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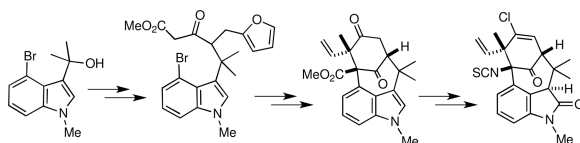
Formal Syntheses of Naturally Occurring Welwitindolinones

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Abstract



The formal syntheses of *N*-methylwelwitindolinone C isothiocyanate, *N*-methylwelwitindolinone C isonitrile, *N*-methylwelwitindolinone D isonitrile, 3-hydroxy-*N*-methylwelwitindolinone C isothiocyanate, and 3-hydroxy-*N*-methylwelwitindolinone C isonitrile is reported. The synthesis features several novel processes, including a Lewis acid mediated coupling between a benzylic-type heteroaromatic alcohol and a highly functionalized silyl ketene acetal, an intramolecular enolate arylation, and a regioselective, Pd(0)-catalyzed π -allylic cyclization of a γ -benzoyloxy enone moiety that is revealed by unmasking a furan ring.

Several novel indole alkaloids, including *N*-methylwelwitindolinone C isothiocyanate (**1**) and *N*-methylwelwitindolinone C isonitrile (**2**), were isolated by Moore and coworkers from the extracts of the blue-green cyanobacteria *Hapalosiphon wetwitschii* and *Westiella intracta* in 1994 (Figure 1).¹ These compounds, which were collectively named welwitindolinones and possess a unique bicyclo[4.3.1]decane ring system, were isolated together with the related fisherindoles and hapalindoles, and a putative biogenetic relationship among these alkaloids was proposed.¹ The related alkaloids 3-hydroxy-*N*-methylwelwitindolinone C isothiocyanate (**3**), 3-hydroxy-*N*-methylwelwitindolinone C isonitrile (**4**), and *N*-methylwelwitindolinone D isonitrile (**5**) with the same skeletal framework were later isolated from the cyanophytes *Fischerella muscicola* and *Fischerella major*.² These natural products exhibit a number of useful biological properties, including antifungal and larvicidal activities, microtubule depolymerization, and the ability to reverse P-glycoprotein-mediated multidrug drug resistance (MDR) in human cancer cells.³

Owing to their novel structures and exciting biological activities, the welwitindolinone family of natural products has captured the attention of many in the synthetic community, and these efforts have been chronicled in numerous publications over the past 15 years.⁴ Despite these extensive efforts, **1**,^{5,6} **2**,^{6,7} **3**,^{6,7} **4**,^{6,7} and **5**⁸ succumbed to total synthesis only very recently. We now report the details of some of our work in the area that has culminated in the formal syntheses of the naturally occurring welwitindolinones **1–5**.

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Supporting Information Available: Experimental procedures and ¹H NMR spectra for all new compounds, plus CIF files representing X-ray coordinates for compound **6** are included. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Our approach to the welwitindolinones **1–5** is outlined in retrosynthetic format in Scheme 1 and features refunctionalization of the advanced common intermediate **6**, which is accessed by the stereoselective methylation of the dienolate derived from **7**. We envisioned that the tetracycle **7** could be formed via a novel allylic alkylation of enone **8**. Although there are a plethora of examples of π -allylic alkylations,⁹ we are aware of no precedent for a Pd(0)-catalyzed π -allylic alkylation of a γ -acyloxy enone moiety as found in **8** that proceeds alpha to the carbonyl group. This construction would thus represent a novel advance that could prove to be of broader utility. The synthesis of **8** from **9** features formation of the tricyclic core of the welwitindolinones by an enolate arylation, which is preceded in our earlier work in the area,^{4v} and the oxidative unmasking of a furan ring to reveal the latent γ -acyloxy enone subunit. Access to **9** then requires trapping of the carbocation generated from the known alcohol **11**^{4v} with the π -nucleophile **10** via a vinylogous Mannich-like reaction¹⁰ utilizing methodology that we previously developed specifically for this bond forming step.¹¹

The first task required the synthesis of the silyl ketene acetal **10**. In the event, γ -alkylation of the dianion of methyl acetoacetate (**12**)¹² with furfuryl chloride (**13**)¹³ furnished ketoester **14** (Scheme 2). Subsequent deprotonation of **14** with NaHMDS followed by trapping with TMSCl gave **10** as a single isomer,¹⁴ which was used directly without purification.

The methyl ketone **15**, which was prepared from commercially available 4-bromoindole in two steps,^{4v} was treated with methylmagnesium bromide to give the somewhat labile alcohol **11**, which was treated immediately with silyl ketene acetal **10** in the presence of TMSOTf to deliver ketoester **9** as a mixture (ca 4:1) of keto and enol tautomers in 60% yield over two steps. (Scheme 3). Construction of the seven-membered carbocyclic ring was then achieved to give **16** in 89% yield via a Pd(0)-catalyzed intramolecular enolate arylation that was optimally promoted with PEPPSI-IPr¹⁵ in the presence of NaO*t*-Bu. Initial attempts to selectively oxidize the furan ring in **16** were unsuccessful because the enol moiety in **16** cyclized onto the intermediate unsaturated keto aldehyde, thus leading to unwanted byproducts. This troublesome side reaction was avoided simply by protecting **16** as its *tert*-butyldimethylsilyl enol ether **17**. In practice, the enolate arylation and enol protection steps were performed without purification of the intermediate **16**.

The selective oxidative cleavage of the furan moiety of **17** proved to be considerably more challenging than originally anticipated, primarily because of competing halogenation of the indole ring. Numerous reagents and conditions were screened. Br₂ and dibromohydantoin in aqueous solvents gave low yields of **18** along with significant amounts of overbrominated products in which bromine atoms had been introduced onto the indole ring. Use of *N*-chlorosuccinimide (NCS) in aqueous solvents led only to chlorination of the furan and indole rings; no aldehyde was detected in the reaction mixtures. MeReO₃/urea hydrogen peroxide oxidized the indole moiety while leaving the furan ring intact.¹⁶ Dimethyldioxirane (DMDO) and magnesium monoperoxyphthalate (MMPP) gave mixtures of products, whereas use of singlet oxygen produced the *Z*-isomer of **18** in only about 20% yield.

We eventually discovered that treating **17** with *N*-bromosuccinimide (NBS) in aqueous DMF gave aldehyde **18** in 34% yield, together with 7% of a brominated derivative of **18** and 6% of a brominated derivative of **17**. Selective reduction of the aldehyde moiety in **18** was initially somewhat problematic because mixtures of 1,2- and 1,4-reduction products were formed. However, we discovered that *tert*-BuNH₂BH₃¹⁷ reduced **18** to give alcohol **19** in 82% yield, and no overreduction of the ketone moiety was observed. *O*-Benzoylation of alcohol **19** with BzCl gave **20**, thereby setting the stage for the pivotal intramolecular π -allylic alkylation. Although the acetate analog of **20** was also prepared, it was found to be less stable and gave lower yields in the cyclization.

Deprotection of the silyl enol ether moiety in **20** with TBAF provided the enol **21**, which was treated directly with $\text{Bu}_3\text{SnOMe}^{18}$ and Pd_2dba_3 in the presence of trifurylphosphine to deliver a mixture (5.8:1:3.5) of enones **22** and **23** and vinyl ketone **7** (Scheme 4). When this mixture of **22**, **23**, and **7** was deprotonated with freshly prepared NaHMDS under equilibrating conditions, the dienolate thus generated was methylated with MeI to furnish **6** as a single diastereomer. The structure of **6** was unequivocally established by X-ray crystallography. At this stage, the entire carbon skeleton of the welwitindolinones **1–5** had been assembled, but several functional group manipulations were needed.

The primary challenge at this juncture was the conversion of the ketone functional group into the vinyl chloride **24**, and a number of one-step methods are known. However, in a number of preliminary experiments, we found that treating ketone **6** with PCl_5 ,¹⁹ WCl_6 ,²⁰ $\text{PPh}_3/\text{CCl}_4$,²¹ $\text{P}(\text{OPh})_3/\text{Cl}_2$,²² and $\text{Sc}(\text{OTf})_3/\text{AcCl}$ ²³ under a variety of established conditions and modifications thereof did not furnish any of the desired vinyl chloride **24**. Other protocols for transforming ketones into vinyl chlorides were also examined. For example, the reaction of hydrazones with NCS is known to generate vinyl chlorides.²⁴ Initial efforts to prepare the hydrazone of **6** led solely to extensive reduction of the pendant vinyl group, which presumably occurred because dimide was generated *in situ*. However, even when **6** was treated with hydrazine under rigorous exclusion of oxygen and trace metals, no hydrazone formation was observed, even under forcing conditions that led to the formation of uncharacterizable mixtures. Because this protocol was used successfully by Rawal to prepare the vinyl chloride of a closely related ketone, additional work is perhaps indicated.⁶ The ketone **6** was also converted into its vinyl triflate by sequential reaction with LiHMDS and Comins' reagent, but preliminary attempts to convert this triflate to a vinyl stannane following a protocol used by Garg⁵ for a related substrate were unsuccessful. Rawal observed an unusual rearrangement for a closely related enol triflate having a bridgehead aldehyde instead of an ester,^{4z} although we observed no such reaction.

We continue to explore methods to effect the conversion of ketone **6** into the vinyl chloride **24** in order to complete a total synthesis of *N*-methylwelwitindolinone C isothiocyanate (**1**). However, we decided to exploit an opportunity to complete the formal syntheses of the welwitindolinones **1–5** by intercepting a pivotal intermediate that Rawal has converted into these natural products. In the event, global reduction of **6** with LiAlH_4 gave an intermediate triol that underwent facile oxidation with Dess-Martin periodinane to furnish aldehyde **25** in 89% yield over two steps (Scheme 5). Spectral data (^1H and ^{13}C NMR) for the synthetic **25** thus obtained are consistent with those reported.⁸ Inasmuch as Rawal and coworkers have converted **25** into welwitindolinones **1–5**,^{6,8} its preparation by the route outlined in this account constitutes a formal synthesis of these alkaloids.

In summary, the formal syntheses of welwitindolinones **1–5** were successfully completed by the independent synthesis of the aldehyde **25**, a key intermediate in Rawal's syntheses of these alkaloids.^{6,8} The synthesis features a number of interesting steps. The first of these is a Lewis acid mediated coupling that involves a variant of a vinylogous Mannich reaction in which a benzylic-type carbocation is trapped by a highly functionalized π -nucleophile. Other highlights include an intramolecular enolate arylation to form a seven-membered ring and a novel, regioselective π -allylic alkylation of a γ -acyloxy enone moiety to construct the tetracyclic core of the welwitindolinones.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

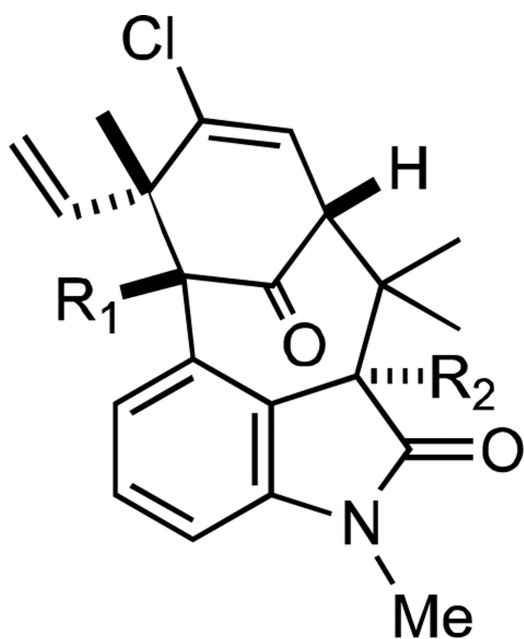
Acknowledgments

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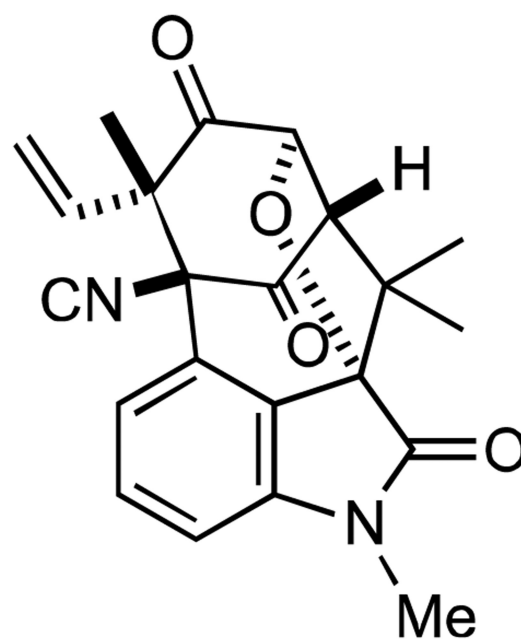
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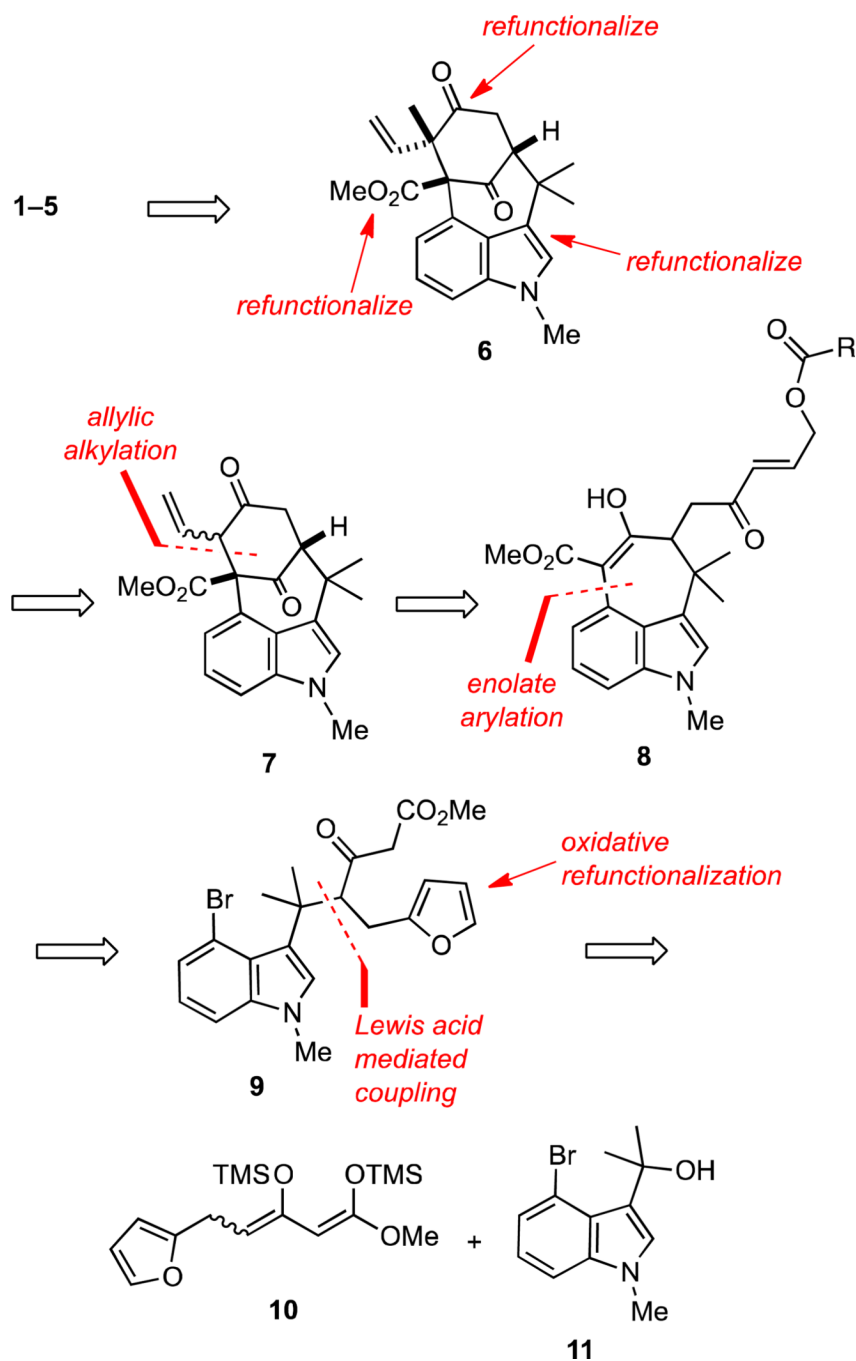


- 1:** $R_1 = \text{NCS}$, $R_2 = \text{H}$
2: $R_1 = \text{NC}$, $R_2 = \text{H}$
3: $R_1 = \text{NCS}$, $R_2 = \text{OH}$
4: $R_1 = \text{NC}$, $R_2 = \text{OH}$

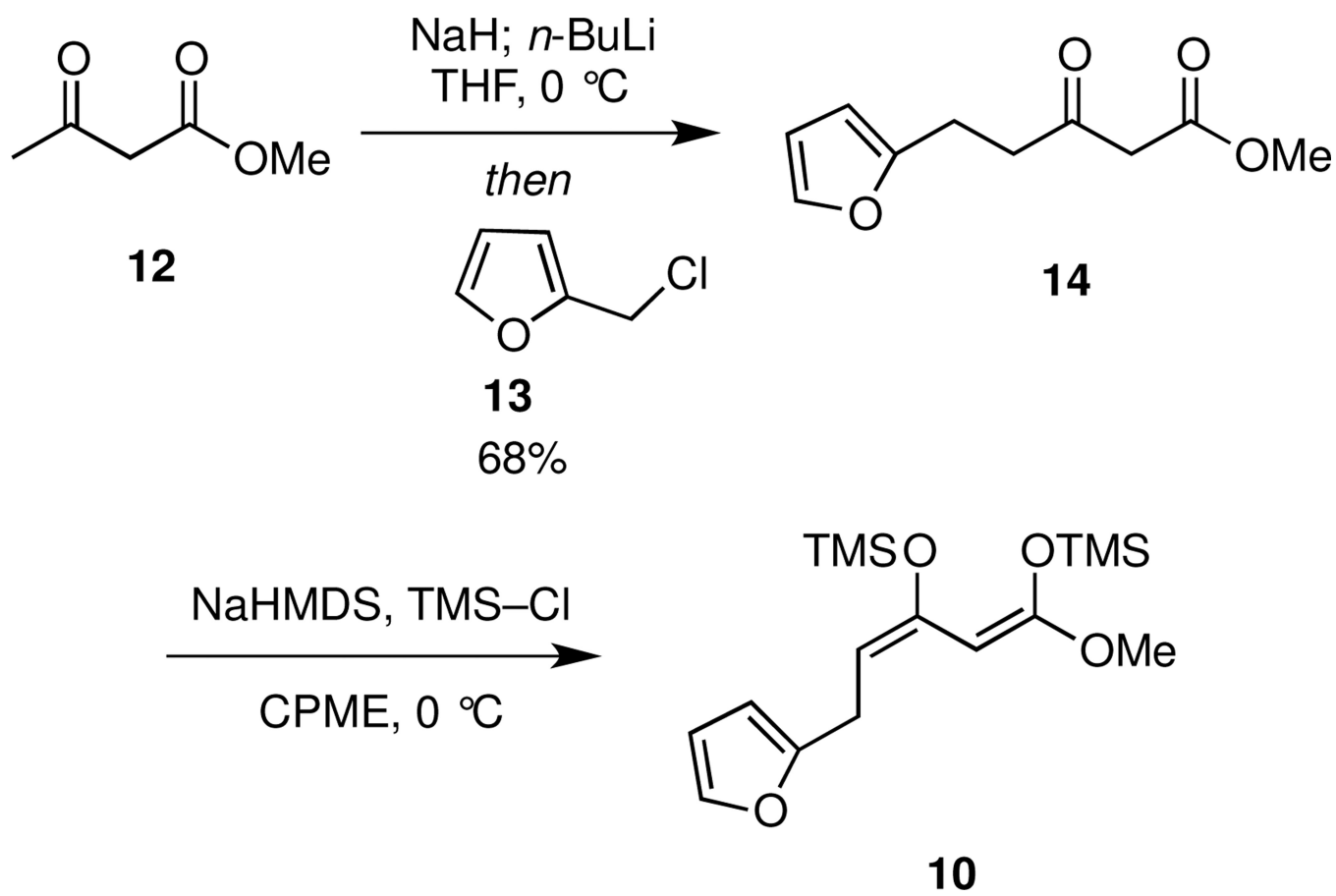


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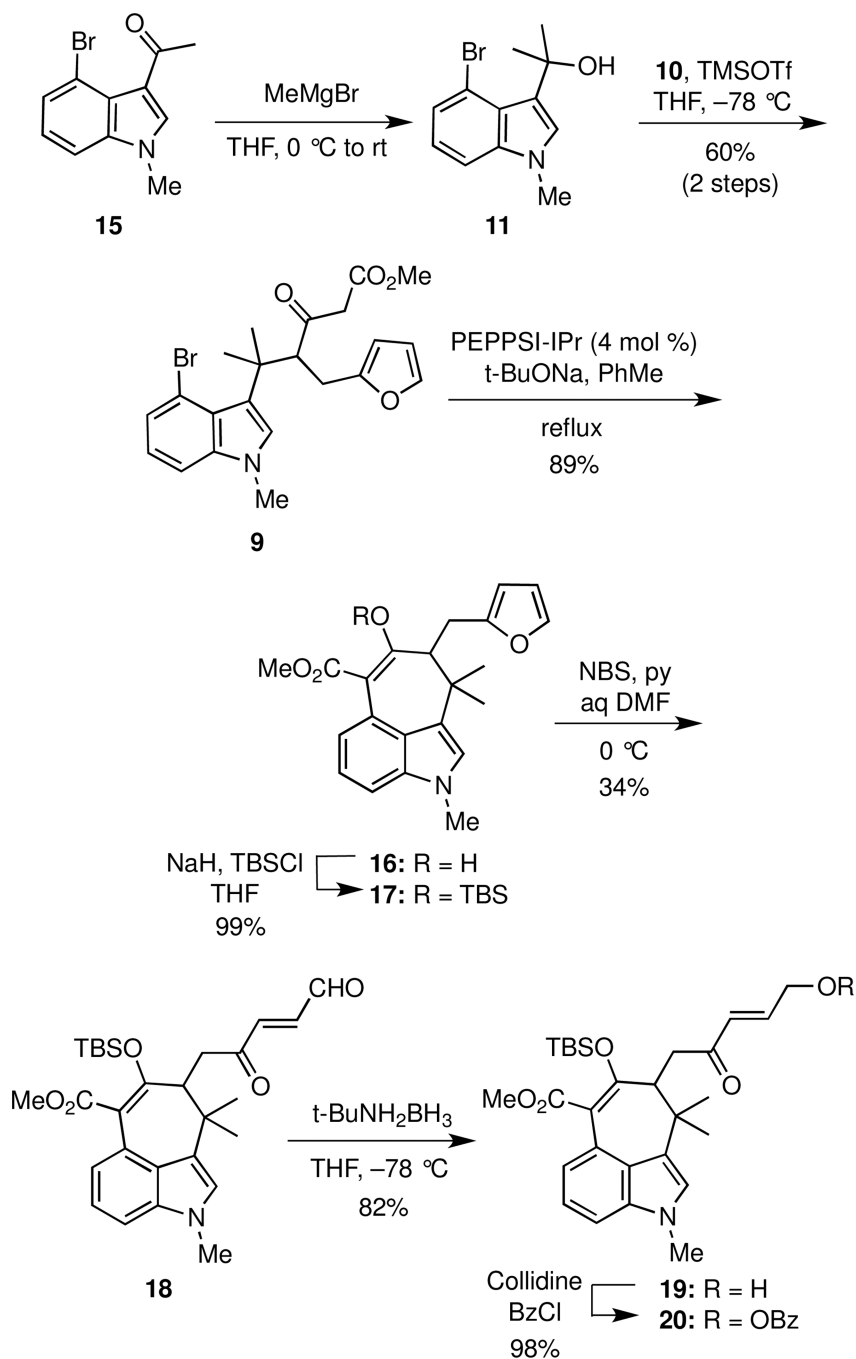
Figure 1.
Representative welwitindolinone alkaloids



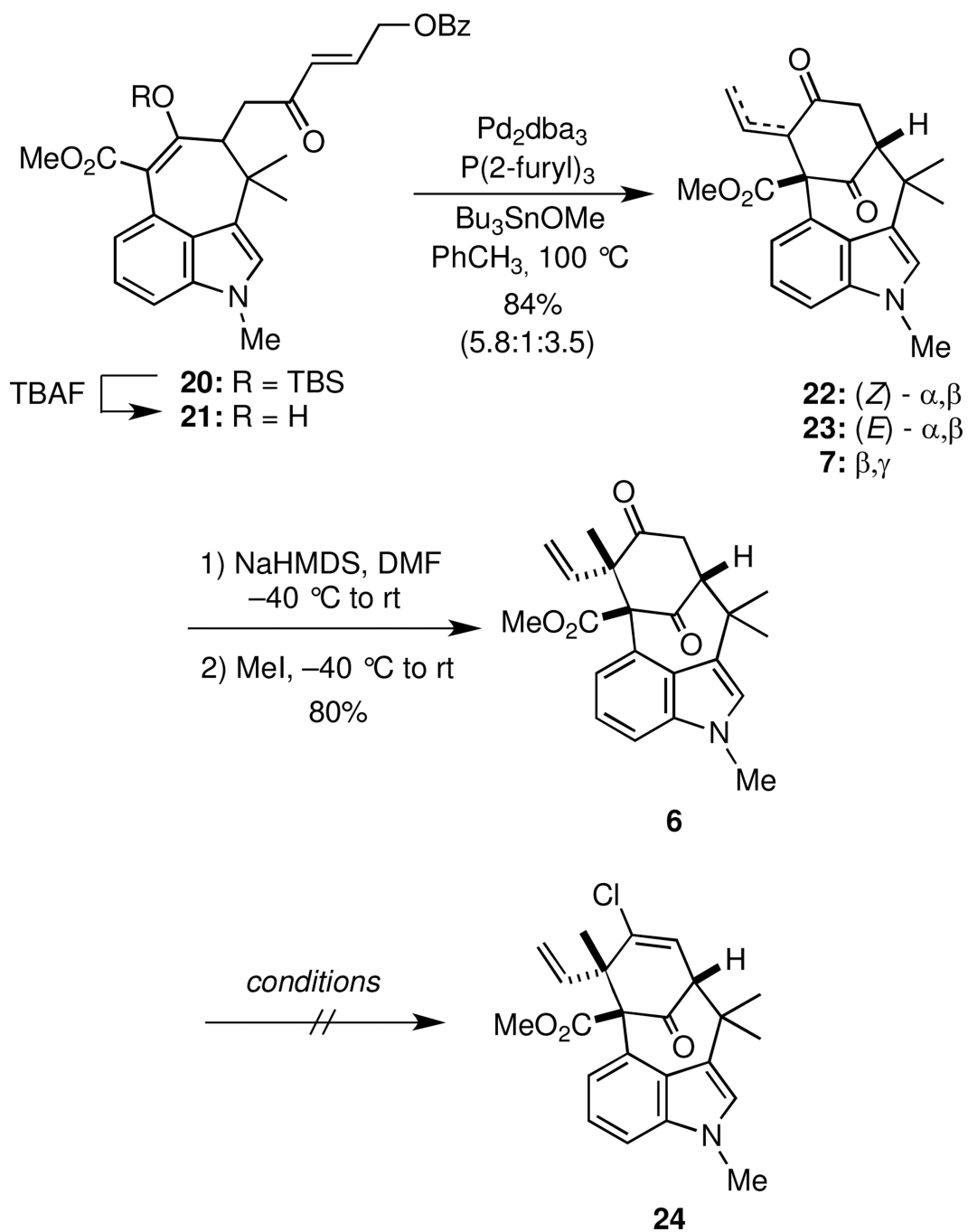
Scheme 1.
Retrosynthetic approach to welwitindolinone alkaloids



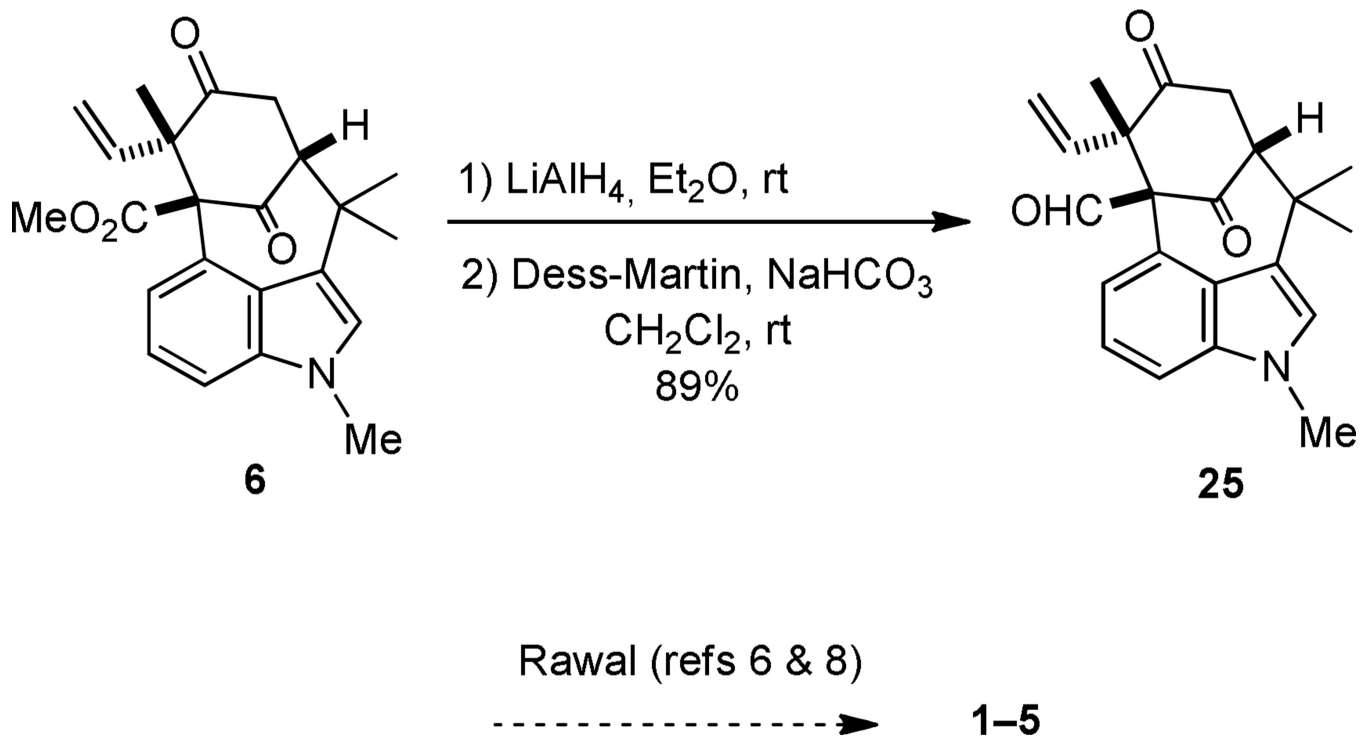
Scheme 2.
Synthesis silyl ketene acetal **10**



Scheme 3.
Synthesis of benzoate **20**



Scheme 4.
Side chain elaboration



Scheme 5.
Completion of Formal Synthesis