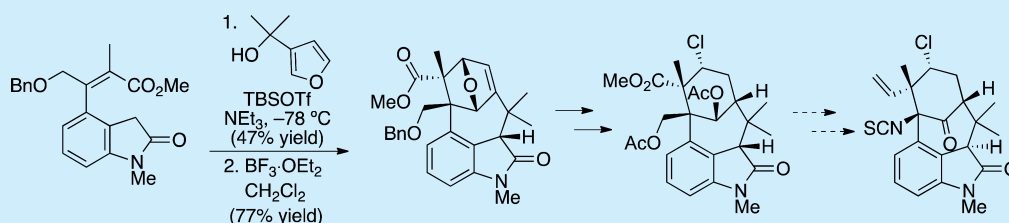


Progress toward the Total Synthesis of *N*-Methylwelwitindolinone B Isothiocyanate

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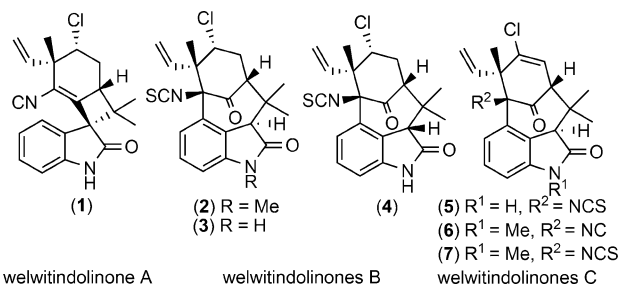
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## Supporting Information



**ABSTRACT:** Progress toward the welwitindolinone alkaloid *N*-methylwelwitindolinone B isothiocyanate is reported. A key reaction to synthesize the [4.3.1] bicycle embedded in the core of the molecule is a furan type 2 intramolecular Diels–Alder reaction with a tetrasubstituted dienophile, which sets the two vicinal quaternary centers present in the natural product. The sterically encumbered cycloaddition precursor was synthesized using a Horner–Wadsworth–Emmons reaction followed by a Suzuki cross-coupling reaction. Finally, introduction of the secondary alkyl chloride was achieved by a regio- and diastereoselective opening of a [2.2.1] oxobicycloheptane functionality.

The welwitindolinone alkaloids were isolated from the blue-green algae (cyanobacteria) *Hapalosiphon welwischii*, *Westiella intricata*, *Fischerella muscicola*, and *Fischerella major* (Figure 1).<sup>1</sup> These molecules have been of significant interest



**Figure 1.** Representative members of the welwitindolinone alkaloids.

to the synthetic chemistry community because of the challenges associated with synthesizing the densely packed, highly functionalized cyclohexane or cyclohexene core present in these alkaloids as well as their interesting bioactivities.

Several of the welwitindolinones were found to possess significant activity after isolation and screening of their biological properties.<sup>2</sup> The lipophilic extract of *W. intricata* was found to be fungicidal, and upon purification, welwitindolinone A isonitrile (1) was identified as an antifungal agent. More intriguing was the discovery that *N*-methylwelwitindolinone C isothiocyanate (7) reverses multiple drug resistance (MDR) in vinblastine-resistant breast and ovarian cancer cells by inhibiting P-glycoprotein. While welwitindolinone C isothiocyanate (5) and *N*-methylwelwitindolinone C isonitrile (6) were also found to possess MDR activities, *N*-

methylwelwitindolinone B isothiocyanate (2), welwitindolinone B isothiocyanate (3), and 3-*epi*-welwitindolinone B isothiocyanate (4) were not surveyed for their bioactivities.

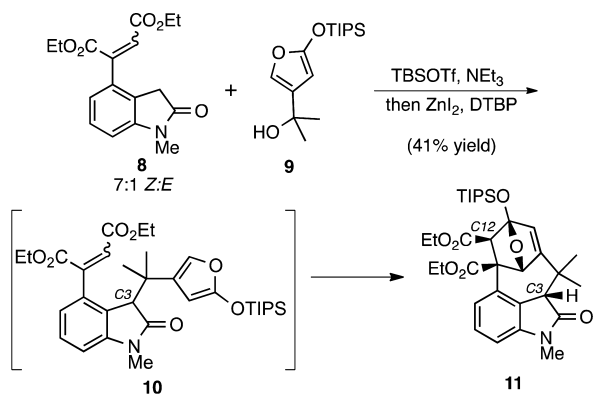
Because of their intriguing structures and bioactivities, the welwitindolinones have become popular synthetic targets. Welwitindolinone A isonitrile (1) was the first of these alkaloids to be synthesized, with the Baran and Wood groups each publishing innovative approaches to accomplish its total synthesis.<sup>3</sup> Other efforts toward the welwitindolinones have mainly focused on the synthesis of MDR inhibitor 7, with numerous groups reporting approaches to the core of the [4.3.1] bicyclic welwitindolinones.<sup>4</sup> The Rawal group reported the synthesis of 7<sup>5</sup> following their groundbreaking synthesis of *N*-methylwelwitindolinone D isonitrile (not pictured).<sup>6</sup> Furthermore, they also employed their enolate arylation strategy in the synthesis of 20,21-dihydro *N*-methylwelwitindolinone B isothiocyanate.<sup>7</sup> The Garg group has likewise synthesized several members of the welwitindolinone alkaloids, while the Martin group has completed a formal synthesis intercepting a late-stage Rawal intermediate.<sup>8</sup> There have been no reports of the total synthesis of any of the welwitindolinones B.

Our group has previously investigated a furan type 2 intramolecular Diels–Alder (T2IMDA) reaction approach toward the synthesis of 7 (Scheme 1).<sup>9</sup> Alkylation of oxindole 8 with alcohol 9 leads to the formation of cycloaddition precursor 10 which then cyclizes to provide 11. The core of 7 was rapidly formed through this methodology as a single diastereomer, with the C3 stereocenter setting the other four

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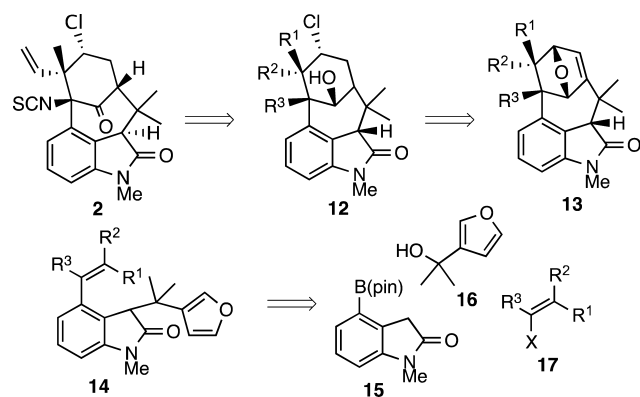
**Scheme 1. Previous Work towards the Synthesis of *N*-Methylwelwitindolinone C Isothiocyanate (7) Reported by the Shea Lab**



stereocenters formed in the product. One drawback of this cycloaddition is that it was not possible to use a more sterically encumbered tetrasubstituted alkene, because furan alcohol **9** is prone to decomposition in the presence of stronger Lewis acids that were necessary to increase the reactivity with a more sterically hindered alkene. We reasoned that it might be beneficial to switch strategies and use a more robust furan diene to target **2**.

We proposed that we could improve our strategy and target welwitindolinones **B** by incorporating the C12 quaternary center through a similar furan T2IMDA with a tetrasubstituted alkene and a furan diene without a silyl protected alcohol (Scheme 2). Retrosynthetically, we envisioned that **2** could be

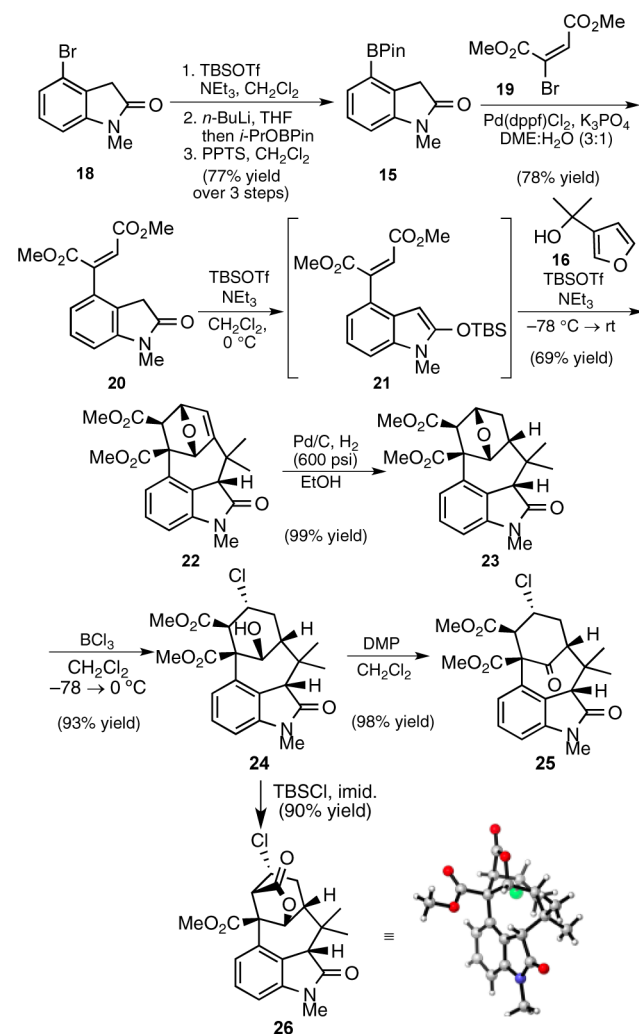
**Scheme 2. Retrosynthetic Analysis of 2**



synthesized through the functionalization of chlorohydrin **12**. The chlorohydrin would be advanced from cycloadduct **13** which would be formed after the T2IMDA reaction of cycloaddition precursor **14**. Alkylation of oxindole **15** with furan alcohol **16** would provide cycloaddition precursor **14**.

Preparation of the core of welwitindolinone **B** was successfully accomplished through a T2IMDA reaction of a model system, which provided a platform to test late-stage chloride installation (Scheme 3). We chose alkene **19** because it was easily accessible and would provide a substrate to test some of the final functional group manipulations. The synthesis commenced by converting *N*-methyl-4-bromooxindole (**18**) to the silyl ketene acetal, followed by lithium halogen exchange and transmetalation to provide pinacol borane **15**. Suzuki cross-coupling of bromomalonate-derived alkene **19** and boronic

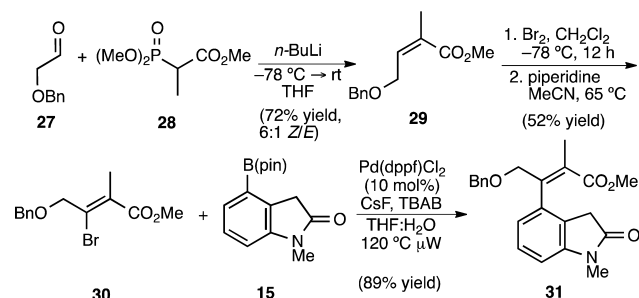
**Scheme 3. Synthesis of the Core of Welwitindolinone B**



ester **15** produced oxindole **20** in good overall yield. The tetracyclic [4.3.1] core of the welwitindolinones was then rapidly obtained via an alkylation–T2IMDA reaction cascade. In one pot, oxindole **20** was converted to silyl ketene acetal **21** which was then treated with excess TBSOTf and furan alcohol **16** to furnish cycloadduct **22** as a single diastereomer with the relative stereochemistry at the C3 position of the oxindole epimeric to that of natural product **2**.<sup>10</sup> The bridgehead alkene of cycloadduct **22** was reduced with complete diastereoselectivity, and oxabicycloheptane **23** was then chlorinated stereo- and regioselectively.<sup>11</sup> To confirm the chloride stereochemistry, alcohol **24** was lactonized (**26**) and the single crystal X-ray structure proved that the chlorinated product was formed as the desired  $\alpha$ -epimer. Alcohol **24** could alternatively be oxidized to form chloroketone **25**. However, conditions for methylation to install the final quaternary center proved elusive, favoring byproducts of alkylation at C3 or elimination of the chloride. The difficulties we encountered while attempting late-stage installation of the quaternary center further highlighted the need to extend the furan T2IMDA reaction methodology to include tetrasubstituted alkenes.

After extensive trials and optimization, we found a Horner–Wadsworth–Emmons/Suzuki cross-coupling strategy was optimal to synthesize alkene **31** (Scheme 4). To this end, aldehyde **27**<sup>12</sup> was treated with lithiated phosphonate **28**<sup>13</sup>

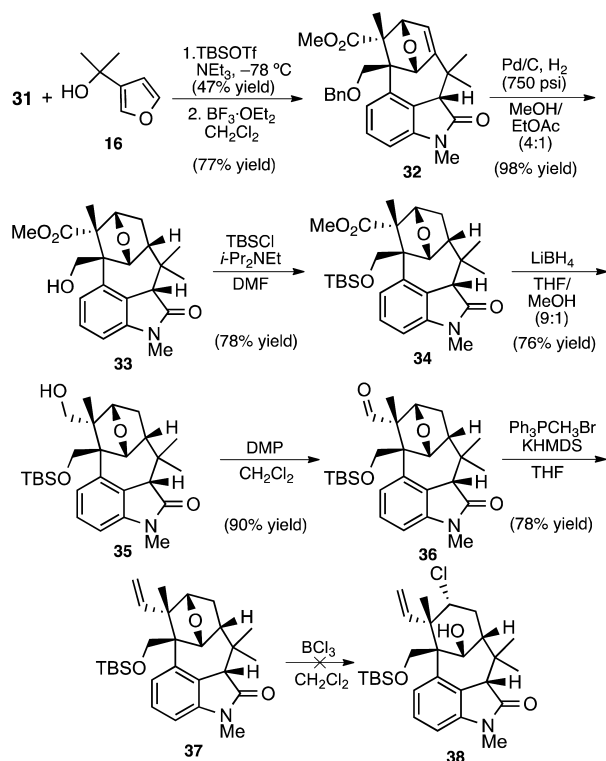
**Scheme 4. Synthesis of Tetrasubstituted Alkene 30 through a Horner–Wadsworth–Emmons/Suzuki Cross-Coupling Strategy**



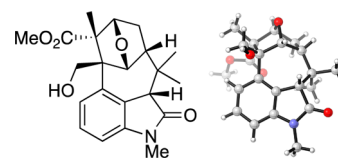
furnishing a separable mixture of trisubstituted alkene **29** in a 6:1 ratio favoring the desired *Z* isomer.<sup>14</sup> Acrylate **29** was then brominated through a two-step sequence to provide vinyl bromide **30**. Suzuki cross-coupling of the bromide and oxindole **15** furnished sterically encumbered dienophile **31** in excellent yield.<sup>15</sup> The sequence conveniently provides a large quantity of the tetrasubstituted alkene for elaboration toward welwitindolinone B (**2**).

We then sought to employ our T2IMDA strategy to diastereoselectively set the two vicinal quaternary centers of **31** (Scheme 5). Alkene **31** was alkylated with furan alcohol **16**. In this case the cycloaddition was found to be slow so the reaction was quenched at  $-78\text{ }^{\circ}\text{C}$  to avoid decomposition of the intermediate triene. The triene was immediately subjected to cycloaddition conditions, and we were pleased to find that  $\text{BF}_3\cdot\text{OEt}_2$  catalyzed the formation of cycloadduct **32** as a single isomer with the vicinal quaternary centers set with the correct

**Scheme 5. Furan Type 2 Intramolecular Diels–Alder Reaction with Tetrasubstituted Alkene 30 and Elaboration toward 2**



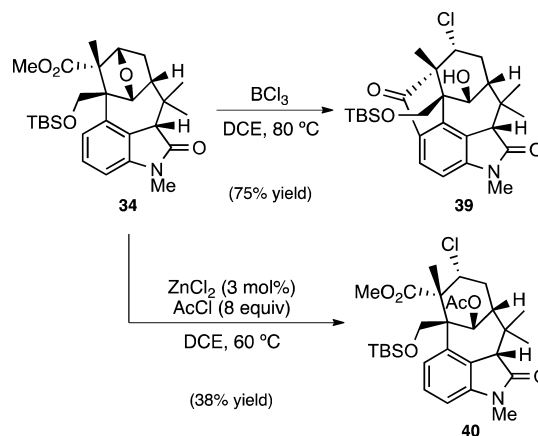
relative stereochemistry and in good overall yield. Moreover, oxindole **31** is the most densely functionalized dienophile reported for use in a T2IMDA reaction to date. Cycloadduct **32** was then diastereoselectively reduced with concomitant benzyl group deprotection to afford alcohol **33**. The X-ray crystal structure of **33** confirmed the relative stereochemistry (Figure 2). Silyl protection of alcohol **33** was followed by a  $\text{LiBH}_4$



**Figure 2.** Crystal structure of **33**.

mediated reduction and DMP oxidation of ester **34** to aldehyde **36**. Wittig olefination of aldehyde **36** cleanly provided alkene **37**. At this stage we were disappointed to find that the previously established chlorination conditions did not provide any of the desired chlorohydrin **38**. Likewise, subjecting aldehyde **36** or alcohol **33** to the chlorination conditions did not furnish any of the desired products. Alternatively, attempts to chlorinate **34** were more fruitful if the reaction conditions were modified to use dichloroethane and heated to  $80\text{ }^{\circ}\text{C}$ ; however, chlorination was accompanied by a Friedel–Crafts acylation reaction to form cyclopentene **39** (Scheme 6). Improved conditions for the chlorination are still under investigation with alternate substrates.

**Scheme 6. Chlorination of 34**



Several other acids were also assayed to find alternate conditions for the chlorination of ether **34**, and we were excited to find that  $\text{AcCl}$  in the presence of catalytic  $\text{ZnCl}_2$  provided a modest yield of chlorinated product **40**.<sup>16</sup> Efforts to optimize the reaction conditions were not fruitful; however, this chlorination procedure offers an alternative strategy to eventually complete the total synthesis.

The welwitindolinone alkaloids remain a source of vibrant, new chemistry, and these molecules continue to be a challenge to synthetic organic chemists. We have established conditions to synthesize the carbon skeleton of welwitindolinone B and were able to set three out of five stereocenters using a furan T2IMDA reaction including the two vicinal quaternary centers. The major challenge left to complete the welwitindolinones B is the development of a reaction sequence to

introduce both the alkyl chloride and vinyl quaternary center, an installation of the isothiocyanate. Our progress toward the synthesis of *N*-methylwelwitindolinone B isothiocyanate (**2**) represents a concise and novel entry into this family of alkaloids.

## ■ ASSOCIATED CONTENT

### ■ Supporting Information

Experimental details and procedures, compound characterization data, copies of  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

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