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

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Supporting Information

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 10 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 anticancer 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 thought to be a suitable

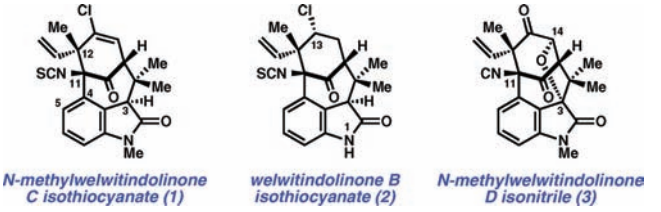
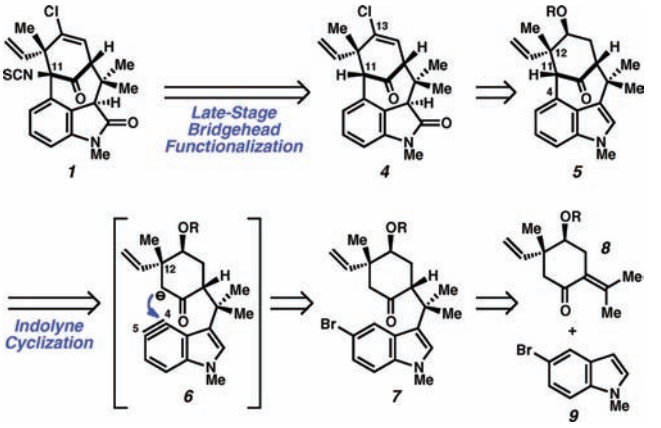


Figure 1. [4.3.1]-Bicyclic welwitindolinones **1**−**3**.

Scheme 1



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 silyl ether **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.

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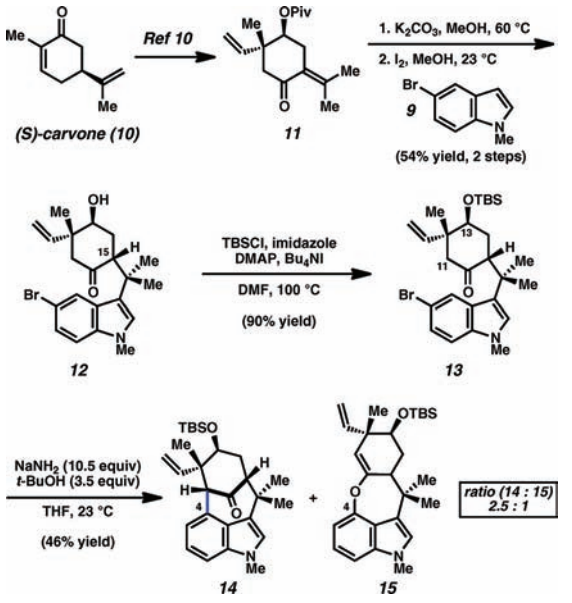
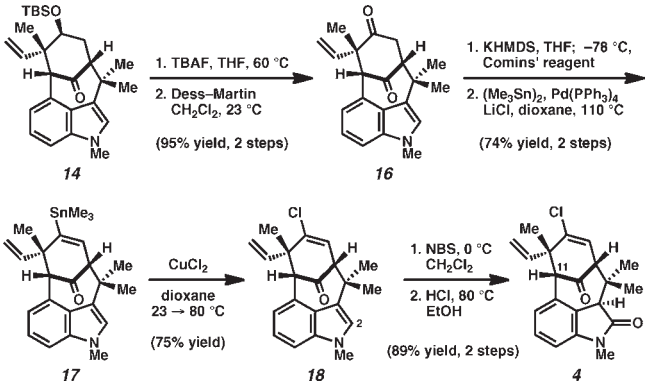
Scheme 2



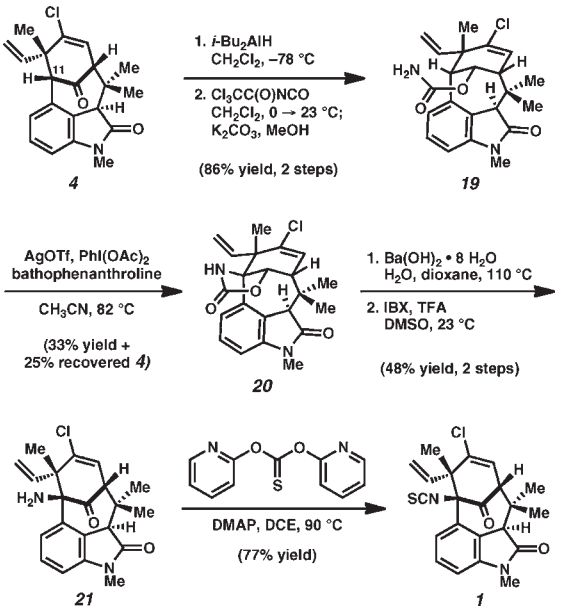
Scheme 3



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

Scheme 4



been used to construct five-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** were identical in all respects to those reported for the natural product.[1a,27]

In summary, we have achieved the first total synthesis of *N*-methylwelwitindolinone C isothiocyanate (**1**). Our enantiospecific 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.

■ ASSOCIATED CONTENT

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

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(14) Variations in reaction conditions (e.g., temperature, stoichiometry, counterion, etc.) did not lead to improvements in the conversion of **13** to **14**.

(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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