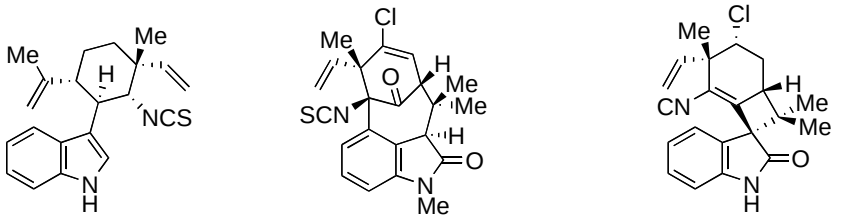
Developments Toward the Synthesis of the Welwitindolinone Alkaloids

Reported by Russell C. Smith November 28, 2005

INTRODUCTION

The continued search for biologically active and structurally diverse natural products led to the isolation of a new class of indole alkaloids from strains of cyanobacteria found in Australia. In 1987, Moore and co-workers reported the isolation and characterization of a series compounds from the cultured cyanophyte *Hapalosiphon fontinalis*.[1] Hapalindole Q (**1**), which contains a novel isonitrile moiety, was one of 18 hapalindoles isolated from the terrestrial blue-green algae. Further work from this group led to the isolation of a group of structurally more diverse indole alkaloids from similar Australian soil samples. The major compound isolated from *Hapalosiphon welwitschii* was *N*-methylwelwitindolinone C isothiocyanate (**2**).[2] The structural architecture of this molecule is compelling: it contains four stereogenic centers, three quaternary carbons and a complex bicyclo[4.3.1]decane ring system. Another compound isolated from these extracts—lending additional structural diversity—was welwitindolinone A (**3**), a molecule that contains a stereodefined neopentyl chlorine atom as well as a strained spiro-fused cyclobutane.[2] The high structural complexity and biological activity of these molecules makes them compelling targets for total syntheses.



(+)-Hapalindole Q **1**

N-methylwelwitindolinone C isothiocyanate **2**

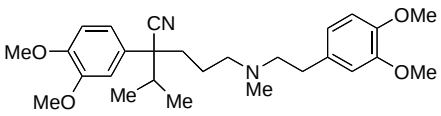
(+)- Welwitindolinone A **3**

Figure 1. Structures of Hapalindole Q **1**, *N*-Methylwelwitindolinone C Isothiocyanate **2**, and Welwitindoline A **3**.

BIOLOGICAL ACTIVITY

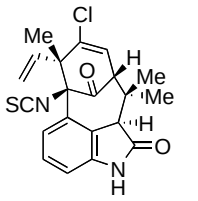
The members of the welwitindolinone alkaloids have shown a wide range of biological activity. The most important use for *N*-methylwelwitindolinone C isothiocyanate (**2**) is as a multiple drug resistance reversing agent. Multiple drug resistance (MDR) is a common problem in many cancer chemotherapies, and it is thought to derive from the ability of the carcinogenic cells to export active drugs from the cell and therefore reducing their cytotoxicity.[3] This process has been linked to the accumulation of P-glycoprotein, P-170, in the cell during the onset of MDR.[4] Therefore, efforts have been made to identify chemical agents that can reverse MDR. Verapamil (**4**) has been shown to competitively bind to P-glycoprotein *in vitro*; however, the high cytotoxicity of this compound is

problematic. Smith and co-workers found that compound **2** was a more potent MDR reversing agent than verapamil, being active at doses as low as 0.1 μM in MCF-7/ADR cells.[3] Zhang and Smith have shown that welwitindolinone C isothiocyanate (**5**) can disrupt microtubule formation in SK-OV-3 carcinoma cells and thus promote cell cycle arrest.[5] Compounds **1** and **3** also exhibit antibacterial[1] and antifungal[2] properties, respectively.



Verapamil
4

Figure 2. Structure of Verapamil



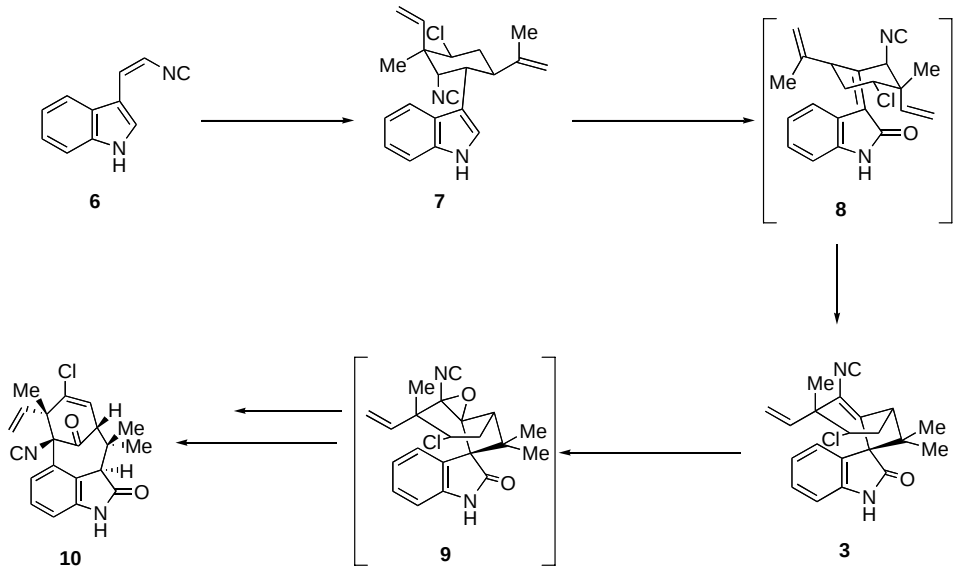
Welwitindolinone C isothiocyanate
5

Figure 3. Structure of Welwitindolinone C Isothiocyanate

PROPOSED BIOSYNTHETIC PATHWAY

Moore and co-workers proposed that the chlorine- and isonitrile-containing molecules isolated from *H. welwitschii* derive from a common precursor, with 12-*epi*-hapalindole E isonitrile **7** being the common intermediate in the biogenesis of many of the compounds, including welwitindolinone A and *N*-methylwelwitindolinone C isonitrile. Compound **7** is believed to derive from a chloronium ion-induced cyclization of 3-((Z)-2'-isocyanoethenyl)indole **6** and geranyl pyrophosphate.[2] The isonitrile group is thought to originate from glycine and cyanide, with the thioisocyanate being obtained from an inorganic sulfur-containing species.[6] Oxidation of the indole **7** would give rise to the oxindole intermediate **8**, which could undergo an acid- or enzyme-catalyzed cyclization leading to compound **3**. Generation of an isocyano epoxide **9** could then give rise to *N*-methylwelwitindolinone C isonitrile **10** (Scheme 1)**.**

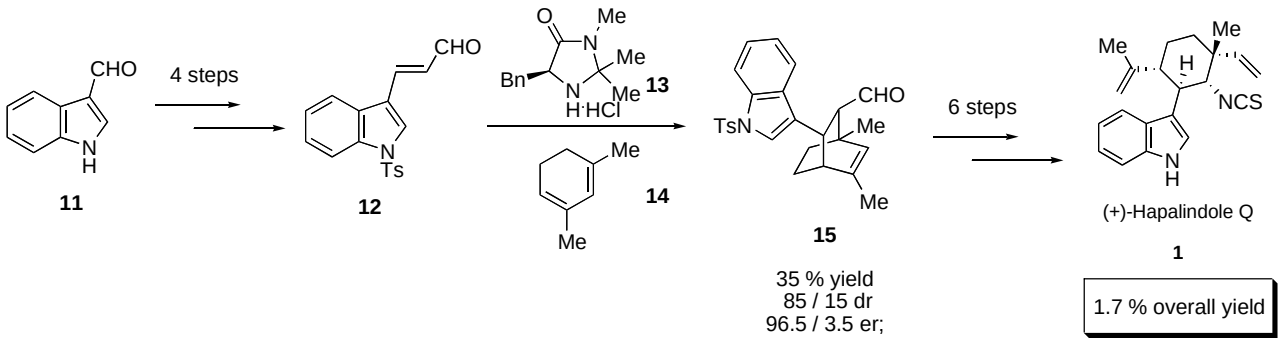
Scheme 1. Proposed Biosynthetic Pathway to Welwitindolinone A **3** and *N*-Methylwelwitindolinone C Isonitrile **10**.



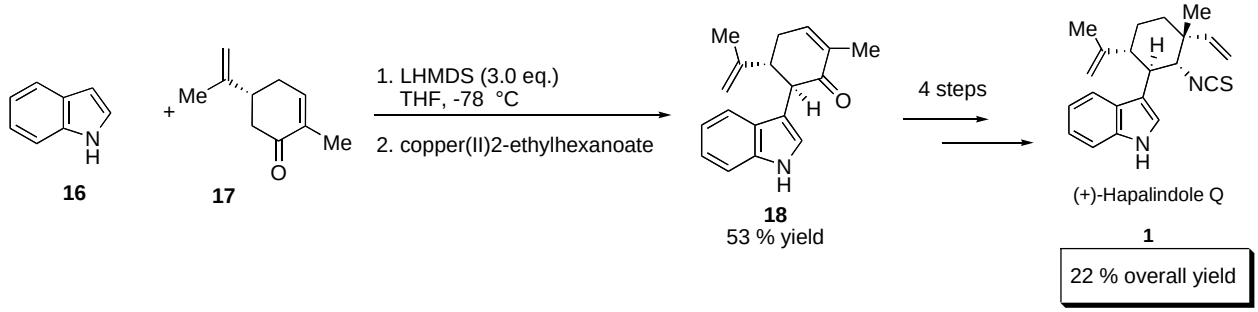
SYNTHESES OF (+)-HAPALINDOLE Q

Because of its intriguing carbon skeleton, this class of natural products has garnered significant attention from synthetic chemists. (+)-Hapalindole Q (**1**) offers two noteworthy structural features: First, the core of the system contains an indole moiety that is connected to a cyclohexyl ring through a stereodefined C-C bond. Second, the cyclohexyl ring contains four contiguous stereogenic centers, one of which is attached to an isothiocyanate. In 2001, Kinsman and Kerr described a racemic synthesis of compound **1** that focused on the formation of the cyclohexyl ring and proceeded in eight steps and 12.8% overall yield.[7] Using the technology from their racemic synthesis, Kerr and co-workers developed an enantioselective approach to **1** using an organomediated Diels-Alder reaction. The required enal dienophile **12** was prepared in four steps from indole **11**. With the dienophile in hand, an asymmetric Diels-Alder reaction with diene **14** was performed using an amino acid-derived organocatalyst **13** to give the bicyclo[2.2.2]octene adduct **15** with good enantioselectivity (96.5/3.5 er) and reasonable diastereoselectivity (85/15 dr). The bicyclic system was elaborated to the natural product in 6 steps and 1.7% overall yield (Scheme 2).[8] In 2004, Baran and co-workers set out to simplify the synthesis by using (R)-carvone as the precursor for the cyclohexane moiety. Deprotonation of both indole and (R)-carvone using LHMDS in THF at -78 °C, followed by oxidative coupling using copper(II) 2-ethylhexanoate, provided the cross-coupled product **18** in 53% isolated yield. Indole **18** was converted to **1** in 6 steps and 22% overall yield (Scheme 3).[9]

Scheme 2. Total Synthesis of **1** using an Organomediated Diels-Alder Reaction.



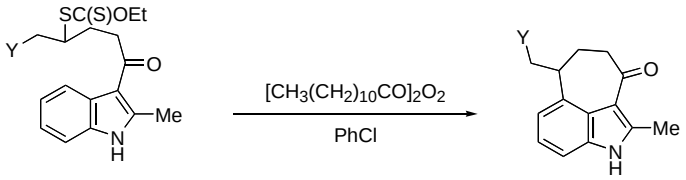
Scheme 3. Total Synthesis of **1** via Direct Coupling of Indole with Carbonyl Compounds.



SYNTHESIS OF THE *N*-METHYLWELWITINDOLINONE C CARBON SKELETON

A seven-membered ring fused with an aromatic system is found in a variety of natural products, including *N*-methylwelwitindolinone C. Thus, the welwitindolinone carbon skeleton provides an interesting challenge for the development of methods to form such complex ring systems. Kaoudi and co-workers developed a radical annulation to form the seven-membered ring with a carbonyl functionality present. In this system, xanthates are used as precursors from which radicals can be generated under tin-free conditions via a chain or non-chain process; these radicals then add to unactivated olefins or aromatic systems (Scheme 4).[10]

Scheme 4. Annulation of 7-Membered Rings Using Xanthate-Mediated Radical Formation

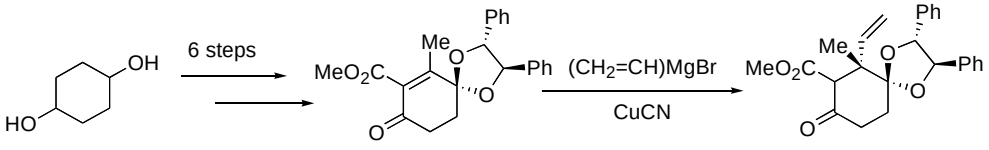


19
Y = OAc, CN, CH_2CO_2Et

20

Konopelski and co-workers recognized that not only would there be problems in linking the cyclohexanone to the oxindole, preparation of the required cyclohexanone itself would also be challenging. Therefore, in 1998, he and his associates prepared a cyclohexanone intermediate **23** that would be used for the total synthesis of isothiocyanate natural product **2**; their route started from 1,4-cyclohexanediol (Scheme 5).[11] Later, Konopelski and co-workers attempted to couple intermediate **23** to the indole using aryllead(IV) chemistry. Unfortunately, whereas simple model cyclic β-ketoesters (e.g. **25**) could be coupled with the aryl lead indole **24** (although with poor diastereoselectivity), all efforts to couple the natural product precursor, the more hindered intermediate **23**, failed to give any product formation (Scheme 6).[12]

Scheme 5. Preparation of Cyclohexanone Intermediate **23**

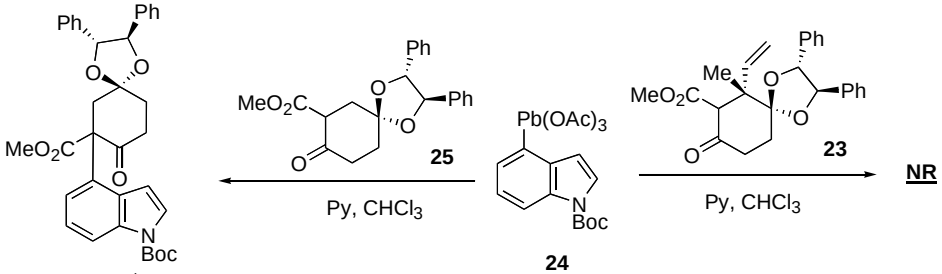


21

22
33 %

23
85 %

Scheme 6. Attempts at Coupling **23** with 4-Indole lead(IV) Triacetate



quant
dr = 2.0/ 1.0
26

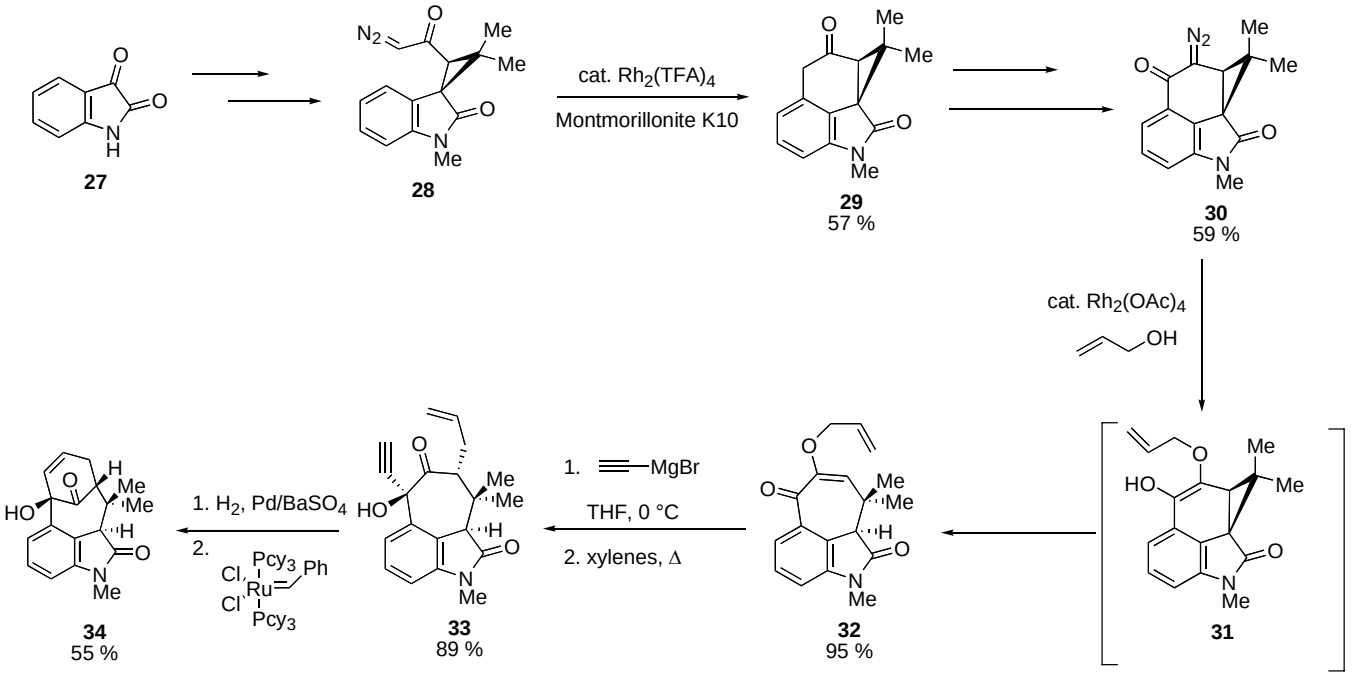
25

24

23

Another approach for forming the seven-membered cyclic system of **2** relies upon transition metal-catalyzed aryl C-H functionalization. Many groups have investigated α-diazo carbonyl compounds as precursors of metal carbenoids, reactive intermediates that are known to undergo aryl C-H insertion.[13] Lopez-Alvarado and co-workers were successful in forming three contiguous stereocenters through a Michael addition, but found that further elaboration to the desired diazo compound was futile.[14] Jung and co-workers were able to access the required α–diazo carbonyl species easily from the β-keto acid, but subsequent aryl C-H insertion proved problematic.[15] However, Wood and co-workers successfully utilized a rhodium carbenoid to effect the required aryl C-H insertion in their synthesis of the full tetracyclic core of **2**. Starting from isatin **27**, formation of α-diazo ketone **28** was accomplished in 5 steps, in overall good yield. Initial attempts at aryl C-H insertion using $Rh_2(TFA)_4$ as a catalyst provided a complex mixture that contained only small amounts of insertion product **29**. Addition of Montmorillonite K10, a mildly Lewis acidic clay, suppressed the formation of side products, and the desired cyclized material **29** was formed in moderate yield. Compound **29** was then converted to the second α-diazo ketone **30**, which rapidly coupled with allyl alcohol to furnish enol intermediate **31**. After cyclopropane opening to cycloheptanone **32**, treatment with ethynyl magnesium bromide and subsequent Claisen rearrangement gave α-allyl ketone **33**. Following partial hydrogenation and ring-closing metathesis, the completed tetracyclic core of **2** was achieved (Scheme 7).[16]

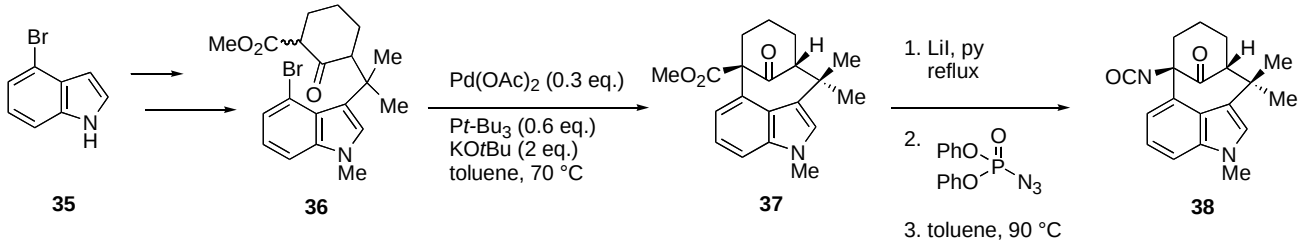
Scheme 7. Preparation of the Carbon Skeleton of **2** Using Rh-Carbenoid Aryl C-H Insertion.



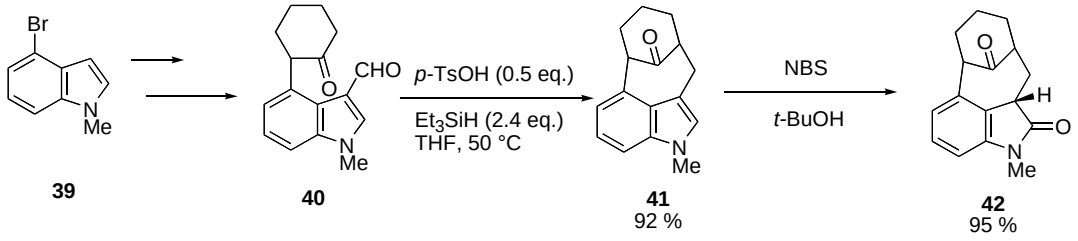
Further developments in the area of transition-metal catalysis have provided methods for enolate insertion into aryl C-H bonds under palladium catalysis.[17] The first example, reported by MacKay and

co-workers, started from 4-bromoindole and accessed the indole adduct through a Lewis acid-mediated alkylation. The resulting ketoester **36** underwent Pd-catalyzed enolate arylation to give the desired bicyclo[4.3.1]decanone ring system. The ester function in **36** was converted into the isocyanate, providing a rapid synthesis (10 steps, 31% overall yield) of a product (**38**) having the complex welwitindolinone C carbon skeleton (Scheme 8).[18] Baudoux and co-workers reported a similar route to the welwitindolinone skeleton, but they used an intermolecular Pd-catalyzed enolate arylation followed by an acid-mediated ring closure under reducing conditions to give the bicyclic carbon skeleton. This route provided facile access to the oxindole, but the cyclohexanone portion was not further elaborated (Scheme 9).[19]

Scheme 8. Synthesis of *N*-methylwelwitindolinone Skeleton Using a Pd-catalyzed Enolate Arylation.



Scheme 9. Preparation of the Welwitindolinone Alkaloid Skeleton Via Cyclization of an Indolecarboxaldehyde



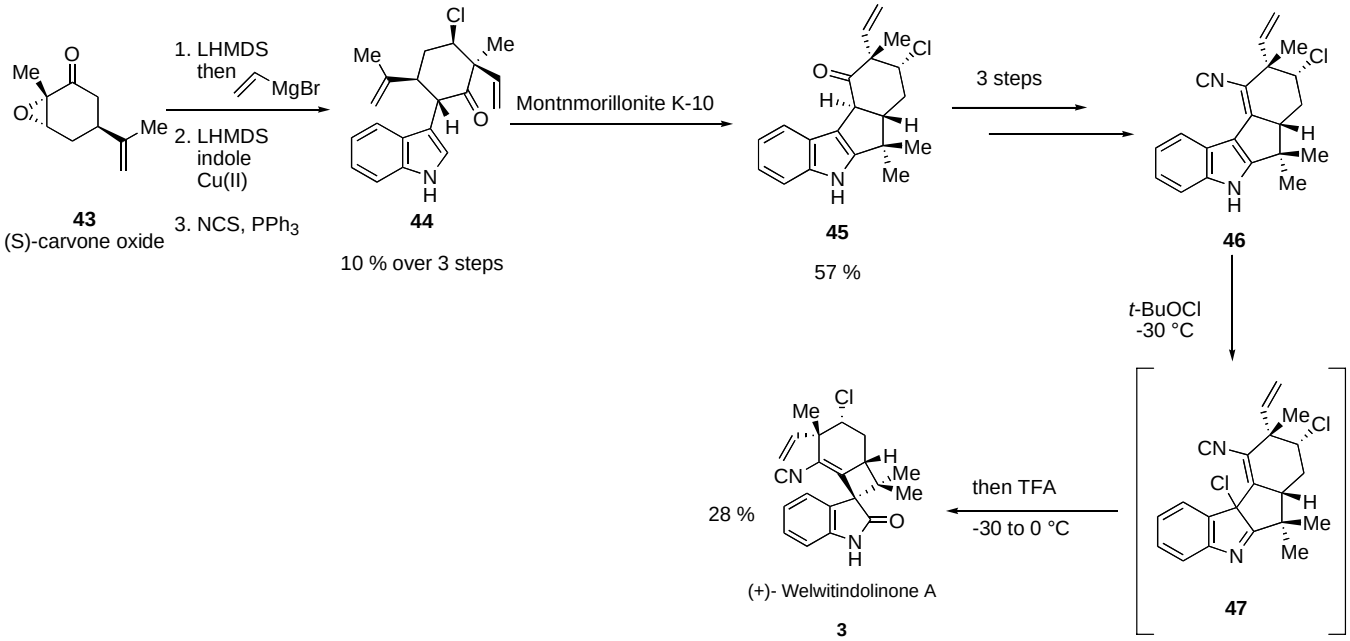
TOTAL SYNTHESIS OF WELWITINDOLINONE A

Baran 2005

Despite its interesting biological activity, only recently have there been reports of synthetic efforts toward welwitindolinone A itself (**3**). The highly functionalized and sterically crowded oxindole containing a spiro-fused cyclobutane, as in this target molecule, appears on cursory inspection to be thermodynamically unstable. Recently, Baran and co-workers have reported the first total synthesis of **3** using the technology developed in their synthesis of (+)-hapalindole Q. Starting with (S)-carvone oxide, they prepared the quaternary carbon containing the allyl moiety in one step, albeit in low yield (30%). Introduction of the neopentyl chlorine atom was accomplished using *N*-chlorosuccinimde, and coupling with indole, performed under conditions previously reported, gave the indole adduct **44** in 55% yield.[9] Simple functionalization of the cyclohexyl moiety provided **46** in 4 steps. Compound **46** could be

converted into **3** via a facile ring contraction using *t*-BuOCl in THF followed by treatment with trifluoroacetic acid (Scheme 10). This provided welwitinoldinone A utilizing a protecting group-free synthesis in a 0.1% overall yield.[20]

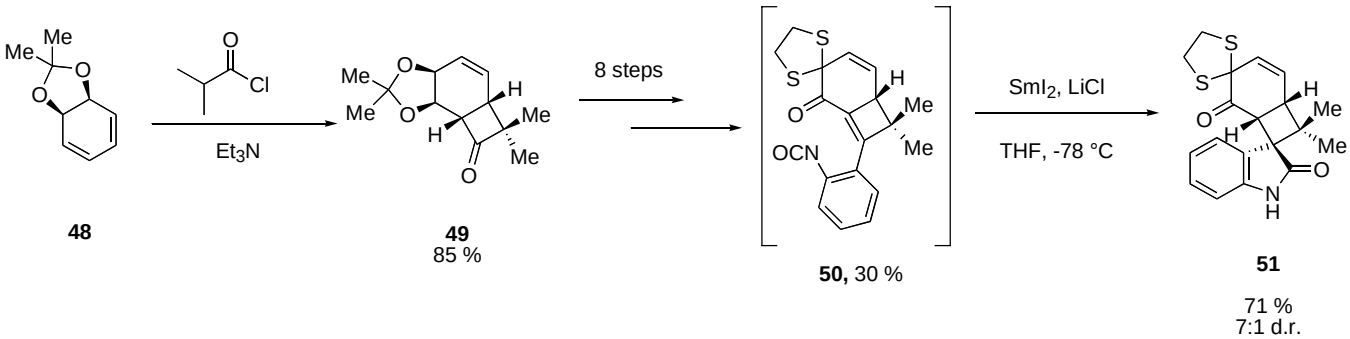
Scheme 10. Baran's Synthesis of Welwitindolinone A



Wood 2005

In 2004, Wood and co-workers reported their efforts towards the total synthesis of **3**. Recognizing that the sensitive vinyl isonitrile could be formed from a ketone, they set out to synthesize intermediate **51.** Starting from commercially available cyclohexadiene acetonide **48**, a stereo- and regioselective [2+2] cycloaddition provided the necessary cyclobutane functionality. Further synthetic manipulations provided isonitrile **50** in 8 steps, which was subjected to a SmI_2-mediated reductive coupling to provide oxindole **51** (Scheme 11).[21] Wood and co-workers have recently accomplished the total synthesis of **3** in a 4.5% overall yield.[22]

Scheme 11. Formation of Key Intermediate in Synthesis of Welwitindolinone A



CONCLUSION

The welwitindolinone family of structurally complex compounds poses significant challenges for the synthetic community. Only two groups have completed the total synthesis of Welwitindolinone A, but many have attempted to gain access to these complex welwitindolinone structures. Baran and co-workers exemplified the utility of a protecting group-free synthesis of welwitindolinone A using a ring contraction strategy. On the other hand, Wood and co-workers sought to install the cyclobutane functionality early in their synthesis and developed a samarium-mediated cyclization to form the spiro-fused indole intermediate. Due to its important biological activity, further work should be directed at improving access to *N*-methylwelwitinoldinone C and its analogs. It would also be interesting to test the viability of Welwitindolinone A as an intermediate for the preparation of *N*-methylwelwitinoldinone C, as proposed in the biosynthetic pathway.

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