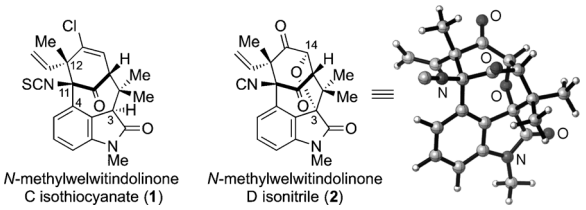
Natural Product Synthesis

DOI: 10.1002/anie.201307464

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

*Evan D. Styduhar, Alexander D. Huters, Nicholas A. Weires, and Neil K. Garg**

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

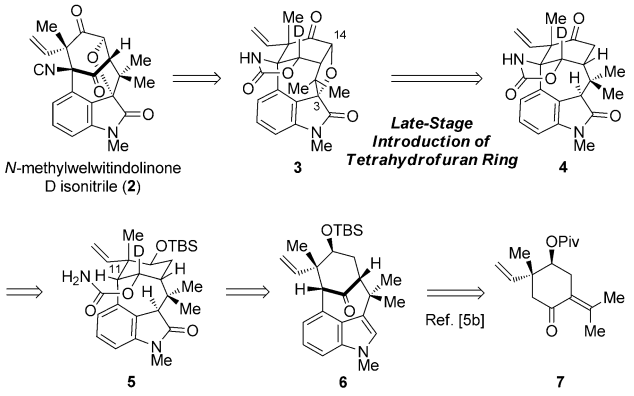


Scheme 1. Welwitindolinones **1** and **2**.

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.

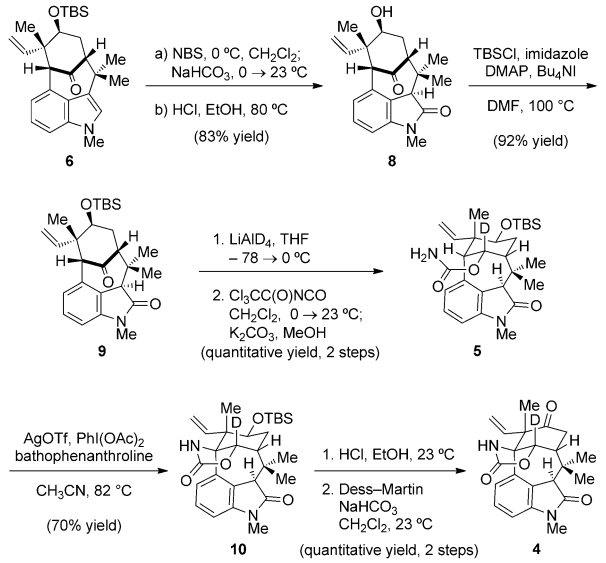
hinge on our ability to perform chemoselective and diastereoselective manipulations adjacent to the two carbonyl groups. The cyclic carbamate was thought to be accessible using an intramolecular nitrene insertion reaction[9] involving oxindole substrate **5**. Substrate **5** would be derived from ketone **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

[*] E. D. Styduhar, A. D. Huters, N. A. Weires, Prof. N. K. Garg
Department of Chemistry and Biochemistry
University of California
Los Angeles, CA 90095 (USA)
E-mail: neilgarg@chem.ucla.edu
Homepage: http://www.chem.ucla.edu/dept/Faculty/garg/Garg_Group/Home.html

[**] We are grateful to the NIH-NIGMS (R01 GM090007), Boehringer Ingelheim, DuPont, Eli Lilly, Amgen, AstraZeneca, Roche, the A. P. Sloan Foundation, the S. T. Li Foundation, the Dreyfus Foundation, the University of California, Los Angeles, Bristol-Myers Squibb (A.D.H.), the NSF (N.A.W., DGE-1144087), and the Foote Family (A.D.H. and E.D.S.) for financial support. We thank the Garcia-Garibay laboratory (UCLA) for access to instrumentation and Dr. John Greaves (UC Irvine) for mass spectra. These studies were supported by shared instrumentation grants from the NSF (CHE-1048804) and the National Center for Research Resources (S10RR025631).

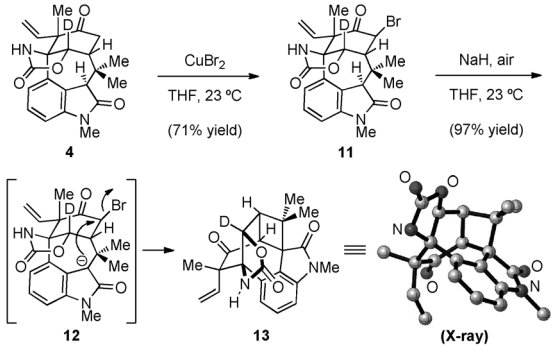
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201307464.



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

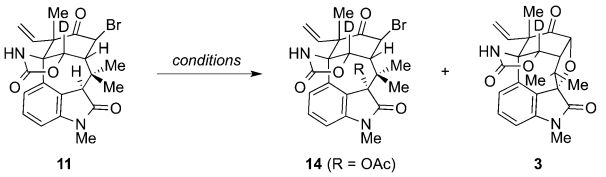


Scheme 4. Unexpected formation of cyclobutane **13**.

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

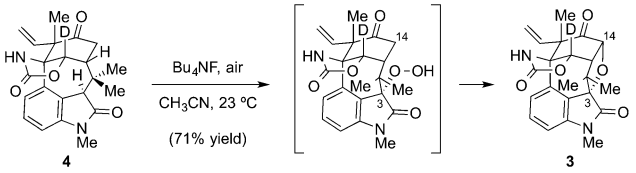
As a workaround, we opted to introduce a protected hydroxy group directly onto C3 of substrate **11**. $Mn(OAc)_3$ was deemed a potential reagent for selective C3 acetoxylation, based on its use in benzylic acetoxylation reactions.[15] Treatment of oxindole **11** with $Mn(OAc)_3$ in AcOH at 80 °C provided 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**.



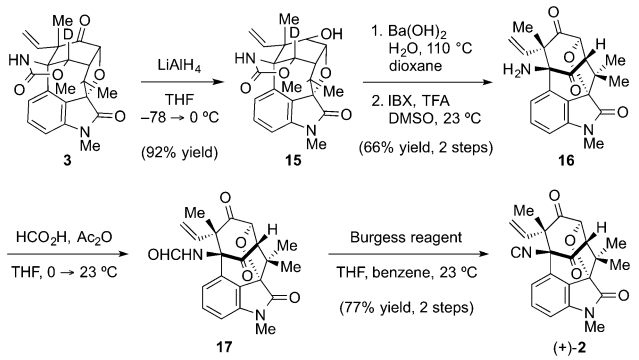
Entry	Conditions	Conversion to products **14** [%]	**3** [%]
1	$Mn(OAc)_3$ (4.0 equiv), AcOH, 80 °C	74	0
2	$Mn(OAc)_3$ (4.0 equiv), AcOH, 150 °C	2	53
3	$Mn(OAc)_3$ (4.0 equiv), AcOH, 80 °C; K_2CO_3, MeOH, H_2O, 70 °C	0	56

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**.

Received: August 24, 2013
Published online: October 2, 2013

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**.

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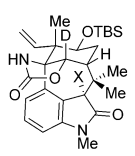
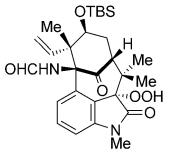
[19] Treatment of **4** with TBAF (3.0 equiv) and MeOD (50.0 equiv) in CH_3CN under an atmosphere of N_2 at ambient temperature gave 40% deuterium incorporation at C3 after 10 min, whereas treatment under the same conditions for 1 h gave 50% deuterium incorporation at C3 and 25% deuterium incorporation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

