

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*.<sup>1</sup> Ten welwitindolinones have been identified to date, nine of which possess [4.3.1]-bicyclic cores (e.g., 1–3, Figure 1).<sup>2</sup> 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.<sup>3,4</sup> 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.<sup>5</sup>

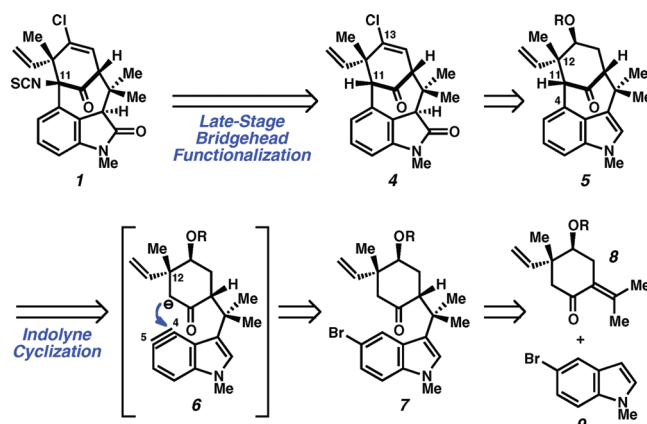
With the aim of synthesizing alkaloids 1–3 and other family members, we selected 1 as our initial synthetic target. Of note, welwitindolinone 1 was uniquely found to reverse P-glycoprotein-mediated multiple drug resistance (MDR) to a variety of anti-cancer drugs in human cancer cell lines and is therefore a promising lead for the treatment of drug-resistant tumors.<sup>6</sup> 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).<sup>7</sup> The use of an indolyne intermediate<sup>8,9</sup> 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



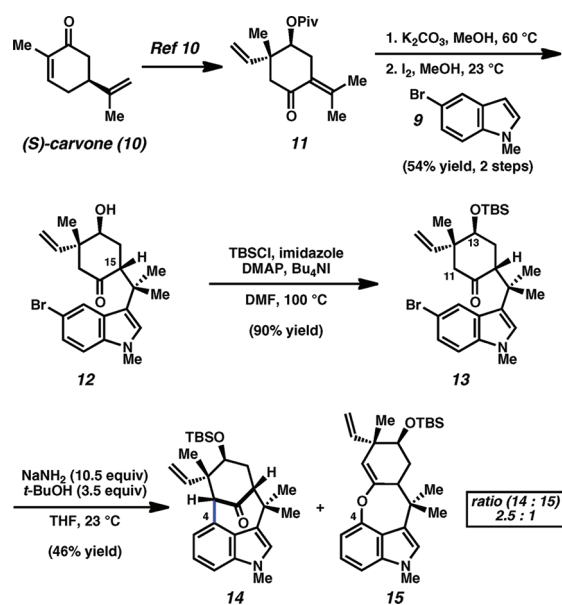
precursor to the desired indolyne via the classic dehydrohalogenation method for aryne generation. Finally, cyclohexyl derivative 8 and indole 9 were identified as suitable starting fragments.

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.<sup>10</sup> Subsequent pivalate cleavage, followed by I<sub>2</sub>-promoted addition of bromoindole 9,<sup>11</sup> furnished adduct 12 in 54% yield over two steps.<sup>12</sup> 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<sub>2</sub> and *t*-BuOH in THF at ambient temperatures<sup>3b,13</sup> led to indolyne adducts 14 and 15 in a combined 46% yield (2.5:1 ratio).<sup>14,15</sup> Although *O*-arylated product 15 was observed,<sup>16</sup> the major product 14 possesses the desired [4.3.1]-bicyclic framework of the natural product and is available in gram quantities.<sup>17</sup> Moreover, it was believed that bicycle 14 was suitably functionalized to allow for the ultimate completion of the natural product synthesis.

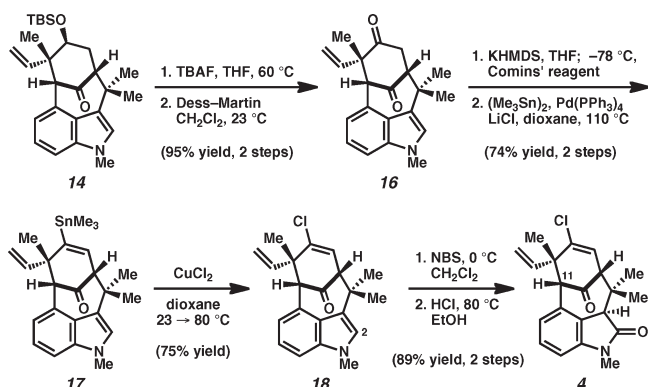
Received: July 14, 2011

Published: August 07, 2011

Scheme 2



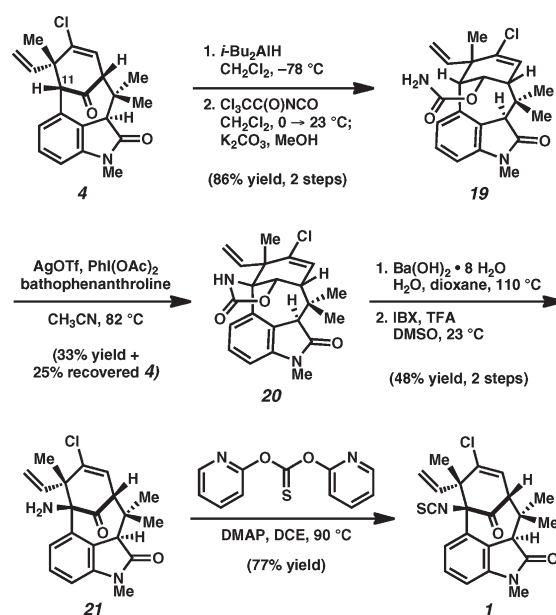
Scheme 3



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.<sup>18</sup> Exposure of 17 to  $CuCl_2$  in dioxane afforded vinyl chloride 18.<sup>19</sup> To arrive at the necessary oxindole, a two-step procedure involving sequential C2 bromination and hydrolysis was employed to deliver late-stage intermediate 4.<sup>7</sup>

With intermediate 4 lacking only the isothiocyanate substituent, we turned our attention to functionalization of the sterically congested C11 bridgehead position.<sup>20</sup> Unfortunately, attempts to substitute C11 through intermolecular processes were unsuccessful.<sup>21</sup> As a workaround, we postulated that an intramolecular nitrene C–H insertion might be more fruitful.<sup>22,23</sup> Ketone reduction of 4 proceeded efficiently using  $i-Bu_2AlH$  to furnish a secondary alcohol intermediate as a single diastereomer (Scheme 4). Subsequent carbamylation furnished 19,<sup>23</sup> 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.<sup>24</sup> Although use of Rh catalysis furnished ketone 4 rather than the desired product 20,<sup>25</sup> Ag catalysis<sup>24b,c</sup> was found to be more effective. Upon treatment of 19 with AgOTf, bathophenanthroline, and PhI(OAc)<sub>2</sub> 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<sup>3m,26</sup> furnished 1. Spectral data for synthetic 1 were identical in all respects to those reported for the natural product.<sup>1a,27</sup>

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 indolene 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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## ■ ACKNOWLEDGMENT

The authors are grateful to the NIH-NIGMS (R01 GM090007), Boehringer Ingelheim, DuPont, Eli Lilly, Amgen, the University of

California, Los Angeles, the ACS Organic Division (fellowship to K.W.Q.), Bristol-Myers Squibb (fellowship to K.W.Q.), and the Foote Family (fellowships to A.D.H. and K.W.Q.) for financial support. We thank the Garcia-Garibay laboratory (UCLA) for access to instrumentation, Prof. Justin Du Bois for helpful discussions, Dr. John Greaves (UC Irvine) for mass spectra, and Xia Tian, Haoxuan Wang, and Sonam Kumar for experimental assistance.

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