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Synthesis of the Bicyclic Welwitindolinone Core via an Alkylation/Cyclization Cascade Reaction

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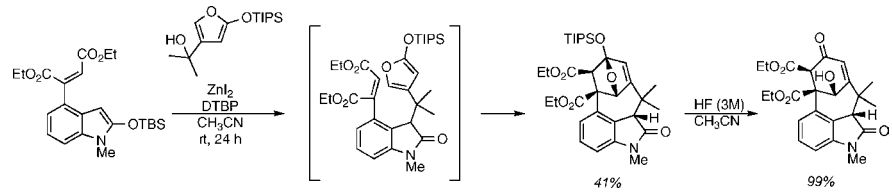
ABSTRACT



Synthesis of an advanced welwitindolinone intermediate via an alkylation/cyclization reaction is reported. The key step involves a one pot Lewis acid-mediated alkylation of a silylketene aminal with a furan alcohol followed by an intramolecular cyclization. The reaction is stereoselective and takes place at low temperature. The cycloadduct was highly functionalized and contains the welwitindolinone core structure.

Multiple-drug-resistance (MDR) is known to operate via several pathways to diminish the effectiveness of anticancer medicines used in chemotherapy.[1] Drug efflux via upregulated production of *P*-glycoprotein, a membrane transport protein for lipophilic molecules, is the most commonly observed MDR mechanism.[2] Agents that inhibit *P*-glycoprotein and/or are active against MDR cells have significant value in cancer treatment due to their potential application as single and combination therapies in the treatment of MDR tumors.[3]

In studies directed toward the discovery of biologically active natural products of blue-green algae (cyanobacteria), Moore isolated the welwitindolinone alkaloids (Figure 1) from *Hapalosiphon welwitschii* and *Westiella intricata*.[4] The welwitindolinone family is divided into three subgroups: welwitindolinone A (**1**), welwitindolinones B (**2**−**4**), and welwitindolinones C (**5**−**7**). *N*-Methylwelwitindolinone C isothiocyanate (**7**), the major component of the lipophilic extract, was found to possess antifungal activity and reverse MDR in vinblastine-resistant cell lines through inhibition of the drug-efflux ability of *P*-glycoprotein.[5] Welwitindolinone

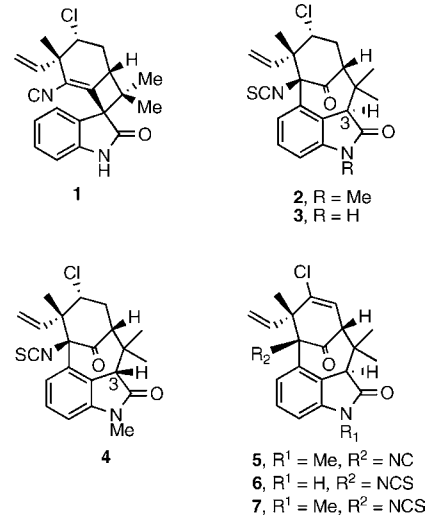


Figure 1. Welwitindolinone alkaloids.

(1) Longley, D.; Johnston, P. *J. Pathol.* **2005**, *205*, 275–292.
(2) Szakacs, G.; Paterson, J. K.; Ludwig, J. A.; Booth-Genthe, C.; Gottesman, M. M. *Nat. Rev. Drug Discov.* **2006**, *5*, 219–234.
(3) Aller, S. G.; Yu, J.; Ward, A.; Weng, Y.; Chittaboina, S.; Zhuo, R.; Harrell, P. M.; Trinh, Y. T.; Zhang, Q.; Urbatsch, I. L.; Chang, G. *Science* **2009**, *323*, 1718–1722.
(4) Stratmann, K.; Moore, R. E.; Bonjouklian, R.; Deeter, J. B.; Patterson, G. M. L.; Shaffer, S.; Smith, C. D.; Smitka, T. A. *J. Am. Chem. Soc.* **1994**, *116*, 9935–9942.

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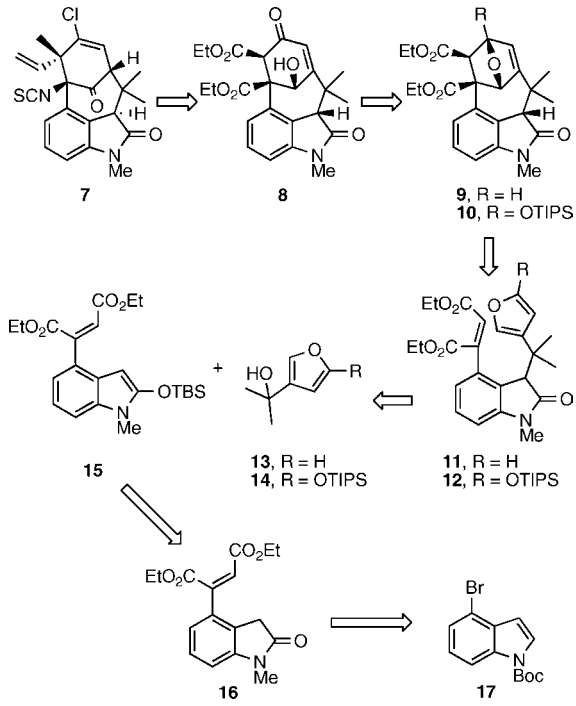
C **6** was later identified as a tubulin-interacting agent demonstrating activity against drug-resistant tumors.[6] Structurally, these molecules are comprised of an oxindole ring linked to a terpenoid ring system containing three quarternary centers, chlorine substitution, and either an isonitrile or isothiocyanate moiety. In contrast to the other B and C welwitindolinones, **4** is epimeric at C-3.

Elegant syntheses of welwitindolinone A isonitrile (**1**) have been completed in the laboratories of Wood[7] and Baran.[8] However, in spite of many strategies,[9,10] no total syntheses of the B or C welwitindolinones have been reported.

In an earlier report, our laboratory disclosed a method for the synthesis of the [4.3.1] welwitindolinone core using a type 2 intramolecular Diels−Alder (IMDA) reaction.[10i] Although this route established proof of concept by providing short access to the welwitindolinone skeleton, we sought to develop a more expedient strategy for preparing the welwitindolinones.

The retrosynthetic strategy for the total synthesis of *N*-methylwelwitindolinone C isothiocyanate (**7**) constructs the bridged tetracyclic system using an intramolecular cycloaddition reaction (Scheme 1). Compound **8** possesses

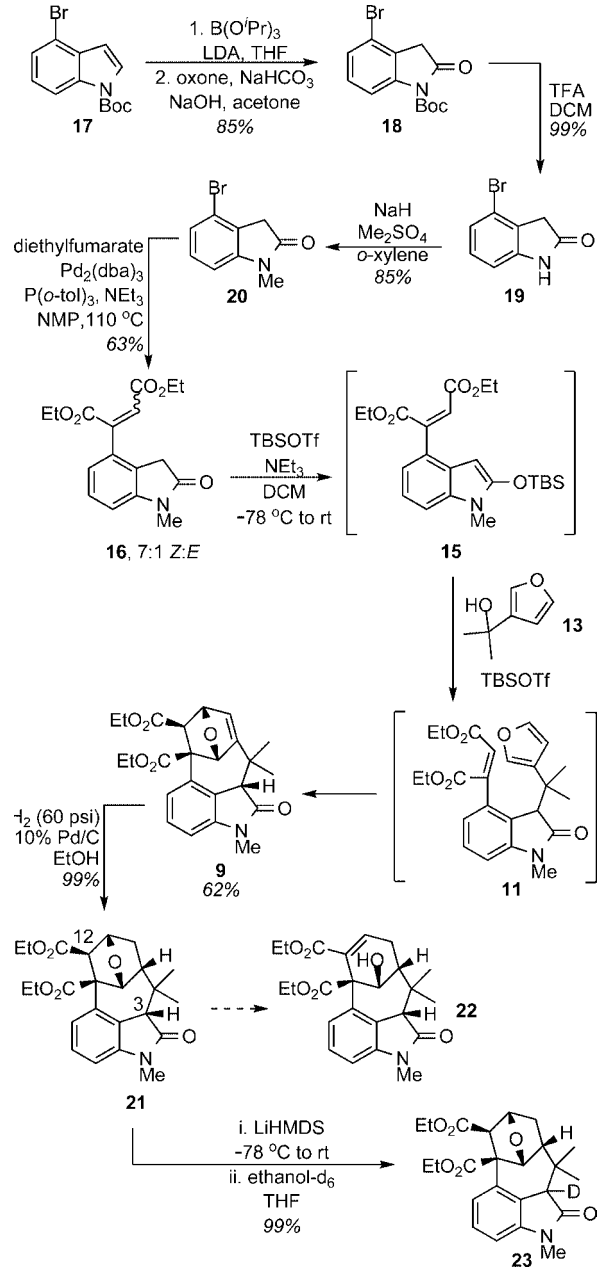
Scheme 1. Retrosynthetic Analysis



the welwitindolinone core structure, several functional handles, and could be accessed from either the bridged pentacycle **9** or **10**. The key transformation in our strategy is the formation of pentacyclo[4.3.1] oxindole **9** or **10** via cycloaddition of intermediate **11** or **12**, respectively, which in turn was envisioned to arise from alkylation of silyl ketene aminal **15** with substituted furan **13** or **14**. Compound **15** would arise from vinyl oxindole **16**, which would be derived from *N*-Boc-4-bromoindole (**17**).[11]

The synthesis began from the known indole **17** prepared from 4-bromo-indole[12] (Scheme 2). *N*-Boc-4-bromo-indole

Scheme 2. Synthesis of Welwitindolinone Core



(**17**) was oxidized to afford *N*-Boc-4-bromo-oxindole (**18**) via 2-indolyl boronic acid.[13] 4-Bromo-oxindole (**19**),[14] prepared by removal of the Boc group of oxindole **18**, was N-methylated to yield 4-bromo-*N*-methyl-oxindole (**20**). Vinylation of oxindole **20** with diethylfumarate via a Heck

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(6) Zhang, X.; Smith, C. *Mol. Pharmacol.* **1996**, *49*, 288–294.

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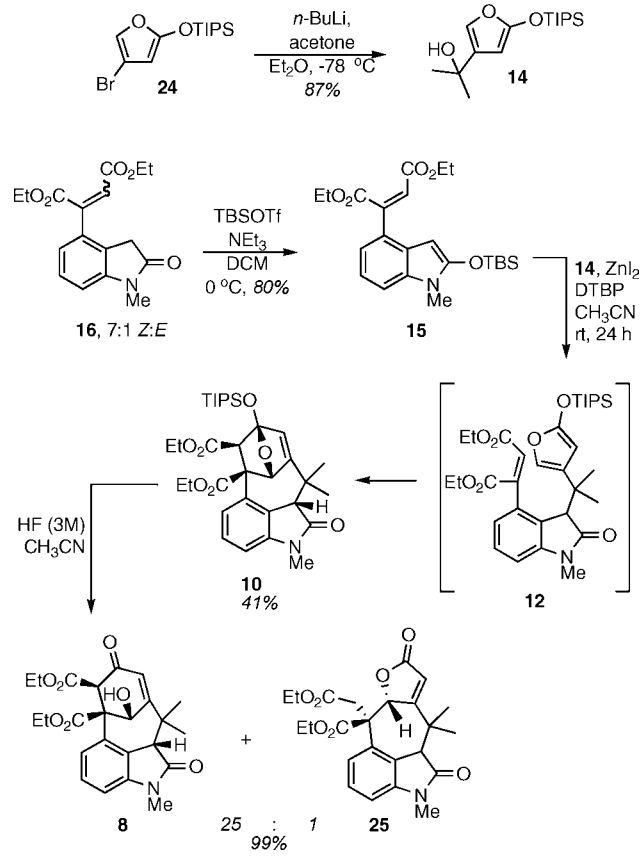
coupling[15] furnished oxindole **16** as a mixture of olefin isomers. Vinyl oxindole **16** was treated with TBSOTf to form silyl ketene aminal **15** *in situ*. Compound **15** subsequently underwent alkylation upon treatment with furan alcohol **13** (R = H)[16] to yield Diels−Alder precursor **11**. Experimental evidence suggests that the acid byproduct of the silylation reaction facilitates ionization of the furan alcohol to produce the reactive electrophilic species.[17] At this low temperature, cyclization of intermediate **12** produced oxa-bicyclo[4.3.1] adduct **9** as a single diastereomer in 62% yield from **16** in a one pot cascade reaction. Cycloadduct **9** contains two all-carbon quaternary centers, and all but two carbon atoms of the B and C welwitindolinones. The relative configuration of the stereogenic carbons of cycloadduct **9** was confirmed by X-ray crystallography. The esters, oxygen bridge, and C-3 hydrogen are positioned on the same face of the molecule. Hydrogenation of cycloadduct **9** produced oxo-bridged **21** as a single diastereomer via addition exclusively to the exo face of the bicyclic system.

On the basis of an analogy to a related system using LiHMDS,[18] we envisioned a base-induced ring-opening of **21** to afford **22** via an elimination mechanism. Unfortunately, the desired product was not formed. Treatment of **21** with 1.3 equiv of LiHMDS followed by quenching with ethanol-d_6 resulted in complete and exclusive incorporation of deuterium at C-3 to yield **23**. This deuterium labeling experiment indicated that the C-3 proton of the oxindole was removed selectively over the C-12 proton. Treatment of **21** with up to 4 equiv of base did not result in the formation of **22**.

An alternative synthetic route employing silyloxyfuran **14** (R = OTIPS) for the alkylation of silylketene aminal **16** was pursued (Scheme 1). This sequence accesses ketone intermediate **8** in fewer steps and circumvents the problematic base mediated oxo-bridge opening reaction through the use of a labile silyl ketal.

Silyloxyfuran **14** was prepared by from furan **24**[19] via metal−halogen exchange followed by 1,2-addition to acetone (Scheme 3). Due to the sensitivity of **14** to the acidic conditions used in the alkylation of des-silyloxyfuran **13**, an alternative alkylation strategy was devised. Silylketene aminal **15** was isolated as the *Z*-isomer exclusively from a 7:1 (*Z*:*E*) mixture of **16**.[20] Lewis acids and solvents were evaluated for their ability to effect the desired alkylation reaction. ZnI_2 in acetonitrile enabled the alkylation of **15** with furan alcohol **14** to prepare furan **12** which underwent intramolecular cyclization to yield cycloadduct **10** as single

Scheme 3. Alternate Route to Welwitindolinone Core



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diastereomer in 41% yield. The relative stereochemistry of **10** was verified by X-ray crystallography (Figure 2). This

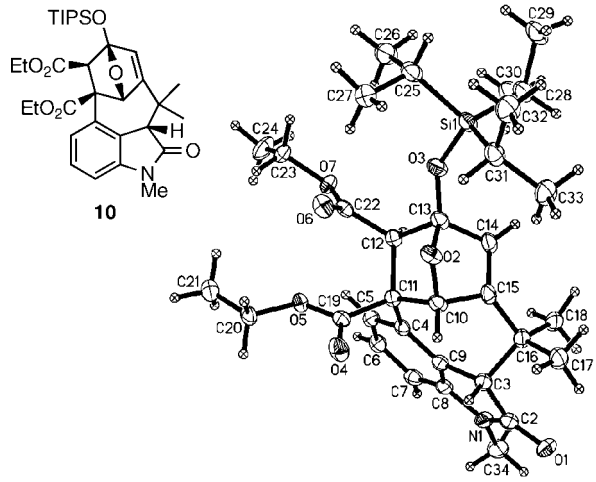

Figure 2. ORTEP drawing of **10**.

cascade reaction prepares a highly functionalized welwitindolinone core structure containing two all-carbon quaternary centers, sets two stereocenters, and assembles all but two carbon atoms of the B and C welwitindolinone skeleton from simple materials in short fashion. Desilylation of **10** with HF yielded a 25:1 mixture of the desired alcohol **8** to lactone **25**. Compound **8** was observed to isomerize to lactone **25** under basic solutions or during silica gel flash chromatography.[21]

Although the configuration of compound **8** at C-3 matches **4**, it is epimeric relative to the other welwitindolinones. Molecular modeling studies were pursued to gain insight concerning the relative stabilities about the epimerizable center at C-3 (Figure 3). Compound **26** with C-3 hydrogen beta was calculated to be 4.4 kcal/mol lower in energy than the C-3 epimer (epi-**26**) (DFT PBEPBE 6-311G*). At this same level of theory, the natural diastereomer of

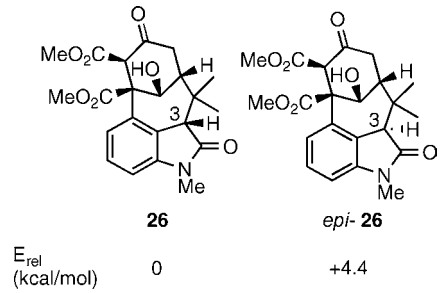

Figure 3. Relative energy of C-3 epimers of **26**.

N-methylwelwitindolinone C isothiocyanate (**7**) is calculated to be 3.9 kcal/mol lower in energy than its C-3 epimer (DFT PBEPBE 6-311G*). This result suggests that an advanced synthetic intermediate can adopt the α-H configuration at C-3.

In conclusion, a highly functionalized welwitindolinone core structure **8** has been prepared in 8 steps from *N*-Boc-4-bromoindole (**17**) using an alkylation/cyclization cascade reaction. The relative stereochemistry of **9** and **10** has been confirmed by X-ray crystallography. Future work will focus on installation of the remaining quaternary center and functional group manipulations to prepare *N*-methylwelwitindolinone C iosthiocyanate (**7**) and the related welwitindolinones.

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Supporting Information Available: Experimental procedures, spectroscopic data (^{1}H, ^{13}C) for new compounds, and CIF files for compounds **9** and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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