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Total Synthesis of (±)-Welwitindolinone A Isonitrile

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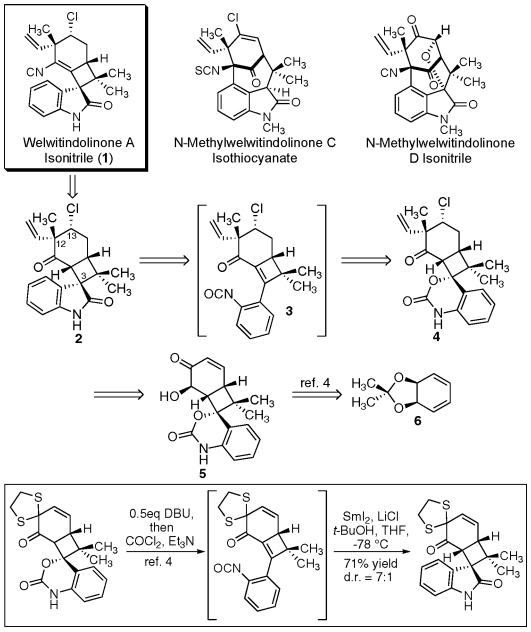
Welwitindolinone A isonitrile (**1**) is one of several related oxindole-containing alkaloids isolated from blue-green algae by Moore and co-workers in 1994.[1] Among the known welwitindolinones, the only one comprised of a highly functionalized spirocyclobutane oxindole carbon skeleton is **1**, and consequently, it has been postulated to serve as the biosynthetic precursor to the remaining congeners (cf. welwitindolinones C and D in Scheme 1).[1a] Although isolation and structural characterization of the welwitindolinones was driven by their biological activities (**1** is an antifungal agent), our interest in **1** was piqued by its densely packed and diverse array of synthetically challenging functional groups.[2] Herein we report an efficient total synthesis of (±)-**1** that exemplifies the strategic and methodological advances molecules of this complexity inspire.

From a retrosynthetic perspective (Scheme 1), we initially envisioned an approach wherein the vinyl isonitrile is derived from a ketone (**2**).[3] Although this disconnection reveals a number of standard bond forming strategies, there appeared to be a paucity of methods capable of efficiently delivering the requisite C3 and C12 all-carbon quaternary centers. To address this deficiency, we developed a mild SmI_2-mediated synthesis of spiro-oxindoles (Scheme 1, boxed structures) that enables access to **2** from cyclic urethane **4** via aryl isocyanate **3** (vide infra).[4] In addition to providing a new oxindole synthesis, these initial investigations demonstrated that known cyclohexadiene **6** could be readily converted to hydroxy-enone **5** (six steps and 56% overall yield), a compound we viewed as a potential precursor to **4**.

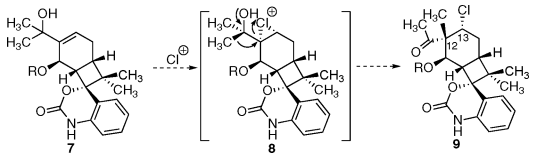
Having outlined a general approach and developed a method for assembling the oxindole,[4] we began considering specific tactics for the stereocontrolled introduction of both the C12 quaternary center and the adjacent neopentyl chlorine found in key intermediate **4**. Rather than address these challenges separately, we devised an approach wherein a chloronium ion induced semi-pinacol rearrangement delivers both simultaneously (see **7** → **8** → **9** in Scheme 2).[5] In this event, the C12/C13 relative stereochemistry would be dictated by mechanism (methyl migration *anti* to chloronium ion), while the overall stereocontrol would derive from diastereoface selective formation of the intermediate chloronium ion. Importantly, since both potential migrating groups of tertiary alcohol **7** are methyl, success would depend only upon chloronium ion facial selectivity. Given the rigid, bicyclic nature of **7**, diastereoface selectivity was anticipated; however, of concern was the likelihood that chlorination would occur from the least hindered convex face and result in formation of the *undesired* stereoisomer (not shown). Though somewhat speculative, we hoped to override this intrinsic bias and promote formation of the illustrated chloronium ion (**8**, Scheme 2) by installing a sufficiently large protecting group (R) on the C11 secondary hydroxyl.

Implementing this approach required a tertiary allylic alcohol substrate (**12**) which, as outlined in Scheme 3, was prepared from

Scheme 1



Scheme 2



hydroxy-enone **5** using a sequence that begins with TIPS protection followed by sequential treatment of the derived enone with LHMDS (to transiently protect the cyclic urethane as the lithium amide), L-selectride, and *N*-phenyltriflimide. The derived enol triflate (**10**) was then subjected to Pd-catalyzed CO insertion in the presence of methanol to provide enoate **11**, which was treated with excess methylmagnesium bromide/anhydrous cerium trichloride to deliver **12**. After considerable experimentation with a variety of chlorine sources, we were delighted to find that treatment of **12** with dilute aqueous sodium hypochlorite and cerium trichloride heptahydrate[6] induces rearrangement of **12** to a *single* chloro-ketone diastereomer (**13**) in 78% isolated yield!

Having successfully implemented the semi-pinacol chemistry, we next installed the C12 vinyl moiety and advanced to cyclization precursor **4** by first desilylating **13** under mild conditions using aqueous fluorosilicic acid[7] in warm acetonitrile. The resulting β-hydroxy ketone was reduced using tetramethylammonium triacetoxyborohydride[8] to give a single diastereomer of diol **14**, a crystalline solid which proved suitable for single-crystal X-ray diffraction, thus providing definitive proof that the semi-pinacol rearrangement had furnished the desired relative stereochemistry.[9]

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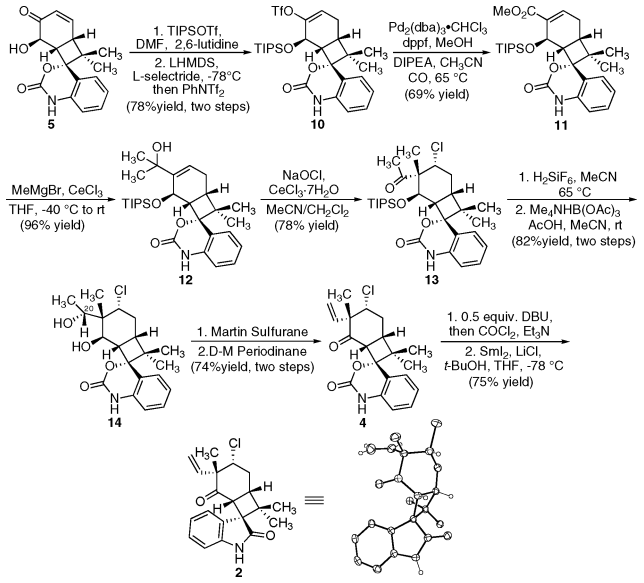
Scheme 3

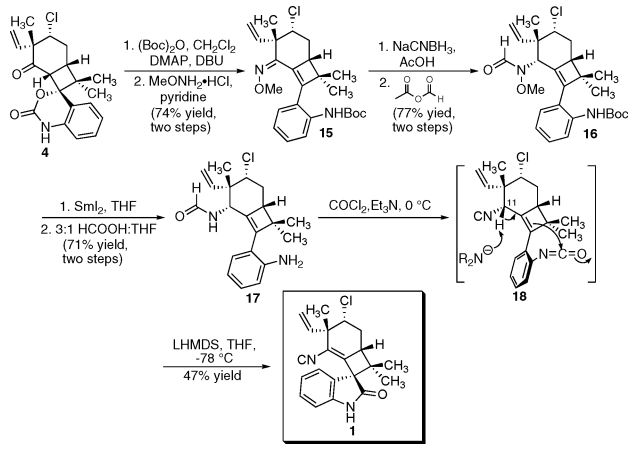


Selective dehydration of the less-hindered C20 alcohol in **14** using Martin sulfurane[10] was followed by oxidation of the remaining alcohol using the Dess-Martin periodinane[11] to give cyclization precursor **4** in good yield. Treatment of ketone **4** with DBU induced elimination of CO_2 to furnish the aniline, which was converted in situ (phosgene/Et_3N) to the corresponding isocyanate (**3**, Scheme 1). In accord with our preliminary studies,[4] exposure of the crude isocyanate to a preformed mixture of SmI_2 and LiCl in THF at −78 °C delivered oxindole **2** in 75% yield with complete diastereocontrol. The stereochemical assignment was confirmed by single-crystal X-ray diffraction and is consistent with bond formation on the less-hindered convex face of the bicyclo[4.2.0]octane skeleton.[9]

With oxindole **2** in hand, we initiated efforts to install the vinyl isonitrile. Unfortunately, **2** proved to be a remarkably unreactive intermediate, and all attempts to convert it to the natural product failed.[12] As a result, we refocused our efforts on an approach wherein the C11 nitrogen would be introduced prior to oxindole formation. To this end, urethane **4** was converted to oxime **15** via a one-pot Boc-protection/CO_2-elimination sequence that was followed by treatment of the derived enone with methoxylamine hydrochloride in pyridine at 65 °C. Unfortunately, α,β-unsaturated oximes of this type proved unreactive toward the previously described SmI_2-mediated reductive cyclization, therefore necessitating development of an alternative method for accessing the oxindole. At this juncture, we recognized that a similar cyclization could potentially be applied to isocyano-isocyanate **18** by taking advantage of the known propensity of isonitriles to undergo α-deprotonation when exposed to strong base (Scheme 4).[13] Access to the requisite cyclization substrate (**18**) was gained from **15** via sodium cyanoborohydride reduction followed by formylation, SmI_2-mediated N−O bond cleavage, Boc-deprotection, and one-pot dehydration/isocyanate generation (phosgene/Et_3N).[14,15] Importantly, the reduction of **15** occurs exclusively from the convex face, thus furnishing a pseudoaxial C11 proton that is poised for subsequent deprotonation. With regard to the latter, we were pleased to find that exposure of crude isocyano-isocyanate **18** to LHMDS at −78 °C provided **1** as a *single diastereomer* in moderate yield.

In conclusion, we have developed an efficient synthesis of (±)-**1** (2.5% overall yield with an average yield of 81%). Importantly,

Scheme 4



this synthesis inspired the development of new methods for the construction of spiro-oxindoles and improved procedures for chloronium ion induced semi-pinacol rearrangement. To our knowledge, this represents the first example of a chloronium ion induced semi-pinacol rearrangement in the context of a natural product total synthesis and demonstrates the utility of this reaction for the synthesis of α-chloro-quaternary centers, such as those found in the welwitindolinones and related natural products.

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Supporting Information Available: Experimental and characterization details (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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