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 welwitindolines, 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. welwitindolines C and D in Scheme 1).1a Although isolation and structural characterization of the welwitindolines 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 SmI2-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,5 we began considering specific tactics for the stereocontrolled introduction of both the C12 quaternary center and the adjacent neopentyl chlorine found in key intermediate 7. 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 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 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 heptahydrate6 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 acid7 in warm acetonitrile. The resulting β-hydroxy ketone was reduced using tetramethylammonium triethoxyborohydride8 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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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\(_3\)N) to the corresponding isocyanate (3, Scheme 1). In accord with our preliminary studies,\(^4\) exposure of the crude isocyano-isocyanate \((\text{3})\) to the corresponding isocyanate (1) furnished oxindole 2 in 75% yield with complete diastereoselection. 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 to give cyclization intermediate, and all attempts to convert it to the natural product total synthesis and demonstrates the utility of this reaction for the synthesis of \(\alpha\)-chloro-quatery 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.

References


(9) See Supporting Information for crystallographic data.


(12) Screening included (but was not limited to) N-nucleophiles, such as NH\(_2\)OH, RN\(_2\)NHMe, RN\(_2\)H, RSONH\(_2\), and NH\(_2\) under acidic and basic conditions at ambient and elevated temperatures.


(14) All attempts to reduce oxime 15 directly to the amine failed to give the desired product.