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Total Synthesis of (−)-*N*-Methylwelwitindolinone B Isothiocyanate via a Chlorinative Oxabicycle Ring-Opening Strategy

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Supporting Information

ABSTRACT: The first total synthesis of *N*-methylwelwitindolinone B isothiocyanate is reported. The route features several key steps, including a regio- and diastereoselective chlorinative oxabicycle ring-opening reaction to introduce the challenging alkyl chloride motif.

The total synthesis of indole alkaloids continues to be a fruitful area of scientific pursuit. One particular class of molecules that has provided an exciting arena of chemical discovery is the welwitindolinone natural products, wherein the majority of congeners contain a [4.3.1]-bicyclic core (e.g., **2**−**4**, Figure 1).[1,2] Since Moore's first isolation report in 1994,[3]

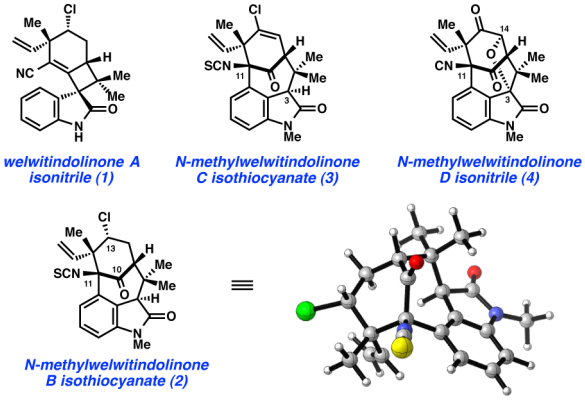


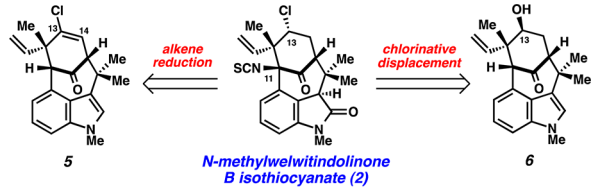
Figure 1. Welwitindolinones **1**−**4**.

roughly 25 manuscripts describing efforts toward these complex structures have appeared from many research groups worldwide.[2b,4] The majority of initially reported studies established a variety of methods for assembling the [4.3.1]-bicyclic core, and subsequent efforts have focused on completing the total syntheses. Toward this latter end, the most recent publications describe formal[5] as well as total syntheses of **3**, **4**, and C3-oxidized variants of **3**.[6,7]

Although [4.3.1]-bicyclic welwitindolinones in the C- and D-"series" have been synthesized (e.g., **3** and **4**), compounds in the B- "series" (e.g., **2**) have yet to be prepared by total synthesis.[4u,y] Structurally, **2** is quite similar to **3** with the key difference being a variation in the oxidation state at C13.[8,9] However, this seemingly simple change is deceptive, as the alkyl chloride resides on the more congested face of the [4.3.1]-bicycle, adjacent to a quaternary center,[10] and thus presents a formidable challenge with regard to synthesis. In addition to this subtle feature, the alkyl chloride in these systems is prone to undergo a variety of undesirable side reactions under basic reaction conditions.[4y,11] Herein, we describe our efforts toward (−)-**2** and the first total synthesis of this elusive natural product.

In our initial efforts, we considered several approaches to **2** that ultimately proved unsuccessful (Scheme 1). In what can be

Scheme 1. Failed Approaches toward Installation of the Alkyl Chloride



considered the most direct assault, we envisioned **2** as arising from C13−14-reduction of **5** or a related derivative. However, attempts to realize this strategy were thwarted by the facile reduction of the terminal olefin.[12] We also pursued a strategy wherein the alkyl chloride would derive from alcohol **6** by activation and chlorination with stereochemical inversion. Similar to the observations made by Rawal,[4u] we found that the proximal vinyl group underwent formal migration to C13 upon activation of the alcohol.[13] Even in the absence of the vinyl group, the chlorination is known to be difficult and only proceeds under specialized conditions,[4u] as the necessary approach of a chloride nucleophile is somewhat hampered by the steric congestion of the bicyclic scaffold.[14]

After numerous failed attempts to advance late-stage intermediates from our previous synthesis, we devised the alternative retrosynthetic plan highlighted in Scheme 2. In this revised approach, it was envisioned that **2** would arise from oxazolidinone **7** by late-stage cleavage of the carbamate and further manipulation, all in the presence of the sensitive alkyl chloride. In turn, oxazolidinone **7** would derive from nitrene insertion of carbamate **8**.[15] We have previously studied related insertion reactions for C11 functionalization of welwitindolinone scaffolds, but in all prior cases the substrates possessed the opposite stereochemical configuration at C10.[7] Thus, the attempted nitrene insertion of **8** would serve as an opportunity to probe the generality of this method for C11 functionalization. In a critical transformation, we sought to introduce the

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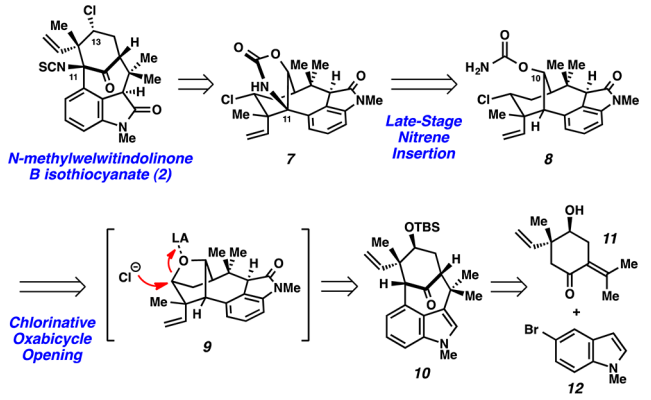
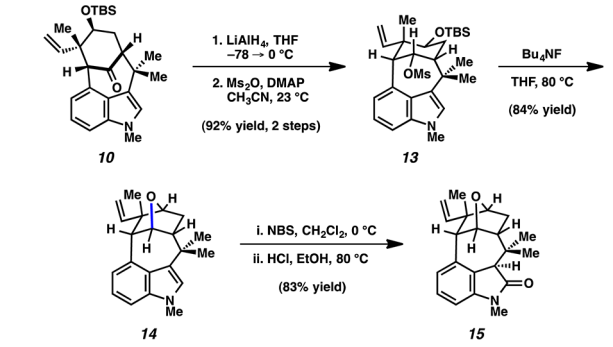
Scheme 2. Modified Retrosynthetic Plan for the Total Synthesis of (−)-2



alkyl chloride of **8** by performing a regio- and diastereoselective chlorinative ring opening of an oxabicycle-containing intermediate (see transition structure **9**). This transformation, largely inspired by Shea's seminal studies,[4y] could provide a solution to the challenge faced earlier. Namely, the necessary approach of the chloride appeared favorable, owing to the restricted conformation of the oxabicycle unit.[16] Importantly, the oxabicycle was envisioned to be readily available from indole **10**, which is accessible from enantioenriched carvone derivative **11** and indole **12** in three steps using our previously established procedure involving an indolyne cyclization.[7a,17]

To implement the plan illustrated in Scheme 2, we first targeted construction of oxabicycle **15** (Scheme 3). To this end,

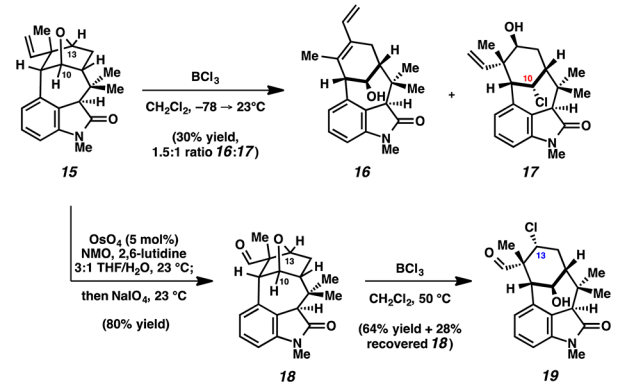
Scheme 3. Elaboration of 10 to Oxabicycle 15



ketone **10** was elaborated to mesylate **13** in two steps involving reduction with $LiAlH_4$ followed by sulfonylation. Upon treatment of **13** with Bu_4NF in THF at 80 °C, desilylation readily occurred with concomitant cyclization to afford oxabicycle **14** in 84% yield. Subsequently, a one-pot oxidation/hydrolysis protocol was used to elaborate **14** to the corresponding oxindole **15**, which was formed as a single diastereomer.

With rapid access to oxabicycle **15**, we were poised to attempt the key chlorinative ring-opening reaction (Scheme 4).[18] We surveyed several conditions that have previously been used for related transformations such as $ZnCl_2$ and acetyl chloride,[19] ethanolic HCl,[20] and $TiCl_4$.[21] Although the use of most reaction conditions led to the recovery of starting material or decomposition, treatment of **15** with BCl_3[22] led to consumption of the substrate with opening of the oxabicycle. Unfortunately, the two products obtained were **16**, which had

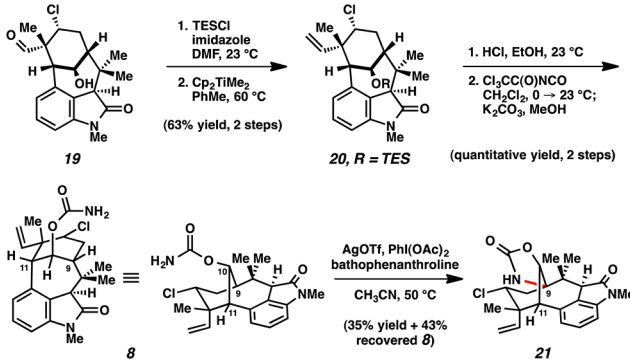
Scheme 4. Chlorinative Oxabicycle Opening Studies



undergone formal vinyl migration, and **17**, an unproductive constitutional isomer of the desired product, which forms as a result of undesired chloride attack at C10 (rather than C13). In hope of avoiding the vinyl migration, and to perturb the electronic environment at C13,[4u] alkene **15** was exposed to modified oxidative cleavage conditions,[23] which furnished aldehyde **18**. To our delight, treatment of **18** with BCl_3 in CH_2Cl_2 at 50 °C delivered the desired chlorinated product **19** in 64% yield. Of note, **19** was obtained as a single diastereomer and the analogous undesired regioisomer was not observed.[24]

Having introduced the alkyl chloride, we turned our attention to installing the C11 nitrogen substituent via the key nitrene insertion reaction (Scheme 5). The requisite

Scheme 5. Attempted Nitrene Insertion of Substrate 8



substrate for this transformation (**8**) was accessed from **19** in four steps that began with conversion to silyl ether **20** using a protection/olefination sequence.[25] Deprotection of **20** followed by carbamoylation delivered the nitrene insertion substrate **8** in quantitative yield over two steps. As mentioned above, our previous studies of related nitrene insertion reactions were performed on substrates epimeric at C10.[7] Although these prior attempts routinely delivered the desired C11-functionalized products, Ag-[26] or Rh-promoted[27] nitrene insertion reactions of **8** were regrettably found to predominantly furnish **21**, the product of nitrene insertion into the C9−H bond.[28]

To test if the formation of **21** was strictly an artifact of the stereochemical configuration, we prepared the corresponding C10 epimer of nitrene insertion substrate **8** (Scheme 6). To that end, oxidation of alcohol **19**, followed by Wittig olefination, afforded ketone **22**. Subsequent reduction of **22** with $LiAlD_4$[29] occurred with complete diastereoselectivity to furnish an alcohol intermediate, which was carbamoylated to

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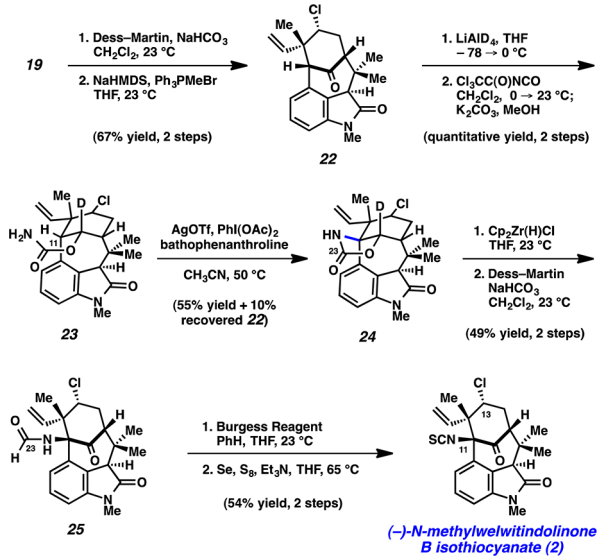
Scheme 6. Nitrene Insertion, Oxazolidinone Cleavage, and Completion of (−)-2



provide **23**. Fortunately, carbamate **23** proved to be a viable substrate for the desired nitrene insertion reaction; upon treatment of **23** with AgOTf, $PhI(OAc)_2$, and bathophenanthroline in CH_3CN at 50 °C, we obtained the C11 functionalized product **24** in 55% yield with 10% recovered **22**. The dichotomy regarding the nitrene products derived from substrates **8** and **23** underscores the subtleties often seen in late-stage manipulations in total synthesis. Moreover, the successful formation of **24** is noteworthy in that He's Ag-based nitrene insertion conditions[26] tolerate the sensitive alkyl chloride unit.

From insertion product **24**, all that remained to complete the total synthesis of **2** was cleavage of the carbamate, followed by oxidation and *N*-functionalization. Despite previously having success with carbamate hydrolysis on related compounds, we found that treatment of **24** with $Ba(OH)_2$ led to decomposition of the alkyl chloride. This led us to develop a milder means for cleaving the carbamate. Prompted by Snieckus' recent report of cleaving *N,N*-dialkylcarbamate derivatives of phenols,[30] cyclic carbamate **24** was exposed to Schwartz' reagent in THF (Scheme 6). Gratifyingly, the carbamate was cleaved selectively to give an amidoalcohol intermediate, where C23 of **24** had conveniently been retained as a formyl group on the bridgehead nitrogen. Oxidation of the alcohol intermediate delivered **25**. With the chloride still intact, dehydration with Burgess reagent and sulfurization[31] afforded (−)-*N*-methylwelwitindolinone B isothiocyanate (**2**). Analytical data for (−)-**2** were found to be identical to those of the natural material in all respects.

In summary, we have completed the first total synthesis of (−)-*N*-methylwelwitindolinone B isothiocyanate (**2**) in 15 steps from indolyne cyclization product **10**. Critical to the success of our enantiospecific route is the use of a regio- and diastereoselective chlorinative oxabicycle ring-opening reaction to introduce the challenging alkyl chloride. To complete the synthesis, a number of steps were taken, including substrate-specific installation of the C11 nitrogen substituent and oxazolidinone cleavage, all of which proceeded in the presence of the alkyl chloride motif. With our completed synthesis of (−)-**2**, all structural classes of the welwitindolinones are now accessible by synthetic chemistry.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental and compound characterization data. 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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(8) The 3D representation of **2** was obtained using B3LYP/6-31G* calculations (geometry optimization), using MacSpartan software.

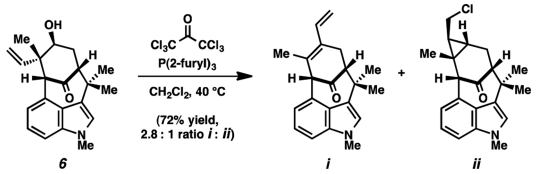
(9) Image prepared using CYLview: Legault, C. Y. *CYLview*, 1.0b; Université de Sherbrooke: Québec, Montreal, Canada, 2009; http://www.cylview.org.

(10) Related natural products, such as **1**, also bear a similar motif where an alkyl chloride resides adjacent to a quaternary center, albeit not on a [4.3.1]-bicyclic scaffold. For elegant approaches to this motif, see ref 2.

(11) Huters, A. D.; Styduhar, E. D.; Weires, N. A.; Garg, N. K. University of California, Los Angeles, CA, 2012, unpublished work.

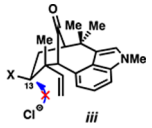
(12) In related studies, efforts to reduce the vinyl chloride in compounds lacking the terminal olefin either led to recovery of starting material or over-reduction to cyclohexyl compounds lacking the chloride.

(13) Subjection of **6** to Rawal's chlorination conditions resulted in vinyl migration and cyclopropanation products **i** and **ii**; see ref 4u.



6 *i* *ii*

(14) As seen in transition structure **iii** below, approach of the chloride is obstructed, whereas the vinyl group is poised to react at C13.



iii

(15) For a review on C–N bond forming reactions involving C(sp^3)–H bonds, see: Jeffrey, J. L.; Sarpong, R. *Chem. Sci.* **2013**, *4*, 4092.

(16) Although this strategy would not preclude the possibility of vinyl group migration, it was anticipated that the ease of chlorination would be considerably greater. As such, it was hoped that the necessary chlorinative displacement could compete with the undesired vinyl group migration.

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(18) Attempts to achieve the chlorinative ring opening of indolooxabicycle **14** resulted in undesired byproducts and decomposition.

(19) Treatment of **15** with $ZnCl_2$ and acetyl chloride resulted in the acetylated derivative of **17** in ca. 40% yield; see: Clive, D. L. J.; Sannigrahi, M.; Hisaindee, S. *J. Org. Chem.* **2001**, *66*, 954.

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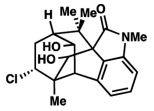
(24) Compound **iv** (single diastereomer, unassigned) commonly forms as a minor byproduct of this transformation, presumably by way of an intramolecular aldol reaction.



iv

(25) All attempts to directly olefinate aldehyde **19** were unsuccessful. Attempts to olefinate the TES ether derivative of **19** using Wittig olefination protocols led to an aldol reaction (i.e., the TES ether analog of compound **iv**; see ref 24).

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(28) Use of the sulfamate derivative of **8** under Rh-catalysis also facilitated C9 insertion.

(29) We also carried out the corresponding sequence with $LiAlH_4$, which gave the proteo derivative of carbamate **23**. When employed in the nitrene insertion reaction, we obtained a 1:1.4 ratio of the desired insertion product to ketone **22**. Consistent with our previous findings on alternate substrates, the strategic use of deuterium minimizes an undesirable competitive reaction, thus giving synthetically useful yields of the desired nitrene insertion product; see ref 7b, 7c.

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