Natural Product Synthesis

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# Enantiospecific Total Synthesis of *N*-Methylwelwitindolinone D Isonitrile**

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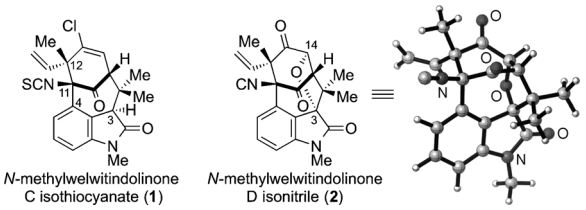
The welwitindolinone family of natural products (e.g., **1**,**2**, Scheme 1) has attracted tremendous attention from the synthetic community over the past two decades.[1–5] Interest in these compounds stems from their promising biological

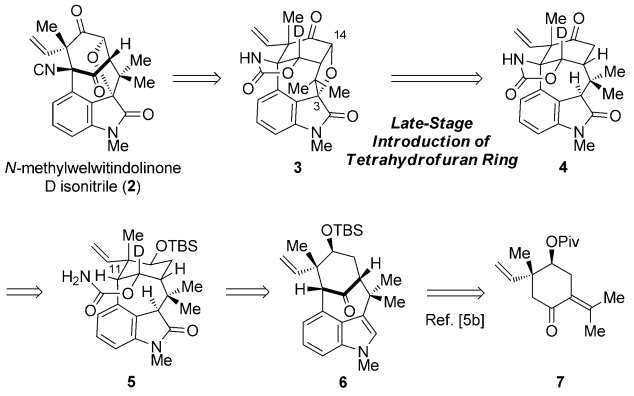



***Scheme 1.*** Welwitindolinones **1** and **2**.

profiles, in addition to their compact, yet daunting structures. Synthetic efforts toward the welwitindolinones have led to at least ten methods for building the bicyclo[4.3.1] core that is common to most of these natural products.[1,4] However, the sheer difficulty associated with late-stage manipulations has plagued most synthetic routes and only a few completed syntheses have been reported in recent years.[5]

One exceptionally challenging synthetic target is *N*-methylwelwitindolinone D isonitrile (**2**).[6,7] The compound possesses five stereocenters, two quaternary carbon centers, and a heavily substituted cyclohexyl ring. Compared to other related family members, **2** also possesses an ether linkage between C3 and C14. Thus, a successful synthesis of **2** would not only have to assemble the congested oxindole-fused bicyclo[4.3.1] framework, but would also have to allow for introduction of the ethereal linkage on the sterically congested face of the bicycle. Highlights of synthetic efforts toward **2** include the assembly of the spirocyclic oxindole reported by the research group of Wood[8] and the elegant total synthesis of (±)-**2** reported by Rawal and co-workers in 2011.[5a] Herein, we report our synthetic forays toward **2**, which culminate in an enantiospecific synthesis.

Our retrosynthetic plan for the synthesis of **2** is presented in Scheme 2. The natural product would be accessed from **3** through late-stage manipulations. In a key disconnection, the tetrahydrofuran ring would be installed from keto oxindole derivative **4**. Of note, the ability to elaborate **4** to **3** would




***Scheme 2.*** Retrosynthetic analysis of **2**. TBS = *tert*-butyldimethylsilyl, Piv = pivaloyl.

hinge on our ability to perform chemoselective and diastereoselective manipulations adjacent to the two carbonyl groups. The cyclic carbamate was thought to be accessible using an intramolecular nitrene insertion reaction[9] involving oxindole substrate **5**. Substrate **5** would be derived from ketone **6**, which in turn can be readily prepared from known carvone derivative **7**[10] in just four steps using our previously established procedure involving an indolyne cyclization.[5b,11]

Our approach toward implementing the retrosynthetic plan is highlighted in Scheme 3. Indole **6** was converted to oxindole **8** using a one-pot oxidation/hydrolysis sequence. As the acidic conditions led to desilylation, reprotection of the alcohol was necessary to provide **9**. Deuteride reduction and carbamoylation proceeded without event to furnish **5** in quantitative yield. Exposure of **5** to Ag-promoted nitrene insertion conditions[5e,12] furnished **10** in 70% yield. Note that attempts to use the proteo analogue of **5** gave only 44% yield of the corresponding insertion product, along with 19% of recovered ketone **9**. Consistent with our previous findings on

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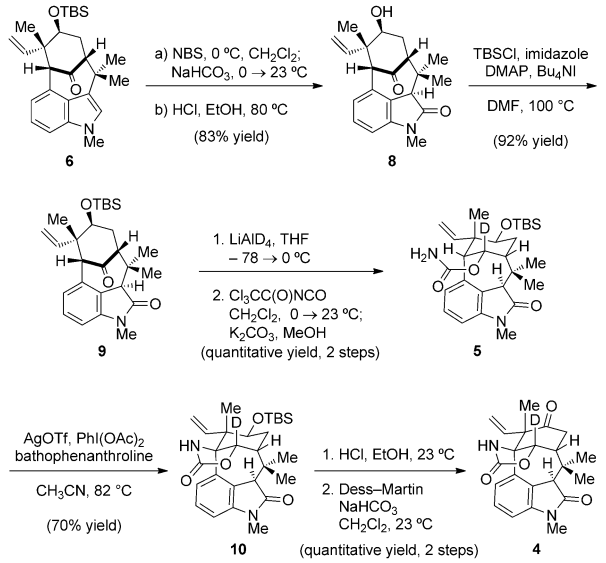
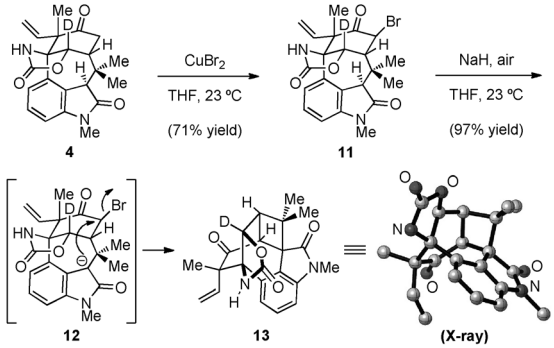



***Scheme 3.*** Elaboration of **6** to keto oxindole **4**; NBS = *N*-bromosuccinimide, DMAP = 4-dimethylaminopyridine, DMF = dimethylformamide, THF = tetrahydrofuran, Tf = trifluoromethanesulfonyl, OAc = acetate, bathophenanthroline = 4,7-diphenyl-1,10-phenanthroline, Dess–Martin = 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one.

an alternate substrate,[5e] the strategic use of deuterium minimizes an undesirable competitive reaction, thus giving synthetically useful yields of the desired insertion product **10**. From **10**, a standard deprotection/oxidation sequence delivered key intermediate **4**.

Many attempts to introduce the tetrahydrofuran ring from **4** were put forth. Unfortunately, efforts toward site-selective functionalization of one carbonyl over the other via enol ethers were unsuccessful. After considerable experimentation, it was found that the keto carbonyl could be α-functionalized first upon treatment of **4** with $CuBr_2$ in THF at ambient temperature to yield **11** as a single diastereomer (Scheme 4). It was hoped that C3 oxidation would provide an alcohol intermediate that would cyclize to give the necessary tetrahydrofuran ring. However, upon treatment of **11** with C3 oxidation conditions,[5e] the desired oxidation and cyclization did not occur. Instead, we unexpectedly obtained cyclobutane **13** in high yield, presumably through direct cyclization of the oxindole enolate (see transition structure **12**).[13] X-ray

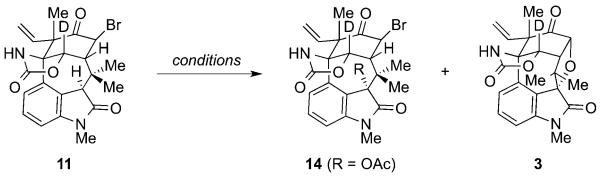



***Scheme 4.*** Unexpected formation of cyclobutane **13**.

analysis of a single crystal of **13** validated our structural assignment.[7,14]

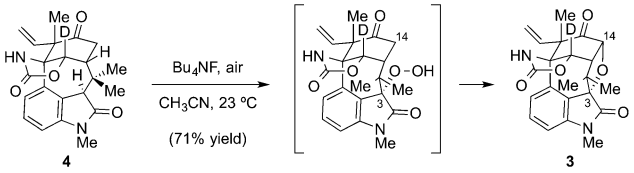
As a workaround, we opted to introduce a protected hydroxy group directly onto C3 of substrate **11**. $Mn(OAc)_3$ was deemed a potential reagent for selective C3 acetoxylation, based on its use in benzylic acetoxylation reactions.[15] Treatment of oxindole **11** with $Mn(OAc)_3$ in AcOH at 80 °C provided acetoxylated product **14** (Table 1, entry 1). Interestingly, when the corresponding reaction was conducted at 150 °C, we obtained a 53% yield of **3**, which possesses the desired tetrahydrofuran ring. Alternatively, **3** could also be prepared in one pot by performing the acetoxylation at 80 °C, removing the volatiles, and exposing the crude intermediate to $K_2CO_3$ in MeOH and $H_2O$ at 70 °C.

***Table 1:*** Conversion of **11** to acetate **14** and cyclized product **3**.




| Entry | Conditions | Conversion to products **14** [%] | **3** [%] |
|---|---|---|---|
| 1 | $Mn(OAc)_3$ (4.0 equiv), AcOH, 80 °C | 74 | 0 |
| 2 | $Mn(OAc)_3$ (4.0 equiv), AcOH, 150 °C | 2 | 53 |
| 3 | $Mn(OAc)_3$ (4.0 equiv), AcOH, 80 °C; $K_2CO_3$, MeOH, $H_2O$, 70 °C | 0 | 56 |

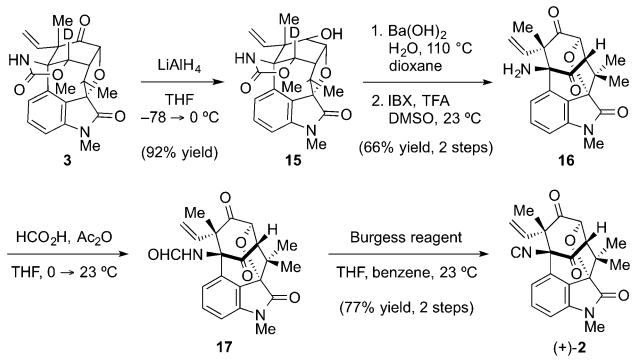
We also explored the feasibility of directly converting keto oxindole **4** to **3** (Scheme 5). Of note, the Wood research group was able to elegantly install a tetrahydrofuran ring from a keto oxindole substrate using basic conditions and $O_2$.[8] Despite the modest yield, this key precedent laid the groundwork for additional experimentation. We found that simple exposure of **4** to tetrabutylammonium fluoride (TBAF) in




***Scheme 5.*** Double C–H functionalization of substrate **4** to install the tetrahydrofuran ring.

acetonitrile in the presence of air efficiently delivered **3**.[16] In previous studies, we[17] and others[18] have found that TBAF/air can facilitate C3 oxidation of oxindoles containing the welwitindolinone scaffold, but the use of TBAF/air to build an ethereal linkage through double C–H functionalization was unknown. Notably, the use of other bases in place of TBAF, such as $K_2CO_3$ and $Cs_2CO_3$, also promoted the formation of **3**, albeit in lower yields. It is likely that this efficient method for introducing the tetrahydrofuran ring proceeds by initial diastereoselective C3 oxidation, followed by cyclization.[19]




***Scheme 6.*** Completion of (+)-**2**; dioxane = 1,4-dioxane, IBX = 2-iodoxybenzoic acid, TFA = trifluoroacetic acid, DMSO = dimethylsulfoxide, Burgess reagent = methyl *N*-(triethylammoniumsulfonyl)carbamate.

Related C3-peroxy compounds have been observed in our studies[20] and in those of the Wood research group.[8]

To complete the total synthesis, it remained to elaborate the cyclic carbamate to the ketone and isonitrile functional groups present in **2** (Scheme 6). Unexpectedly, attempted hydrolysis of **3** led to cyclohexyl ring fragmentation, a process that was attributed to the reactivity of the ketone. To circumvent this, ketone **3** was reduced to alcohol **15** with $LiAlH_4$. Fortunately, upon exposure of **15** to hydrolysis conditions, cyclohexyl ring fragmentation was not observed. Hydrolysis gave the desired diol intermediate, which was oxidized with IBX to provide diketone **16**. Finally, formylation provided **17**, which was directly exposed to standard dehydration conditions to deliver (+)-**2**.

In summary, we have completed the enantiospecific total synthesis of *N*-methylwelwitindolinone D isonitrile. Several unexpected hurdles, including the formation of the unusual cyclobutane-containing compound **13** were overcome en route to the natural product. Our total synthesis features a double C–H functionalization of keto oxindole **4** to introduce the tetrahydrofuran ring of **2** and is achieved in 17 steps from readily available carvone derivative **7**.

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**Keywords:** C–H functionalization · natural products · nitrene insertion · total synthesis · welwitindolinone

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[13] Variations in reaction conditions (e.g., employing a variety of bases, saturating with $O_2$) did not overcome the formation of **13**.

[14] CCDC 960226 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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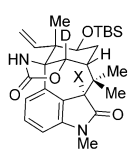
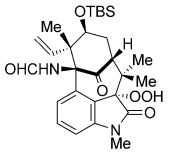
[19] Treatment of **4** with TBAF (3.0 equiv) and MeOD (50.0 equiv) in $CH_3CN$ under an atmosphere of $N_2$ at ambient temperature gave 40% deuterium incorporation at C3 after 10 min, whereas treatment under the same conditions for 1 h gave 50% deuterium incorporation at C3 and 25% deuterium incorporation at C14.

[20] Efforts to isolate the putative peroxy species (Scheme 5) have been unsuccessful; however, we have isolated several related compounds, such as **I** and **II**, by oxidation of the corresponding oxindoles.




I (X = OOH)




II