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Rapid Access to the Welwitindolinone Alkaloid Skeleton by Cyclization of Indolecarboxaldehyde Substituted Cyclohexanones

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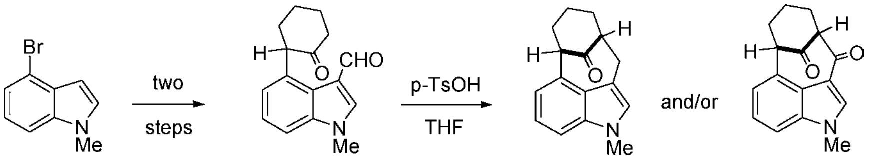
ABSTRACT

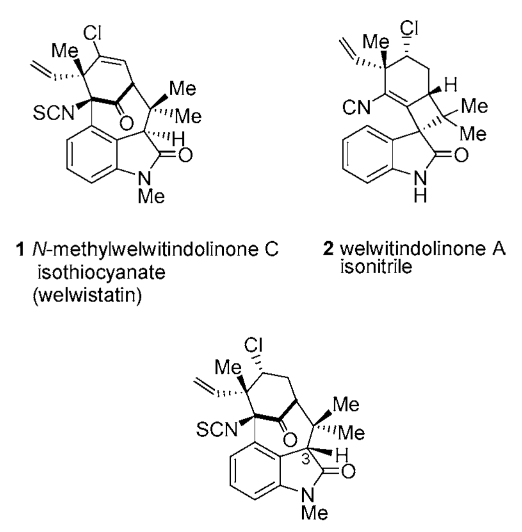


A very rapid access to cyclohexanone-bridged indole systems was established by an acid-mediated ring closure of appropriately substituted indole aldehydes, which involved an apparent disproportionation of an aldol-like intermediate. One of the bridged indole intermediates was further transformed into an oxindole having the essential skeleton of the Welwitindolinone alkaloids.

In 1994, Moore and co-workers described the isolation of a family of unusual alkaloids from the blue−green algae *Hapalosiphon welwitschii* and *Westiella intricata* Borzi, including the structures of *N*-methylwelwitindolinone C isothiocyanate **1** (also known as welwistatin), welwitindolinone A isonitrile **2**, and a number of related structures, including oxindole **3**, which is epimeric at C-3 with respect to welwistatin (Figure 1).[1,2]

Welwistatin has established biological activities, including reversal of P-glycoprotein-mediated multiple-drug-resistance (MDR), larvacidal activities, and microtubule effects that result in inhibition of cancer cell proliferation.[3,4] The isonitrile **2**, which is a proposed biosynthetic precursor to welwistatin (and welwitindolinones B and D), shows antifungal activity.

The interesting biological activities of these compounds, combined with their fascinating and synthetically challenging structures, make them attractive targets for synthesis. However, progress in this area has been surprisingly limited, with only Wood's group describing substantive approaches to both **1** and **2**.[5,6] The work to date has recently been reviewed.[7]



1 *N*-methylwelwitindolinone C isothiocyanate (welwistatin)

2 welwitindolinone A isonitrile

3

Figure 1. Structures of **1**−**3**.

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(1) Stratmann, K.; Moore, R. E.; Bonjouklian, R.; Deeter, J. B.; Patterson, G. M. L.; Shaffer, S.; Smith, C. D.; Smitka, T. A. *J. Am. Chem. Soc.* **1994**, *116*, 9935.

(2) See also: Jimenez, J. I.; Huber, U.; Moore, R. E. *J. Nat. Prod.* **1999**, *62*, 569.

(3) Smith, C. D.; Zilfou, J. T.; Stratmann, K.; Patterson, G. M.; Moore, R. E. *Mol. Pharmacol.* **1995**, *47*, 241.

(4) Zhang, X.; Smith, C. C. *Mol. Pharmacol.* **1996**, *49*, 288.

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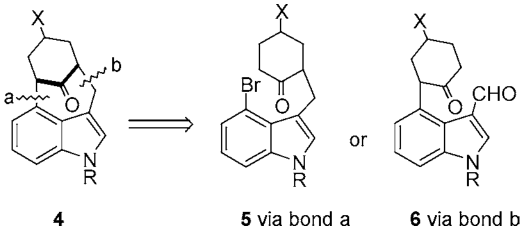
We became interested in the synthesis of these compounds (especially **1**) via bridged indole intermediates, such as **4**, as part of project examining bridgehead metalation chemistry.[8] We believed that key intermediates, such as **4** (where X is a protected alcohol or ketone function), would be available by strategic disconnection at either bond a or bond b, the forward reactions involving either intramolecular enolate arylation of **5** or aldol-type reaction of **6** (Scheme 1).

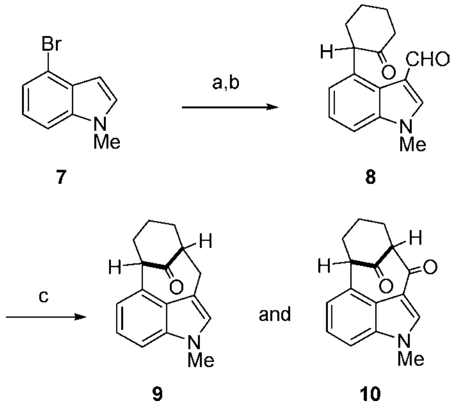
Scheme 1



After our initial efforts to cyclize ketone **5** (X = H) and similar structures (obtained through indole Michael addition to appropriate enones) proved unsuccessful, we turned instead to the synthesis and reactions of indole aldehydes of structure **6**. Similar intermediates have been accessed previously by Deng and Konopelski, who utilized an indole−lead partner in a key coupling process with an elaborated cyclohexanone.[6a]

Palladium-catalyzed coupling of cyclohexanone with bromoindole **7**, under conditions based on those described by Buchwald,[9] gave a product ketone, which on subsequent Vilsmeier−Hack formylation then gave indole **8** (=**6** where X = H and R = Me) (Scheme 2).[10] Attempted aldol-type ring closure of **8** by reaction with bases ranging from $Ca(OH)_2$ to LDA gave no sign of the desired product. In contrast, exposure to acidic conditions gave rise to two bridged structures, methylene-bridged product **9** and diketone **10**, in roughly equal amounts.

Scheme 2[a]



[a] Reagents: (a) cyclohexanone, $Pd(OAc)_2$ (1 mol %), K_3PO_4 (2.3 equiv), (2-biphenyl)dicyclohexylphosphine (2.5 mol %), THF, 100 °C (sealed tube), 24 h, 51−73%; (b) $POCl_3$, DMF, 0 °C, then KOH (aq) 75%; (c) *p*-TsOH (0.5 equiv) THF, 50 °C, 24 h, 60% (**9**:**10** ca. 1:1).

This unexpected but pleasing result was confirmed by detailed spectroscopic analysis of both compounds, the structure of indole **9** also being secured by subsequent X-ray crystallographic analysis (Figure 2).

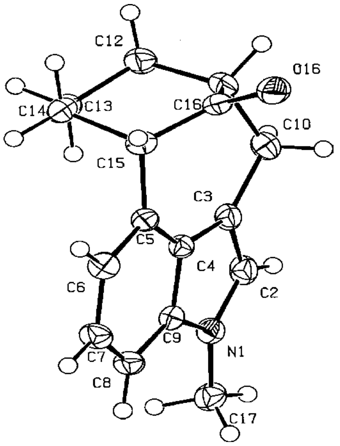
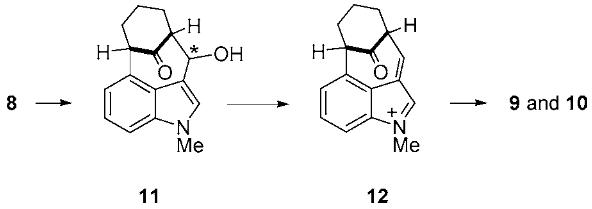


Figure 2. ORTEP drawing of indole **9**.

The reaction can be rationalized by invoking initial aldol condensation to give **11**, followed by dehydration to give **12** (both of these steps might be expected to be reversible). Hydride transfer from C* of **11** to the corresponding position in the extended iminium species **12** effects disproportionation of **11**, leading to the observed products (Scheme 3).

Scheme 3



Although this was a very exciting result, the formation of two products was clearly problematic, and we sought

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(5) (a) Wood, J. L.; Holubec, A. A.; Stoltz, B. M.; Weiss, M. M.; Dixon, J. A.; Doan, B. D.; Shamji, M. F.; Chen, J. M.; Heffron, T. P. *J. Am. Chem. Soc.* **1999**, *121*, 6326. (b) Ready, J. M.; Reisman, S. E.; Hirata, M.; Weiss, M. M.; Tamaki, K.; Ovaska, T. V.; Wood, J. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1270.

(6) For other synthetic efforts, see: (a) Deng, H. B.; Konopelski, J. P. *Org. Lett.* **2001**, *3*, 3001. (b) Jung, M. E.; Slowinski, F. *Tetrahedron Lett.* **2001**, *42*, 6835. (c) Lopez-Alvarado, P.; Garcia-Granda, S.; Alvarez-Rua, C.; Avendano, C. *Eur. J. Org. Chem.* **2002**, 1702.

(7) Avendano, C.; Menéndez, J. C. *Curr. Org. Synth.* **2004**, *1*, 65.

(8) (a) Blake, A. J.; Giblin, G. M. P.; Kirk, D. T.; Simpkins, N. S.; Wilson, C. *Chem. Commun.* **2001**, 2668. (b) Giblin, G. M. P.; Kirk, D. T.; Mitchell, L.; Simpkins, N. S. *Org. Lett.* **2003**, *5*, 1673.

(9) (a) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360. (b) For a relevant review, see: Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234.

modified conditions that would give just one product. We expected that iminium **12** might be intercepted by alternative nucleophiles and that inclusion of an appropriate reaction partner would therefore preclude intermolecular hydride transfer from **11**. Satisfyingly, repeating the PTSA cyclization reaction of **8** in the presence of a powerful external source of hydride, namely, Et_3SiH (2.4 equiv), resulted in the formation of **9** as the sole product in 92% yield.[11] Conversely, running the reaction in the presence of a hydride acceptor (DDQ) gave only the diketone **10**, although in a more modest 45% yield.

Of key interest was the conversion of our indole structures into the corresponding oxindoles, which are more closely related to natural products, such as **1** and **3**. To this end, exposure of indole **9** to NBS in 95% ^{t}BuOH at room temperature gave rise to a single oxindole product **13** in 52% yield (Figure 3).[6a,12]

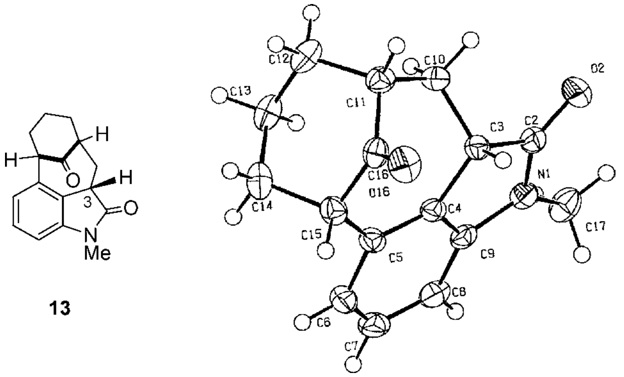

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Figure 3. Schematic and ORTEP of product **13**.

We were able to unequivocally establish the structure of the product **13** by X-ray crystallography. The C-3 stereochemistry presumably arises by least hindered protonation from the convex face of the bridged system and makes **13** a relative of the minor alkaloid **3**, rather than welwistatin **1**, which is epimeric at this center.[12]

In summary, the new cyclization chemistry described here gives extremely short access (three steps) to the bridged framework of the Welwitindolinone alkaloids, and the products synthesized appear to be suitable for further manipulation toward the natural products and their close analogues.[13,14]

Acknowledgment. We thank the Engineering and Physical Sciences Research Council (EPSRC) for a Fellowship to J.B., and also for funding for an X-ray diffractometer.

Supporting Information Available: Description of experimental procedures described, and characterization data for new compounds, including CIF X-ray data for compounds **9** and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) This result contrasts with one described by Deng and Konopelski in ref 6a, in which a similar substrate underwent cyclohexanone (rather than indole) formylation.

(11) (a) Appleton, J. E.; Dack, K. N.; Green, A. D.; Steele, J. *Tetrahedron Lett*. **1993**, *34*, 1529. (b) Mahadevan, A.; Sard, H.; Gonzalez, M.; McKew, J. C. *Tetrahedron Lett.* **2003**, *44*, 4589.

(12) Effective C-3 epimerization under has not been possible to date (e.g., using protic conditions, NaOMe-MeOH).

(13) Further preliminary work has demonstrated that the new cyclization is viable starting with keto aldehyde **6**, where X = OPMB. We have also shown that bridgehead silylation of ketone **9** is possible.

(14) While our manuscript was under review, an intramolecular arylation approach to similar bridged indoles appeared. See: MacKay, J. A.; Bishop, R. L.; Rawal, V. H. *Org. Lett.* **2005**, *7*, 3421.