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Total Synthesis of Oxidized Welwitindolinones and (−)-*N*-Methylwelwitindolinone C Isonitrile

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Supporting Information

ABSTRACT: We report the total synthesis of (−)-*N*-methylwelwitindolinone C isonitrile, in addition to the total syntheses of the 3-hydroxylated welwitindolinones. Our routes to these elusive natural products feature the strategic use of a deuterium kinetic isotope effect to improve the efficiency of a late-stage nitrene insertion reaction. We also provide a computational prediction for the stereochemical configuration at C3 of the hydroxylated welwitindolinones, which was confirmed by experimental studies.

Since the reports of their isolation in 1994 and 1999,[1] the welwitindolinone natural products have captivated synthetic chemists worldwide.[2] To date, nine welwitindolinones with [4.3.1]bicyclic frameworks have been discovered (e.g., **1**−**5**, Figure 1), some of which show promising activity against

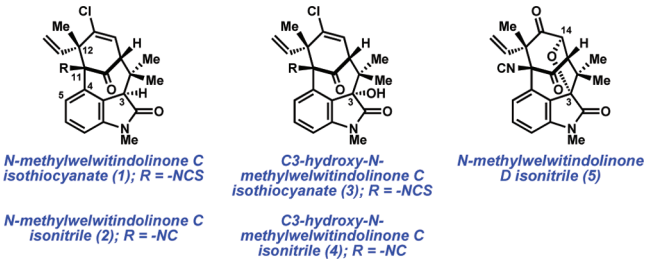


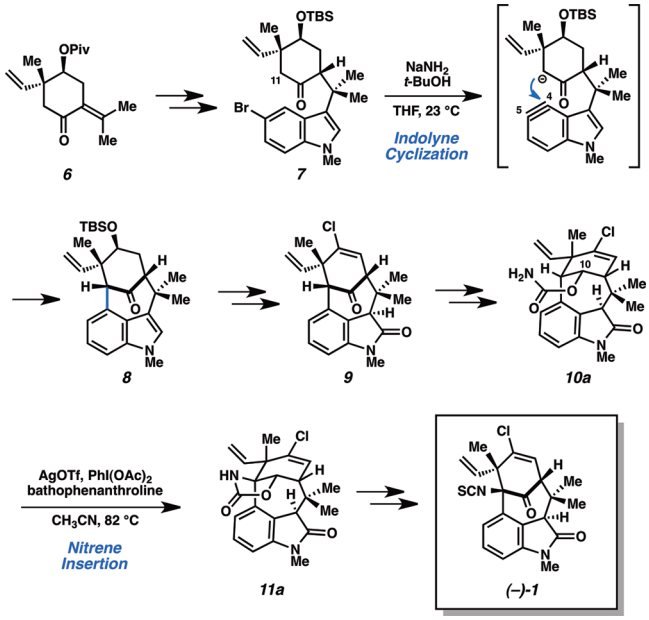
Figure 1. Welwitindolinones **1**−**5**.

drug-resistant cancer cells.[3] The dense array of functional groups that decorate the compact structure of these targets has taunted chemists for nearly two decades. More than 15 laboratories have reported progress toward these intriguing natural products, resulting in many elegant approaches to the bicyclic core.[4,5] The strategies used respectively by our laboratory and Rawal's have recently facilitated the first two syntheses of these elusive natural products.[6,7] However, syntheses of several challenging members of the welwitindolinone family of natural products have not been reported.[8]

In this Communication, we report the total syntheses of three natural products in the welwitindolinone C series: (−)-**2**, (−)-**3**, and (−)-**4**. The latter two of these targets represent the so-called "oxidized welwitindolinones", whose configuration at C3 had not been unambiguously defined. We also describe the strategic manipulation of a kinetic isotope effect to improve the efficiency of a challenging C−H activation/nitrene insertion reaction, which takes place late-stage in the total syntheses to forge a critical C−N bond.

A summary of our recent total synthesis of (−)-**1**[7] is shown in Scheme 1. Known carvone derivative **6** was elaborated to

Scheme 1



bromoindole **7** over three synthetic steps. Subsequent treatment of **7** with $NaNH_2$ and *t*-BuOH in THF facilitated an indolyne cyclization to afford **8**, which possesses the desired [4.3.1]bicycle. Bicycle **8** was elaborated to ketone **9**, which lacked only the isothiocyanate functional group. Thus, ketone **9** was readily converted to carbamate **10a**, the substrate for a critical nitrene C−H insertion reaction.[9−11] We were delighted to find that the desired C−H functionalization took place to afford **11a** upon exposure of substrate **10a** to the Ag-promoted conditions described by He.[11b,c] Insertion product **11a** was elaborated to the elusive natural product (−)-**1** over three additional transformations.

In order to facilitate syntheses of the remaining natural products in the welwitindolinone C series, we sought to first

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improve the efficiency of the late-stage nitrene insertion reaction (i.e., **10a**→**11a**, Scheme 1), which had proceeded in a modest 33% yield. It was noted that a major byproduct of the insertion step was ketone **9**, which presumably formed through the undesired insertion of the intermediate nitrene species into the C10 C−H bond.[12] We hypothesized that replacing the problematic hydrogen with deuterium would subdue the undesired insertion process, thereby favoring the desired functionalization event.[13] The deuterated substrate **10b** was readily prepared by a sequence involving reduction of ketone **9** with super deuteride, followed by carbamoylation (Figure 2).

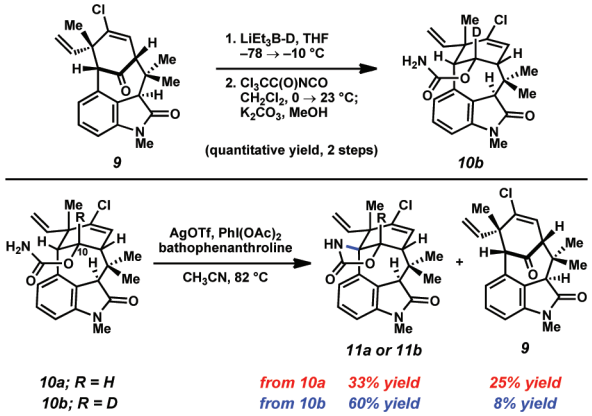
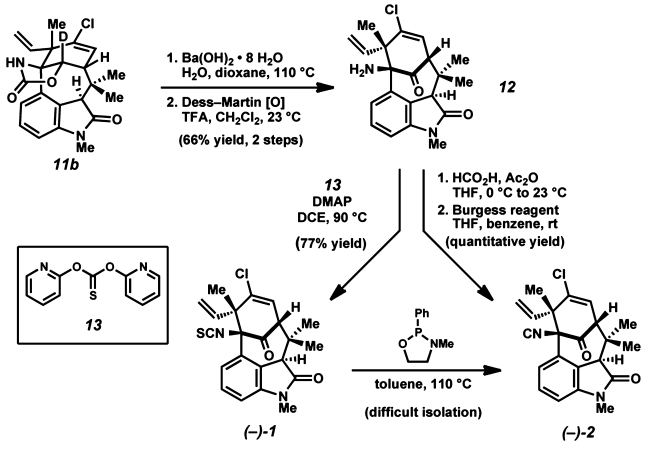


Figure 2. Nitrene insertion of substrates **10a** and **10b**.

We were delighted to find that exposure of this substrate to our optimal reaction conditions for nitrene insertion furnished the desired product **11b** in 60% yield, while the formation of ketone **9** was diminished. The strategic use of a deuterium kinetic isotope effect in total synthesis is rare,[14] and the present study marks the first use of this approach to facilitate a C−H functionalization event en route to natural products.

With improved access to a C11 *N*-functionalized product, we explored elaboration of **11b** to several welwitindolinone natural products. Hydrolysis of the carbamate, followed by Dess−Martin oxidation, proceeded smoothly to furnish aminoketone **12** (Scheme 2). Subsequent elaboration of **12** delivered *N*-

Scheme 2



methylwelwitindolinone C isothiocyanate (−)-**1**, as we have shown previously.[7] Exposure of this natural product to Rawal's desulfurization conditions provided (−)-*N*-methylwelwitindolinone isonitrile (**2**) as the major product.[6] Unfortunately, purification of the crude natural product proved difficult.[15] As a workaround, aminoketone **12** was subjected to sequential formylation[4s] and dehydration[4m] to afford the desired natural product (−)-**2** in quantitative yield.[16] Spectral data for synthetic (−)-**2** were in accord with those provided for natural (−)-**2** in the isolation report.[1a]

We next pursued total syntheses of the C3-hydroxylated welwitindolinones, the two oxidized welwitindolinones that had not been synthesized previously. Furthermore, the stereochemical configuration of these natural products at C3 had not been rigorously established spectroscopically but rather had been assigned by analogy to the non-hydroxylated welwitindolinone natural products.[17] In our first attempts toward these natural products, aminoketone **12** was treated with various bases, with the reaction vessels under standard atmospheric conditions to allow for air-oxidation. Although the corresponding C3-oxidized product was formed and could be manipulated further, low yields and irreproducibility hampered our efforts. However, direct oxidation of the non-hydroxylated natural products was found to be a more fruitful strategy (Figure 3). It

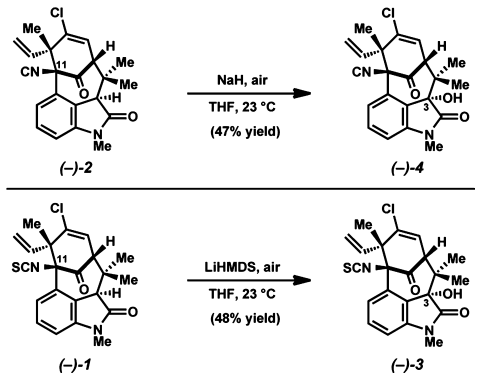


Figure 3. Total synthesis of oxidized welwitindolinones **3** and **4**.

should be noted that related aerobic oxidations of oxindoles have been reported,[18] including an impressive example in the context of the welwitindolinones.[19] Treatment of (−)-*N*-methylwelwitindolinone C isonitrile (**2**) with NaH in the presence of air provided (−)-3-hydroxy-*N*-methylwelwitindolinone C isonitrile (**4**). Similarly, oxidation of (−)-*N*-methylwelwitindolinone C isothiocyanate (**1**) delivered (−)-3-hydroxy-*N*-methylwelwitindolinone C isothiocyanate (**3**). Both oxidations occurred selectively to furnish single diastereomers of hydroxylated products while leaving the sensitive C11 functional groups undisturbed.

For each of the natural products synthesized, our synthetic samples matched the natural materials by spectroscopic means.[1b,20] However, for the hydroxylated welwitindolinones, the C3 stereochemistry remained to be unambiguously established. Since computational predictions for ^{1}H and ^{13}C NMR chemical shifts have proven valuable in elucidating stereochemical configurations of natural products,[21,22] we calculated the ^{1}H and ^{13}C NMR chemical shifts for the C3 epimers of welwitindolinones **3** and **4**.[23] In both cases, the computed chemical shifts for the C3(*S*) diastereomer matched the experimental data better than did the computed shifts for the C3(*R*) diastereomer. For example, although computed ^{13}C shifts for **4** and *epi*-**4** deviated from the experimental shifts by similar amounts [mean absolute deviations (MADs) of 2.13

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and 2.69 ppm, with largest outliers off by 5.59 and 5.34 ppm for **4** and *epi*-**4**, respectively], computed ^{1}H shifts for **4** matched the experimental values much more closely than did computed shifts for *epi*-**4** [MADs of 0.08 (0.05 without the OH proton included) and 0.36 ppm (0.34 without the OH proton included), with largest C−H outliers off by 0.13 and 0.79 ppm for **4** and *epi*-**4**, respectively]. Similar results were obtained for **3**.[23] We therefore propose that the stereochemical configuration at C3 is *S* in **3** and **4**, in accord with the hypothesis made by the isolation chemists.[1b]

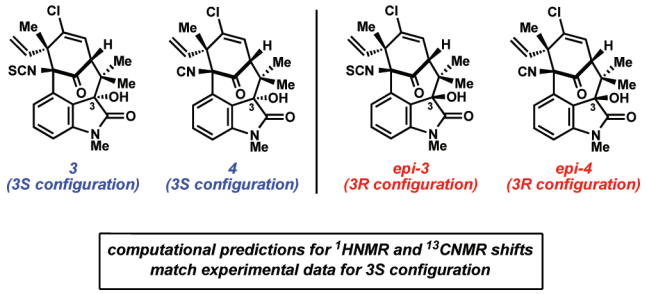
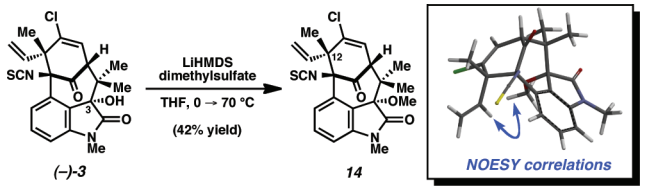


Figure 4. Structures of **3** and **4**, in addition to C3 epimers, and summary of computational findings.

To provide evidence for this stereochemical assignment, (−)-3-hydroxy-*N*-methylwelwitindolinone C isothiocyanate (**3**) was treated with LiHMDS and dimethylsulfate (Scheme 3).

Scheme 3



Despite the severely hindered nature of the tertiary alcohol, methylation proceeded to provide ether **14**. 2D-NOESY experiments of **14** showed correlations between the methoxy protons and the protons of the vinyl group at C12, thus supporting the proposed C3(*S*) configuration.[24] This result further validates the promising use of computational chemistry to establish stereochemical assignments on complex molecules.[21,22]

In summary, we have completed the total syntheses of several elusive welwitindolinone natural products. Our routes to these natural products feature the strategic use of a deuterium kinetic isotope effect to improve the efficiency of a late-stage nitrene insertion reaction. We also provide a computational prediction for the stereochemical configuration at C3 of the hydroxylated welwitindolinones **3** and **4**. This prediction was confirmed by experimental studies. Our findings are expected to facilitate the total syntheses of other welwitindolinone natural products, while demonstrating the utility of computational chemistry in elucidating stereochemical assignments and the strategic manipulation of kinetic isotope effects in total synthesis.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Complete ref 4s., detailed experimental and theoretical procedures, compound characterization data, and computed coordinates, energies, and chemical shift data for **3**, *epi*-**3**, **4**, and *epi*-**4** . This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Rawal and co-workers have recently achieved this transformation; see ref 8.
(16) Moore and co-workers have shown that (−)-**2** can be converted to (−)-**4** and (−)-**5**, albeit in low yield (5% and 3%, respectively), using a photooxidation procedure. Thus, the synthesis of (−)-**2** also constitutes formal total syntheses of (−)-**4** and (−)-**5**.
(17) The C3 stereochemical configuration of **4** was assigned on the basis of this compound having ^{1}H NMR and CD spectra similar to those of **2**. Further support was obtained by the experiment described in ref 16. The C3 configuration of **3** was assigned by analogy to **4**. See ref 2b.
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(24) The three-dimensional structure shown in Scheme 3 was obtained by geometry optimization calculations (MMFF) using MacSpartan '10 (Wavefunction, Inc., Irvine, CA).