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Concise Synthesis of the Bicyclic Scaffold of *N*-Methylwelwitindolinone C Isothiocyanate via an Indolyne Cyclization

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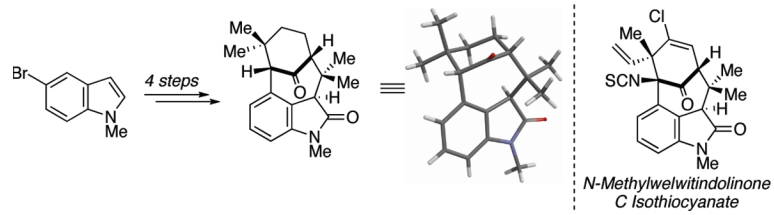
ABSTRACT



A concise synthesis of the *N*-methylwelwitindolinone C isothiocyanate scaffold is disclosed. The approach relies on an indolyne cyclization to construct the [4.3.1]-bicyclic ring system present in the natural product. Subsequent oxidation of the indole core occurs with excellent diastereoselectivity to afford oxindole 2, the structure of which was confirmed by X-ray crystallographic analysis.

N-Methylwelwitindolinone C isothiocyanate (**1**, Figure 1), was first isolated from the blue-green algae *Hapalosiphon welwitschii* in 1994 by Moore and co-workers.[1,2] **1** was found to reverse multiple drug resistance (MDR) to a variety of anticancer drugs, thus rendering it an attractive agent for the treatment of drug-resistant tumors.[3,4] The unique structural framework of **1**, coupled with its impressive biological profile, has attracted considerable attention from the synthetic community over the past decade.[5] Although numerous approaches to **1** have been reported,[6−13] a total synthesis of this unique target has remained elusive. In this communication, we disclose a concise approach to the [4.3.1]-bicyclic core of **1** using an indolyne cyclization.

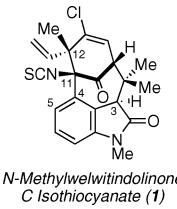


Figure 1. *N*-Methylwelwitindolinone C isothiocyanate (**1**).

With the aim of developing a concise route to the bicycle present in **1**, oxindole **2** was selected as a suitable model system target (Scheme 1). It was envisioned that oxindole **2** could be derived from indole precursor **3** through a diastereoselective oxidation reaction. In the key retrosynthetic

(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*, 9935–9942.

(2) **1** has sometimes been referred to as "welwistatin"; however, as originally defined in ref 3b, "welwistatin" refers to the des-*N*-methyl analogue of **1**.

(3) (a) Smith, C. D.; Zilfou, J. T.; Stratmann, K.; Patterson, G. M.; Moore, R. E. *Mol. Pharmacol.* **1995**, *47*, 241–247. (b) Zhang, X.; Smith, C. D. *Mol. Pharmacol.* **1996**, *49*, 288–294. (c) Avendaño, C.; Menéndez, J. C. *Curr. Med. Chem.* **2002**, *9*, 159–193.

(4) At concentrations as low as 0.1 μM, **1** was found to greatly decrease the IC_{50} of vinblastine, taxol, actinomycin D, cochicines, and daunomycin in MCF-7/ADR drug-resistant breast carcinoma cells.

(5) For a review, see: Avendaño, C.; Menéndez, J. C. *Curr. Org. Synth.* **2004**, *1*, 65–82.

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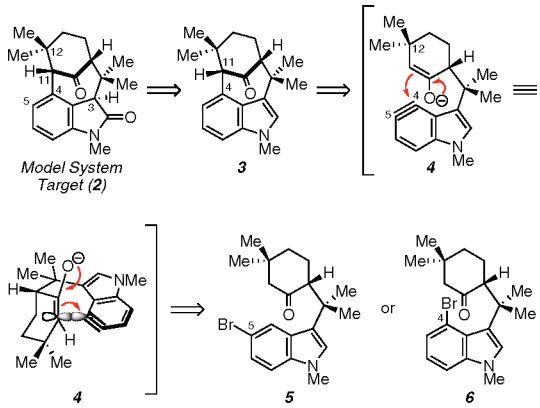
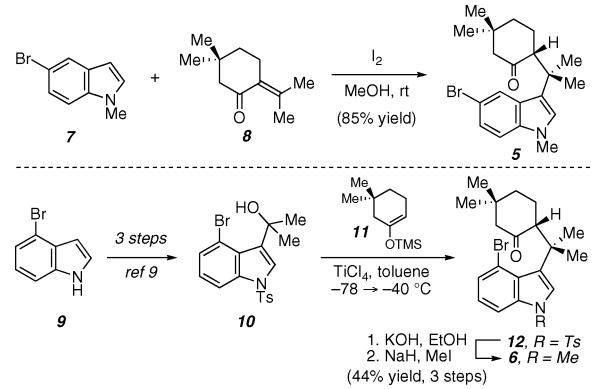
Scheme 1. Indolyne Approach to the Synthesis of **1**



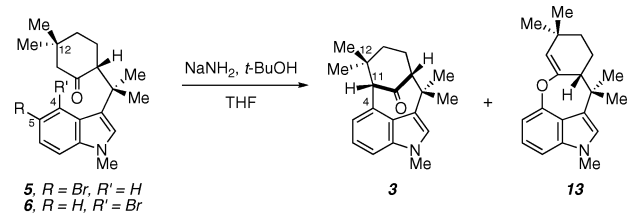
Scheme 2. Synthesis of Bromoindole Substrates **5** and **6**



disconnection, the C4−C11 bond of bicycle **3** would arise via a cyclization of an enolate onto an electrophilic indole, or indolyne[14−16] (see transition structure **4**). Although the enolate participating in this reaction would be adjacent to the congested C12 quaternary center, the desired cyclization seemed favorable given that the intermediate indolyne would be extremely reactive. Furthermore, the stereoelectronics for bicycle formation appeared optimal, as suggested in Scheme 1. Inspired by classic methods for aryne generation,[17] it was envisioned that the desired indolyne intermediate could be accessed in situ from either 5- or 4-brominated substrates, **5** or **6**, respectively.

Our synthetic routes to the desired cyclization precursors **5** and **6** are depicted in Scheme 2. To access 5-brominated substrate **5**, readily available 5-bromo-*N*-methylindole (**7**)[18] was allowed to react with enone **8**[19] in the presence of I_2 in MeOH following the general method described by Wang and co-workers.[20] This approach led to the single-step formation of the 5-brominated cyclization substrate **5** in 85% yield. Unfortunately, the analogous route to 4-brominated substrate **6** was less fruitful.[21] Nonetheless, substrate **6** could be prepared in six steps from 4-bromoindole following the robust approach developed by Rawal.[9] Thus, 4-bromoindole (**9**) was elaborated to known tertiary alcohol **10** over three steps.[9] Upon treatment of **10** with $TiCl_4$ and enoxysilane **11**,[22] Ts-indole **12** was obtained. Subsequently, a two-step detosylation/methyl protection sequence provided the desired substrate **6**.

Table 1. Indolyne Cyclization Experiments



substrate	temperature	yield[a]	ratio (3:13)
5	23 °C	56% (62%)	1.2:1
6	23 °C	no reaction	
6	50 °C	64%	1:1

[a] Combined isolated yield of **3** and **13**. Yield in parentheses reflects yield based on recovered substrate.

Table 1 highlights the results of our efforts to effect the indolyne cyclization of substrates **5** and **6**. Gratifyingly, both substrates could be converted to the desired bicycle **3** upon reaction with $NaNH_2$/*t*-BuOH[23] in THF.[24] Although the yield is modest, several significant aspects of our cyclization results

(6) (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*, 6326–6327. (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*, 1270–1272.

(7) Jung, M. E.; Slowinski, F. *Tetrahedron Lett.* **2001**, *42*, 6835–6838.

(8) (a) Deng, H.; Konopelski, J. P. *Org. Lett.* **2001**, *3*, 3001–3004. (b) Xia, J.; Brown, L. E.; Konopelski, J. P. *J. Org. Chem.* **2007**, *72*, 6885–6890.

(9) MacKay, J. A.; Bishop, R. L.; Rawal, V. H. *Org. Lett.* **2005**, *7*, 3421–3424.

(10) (a) Baudoux, J.; Blake, A. J.; Simpkins, N. S. *Org. Lett.* **2005**, *7*, 4087–4089. (b) Boissel, V.; Simpkins, N. S.; Bhalay, G.; Blake, A. J.; Lewis, W. *Chem. Commun.* **2009**, 1398–1400.

(11) Greshock, T. J.; Funk, R. L. *Org. Lett.* **2006**, *8*, 2643–2645.

(12) Lauchli, R.; Shea, K. J. *Org. Lett.* **2006**, *8*, 5287–5289.

(13) Richter, J. M.; Ishihara, Y.; Masuda, T.; Whitefield, B. W.; Llamas, T.; Pohjakallio, A.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 17938–17954.

(14) For seminal studies involving indolynes, see: (a) Julia, M.; Huang, Y.; Igolen, J. *C. R. Acad. Sci., Ser. C* **1967**, *265*, 110–112. (b) Igolen, J.; Kolb, A. *C. R. Acad. Sci., Ser. C* **1969**, *269*, 54−56. For related studies, see: (c) Julia, M.; Le Goffic, F.; Igolen, J.; Baillarge, M. C. *C. R. Acad. Sci., Ser. C* **1967**, *264*, 118–120. (d) Julia, M.; Igolen, J.; Kolb, A. *C. R. Acad. Sci., Ser. C* **1971**, *273*, 1776–1777.

(15) In a previous study, we demonstrated that indolynes function as practical electrophilic indole surrogates and can also be accessed from indolylsilyltriflate species under mild fluoride-mediated conditions, see: Bronner, S. M.; Bahnck, K. B.; Garg, N. K. *Org. Lett.* **2009**, *11*, 1007–1010.

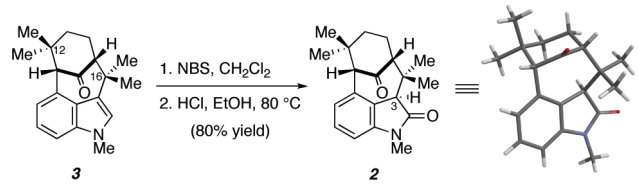
(16) For the preparation of indolynes from dihaloindoles and butyllithium reagents, and subsequent Diels-Alder studies, see: (a) Buszek, K. R.; Luo, D.; Kondrashov, M.; Brown, N.; VanderVelde, D. *Org. Lett.* **2007**, *9*, 4135–4137. (b) Brown, N.; Luo, D.; VanderVelde, D.; Yang, S.; Brassfield, A.; Buszek, K. R. *Tetrahedron Lett.* **2009**, *50*, 63–65. (c) Buszek, K. R.; Brown, N.; Luo, D. *Org. Lett.* **2009**, *11*, 201–204.

(17) For reviews regarding the chemistry of arynes, see: (a) Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, *59*, 701–730. (b) Wenk, H. H.; Winkler, M.; Sander, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 502–528. (c) Sanz, R. *Org. Prep. Proced. Int.* **2008**, *40*, 217–291.

should be noted: (a) the desired *C*-arylated product **3** is the major compound produced in the cyclizations, albeit with *O*-arylated product **13** being formed competitively;[25−27] (b) 4-brominated substrate **6** requires higher temperatures to induce product formation; this result may be explained by the greater acidity of the C4 proton of substrate **5** in comparison to the C5 proton of **6**;[28] (c) whereas the dehydrohalogenation of 5-bromo substrate **5** could plausibly lead to undesirable mixtures of 4,5- and 5,6-indolyne intermediates, formation of the desired 4,5-indolyne appears to be favored; (d) the use of 5-brominated substrate **5** to access bicycle **3** is generally preferred, as the synthesis of **5** is concise, high-yielding, and ultimately begins with inexpensive 5-bromoindole.[29] Moreover, it is notable that a 5-substituted substrate could be used as the synthetic precursor to the desired 4-substituted product. Our studies are the first to describe direct formation of the [4.3.1]-bicycle of **1** through assembly of the C4−C11 bond with an adjacent quaternary center at C12.

To date, most of the disclosed approaches to *N*-methylwelwitindolinone C isothiocyanate (**1**) plan for a late-stage diastereoselective indole oxidation to furnish the oxindole found in the natural product.[8−12] However, only two studies toward this goal have been documented,[10a,30] whereby attempted oxidation of model system substrates predominantly afforded the undesired epimers of the corresponding oxindole products. After extensive experimentation, we have found that bicyclic indole **3** can be cleanly converted to oxindole **2** through a two-step sequence involving treatment with NBS to afford the corresponding C-2 brominated indole, followed by HCl-promoted hydrolysis (Scheme 3). Fortunately, a single diastereomer of product was obtained. X-ray diffraction studies revealed that **2** possessed the desired stereochemical configuration at C3, as depicted.

Scheme 3. Oxidation of **3** and X-ray Structure of Oxindole **2**



In summary, we have developed a concise approach to the bicyclic scaffold of *N*-methylwelwitindolinone C isothiocyanate (**1**). Our strategy involves an expedient synthesis of bromoindole **5**, an indolyne cyclization to forge the congested C4−C11 bond of bicycle **3**, and a diastereoselective oxidation to deliver oxindole **2**. Efforts to access related structures that possess a C11 nitrogen substituent are currently underway in our laboratory, in addition to studies aimed at completing the total synthesis of **1**.

Acknowledgment. The authors are grateful to the University of California, Los Angeles, and Boehringer Ingelheim for financial support. We thank Professor Jung (UCLA), Professor Houk (UCLA), and Dr. Jason Rohde (Ironwood Pharmaceuticals) for pertinent discussions, the Garcia-Garibay laboratory (UCLA) for access to instrumentation, and Dr. John Greaves (UC Irvine) for mass spectra.

Supporting Information Available: Detailed experimental details and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) **7** is commercially available or can be easily prepared in one step from inexpensive 5-bromoindole on a multigram scale, see: Jiang, X.; Tiwari, A.; Thompson, M.; Chen, Z.; Cleary, T. P.; Lee, T. B. K. *Org. Proc. Res. Dev.* **2001**, *5*, 604–608.

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(20) Wang, S.-Y.; Ji, S.-J.; Loh, T.-P. *Synlett* **2003**, *15*, 2377–2379.

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(22) Aggarwal, V. K.; Daly, A. M. *Chem. Commun.* **2002**, 2490–2491.

(23) Caubere, P. *Acc. Chem. Res.* **1974**, *7*, 301–308.

(24) Alternative basic conditions commonly used to promote aryne formation were unsuccessful (e.g., LDA, LHMDS, $Me_2Zn(TMP)Li$).

(25) Prolonged reaction times led to olefin isomerization of enol ether **13** to afford the corresponding tetrasubstituted olefin.

(26) Utilization of the TBS or TIPS enol ether derivatives of **5** did not lead to improvements in yield or selectivity for C-arylation.

(27) Variations in temperature, stoichiometry, and counterion did not lead to improvements in the conversion of **5** to **3**.

(28) Shen, K.; Fu, Y.; Li, J.-N.; Liu, L.; Guo, Q.-X. *Tetrahedron* **2007**, *63*, 1568–1576.

(29) 5-Bromoindole is commercially available from Combi-Blocks, Inc. at a cost of $24 per 25 grams; the cost of 4-bromoindole is $195 per 25 grams.

(30) Greshock, T. J. Ph.D. Dissertation. Pennsylvania State University, University Park, PA, 2006.