Published in final edited form as:
J Am Chem Soc. 2011 April 20; 133(15): 5798–5801. doi:10.1021/ja201834u.

Total Synthesis of *N*-Methylwelwitindolinone D Isonitrile

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Abstract

Described is a concise total synthesis of *N*-methylwelwitindolinone D isonitrile, the first in a family of complex bicyclo[4.3.1]decane-containing indole alkaloids to yield to synthesis. The complete carbon core of the natural product was assembled rapidly through a Lewis acid-mediated alkylative coupling followed directly by a palladium-catalyzed enolate arylation reaction. The final ring of the pentacycle was introduced by an indole oxidation/cyclization, and the isonitrile was installed through the rearrangement of an alde-hyde to an isothiocyanate followed by desulfurization.

In 1994, Moore and coworkers reported the isolation of a novel family of indole alkaloids from the blue-green algae *Hapalosiphon welwitschii* and *Westiella intricata* (**1**–**3**; Figure 1).1 A series of more highly oxidized congeners, including *N*-methylwelwitindolinone D isonitrile (**5**), was later isolated from the terrestrial cyanophytes *Fischerella muscicola* and *Fischerella major*.2 Preliminary evaluation has shown these alkaloids to display a wide variety of biological activities, ranging from antifungal effects to microtubule depolymerization and reversal of P-glycoprotein-mediated multidrug resistance in human carcinoma cells.3,4 With the exception of welwitindolinone A isonitrile (**1**), all members of this family have in common a carbon framework that fuses the 3- and 4-positions of an oxindole to the 2- and 6-positions of a densely functionalized cyclohexanone moiety, so as to produce the characteristic bicyclo[4.3.1]decane ring system. The interesting biological properties and structural challenges presented by these alkaloids have inspired synthesis efforts from numerous laboratories.5 However, despite notable progress, the bridged welwitindolinones (**2**–**5**) have so far eluded these attempts at chemical synthesis.6 Herein we report the first total synthesis of *N*-methylwelwitindolinone D isonitrile (**5**).

Our objective was to develop a route that would enable rapid construction of a functionalized bicyclo[4.3.1]decane unit, suitably adorned with functionality so as to provide access to most members of this family of alkaloids. The initial efforts were focused on *N*-methylwelwitindolinone D isonitrile (**5**), the sole pentacyclic member of the family (Scheme 1). The bridgehead isonitrile moiety was expected to be available from the corresponding isothiocyanate, which in turn could be derived from the neopentyl aldehyde via a little-used oxime rearrangement. The spiro-fused tetrahydrofuran was envisioned to arise from α-hydroxy oxindole (**6**), reminiscent of the proposed biosynthetic precursor to **5**.2 The bicyclo[4.3.1]decane carbon core (**7**) of the natural product would be stitched through a palladium-catalyzed intramolecular enolate arylation of vinylogous acid **8**.5h Further disconnection led to two roughly equal-sized fragments (**9** and **10**) that could be conjoined through a Friedel–Crafts-type alkylation.

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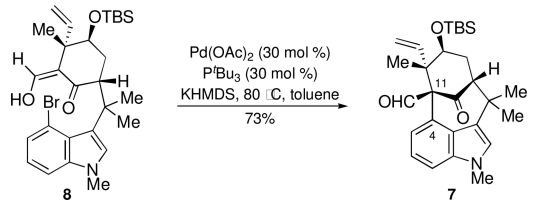
Supporting Information. Experimental details, characterization data, NMR spectra, and X-ray crystal data (CCDC 814975) are available free of charge via the Internet at http://pubs.acs.org.

In preparation for the alkylative coupling, we sought to quickly assemble the two partners, **9** and **10**, from readily available materials (Scheme 2). Vinylogous ester **9** was prepared by addition of vinyl cuprate to the known enone (**11**)5l,7 followed by quenching the intermediate enolate with Zayia's reagent, 2,2,2-trifluoroethyl formate (TFEF).8 Methylation of the resultant vinylogous acid then provided ester **9** in 47% overall yield, accompanied by trace quantities of the C-methylation product, ketoaldehyde **12**. The indole coupling partner (**10**) was prepared from the requisite 3-acetylindole (**13**) upon addition of methylmagnesium bromide.5h,t With the necessary fragments at hand, we set forth for the crucial alkylative coupling. Vinylogous ester **9** was converted to silyl enol ether **14**, which was used without purification (Scheme 3). The reaction of silyl enol ether **14** with *N*-sulfonyl indole **10a** was promoted with $SnCl_4$ and provided the desired product with complete diastereoselectivity, albeit in low yield (ca. 25%).5h,9 Attempts to improve the yield by using other Lewis acids were frustrated by competing dehydration of the tertiary alcohol. Reasoning that a more electron-rich indole would better stabilize the transient benzylic cation, we examined the coupling of **14** with *N*-methylindole alcohol **10b**, which was prepared by an analogous sequence (Scheme 2).10 Best results were obtained when this reaction was promoted with TMSOTf, wherein the weakly basic triflate counterion was expected to be less effective at deprotonation of the benzylic cation.11 Aqueous acidic workup of the reaction mixture afforded vinylogous acid **8** as a single diastereomer in 78% overall yield from **13b** (Scheme 3). The use of the *N*-methyl indole component not only provided the coupled product in high yield, with all carbons found in the natural product, but also avoided the use of the sulfonyl protecting group.

Completion of the bicyclo[4.3.1]decane framework was expected to be accomplished using a palladium-catalyzed intramolecular enolate arylation to form the key C4—C11 bond (eq 1). This transformation presented a notable challenge given that it would set in place vicinal quaternary stereocenters. Moreover, to our knowledge, the transition metal-catalyzed α-arylation of a β-ketoaldehyde is without precedent.12 An evaluation of palladium sources, ligands, bases, and solvents ultimately identified $Pd(OAc)_2$ and tri-*tert*-butylphosphine (1:1) as the optimum catalyst complex. The use of this catalyst system in combination with KHMDS in toluene at 80 °C afforded the desired tetracycle (**7**) in 73% yield. Significantly, this seven-step sequence enabled us to prepare multigram quantities of **7**, which possesses the bicyclo[4.3.1]decane core common to the majority of the welwitindolinones.



(1)

Next, we turned our attention to installation of the spirocyclic tetrahydrofuran, the final ring in the pentacyclic structure of the natural product. To this end, the TBS group in **7** was removed with HF and the resulting alcohol was oxidized using the Dess– Martin reagent (Scheme 4). Given the caged architecture of tetra-cycle **15**, bromination α to the ketone (C14) was expected to occur selectively from the convex face. In the event, deprotonation of **15** with KHMDS and treatment of the resulting enolate with *N*-bromosuccinimide gave rise to bromodione **16** as a single diastereomer, with the halide ideally oriented for subsequent intramolecular displacement from the opposite face. Critical for the displacement reaction was selective introduction of the hydroxyl group at C3, through oxidation of the indole. The options available for this oxidation were dictated by the presence of other oxidizable

functionality present in the molecule, most notably the aldehyde. Among the oxidants examined, dimethyldioxirane (DMDO)13 was found to be the most effective. To our delight, subjection of **16** to a freshly prepared solution of DMDO resulted not only in the desired, diastereoselective oxidation of the indole to the 3-hydroxyoxindole, but in spontaneous cyclization of this intermediate to furnish the desired pentacycle (**17**). X-ray crystal-lography provided unambiguous confirmation of the structure of **17**.

The final hurdle en route to completion of the natural product lay in conversion of the aldehyde functionality to an isonitrile. We had hoped to achieve this transformation by taking advantage of an interesting rearrangement reaction that converts oximes to isothiocyanates.15 Reductive desulfurization of the latter would not only provide access to the sought-after isonitrile, but the general strategy would likely pave the way for the synthesis of additional members of this alkaloid family (e.g., **3a** and **4a**). With this goal in mind, aldehyde **17** was converted to the corresponding oxime **18** (Scheme 5). Following Kim's one-pot protocol,15b **18** was treated with *N*-chlorosuccinimide followed by thiourea (**20**) and triethylamine to give isothiocyanate **19** in 18% yield. We found that the yield of this transformation could be improved through the use of *N,N*′-dialkylthioureas such that the isocyanate could ultimately be prepared in up to 65% yield using propylenethiourea **22**. This transformation is postulated to proceed through a nitrile oxide, which then reacts with the thiourea to give an oxathiazoline through a formal [3+2] cycloaddition reaction. Rearrangement of the putative oxathiazoline then affords the isothiocyanate. Finally, desulfurization of the isothiocyanate was realized using oxazaphospholidine **23**16 to provide *N*-methylwelwitindolinone D isonitrile (**5**) in 54% yield.

In summary, we have successfully completed the total synthesis of *N*-methylwelwitindolinone D isonitrile (**5**), the first member of the bicyclo[4.3.1]decane family to yield to synthesis. The synthesis features a Lewis acid-mediated alkylative coupling in succession with a palladium-catalyzed intramolecular arylation to assemble the tetracyclic carbon scaffold in only seven steps from commercially available materials. Oxidation of the indole with concomitant closure of the spirocyclic ether constructed the final ring of the natural product. An improved protocol was developed for the conversion of the aldehyde to an isothiocyanate, a transformation that has not been exploited previously in total synthesis. This concise route (14 steps, 4.8% overall yield) lays the groundwork for approaches to additional members of the welwitindoli-none alkaloid family.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Generous financial support from the National Cancer Institute of the NIH (R01 CA101438) is gratefully acknowledged. We thank Dr. I. M. Steele for X-ray crystallo-graphic assistance and Dr. A. Jurkiewicz for assistance with NMR spectroscopy.

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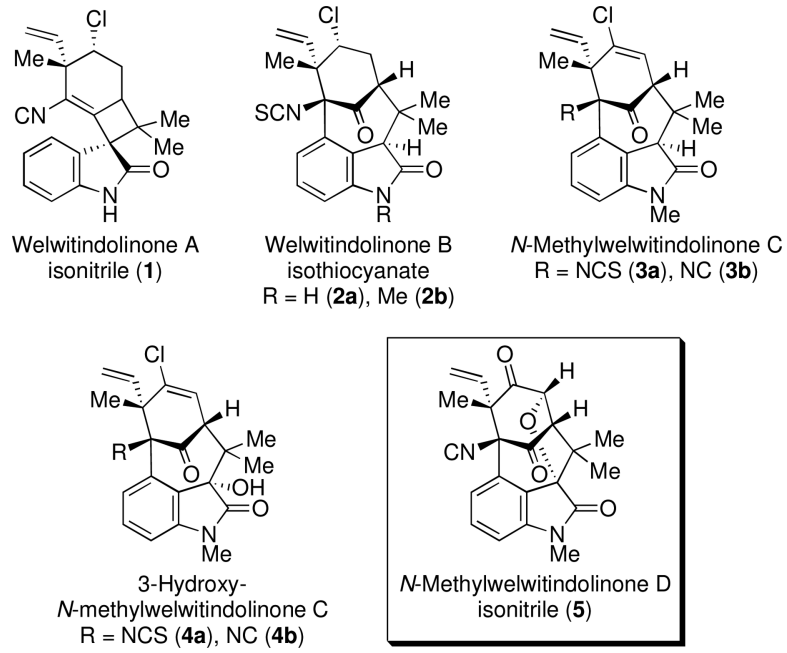
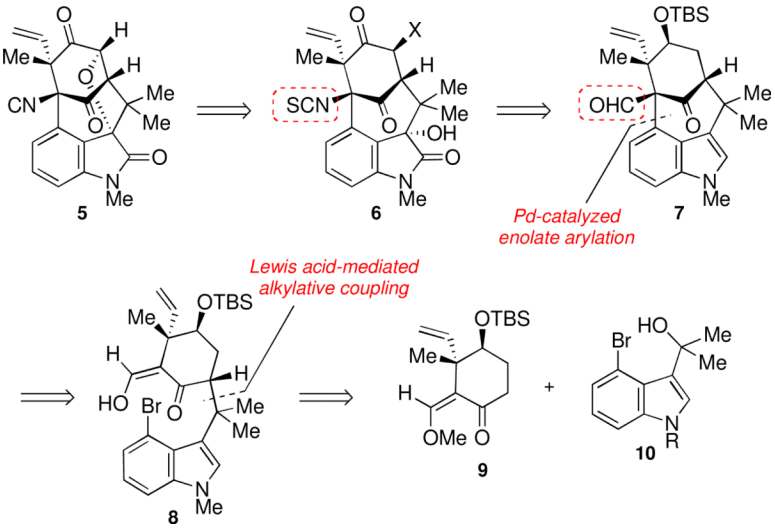
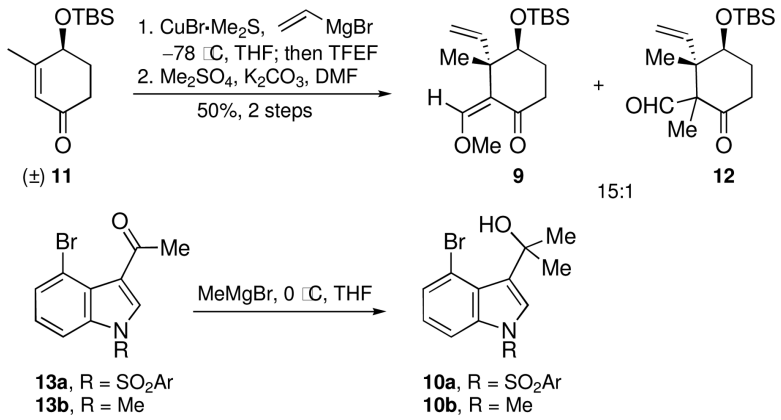


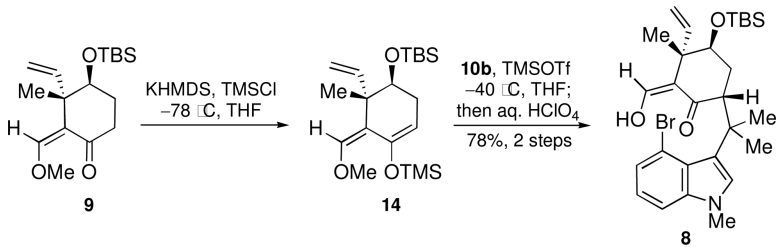
Figure 1.
Representative welwitindolinones



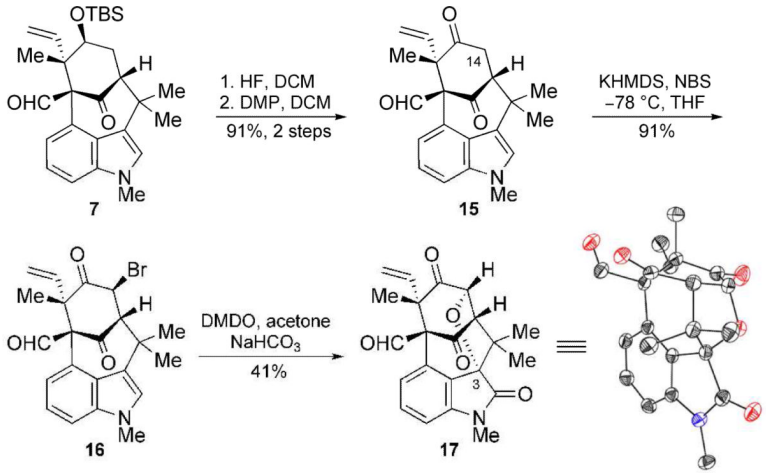
Scheme 1.
Retrosynthetic Analysis of 5



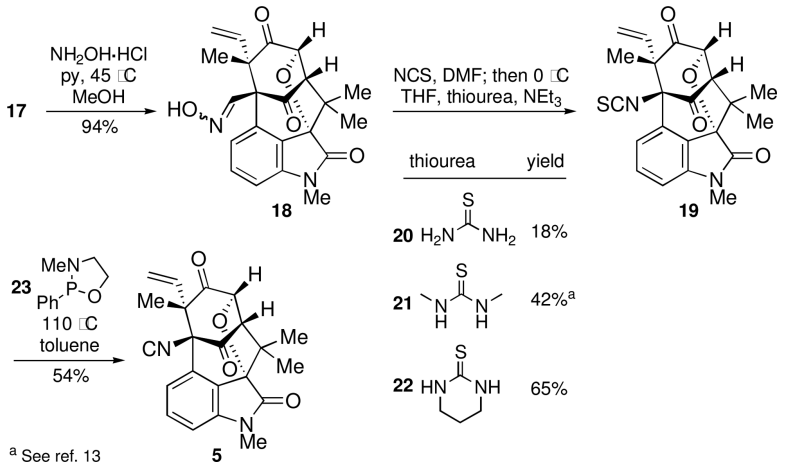
Scheme 2.
Synthesis of Coupling Fragments 9 and 10



Scheme 3.
Synthesis of Cyclization Precursor 8



Scheme 4.
Synthesis of Pentacycle 17



Scheme 5.
Synthesis of *N*-Methylwelwitindolinone D Isonitrile (5)14