 120°C for one hour, affording tetracycle **24**.

Further functionalization of the bare scaffold was then sought by incorporating a furanyl diene (*Scheme 2*). Aldehyde **25** underwent Suzuki coupling with 3-furan boronic acid, which was followed by tosylation of the indole to give **26**. As in the earlier synthesis, installation of the enone *via* Grignard addition followed by oxidation gave Diels-Alder precursor **28**, which



Further Functionalization of the Tetracycle

Scheme 2

was brought immediately on to the cycloaddition without isolation. Fearing retrocycloaddition, Shea and coworkers also limited the temperature of the cycloaddition to 120°C, and obtained cycloadduct **29** in 69% yield over the oxidation and cycloaddition steps. This transformation was the first known example of a T2IMDA reaction employing a furanyl diene, which are known to react poorly in cycloadditions due to their aromatic stability.[21] X-ray crystallography confirmed the successful synthesis of the tetracyclic welwistatin core, incorporating an oxo bridge that could potentially be opened at either C10 or C13 (welwistatin numbering) to further functionalize the molecule.

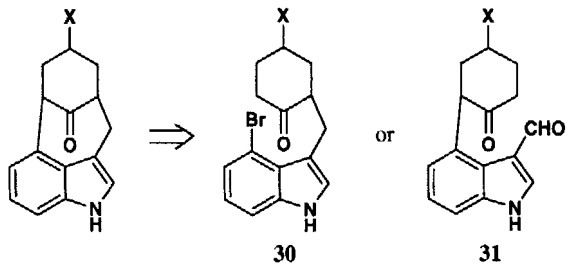
2. Seven-membered Macrocyclic Closure

In 2005, two groups published successful syntheses of the welwistatin core by employing similar strategies: coupling the upper 6-membered ring fragment to the lower indole, and performing an intramolecular 7-membered ring closure to complete the assembly. This approach was also unsuccessfully pursued and reported by the Konopelski laboratory in 2007.[13]

a) Simpkins' Approach

Simpkins and coworkers envisioned closing the seven-membered ring on either the western half of the molecule via enolate arylation on a compound such as **30**, or on the eastern half via an aldol-type reaction of a compound such as **31** (*Scheme 3*).[7] While attempts at western

closure were prevented by inability to synthesize an appropriate arylation precursor resembling **30**, the aldol-type cyclization proved far more fruitful.

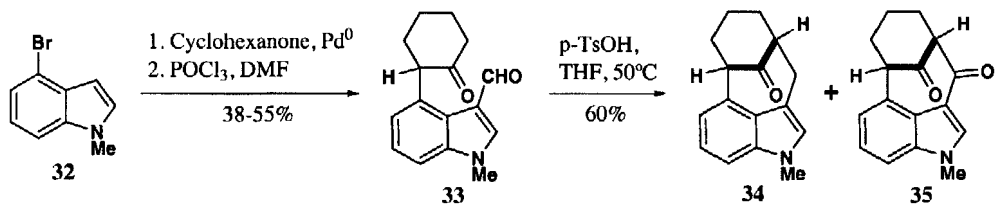


30 **31**

Two Methods of 7-Membered Ring Closure

Scheme 3

Starting from methylated 4-bromoindole **32**, palladium-catalyzed coupling[22] to cyclohexanone followed by formylation gave compound **33**, which was subjected to a variety of aldol-coupling procedures (*Scheme 4*). While no base-catalyzed aldol reactions were successful, treatment with 0.5 equivalents of *p*-TsOH in THF at 50°C for 24 hours gave a 1:1 mixture of compounds **34** and **35** in 60% yield. The structure of **34** was confirmed by X-ray crystallography.

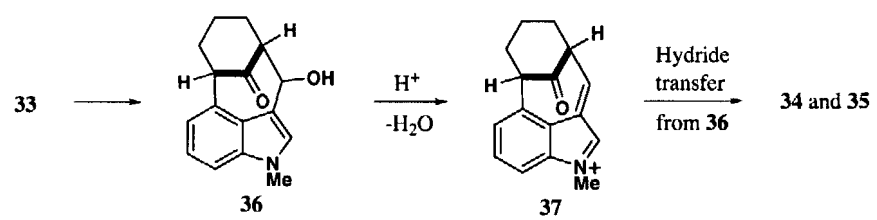


32 **33** **34** **35**

Aldol-Type Closure to Complete the Tetracycle

Scheme 4

A suggested mechanism to explain the mixture of products involves the initial aldol reaction to give, β-hydroxy ketone **36** (*Scheme 5*), which forms **37** *via* protonation of the alcohol functionality and dehydration driven by electron donation from the indole nitrogen. Transfer of a hydride from the hydroxyl carbon of **36** to the equivalent position on the iminium **37** leads to the formation of **34** and **35**. In order to avoid this disproportionation into two products, a competing hydride source (Et_3SiH) was incorporated.[23] This strategy proved successful, giving solely **34** in



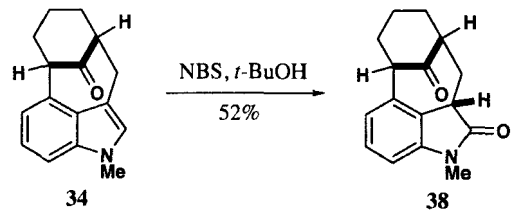
36 **37**

Suggested Disproportionation Mechanism

Scheme 5

92% yield. The proposed disproportionation mechanism was further supported by performing the experiment in the presence of DDQ as a hydride acceptor, which furnished only the diketone **35** in 45% yield.

Simpkins and coworkers then worked to oxidize the tetracycle **34** to the corresponding oxindole (*Scheme 6*). This was achieved by reacting the indole with NBS in 95% *t*-BuOH. The oxindole **38** was obtained in 52% yield as a single diastereomer. Unfortunately, X-ray crystallography demonstrated that the oxidation product is epimeric to natural welwistatin at C3 (the C3



34 **38**

Oxindole Formation

Scheme 6

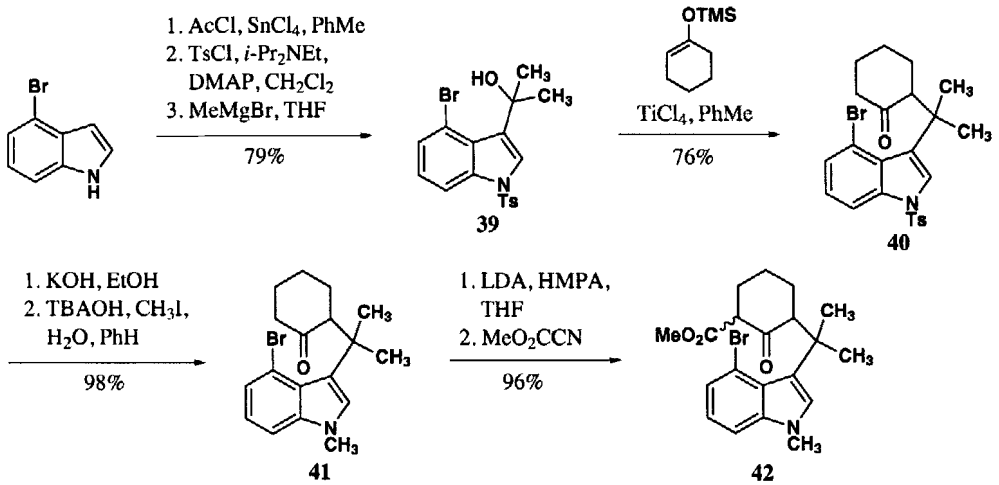
stereochemistry does, however, match that of 3-*epi*-welwitindolinone B isothiocyanate **4**). Nonetheless, the synthesis amounts to the most rapid assembly of a minimally functionalized welwitindolinone C skeleton to date.

b) Rawal's Approach

A further functionalized tetracyclic skeleton was also published in 2005 by Mackay, Bishop and Rawal.[8] In contrast to Simpkins, Rawal's group approached the seven-membered ring closure on the western half of the molecule by way of a palladium-catalyzed intramolecular enolate arylation.

Again starting from 4-bromoindole, Friedel-Crafts acylation followed by *N*-tosylation and methyl Grignard treatment afforded alcohol **39** in 79% over three steps. Coupling to the cyclohexanone unit was performed under Natsume's conditions with cyclohexanone-TMS-enol ether. The model reaction with a non-brominated indole analog proceeded cleanly with $SnCl_4$ as a Lewis acid in >80% yield.[24] However, the yield decreased to 66% with the brominated compound **39**. Substituting $TiCl_4$ as the Lewis acid improved the yield of **40** to 76%. The *N*-tosyl group was then hydrolyzed with KOH and EtOH in 99% yield, and the resultant free indole was methylated with methyl iodide and TBAOH as a phase-transfer catalyst. The enolate coupling partner was assembled by kinetic deprotonation of **41** (LDA) followed by Mander's reagent addition (*Scheme 7*).[25]

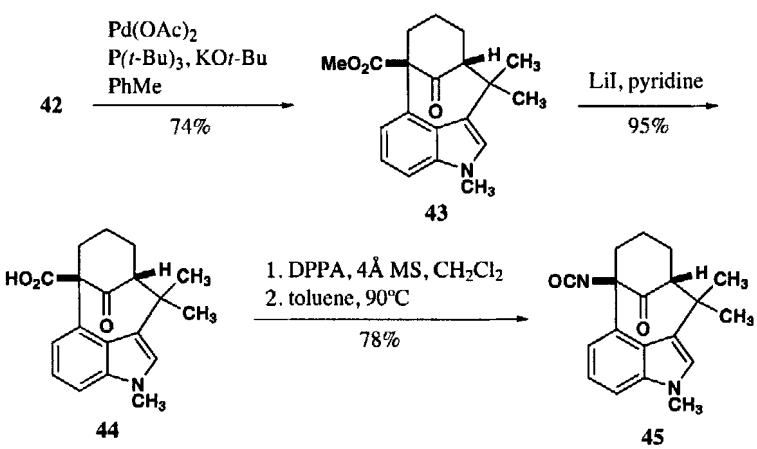
Rawal and coworkers examined a number of experimental conditions for the coupling reaction, settling on a 0.3:0.6 equiv. $Pd(OAc)_2/P(t\text{-}Bu)_3$ catalyst, with KO*t*-Bu as a base and toluene as solvent at 70°C. The cyclization proceeded in under four hours to provide **43** in 74% yield. The structure of the tetracycle was confirmed by X-ray crystallography.



Synthesis of Intramolecular Arylation Precursor **42**

Scheme 7

Prior to this synthesis, no group had installed the requisite nitrogen in the C11 bridgehead position. The group then endeavored to explore a Curtius rearrangement and trap with an alcohol, to give a carbamate-protected amine. To this end, they attempted ester hydrolysis on **43**. Interestingly, the compound resisted basic hydrolysis. Even upon refluxing in $MeOH/H_2O$ with 60 equivalents of LiOH for 22 hours, the reaction gave only incomplete conversion alongside partial decarboxylation of the product. The hydrolytic resistance was explained by analysis of the crystal structure, which shows the cyclohexanone carbonyl positioned in front of one face of the ester carbonyl, while the indole C5 is blocking the other. More accessible in this conformation is the methoxy group, and thus nucleophilic ester cleavage (LiI, pyridine, reflux) was attempted and proceeded cleanly.[26] The acid **44** was isolated in 95% yield, with no decarboxylative decomposition as seen earlier (*Scheme 8*).



Rawal's Successful Tetracycle Closure and Curtius Rearrangement

Scheme 8

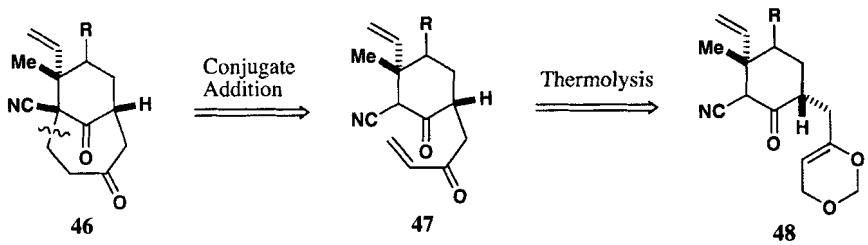
To induce the Curtius rearrangement, compound **45** was then treated with diphenylphosphoryl azide, trimethylamine and 4-methoxybenzyl alcohol.[27] The compound, however, proved resistant to alcohol attack, giving isocyanate **45** as the major product. The isocyanate formation was then optimized to 78% yield by performing the reaction in the absence of the alcohol. The lack of hydrolysis or alcohol reactivity of compounds **43** and **45**, respectively, bears considerable light on the structural constraints imposed by the compact and rigid welwitindolinone C skeleton.

3. Late Stage Indole Annelation (Funk's Approach)

While the intermediates synthesized by Simpkins and Rawal were both notable in their rapid and convergent assemblies of the unique bicyclo[4.3.1]decane ring system, both compounds did lack substitution or functionality at C12 and C13. In 2006, this hurdle was finally cleared by Greshock and Funk, who published the most advanced welwistatin intermediate to date.[9]

Greshock and Funk employed a conceptually different strategy than any of the aforementioned groups, in that rather than synthesizing the bicyclo[4.3.1]decane onto a preassembled indole, their retrosynthesis involved assembling the strained, bridged bicyclic system early followed by a late-stage indole annelation sequence.

Synthesis of the bicyclic system **46** was envisioned using a conjugate addition reaction (*Scheme 9*). The strategy involved the use of 1,3-dioxin moiety (shown in compound **48**) to mask the enone of a Michael precursor, such as compound **47**. The enone can thus be shielded from



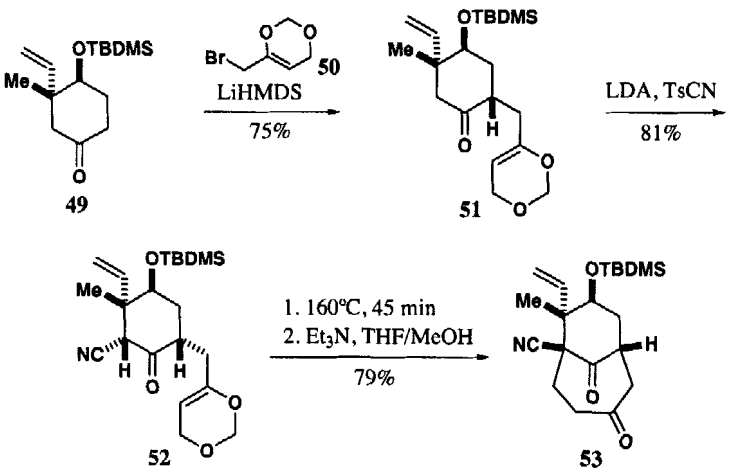
46 **47** **48**

Greshock and Funk's Retrosynthetic Plan for Tetracycle Assembly Via a Masked Enone

Scheme 9

reaction with highly basic nucleophiles until its unveiling. This strategy for constructing both hetero- and carbocycles was previously reported by the group in 2002.[28] This methodology was also covered in the earlier welwitindolinone review.

The synthesis starts with optically pure compound **49**, which was synthesized *via* Fredj's and Polla's elaboration of 3-methylanisole, employing a kinetic enzymatic resolution (*Scheme 10*).[29] Kinetic deprotonation followed by alkylation with compound **50** gave **51** with a high degree of diastereoselectivity (10:1). The selectivity can be attributed to the kinetic enolate undertaking a chair conformation in which both the vinyl and the siloxy groups are equatorial. Axial alkylation on the α-face was presumably preferred to the β-face due to a



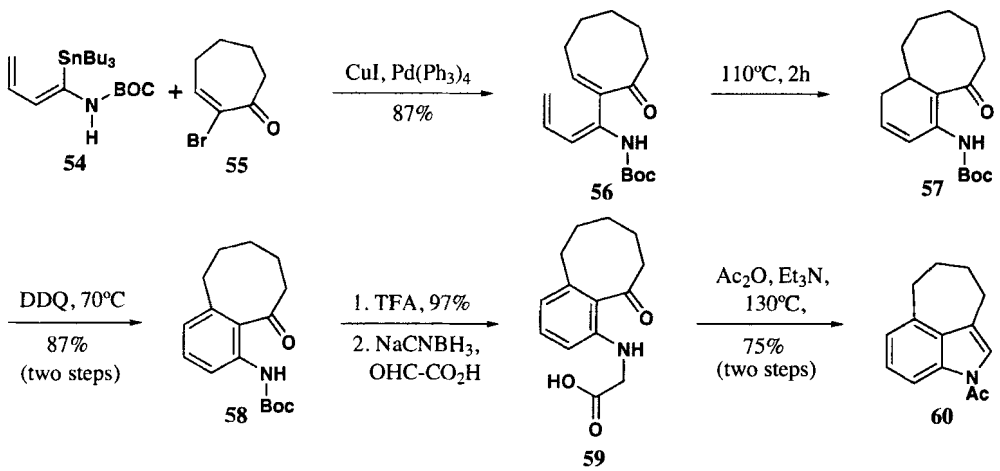
Unveiling of a Masked Enone and Subsequent Conjugate Addition

Scheme 10

resultant flagpole-flagpole interaction with the axial methyl substituent. This diastereoselectivity was further affirmed by 1,3-diaxial (C11 and C15) proton NOE studies on the subsequent cyanide **52**, obtained by cyanation of the regioselectively formed enolate. Note that for this NOE study to be successful the ring conformation has flipped as compared to **49**. This success in cyanation stands in contrast to attempted carboxymethylations, which gave only O-acylated product instead of the desired β-keto ester. The masked enone was then revealed by thermolytic retrocycloaddition of the dioxin. As seen in the earlier model studies, intramolecular conjugate addition to give the seven-membered ring of **53** could be effected upon treatment with triethylamine in MeOH/THF.

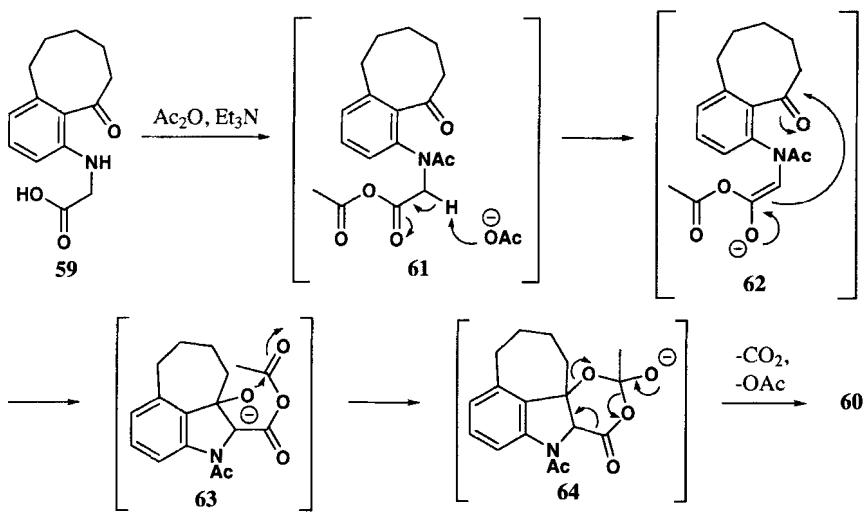
With the bicyclo[4.3.1]decane skeleton established, Greshock and Funk then assembled the requisite functionality for their indole annelation sequence.[30] The methodology involves sequential construction of each indole aromatic ring from acyclic precursors. The 2006 model studies showed the Stille reaction of stannylated diene **54** to α-halogenated enone **55** affords a coupling product **56** that is primed to undergo electrocylic ring closure upon heating to give **57** (*Scheme 11*). DDQ oxidation easily affords the protected aniline **58**. The second cyclization, inspired by Raelianu's studies,[31] occurs when the deprotected aniline nitrogen, after undergoing reductive amination with glyoxylic acid to give **59**, is treated with acetic anhydride and triethylamine at 130°C.

The authors propose the cyclization to indole **60** proceeds by one of two mechanisms. The first potential transformation that could give rise to indole **60** is a Perkin-type condensation following *N*-acylation and anhydride formation to give intermediate **61** (*Scheme 12*). Deprotonation generates enolate **62**, which then attacks the cycloheptanone carbonyl to give tetrahedral intermediate **63**. Attack of the acyl group, followed by the loss of both CO_2 and an acetate anion would then lead to the generation of indole **60**.



Greshock and Funk's Early Indole Annelation Studies

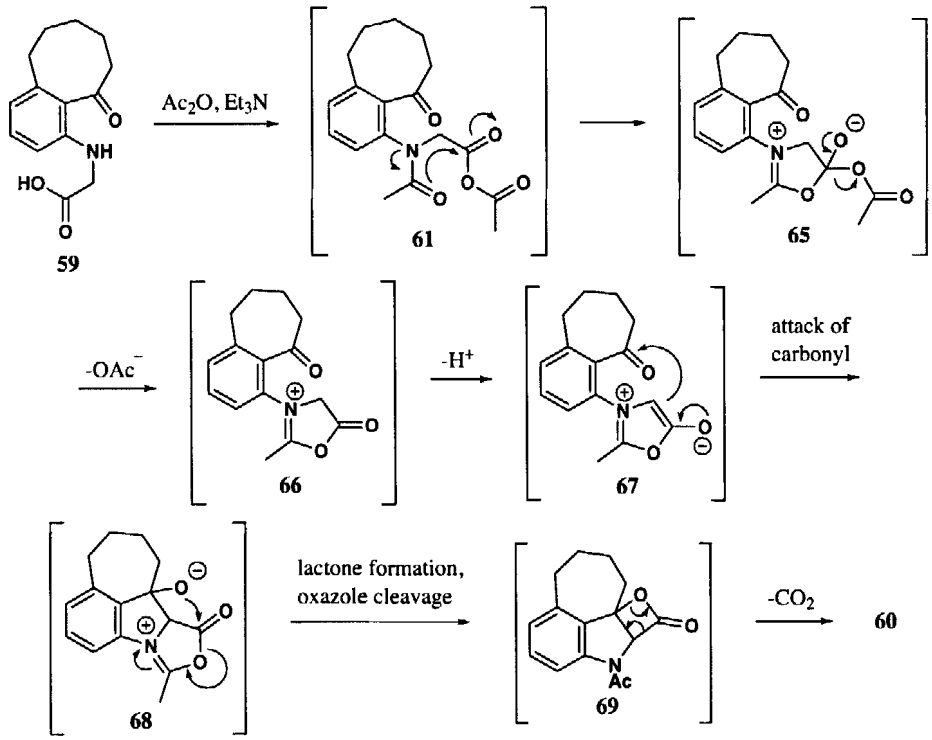
Scheme 11



Greshock and Funk's Indole Formation *via* a Perkin-type Mechanism

Scheme 12

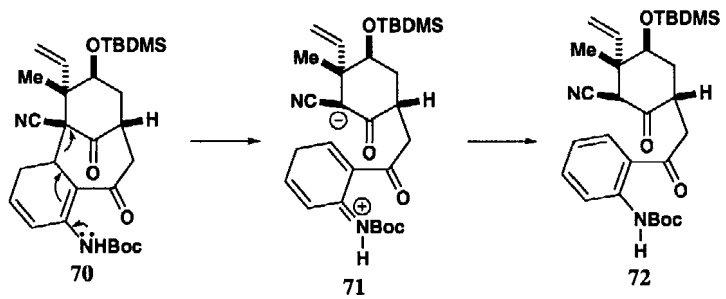
A second potential mechanism, deemed more likely by Greshock and Funk, also begins with the putative *N*-acetylated mixed anhydride **61** (*Scheme 13*). In this sequence, the mixed anhydride functionality is instead subject to nucleophilic attack by the enamide tautomer of the acetylated aniline to give rise to **65**. Subsequent loss of acetate followed by a deprotonation affords münchnone **67**. The münchnone attacks the cycloheptanone carbonyl, and alkoxide **68** would then form β-lactone **69**. Cycloelimination of CO_2 generates the indole **60**. A similar mechanism, giving rise to *N*-acyl pyrroles, is proposed in the literature.[32]



Greshock and Funk's Indole Formation *via* possible Münchnone Intermediate **67**

Scheme 13

Before transforming compound **53** to the α-haloenone Stille coupling partner, it was necessary to reduce the bridgehead carbonyl, which had caused problems in the electrocyclization during earlier studies. It was found that with the carbonyl present, the strained tricyclic system of compound **70** underwent a vinylogous retro-Mannich reaction to open the seven-membered ring, yielding compound **72** (*Scheme 14*).

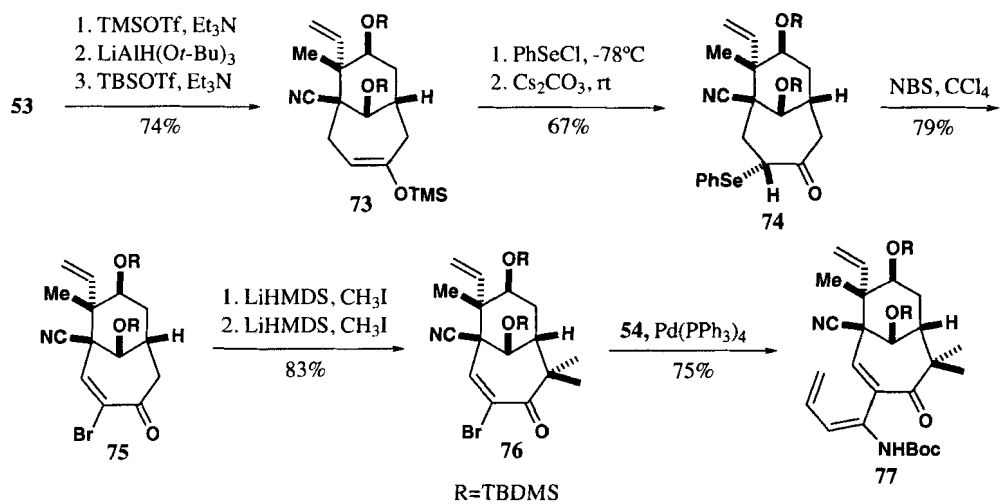


Proposed Retro-Mannich Mechanism

Scheme 14

After initial protection of the less-hindered carbonyl of **53** in the form of a silyl enol ether, the remaining bridgehead carbonyl underwent reduction with $LiAlH(O\text{-}t\text{-}Bu)_3$ (*Scheme 15*).

The reduction proceeded stereoselectively with a 9:1 diastereomeric ratio. The alcohol was then protected as the *t*-butyldimethylsilyl ether to give compound **73**. Initially, the authors converted the silyl enol ether **73** directly to an enone *via* Saegusa oxidation. Unfortunately, attempts to α-halogenate were unsuccessful, and the group instead converted **73** to the selenide by treating with PhSeCl. Cesium carbonate was used to equilibrate the selenides to a 4:1 diastereomeric ratio. The major diastereomer, **74**, was then successfully converted to the α-bromo enone **75** on treatment with excess NBS in CCl_4. Interestingly, the minor epimer only provided the des-bromo enone. The *gem*-dimethyl substituents were then installed by sequential alkylations with LiHMDS and methyl iodide to give **76**. Stille coupling with stannyl diene **54** gave electrocyclization precursor **77**.

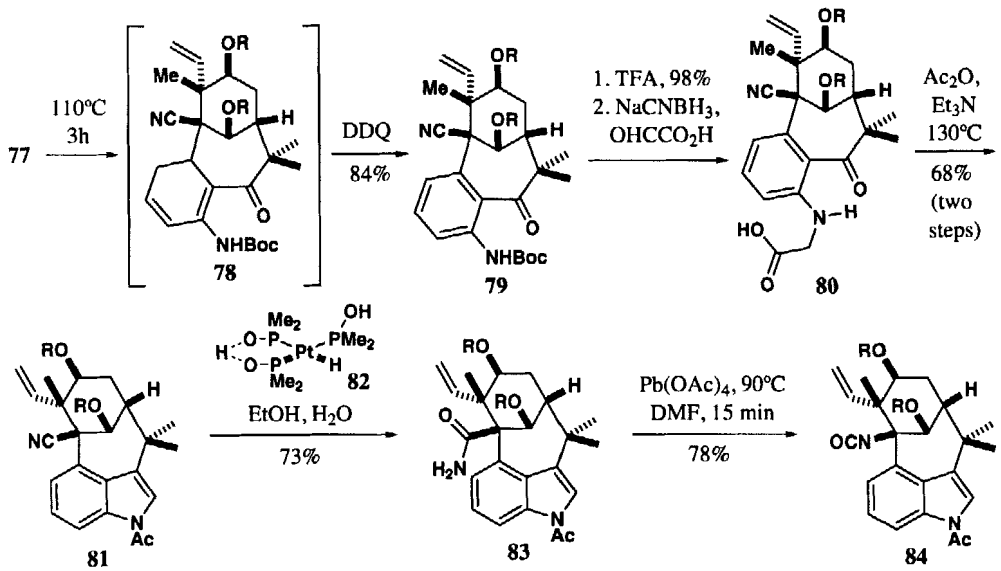


Preparation of α-Halo Enone **76** and Stille Coupling to Give **77**

Scheme 15

Scheme 16 depicts the final stages of the synthesis, in which **77** was cyclized in toluene at 110°C and aromatized in situ upon addition of DDQ to give compound **79**. The final ring closure was performed in an identical manner to the earlier studies. Acid **80** was formed after BOC removal and reductive amination of the free aniline with glyoxylic acid. Treatment with acetic anhydride and triethylamine invoked the expected ring closure, and tetracycle **81** was obtained in 68% yield over the two-step reductive amination/cyclization sequence.

As a final experiment, Greshock and Funk decided to explore the Hoffman rearrangement to establish the bridgehead nitrogen on the congested tetracycle. Though this step lies later in their full synthetic plan, the sterically encumbered environment of the nitrile **81** is unlikely to change during the synthesis endgame, making **81** an appropriate compound for model study. The nitrile was hydrolyzed to amide **83** under mild conditions with Parkins' platinum catalyst **82**,[33] and the Hoffman rearrangement proceeded in only 15 minutes using Baumgarten's conditions ($Pb(OAc)_4$ in DMF, 90°C).[34] Compound **84** is by far the most advanced welwistatin intermediate



Completion of Greshock and Funk's Highly Functionalized Tetracycle **84**

Scheme 16

synthesized to date, possessing the complete carbon framework of the natural product with full substitution at the all-carbon quaternary centers of C12 and C16, a bridgehead nitrogen at C11 and synthetic handles at all carbons requiring further functionalization.

Despite over a decade of frustration in the realm of welwistatin synthesis, the recent work of Rawal, Simpkins, Shea and particularly Funk have provided hope that the synthesis of this dauntingly compact and complex molecule will be achieved in due course.

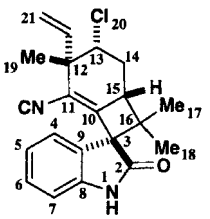
II. TOTAL SYNTHESES OF WELWITINDOLINONE A ISONITRILE

The recent flurry of both activity and achievement in the synthesis of *N*-methylwelwitindolinone C isothiocyanate has been complemented by two total syntheses of the related compound, welwitindolinone A isonitrile (**1**). The Baran group in 2005 published the groundbreaking total syntheses of both (**1**) and 12-*epi*-fischerindole isonitriles G and I (**10** and **13**).[11] While the syntheses of **1** and **10** were originally achieved in 0.3% and 1.1% unoptimized yields, respectively, both were completed in under ten steps from carvone oxide and without the use of protecting groups or excessive oxidation state transformations. The syntheses were later optimized for yield and reported in 2007.[35] The following year, a substantive contributor to the early years of welwitindolinone C synthesis, John Wood, published the total synthesis of (±)- **1** in a 2.5% overall yield.[36]

1. Wood's Synthesis

In the total synthesis of (±)-**1**, Wood encountered a lack of established methods for constructing many of the molecule's unique structural features, notably the introduction of the

all-carbon quaternary centers at C3 and C12 (*Fig. 5*). Early published work from the group first focused on developing a SmI_2-mediated synthesis of spiro-oxindoles that installed the



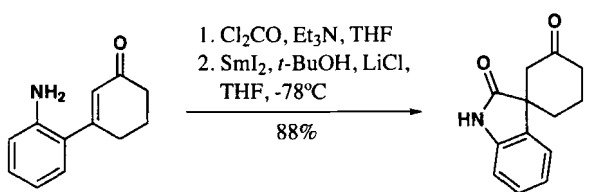
1

Welwitindolinone A Isonitrile Numbering

Fig 5

compound's contiguous all-carbon quaternary centers at C3 and C16 in very good yield and diastereoselectivity.[37] In order to tackle the upper portion of the molecule, Wood's strategy for synthesizing (**1**) hinged on installing the neopentyl chloride and the adjacent C12 quaternary center simultaneously using a chromium-induced semi-pinacol rearrangement.[38]

Approaching first the spiro center, Wood and coworkers envisioned two methods of assembly. The first potential route hinged on formation of the C3-C9 ring bond via established radical[39] or metal-catalyzed[40] methodology. This route was abandoned, however, due to possible thermal instability of a cyclobutene intermediate and concern that the molecule itself would stereochemically direct formation of the undesired isomer. Instead, the group looked to methods for forming the C3-C2 connection. The group focused on Kim, Park, and Kwon's SmI_2-mediated reductive coupling of acrylates and isocyanates to give amides.[41] Model studies were performed on aniline **85** to explore this strategy as a viable route to the desired spirooxindole **86** (*Scheme 17*).



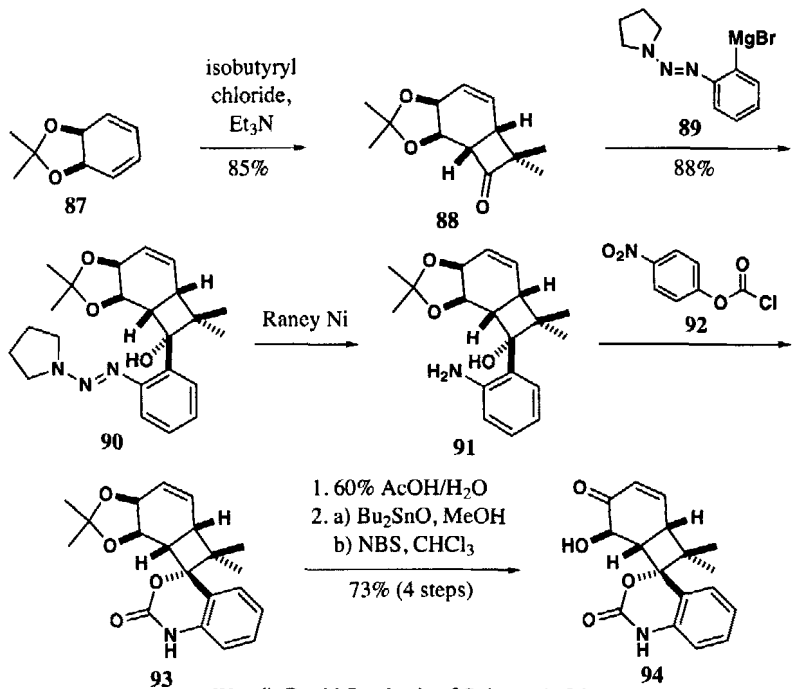
85 86

Wood's Model Spirooxindole Formation

Scheme 17

After treatment of **85** with phosgene and triethylamine to give the isocyanate, reaction with SmI_2 and *t*-BuOH in THF gave **86** in only 5% yield. The reaction was optimized, however, by the incorporation of various additives to modulate the reactivity of the SmI_2. After surveying NiI_2,[42] HMPA,[43] LiBr and LiCl,[44] the most successful additive was shown to be LiCl, which gave desired oxindole formation in 78% yield. The authors note that the in situ generation of $SmCl_2$ upon addition of LiCl to SmI_2 may account for enhanced ketone reduction.

Wood's synthesis commences with cyclohexadiene acetonide **87**, which was reacted with isobutyryl chloride and triethylamine to give the [2+2] cycloaddition product **88** in high yield with full regio- and diastereoselectivity (*Scheme 18*).[45] The cyclobutanone carbonyl was then attacked by ortho-metallated aniline derivative **89** on its convex face.[46] The triazene of **90**

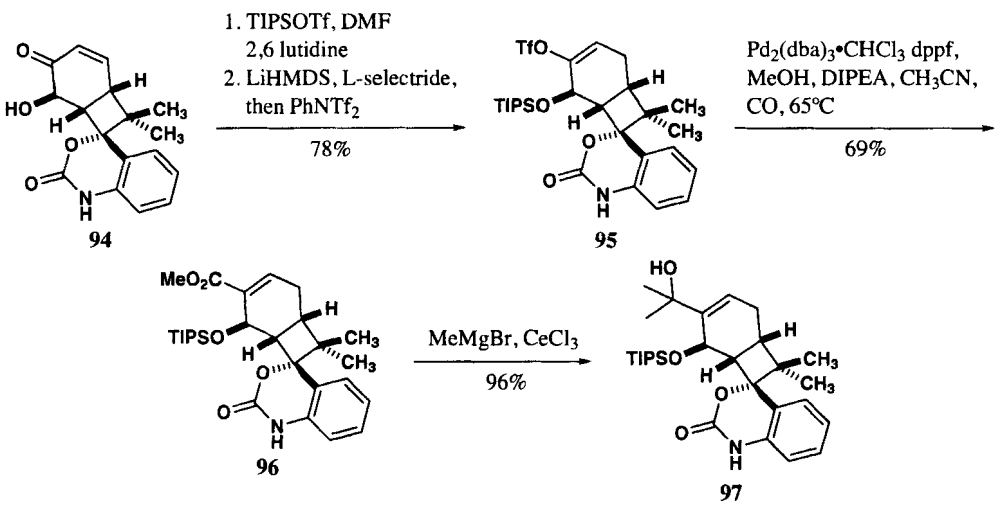


Wood's Rapid Synthesis of Spirocycle **94**

Scheme 18

was then chemoselectively reduced with Raney nickel, and the resultant amine of **91** was tethered to the pendant hydroxyl by reaction with 4-nitrophenyl chloroformate **92** to give compound **93**. Removal of the acetonide with acetic acid in water was followed by allylic oxidation with dibutyltin oxide in refluxing methanol followed by treatment with NBS in chloroform.[47] This four step sequence was completed with a remarkable 73% overall yield to rapidly furnish spirocycle **94**.

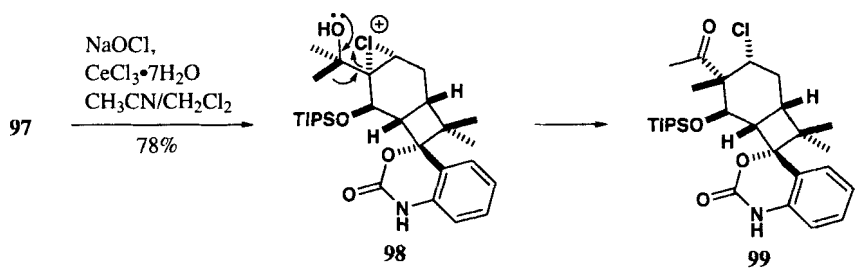
While initial SmI_2-mediated oxindole synthesis model studies were performed early in the synthetic sequence (on an analog of **94** on which the ketone has been protected as a dithiolane), the completed total synthesis employs this transformation on a more advanced intermediate. From **94**, the next synthetic challenge was the installation of the contiguous C12-C13 stereoarray. Protection of the alcohol with TIPSOTf was followed by conversion of the carbonyl to the enol triflate **95** (*Scheme 19*). A carbomethoxy group was then installed using Pd-catalyzed CO insertion to give **96**. Treatment with excess methylmagnesium bromide gave the tertiary allylic alcohol **97** required for the envisioned pinacol rearrangement.



Construction of Pinacol Rearrangement Precursor **97**

Scheme 19

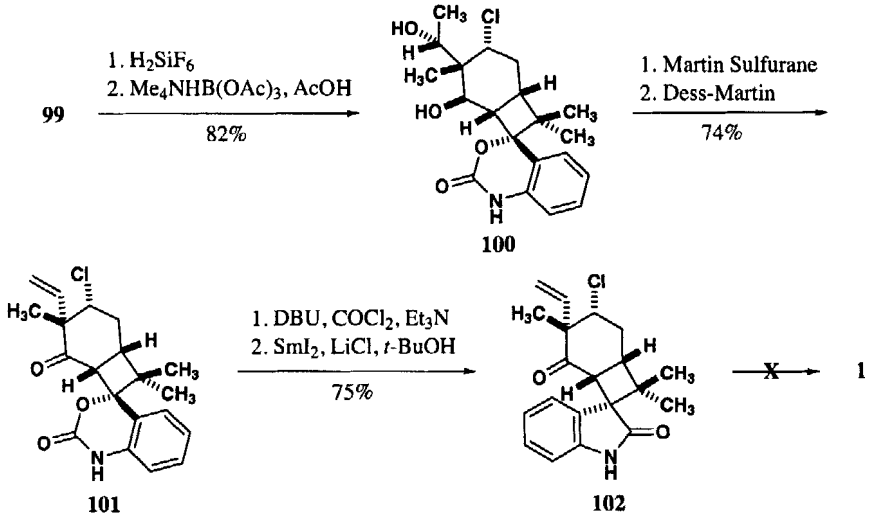
It was hoped that upon exposure to a chlorenium equivalent, **97** would undergo rearrangement as shown in *Scheme 20*. The large TIPS protecting group on the adjacent chiral hydroxyl at C11 had been introduced to impart stereoselectivity in the initial formation of chloronium **98**. Indeed, exposure to aqueous sodium hypochlorite in the presence of cerium trichloride heptahydrate[48] gave **99** in 78% yield as a single diastereomer.



Pinacol Rearrangement of Chloronium Ion **98**

Scheme 20

Removal of the TIPS protection group with H_2SiF_6[49] and ketone reduction with tetramethylammonium triacetoxyborohydride[50] gave alcohol **100** (*Scheme 21*). X-ray crystallography confirmed both the structure of **100** and its existence as the desired single diastereomer. Dehydration with Martin sulfurane furnished the C12 vinyl substituent.[51] The remaining hydroxyl was then oxidized with Dess-Martin periodinane[52] to give ketone **101**, which would ultimately be converted to the sensitive vinyl isonitrile present in the natural product. First, however, the spirooxindole synthesis was attempted.



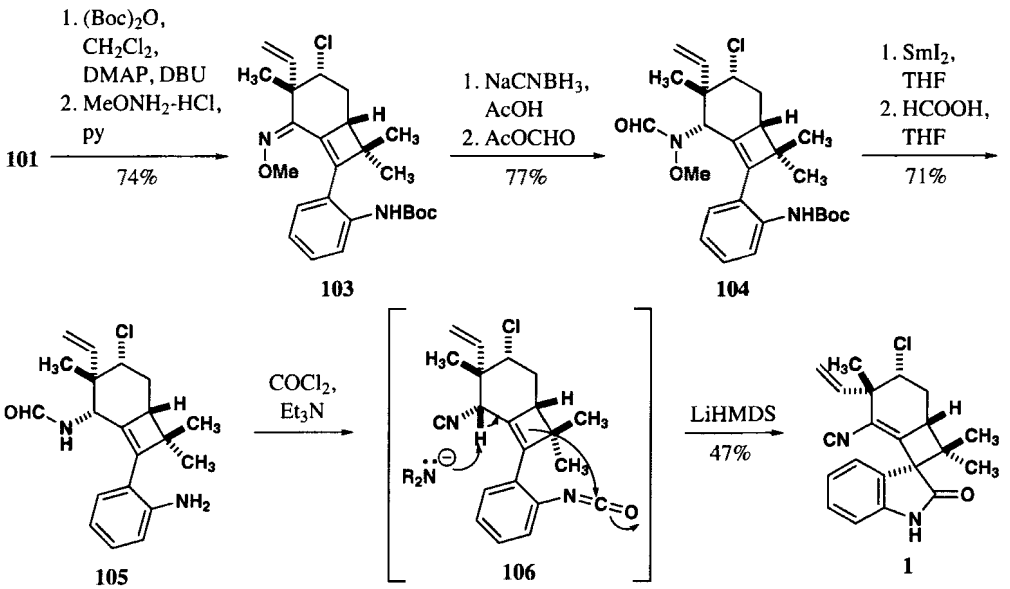
Failed Converstion of Spirooxindole **102** to Welwitindolinone A Isonitrile

Scheme 21

Cyclic carbamate **101** was decarboxylated upon treatment with 0.5 eq DBU with concomitant enone formation, then treated with phosgene and triethylamine. Addition of SmI_2, LiCl, and *t*-BuOH to the crude isocyanate gave spirooxindole **102** in 75% yield over the two steps. The desired stereochemistry of the cyclization was confirmed by X-ray crystallography, and attributed to attack of the isocyanate carbon on the convex face of the molecule.

Just one functional group transformation away from the natural product **1**, compound **102** was subjected to a number of conditions in an effort to install the vinyl isonitrile functionality. The clear unreactivity of ketone **102** prompted the group to step back to compound **101** and install the nitrogen prior to spirooxindole formation. Concomitant aniline BOC-protection and elimination of CO_2 with DBU gave an enone that was converted to α,β-unsaturated oxime **103** with methoxyamine hydrochloride.

When the SmI_2-induced cyclization failed to proceed on this substrate, the group was forced to look for alternative strategy. Instead, oxime **103** was reduced with sodium cyanoborohydride and then formylated. The *N*-methoxy bond was cleaved with SmI_2, and the aniline BOC group was removed to give compound **105**. The final transformation hinged on a similar cyclization to that envisioned earlier. Instead of a reductive acrylate coupling, deprotonation of the isonitrile α-hydrogen with strong base could invoke cyclization.[53] Indeed, after dehydrating the formamide of compound **105** and generating the isocyanate **106** in one pot on treatment with phosgene and triethylamine,[54] addition of the crude product to LiHMDS gave compound **1** in 47% yield (*Scheme 22*).



Completion of the Synthesis

Scheme 22

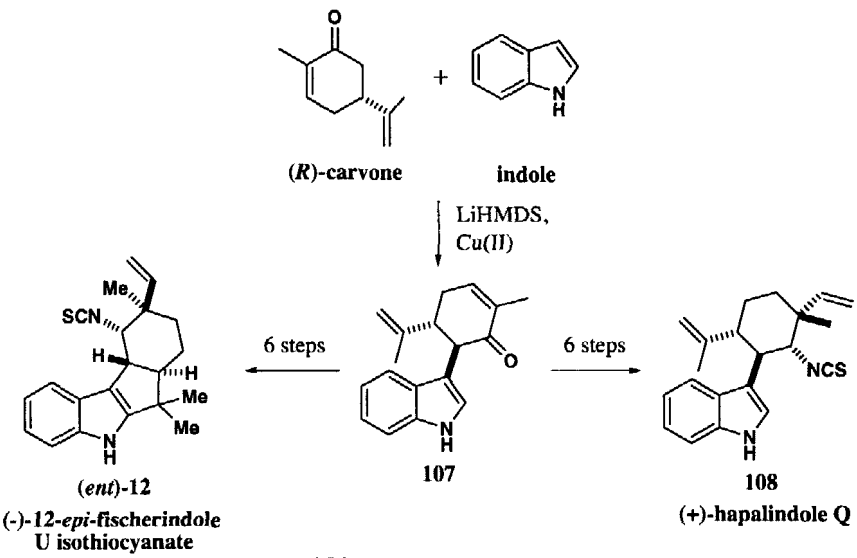
2. Baran's Synthesis and Optimization

In a 2007 article in *Nature*,[35] Baran proposed a new way of thinking about the planning stages of natural product synthesis. In keeping with the ideas of "atom economy" as well as minimizing the number of steps, Baran proposed that the ideal total synthesis should (1) minimize redox reactions that do not form C-C bonds, (2) maximize the ratio of C-C bonding events to total number of steps, (3) maximize convergency, (4) linearly escalate the overall oxidation state of intermediates through the course of the synthesis, (5) incorporate as many cascade reactions as possible in order to elicit maximum structure change per step, (6) limit the use of protecting groups by harnessing the innate reactivity of functional groups, (7) invent new methodology and (8) attempt to follow any known biomimetic pathways so as to aid in the aforementioned ideas.[55] This approach to synthesis, while groundbreaking in both concept and practice, harks back to strategies evoked by early chemists such as Robinson, whose achievements predated the invention of most ubiquitous protecting groups.

In keeping with these ideas, Baran's syntheses of (+)-welwitindolinone A isonitrile (**1**) and the 12-*epi*-fischerindole isonitriles G and I ((-)-**10** and (+)-**13**, respectively),[56] were a revolutionary achievement in the art of total synthesis. Incorporating biomimetic disconnections and a series of elegant cascade reactions, Baran and Richter synthesized all three compounds, each in under 10 steps without the use of protecting groups. The overall yield for the syntheses of **13** and **1** were 6.9% and 1.7%, respectively, from a shared intermediate (compound **112** in *Scheme 24*). The original publication[11] was complemented by the subsequent article in *Nature*, which offered

optimized syntheses for **1** and **13** in addition to protecting-group-free syntheses of related compounds hapalindole U and ambiguine H. As a demonstration of the powerful effect that minimizing steps can have on the optimization process, the yield of the optimized sequence of steps was nearly doubled for **13** (to 13%) and more than tripled for compound **1** (to 5.7%).

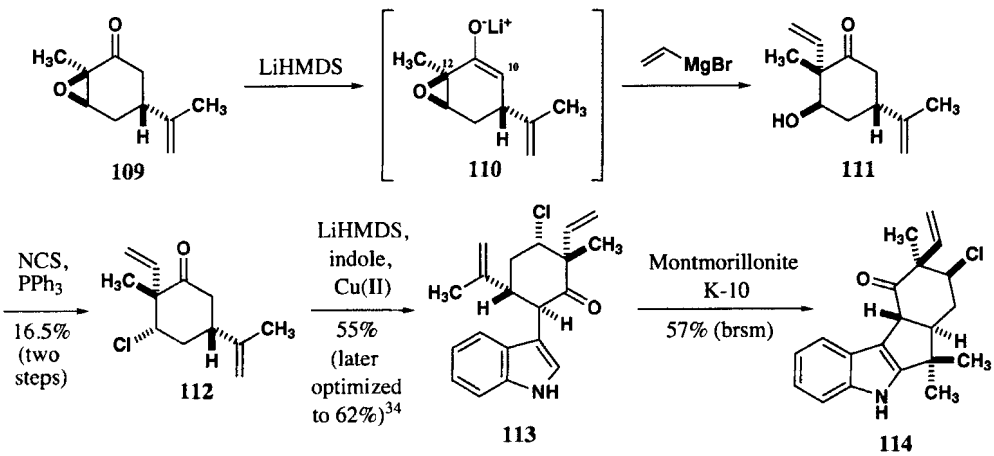
The Baran group's initial foray into the realm of *Hapalosiphon welwitschii*-obtained natural products began with synthetic efforts geared towards the fischerindole and hapalindole families.[57] In addition to being the first total synthesis of any compound in the fischerindole family, Baran and Richter's 2004 publication detailing the total syntheses of 12-*epi*-fischerindole U isothiocyanate (-)-**12** and hapalindole Q (**108**) also served as the first synthetic proof that Moore's original assignment of the absolute stereochemistry of the isolated compound (+)-**12** (*Fig. 2*) was, indeed, correct. In this synthesis, the lone chiral center of (*R*)-carvone was used to direct a diastereoselective coupling with indole to generate **107** as the first step of a divergent 6-step synthesis of both (-)-**12** and **108** (*Scheme 23*).



Baran and Richter's Synthesis of (*ent*)-**12** and (+)-Hapalindole Q from (*R*)-Carvone

Scheme 23

The syntheses of **1, 10 and 13** again employed (*R*)-carvone as the initial source of absolute chirality. All three syntheses commence with the construction of compound **114** from (*R*)-carvone oxide **109** (*Scheme 24*). Following removal of the ketone α-proton to generate lithium enolate **110**, vinylmagnesium bromide is introduced stereoselectively *via* epoxide attack at C12. Epoxy-enolates such as **110** have been shown by Wender to function similarly to a diene monoepoxide.[58] Compound **110** is thus prone to attack at C12, opening the epoxide via an S_N2 mechanism, or at C10, giving the S_N2' epoxide-opened product. Indeed, the low yield in this transformation is attributed by the authors to the competing S_N2' attack.



109 110 111 112 113 114

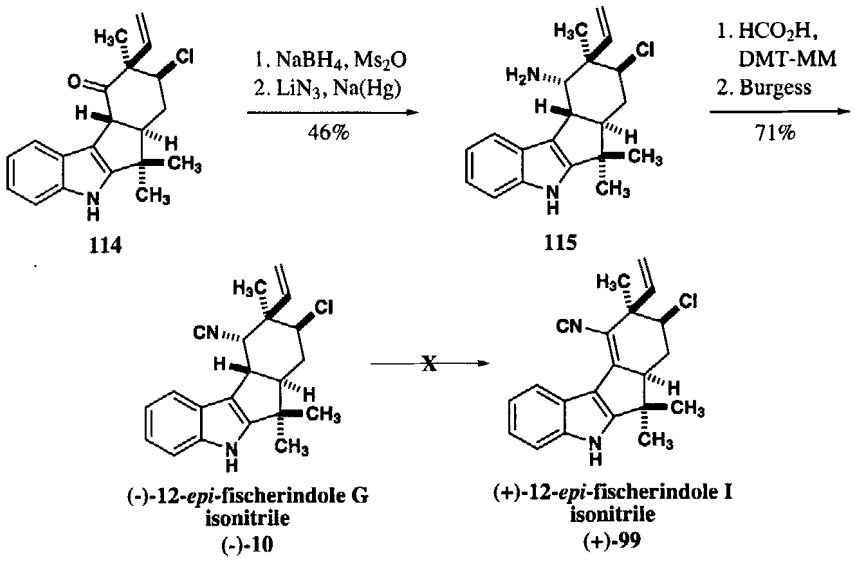
Synthesis of Common Precursor **114**

Scheme 24

The resultant hydroxy group of **111** is transformed to a chloride (with inversion) with *N*-chlorosuccinimide and triphenylphosphine to give compound **112.** Carvone itself has been commonly used as a precursor in fischerindole and hapalindole syntheses and indeed has been used to synthesize an epimer of compound **112.** That synthesis, however was ten steps long with a 10% overall yield.[59] Baran, in contrast, could obtain **112** in two steps in one day, with the 16.5% overall yield still allowing for multigram quantities to be prepared.

The lithium enolate of ketone **112** was then coupled to indole in the presence of copper (II) to provide **113** in 55% yield. Baran's group has also reported the scope and mechanism of such oxidative couplings between indoles/pyrroles and carbonyl compounds.[60] The next step, an acid-catalyzed Friedel-Crafts cyclization, proved problematic. While a number of acids screened gave low yields and multiple side-products, it was eventually discovered that clean product **114** could be obtained by microwaving in 1,2-dichloroethane in the presence of Montmorillonite K-10, along with recyclable starting material.

Compound **114** was viewed as both a precursor for the 12-*epi*-fischerindoles **10** and **13** (following conversion of the ketone into isonitrile and vinylisonitrile groups, respectively) and compound **1** (following an acid-catalyzed ring contraction). Pursuant to the fischerindoles, the carbonyl of **114** was first stereoselectively reduced and mesylated, then displaced with lithium azide (*Scheme 25*). Reduction afforded compound **115.** This sequence was similarly employed by Fukuyama in his synthesis of hapalindole G.[61] Conversion of the newly formed amine to the formamide with formic acid and 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMT-MM) proceeded smoothly, as did Burgess-reagent induced dehydration to give (-)-12-*epi*-fischerindole G ((-)-**10**). Oxidation of isonitrile **10** to the vinyl isonitrile functionality found in **13**, however, did not proceed as expected. A number of oxidizing agents gave either unreacted starting material or decomposition. In addition, the nitrogen stereochemistry at C11



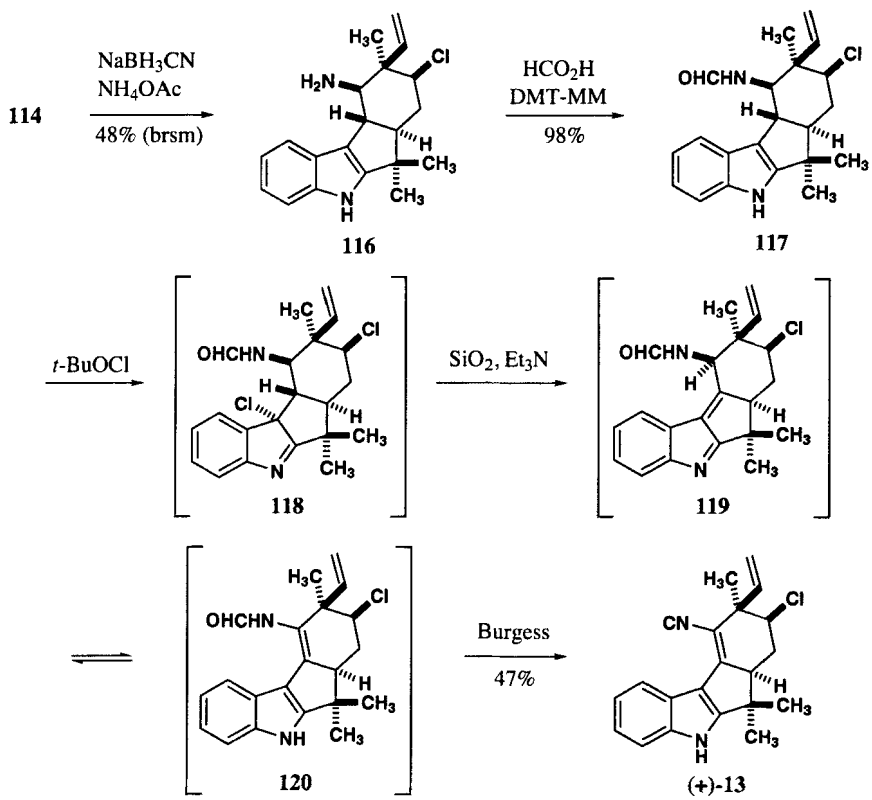
Successful Synthesis of Compound **10**

Scheme 25

hindered the alternative strategy to either chlorinate or hydroxylate the indole in hopes of then eliminating or dehydrating, respectively. While the hydroxylated and chlorinated compounds were both formed, their resistance to further react was explained by the necessity for an unfavorable *syn*-elimination. Therefore an alternative route was sought from compound **114**, with the new strategy being chlorination/elimination prior to the Burgess dehydration on a compound epimeric at the C11 nitrogen.

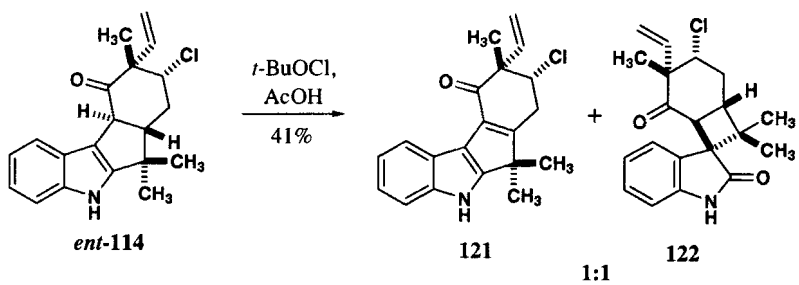
Reductive amination with sodium cyanoborohydride and ammonium acetate gave **116**, which was then formylated to compound **117** in an analogous manner to its epimer **115** (*Scheme 26*). Chlorination with *t*-BuOCl and triethylamine is thought to provide the intermediate **118**, which was then treated with triethylamine-deactivated silica gel to give the desired elimination product **119**. Tautomerization then gave **120**. The final step, Burgess dehydration, furnished the target (+)-**13**. It should be noted that while the stereochemistry as depicted is the enantiomer of compound **13** as originally drawn by Moore (*Fig. 2*), optical rotation data for naturally occuring **13** was not included in Moore's original publication. It can therefore be inferred, based on the known chirality of Baran's starting material, that the isolated compound (as depicted by Moore) would correspond to (-)-**13**.

With both fischerindoles in hand, the group was then poised to transform the enantiomer of precursor (+)-**13** (obtained in the same manner from (*S*)-carvone oxide) into compound **1**. The proposed acid-catalyzed ring contraction was first tested on *ent*-**114**, which was transformed into a 1:1 mixture of **121** and the desired **122** on exposure to *t*-BuOCl and acetic acid in 41% unoptimized yield (*Scheme 27*).



Synthesis of 12-*epi*-fischerindole I isonitrile (**13**)

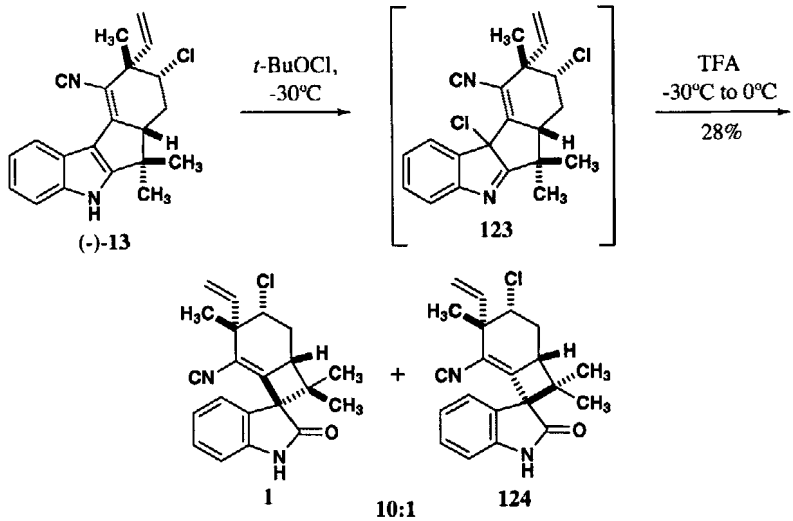
Scheme 26



Model Acid-Catalyzed Ring Contraction

Scheme 27

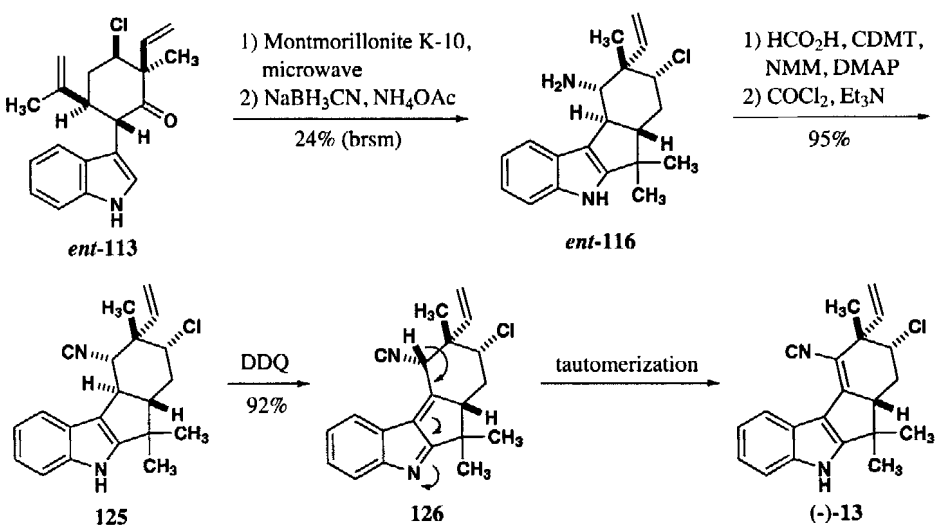
With this success, the enantiomer of vinyl isonitrile **13** was studied as a precursor to compound **1** (*Scheme 28*). The delicate transformation was achieved by treatment with *t*-BuOCl at -30°C, solvent removal, and treatment of the resultant chloride **123** with 1% TFA in THF/H_2O. Compound **1** was isolated in a 10:1 ratio over a second compound presumed to be the C3-epimer **124**.



Completion of the Synthesis of **1**

Scheme 28

The optimized synthesis of **1**, as well as (-)-**13**, was achieved via a slightly altered route (*Scheme 29*). Again starting from (*S*)-carvone, the enantiomer of **113** was synthesized in optimized yield (*Scheme 24*) and transformed into *ent*-**116** by treatment with Montmorillonite K-10 clay with microwave irradiation followed by stereoselective reductive amination in 24%, once again based on recovery of starting material from the acidic clay treatment. Formylation, followed by phosgene dehydration gave compound **125**.

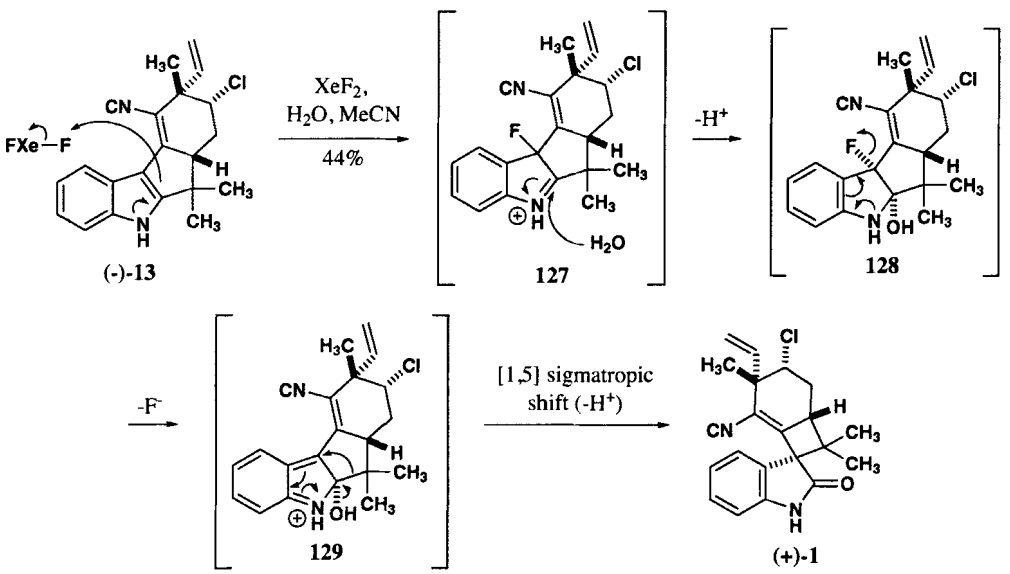


Baran's Optimized Synthesis

Scheme 29

While *t*-BuOCl was the oxidant of choice for the earlier syntheses, the authors postulated that the difficulty in efficiently converting (-)-**10** to (+)-**13** stemmed from the reagent's ability to readily oxidize isonitriles. The group then sought an alternate oxidant, and were able to successfully convert **125** (the C-11 epimer of (+)-**10**) to (-)-**13** by treatment with DDQ in 92% yield. The authors suggest that **13** arises *via* tautomerization of oxidation product **126**.

The final oxidative ring contraction of (-)-**13** to (+)-**1** was then optimized (*Scheme 30*). Relying on the increased hardness of fluorine over chlorine, the authors postulated that fluorohydroxylation of the indole would suppress side-product formation seen in prior chlorohydroxylations. To that end, they developed such a method by treating (-)-**13** with xenon difluoride in the presence of water and acetonitrile, and obtained (+)-**1** in 44% isolated yield as a single diastereomer. The reaction presumably occurs by fluorohydroxylation to intermediate **128**, followed by loss of fluoride to afford intermediate **129**. A [1,5] sigmatropic shift would then give compound **1**.



Baran's Completion of the Optimized Synthesis

Scheme 30

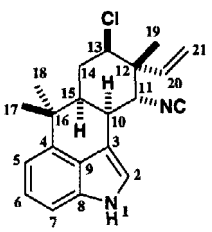
With the optimized route, the Baran group was able to obtain **1** at a scale of nearly 400 milligrams, and compound **13** on a 2 g scale. The approach to total synthesis without protection groups is thus far limited in scope, but the ability of the Baran group to rapidly manipulate the delicate welwitindolinone scaffolds demonstrates the power of brevity when attempting to improve mediocre yields. In addition to the obvious increase in potential product mass, when a synthesis is at a minimum of steps tremendous effort can be directed at both reagent scanning and synthesis reroutes in a relatively short amount of time. Indeed, a way of thinking about synthesis that is now over 100 years old has breathed new life into the synthesis of the welwitindolinones.

III. CONCLUSION

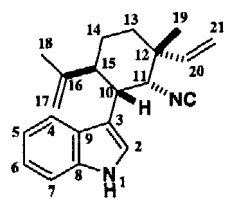
Both compact and complex, sometimes delicate and sometimes surprisingly resilient, the welwitindolinones and their precursors have proven a frustrating challenge for many chemists to date. However, the body of work in welwitindolinone chemistry has clearly turned the corner with the six syntheses presented herein. The widely varied yet uniformly successful efforts towards precursors of **7**, as well as the two uniquely different total syntheses of compound **1** suggest the race to fully assemble a family of extremely potent anticancer compounds may soon come to an exciting finish.[62]

APPENDIX A: THE NAMING OF FISCHERINDOLES G AND I

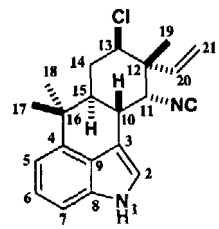
Hapalindoles A and B were isolated by Moore in 1984.[63] Three years later, 20 additional hapalindoles were isolated and given the designations C-Q.[64] The compounds all bear the same number of carbons and significant structural similarities, although some are tetracyclic and others tricyclic. All hapalindoles share stereochemistry at C11 (for those compounds where C11 is sp^3 hybridized), C12, and C13 (for those compounds that have a chlorine atom at C13) with the exception of hapalindole L, which has C12 stereochemistry opposite of the rest of the hapalindoles (*Fig. A1*).



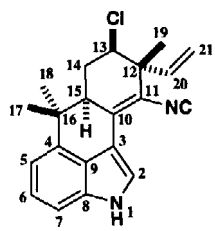
Hapalindole A



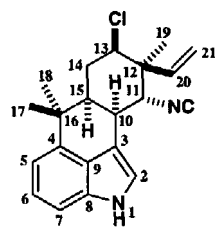
Hapalindole C



Hapalindole G



Hapalindole I



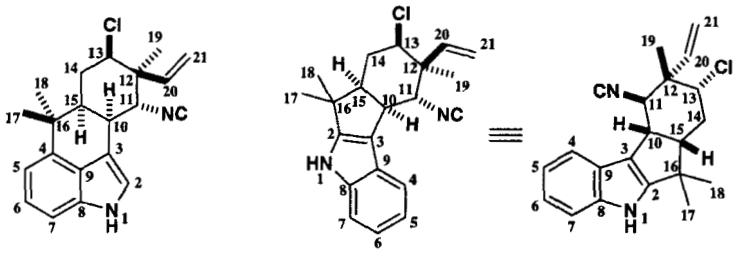
Hapalindole L

Pertinent Hapalindoles Isolated By Moore Between 1984-1987

Fig A1

In 1992 Moore then isolated the first of the fischerindoles,[65] named "fischerindole L." The choice of name was attributed to the fact that the stereochemistries at C10, C11, C12, C13 and C15 all matched that of hapalindole L (*Fig. A2*).

Moore continued this naming pattern in 1994 when he isolated the next four fischerindoles (**10-14**, *Fig. 2*).[1] However, all of the new fischerindoles, while fully matching

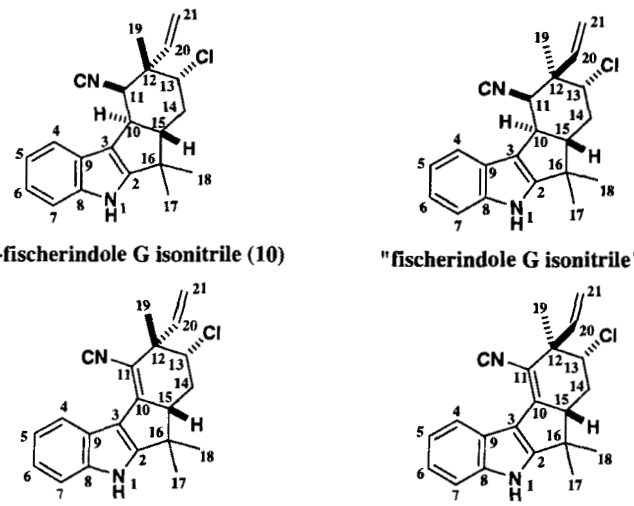


Hapalindole L **Fischerindole L**

Hapalindole and Fischerindole L

Fig A2

fischerindole L and hapalindole L in their stereochemistry, are C12 epimers of their own hapalindole namesakes and therefore named with "12-*epi*" prefixes. It should be noted that "fischerindole G," "fischerindole I," and "fischerindole U," as Moore envisioned them to be configured, have to this date never been isolated (*Fig. A3*).



12-*epi*-fischerindole G isonitrile (10) **"fischerindole G isonitrile"**

12-*epi*-fischerindole I isonitrile (13) **"fischerindole I isonitrile"**

Moore's Nomenclature of Isolated (Left) and
Hypothetical (Right) Fischerindoles

Fig A3

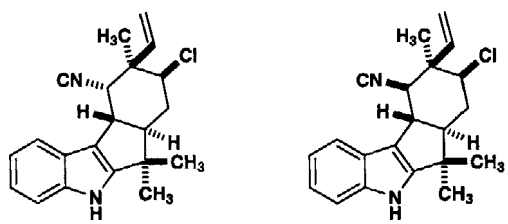
In addition to welwitindolinones and fischerindoles, the 1994 Moore article also identifies four hapalindoles (**14-17**, *Fig. 2*) that are also epimeric to the original hapalindoles C, D, E and F at C12. Moore thus named them with the "12-*epi*" prefix. The major component "12-*epi*-hapalindole E" (**14**, *Fig. 2*) is presumed to be the biogenetic precursor to all of the chlorine-containing isonitrile alkaloids in the extract. The welwitindolinones (**1-9**, *Fig. 1*), which match the "12-*epi*" alkaloids at all stereocenters (when present), were apparently given letter designations without reference to the original hapalindoles.

In their 2004 article detailing a gram-scale process for obtaining hapalindole and fischerindole structures, Baran and Richter detail the synthesis of "12-*epi*-fischerindole U."[57] However, for the subsequent *J. Am. Chem. Soc.* and *Nature* articles reviewed herein, Moore's "12-*epi*" designation is dropped, and compounds **10** and **13** are simply referred to as fischerindoles G and I, respectively.[11,35] For the sake of clarity and consistency in this document, we will refer to the fischerindole compounds with Moore's original nomenclature.

APPENDIX B: STRUCTURAL ERRORS

The naming inconsistency demonstrated in Appendix A is confounded by what we have determined to be drawing errors in various schemes in the Baran publications. We believe that in the text of Baran's 2005 *J. Am. Chem. Soc.* communication,[11] compounds **10** and **13** are drawn correctly with regards to Moore's original structure elucidation. As mentioned previously, Moore had designated these compounds as "12-*epi*-fischerindole G isonitrile" and "12-*epi*-fischerindole I isonitrile," while Baran names them as simply "fischerindole G" and "fischerindole I."

When we analyzed the supporting information of this publication, there was a discontinuity in the stereochemistry of some intermediates, as well as the final product (-) 12-*epi*-fischerindole G isonitrile ((-)-**3** in the paper, (-)-**10** in this review). In the experimental details and in a supplemental information scheme, Baran and Richter have drawn the natural product with opposite C11 stereochemistry to that in the text of the article. The compound that was in the document depicted as (-)-**3** ((-)-**10** in this review) was in fact drawn in the supporting information as the enantiomer of the compound we have depicted in *Scheme 29* as **125** (See *Fig. B1*). The



(-)-12-*epi*-fischerindole G (-)-10 ***ent*-125**

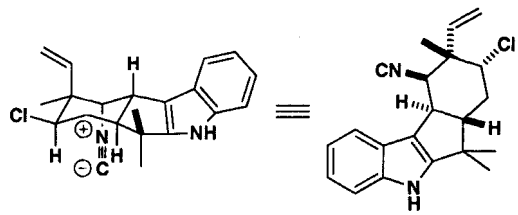
Baran's Depictions of "Fischerindole G" in Text (Left) and Supporting Information (Right) of *J.Am. Chem. Soc.* **2005**, *127, 15394-15396*

Fig B1

supporting information text and synthetic scheme also shows Baran's version of amine **115** (*Scheme 25*) drawn identically to our depiction of amine **116** (*Scheme 26*), with similar stereochemical errors in the drawings of the intermediate mesylate and azide involved in the transformation of **114** to **115**. Compound **116** was used crude without full characterization and therefore does not appear graphically in the supporting information text.

In the ensuing 2007 *Nature* publication,[35] Baran and coworkers present an optimized synthesis of **13** and **1** (compounds **5** and **4**, respectively, in the *Nature* paper). This synthesis is

said to employ the same intermediate compounds as were used in the initial synthetic work, yet in this document the tetracyclic isocyanide precursor to **13**, assumed by us to again be **125**, is isolated, characterized and named as "11-*epi*-fischerindole G " (compound **18** in the *Nature* paper). As shown in *Fig. B2*, close examination of the Baran's depictions, however, reveals that in both the text and the supporting information of the *Nature* document, this isocyanide is drawn with the stereochemistry of "12-*epi*-fischerindole G" (**10**).

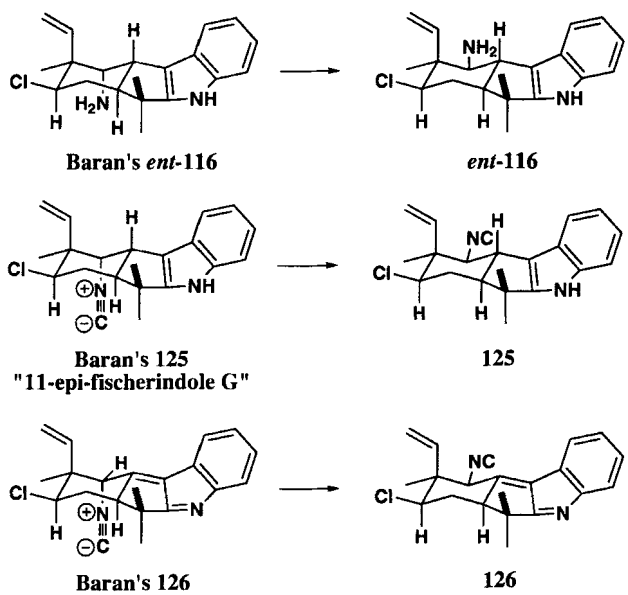


"11-*epi*-fischerindole G" **(+)-10**

Baran's Depiction of "11-*epi*-fischerindole G" in *Nature*, **2007**, *446*, 404-408
Appears To Be "(+)-12-*epi*-fischerindole G" ((+)-**10**)

Fig B2

Assuming that reaction stereoselectivity remains consistent between the two Baran documents, and assuming the aforementioned drawing error in the supporting information of Baran's *J. Am. Chem. Soc.* article, our analysis suggests that the *Nature* depictions of compounds *ent*-**116**, **125** and **126** are also drawn incorrectly with regards to the stereochemistry at C11. *Fig. B3* depicts Baran's drawings as well as what we have interpreted to be structures more consistent



Baran's *ent*-116 ***ent*-116**

Baran's 125
"11-epi-fischerindole G" **125**

Baran's 126 **126**

Our Interpretation of the Correct Depictions (Right)
of Baran's Drawings in *Nature* (Left)

Fig B3

with the reactivity described in the earlier communication. In addition, when redrawn as **125**, Baran's "11-*epi*-fischerindole G" is indeed the C11 epimer of compound **10**. It is perhaps worth noting that the ^{1}H NMR data provided by the Baran group in all publications gives compelling evidence that the compounds synthesized do indeed match the natural products isolated by Moore, and that the apparent incongruities lie only in the aforesaid drawings and the names but not the syntheses themselves.

Acknowledgements.- We thank the NIH (CA98878) for generous support of this work.

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56. Upon examining the literature, we encountered some inconsistencies in the naming and depiction of several compounds between Moore's original isolation paper and the two synthetic papers published by Baran. Our analysis suggests that the confusion is caused by two factors: (1) Baran's renaming of Moore's isolated compounds "12-*epi*-fischerindole G isonitrile" (**10**) and "12-*epi*-fischerindole I isonitrile" (**13**) to "fischerindole G" and "fischerindole I," respectively, and (2) apparent drawing errors in the supporting information of Baran's *J. Am. Chem. Soc.* article[11] that, from our analysis, carries over into both the text and supporting information of the subsequent *Nature* article.[35] These two factors contribute to a single compound, numbered **10** in this review, appearing to have been given three different names over the course of several publications. Appendices A and B will attempt to clarify the inconsistencies.

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(Received February 2, 2008; in final form July 14, 2008)