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Total Synthesis of (–)-*N*-Methylwelwitindolinone C Isothiocyanate

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Abstract

We report the first total synthesis of (–)-*N*-methylwelwitindolinone C isothiocyanate. Our route features a number of key transformations, including an indolyne cyclization to assemble the [4.3.1]-bicyclic scaffold, as well as a late-stage intramolecular nitrene insertion to functionalize the C11 bridgehead carbon en route to the natural product.

The welwitindolinones are a unique class of natural products isolated from the blue-green algae *Hapalosiphon welwitschii* and *Westiella intricata*.[1] Ten welwitindolinones have been identified to date, nine of which possess [4.3.1]-bicyclic cores (e.g., **1**–**3**, Figure 1).[2] Although compact in size, each of these natural products contains a dense array of functionality that has plagued synthetic efforts for nearly two decades. To date, more than ten laboratories have reported progress toward the bicyclic welwitindolinones.[3,4] Whereas these exhaustive efforts have resulted in several elegant methods for bicycle generation, completion of these targets has remained a formidable challenge. In fact, the only total synthesis of a [4.3.1]-bicyclic welwitindolinone was recently achieved by Rawal and co-workers, with their breakthrough synthesis of (±)−**3** in 2011.[5]

With the aim of synthesizing alkaloids **1**–**3** and other family members, we selected **1** as our initial synthetic target. Of note, welwitindolinone **1** was uniquely found to reverse P-glycoprotein-mediated multiple drug resistance (MDR) to a variety of anti-cancer drugs in human cancer cell lines, and is therefore a promising lead for the treatment of drug resistant tumors.[6] The densely functionalized bicyclic framework of **1** presents numerous synthetic challenges, including a 3,4-disubstituted oxindole, a heavily substituted cyclohexyl ring, and a bridgehead isothiocyanate substituent at C11. In this communication, we report the first total synthesis of (–)-*N*-methylwelwitindolinone C isothiocyanate (**1**).

Retrosynthetically, it was envisioned that **1** would be derived from bicycle **4** through late-stage functionalization of the C11 bridgehead position (Scheme 1). In turn, intermediate **4** would arise from indole precursor **5** by introduction of the vinyl chloride and oxindole moieties. In the key complexity generating step, the [4.3.1]-bicycle would be fashioned through intramolecular addition of an enolate onto an in situ-generated “indolyne” species (see transition structure **6**).[7] The use of an indolyne intermediate[8,9] was considered advantageous as the high reactivity of the aryne would permit the assembly of the congested C4–C11 bond linkage, where a tertiary center would be introduced adjacent to the C12 quaternary stereocenter. Of note, the indolyne would be inherently electrophilic, representing an uncommon umpolung of the indole’s typical reactivity. Bromoindole **7** was

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Supporting Information Available. Detailed experimental procedures and compound characterization data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

thought to be a suitable precursor to the desired indolyne via the classic dehydrohalogenation method for aryne generation. Finally, cyclohexyl derivative **8** and indole **9** were identified as suitable starting fragments.

Our synthesis commenced with the concise preparation of the key [4.3.1]-bicycle (Scheme 2). (*S*)-Carvone (**10**) was elaborated to enone **11** using the robust five step procedure reported by Natsume in the enantiomeric series.[10] Subsequent pivalate cleavage, followed by I_2-promoted addition of bromoindole **9**,[11] furnished adduct **12** in 54% yield over two steps.[12] TBS-protection of **12** provided silylether **13**, which in turn was employed in the critical indolyne cyclization. To our delight, treatment of **13** with $NaNH_2$ and *t*-BuOH in THF at ambient temperatures[3p,13] led to indolyne adducts **14** and **15** in a combined 46% yield (2.5: 1 ratio).[14,15] Although *O*-arylated product **15** was observed,[16] the major product **14** possesses the desired [4.3.1]-bicyclic framework of the natural product and is available in gram quantities.[17] Moreover, it was believed that bicycle **14** was suitably functionalized to allow for the ultimate completion of the natural product synthesis.

Having assembled the bicyclic framework of the natural product, we focused efforts on introduction of the vinyl chloride and oxindole moieties (Scheme 3). Desilylation of **14**, followed by Dess–Martin oxidation, smoothly furnished diketone **16**. Subsequently, a sequence involving triflation and Pd-catalyzed stannylation provided vinyl stannane **17**.[18] Exposure of **17** to $CuCl_2$ in dioxane afforded vinyl chloride **18**.[19] To arrive at the necessary oxindole, a two-step procedure involving sequential C2 bromination and hydrolysis was employed to deliver late-stage intermediate **4**.[7]

With intermediate **4** lacking only the isothiocyanate substituent, we turned our attention to functionalization of the sterically congested C11 bridgehead position.[20] Unfortunately, attempts to substitute C11 through intermolecular processes were unsuccessful.[21] As a workaround, we postulated that an intramolecular nitrene C–H insertion might be more fruitful.[22,23] Ketone reduction of **4** proceeded efficiently using *i*-Bu_2AlH to furnish a secondary alcohol intermediate as a single diastereomer (Scheme 4). Subsequent carbamoylation furnished **19**,[23] the key substrate for the critical C–H insertion reaction. The cyclization of carbamate **19** was attempted using a variety of reaction conditions that had previously been used to construct 5-membered oxazolidinones fused to cyclohexyl rings.[24] Although use of Rh catalysis furnished ketone **4** rather than the desired product **20**,[25] Ag catalysis[24b,c] was found to be more effective. Upon treatment of **19** with AgOTf, bathophenanthroline, and $PhI(OAc)_2$ in CH_3CN at elevated temperatures, the desired nitrene insertion took place to deliver oxazolidinone **20** as the major product. Ketone **4** was also recovered, and could be recycled through our synthetic route. Nonetheless, hydrolysis of **20** followed by IBX oxidation generated the penultimate intermediate **21**. With aminoketone **21** in hand, final introduction of the isothiocyanate[3m,26] furnished **1**. Spectral data for synthetic **1** was identical in all respects to that reported for the natural product.[1a,27]

In summary, we have achieved the first total synthesis of *N*-methylwelwitindolinone C isothiocyanate (**1**). Our enantio-specific route proceeds in 17 steps from known carvone derivative **11** and features a number of key transformations, including: (a) an indolyne cyclization to assemble the [4.3.1]-bicycle, (b) late-stage introduction of the vinyl chloride and oxindole moieties, and (c) a nitrene insertion reaction to functionalize the sterically congested C11 bridgehead position. Our synthesis of (–)-(**1**) validates the use of indolynes as intermediates in complex molecule synthesis and provides a promising entryway to the other [4.3.1]-bicyclic welwitindolinones.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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15. The remaining balance of mass in the indolyne cyclization is largely attributed to aminoindole products, which presumably form by intermolecular addition of $^{-}NH_2$ to the indolyne intermediate. Attempts to suppress this undesired reaction pathway have been unsuccessful.
16. *O*-arylated product 15 is often isolated with small amounts of the isomeric tetrasubstituted olefin.
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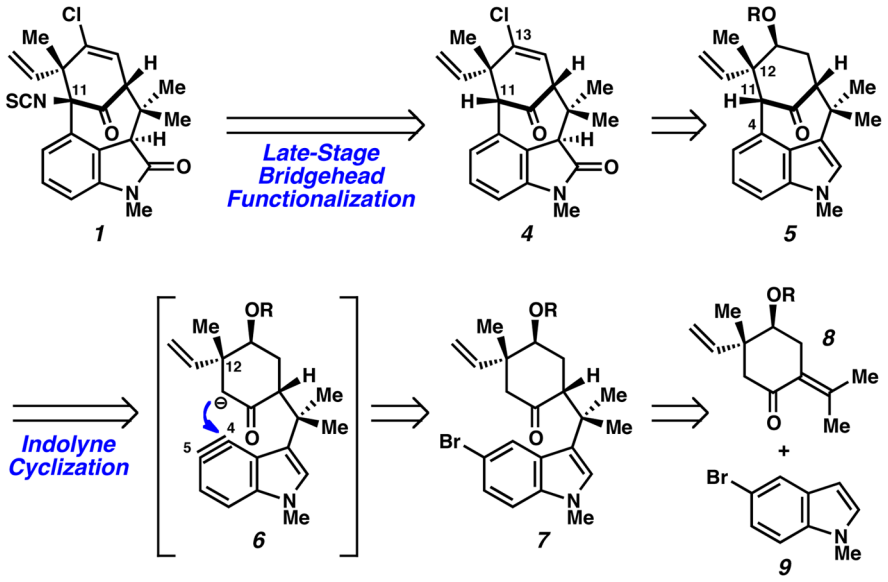
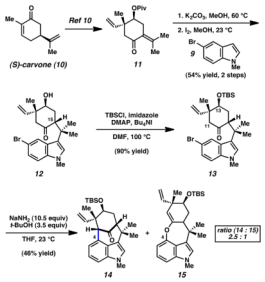
27. A sample of natural 1 was not available for direct comparison.

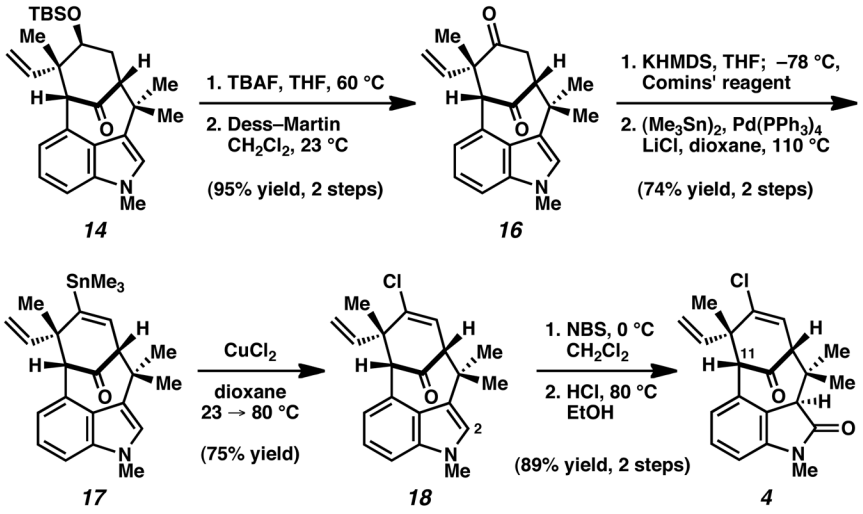
Figure 1.
[4.3.1]-Bicyclic welwitindolinones **1–3**.



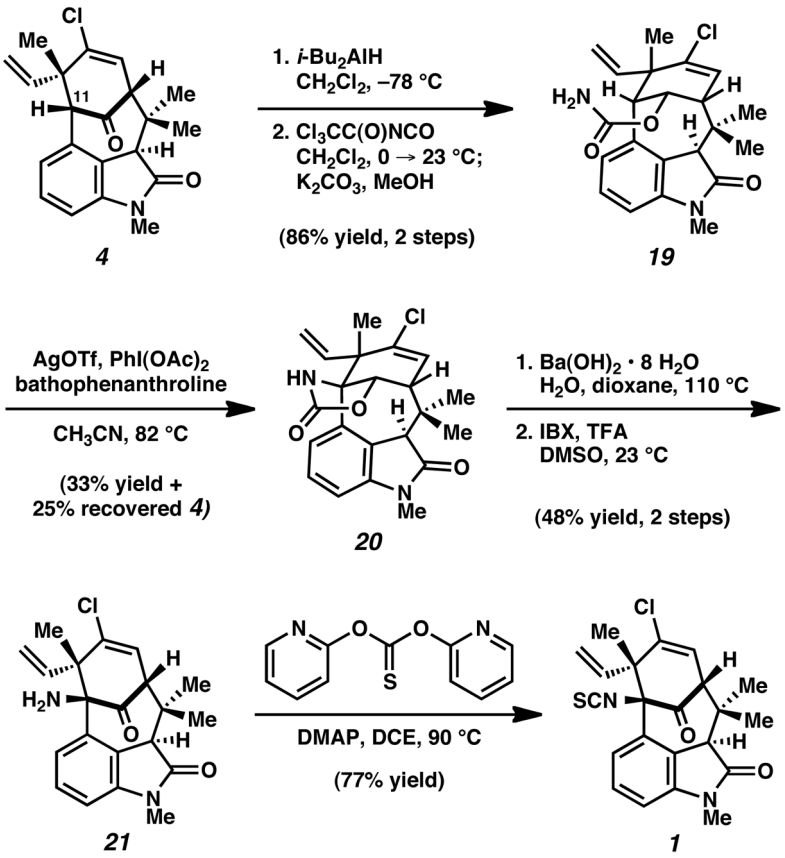
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 4.