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Rapid Synthesis of the *N*-Methylwelwitindolinone Skeleton

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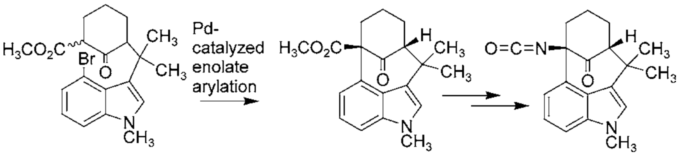
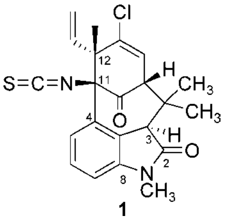
ABSTRACT



An efficient, convergent synthesis of the core bicyclo[4.3.1]decane ring system of welwitindolinones is described. Key steps in the synthesis include an intramolecular palladium-catalyzed enolate arylation reaction to create the desired bicyclic skeleton and a Curtius rearrangement to install the bridgehead isocyanate unit.

A 1994 report described the isolation of a new class of indole alkaloids from the lipophilic extracts of both *Hapalosiphon welwitschii* and *Westiella intricata*.[1] The extracts from these cyanobacteria were found to have potent biological activities, including antifungal, larvacidal, and insecticidal properties. Significantly, the major component from each of these extracts, *N*-methylwelwitindolinone C isothiocyanate (**1**), was shown to reverse multidrug resistance (MDR) in chemotherapeutic cancer treatment.[2]



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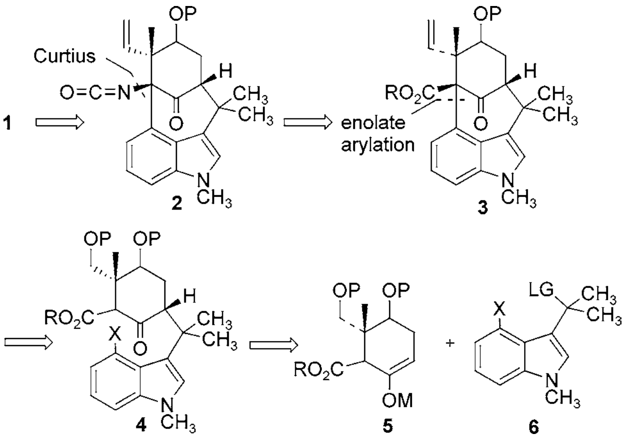
In addition to its striking biological activity, *N*-methylwelwitindolinone C isothiocyanate (**1**) exhibits daunting structural complexity that arises from four stereogenic centers, three quaternary carbons, and a unique bicyclo[4.3.1]decane ring system about an oxindole. While no total synthesis of **1** or any other member of this family of compounds exists to date, there are several reports describing strategies for their synthesis.[3,4] Herein, we report a rapid, convergent synthesis of the core skeleton of **1**. The route features a Lewis acid-mediated alkylative coupling to assemble the carbon framework, a Pd-catalyzed intramolecular enolate arylation reaction[5] to assemble the tetracyclic ring system, and a Curtius rearrangement to install the isocyanate moiety.

Scheme 1



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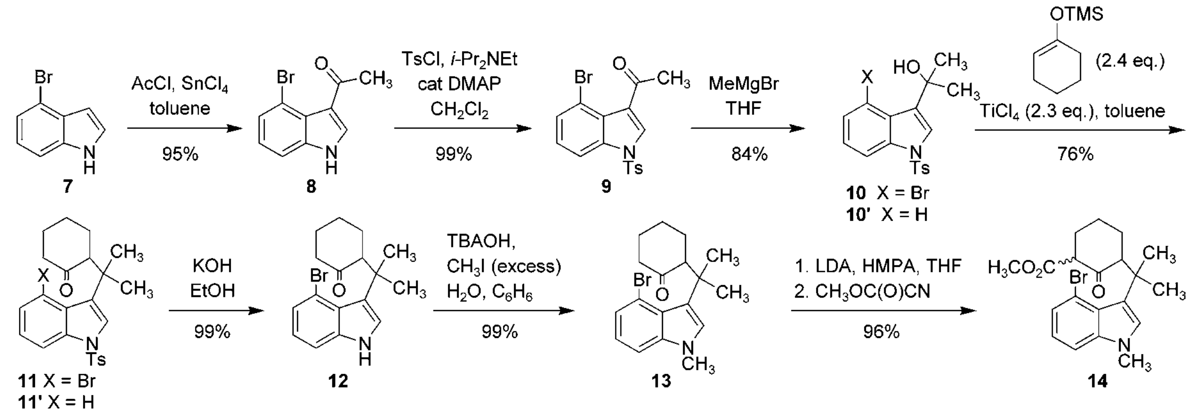
(1) (a) Stratmann, K.; Moore, R. E.; Bonjouklian, R.; Deeter, J. B.; Patterson, G. M. L.; Shaffer, S.; Smith, C. D.; Smitka, T. A. *J. Am. Chem. Soc.* **1994**, *116*, 9935. (b) Jimenez, J. I.; Huber, U.; Moore, R. E.; Patterson, G. M. L. *J. Nat. Prod.* **1999**, *62*, 569.

(2) (a) Smith, C. D.; Zilfou, J. T.; Stratmann, K.; Patterson, G. M. L.; Moore, R. E. *Mol. Pharmacol.* **1995**, *47*, 241. (b) Zhang, X. Q.; Smith, C. D. *Mol. Pharmacol.* **1996**, *49*, 288.

10.1021/ol051043t CCC: $30.25

Scheme 2



The strategy for the synthesis of welwitindolinones is shown in Scheme 1. The key step in the plan involves assembly of the challenging bridged-bicyclic ring system through an intramolecular Pd-catalyzed enolate arylation reaction (**4** → **3**).[6] Although several reports describe the construction of the seven-membered ring of **1** by formation of the C4−C11 bond,[4c,e−g] no one to date has successfully constructed the bicyclo[4.3.1]decane ring skeleton through this means. Our plan was to use a β-keto ester in the cyclization event to allow the arylation reaction to proceed under mild conditions.[5] Importantly, the bridgehead methyl ester in the resulting product would serve as a masked form of the required isothiocyanate. The latter functionality could be revealed when needed via a Curtius rearrangement (**3** → **2**). Finally, enolate arylation precursor **4** would be prepared convergently, through the alkylative coupling of the indole subunit (**6**) to the cyclohexanone unit (**5**).

To test the strategy toward welwitindolinones, we first set out to create the cyclization precursor **14** (Scheme 2). Commercially available 4-bromoindole (**7**) was acylated under Friedel−Crafts conditions to afford ketone **8** (95%). Subsequent tosylation gave protected indole **9** in quantitative yield, which was then treated with MeMgBr, affording tertiary alcohol **10** in 84% yield.

The next task was to introduce the cyclohexanone unit at the benzylic position of **10**. Such couplings are typically carried out by an S$_N$1-type process through the Lewis acid-promoted reaction of a ketone−TMS−enol ether with tertiary or benzylic alkyl halides.[7] For the problem at hand, it was more desirable to use the readily synthesized tertiary alcohol (**10**) directly. When the coupling of cyclohexanone−TMS−enol ether and tertiary alcohol **10′**, lacking the bromine at the 4-position of the indole, was carried out under Natsume's conditions, using SnCl$_4$ as the Lewis acid,[7d,e] the desired alkylation product (**11′**) was obtained in >80% yield. Unfortunately, under the same conditions, the corresponding halogenated indole (**10**) afforded the alkylated product (**11**) in only 66% yield. On the other hand, when the reaction was performed with TiCl$_4$ in toluene, the yield increased to 76%.

Although the natural product (**1**) contains an *N*-methyl indole, the *N*-tosyl-protected indole was used for the alkylation reaction to minimize reaction at the indole 2-position. Deprotection of the tosyl group proceeded uneventfully with potassium hydroxide in ethanol and afforded the free indole **12** in quantitative yield. Methylation under phase transfer conditions then gave **13**, containing the requisite *N*-methyl group. Finally, treatment of **13** with LDA generated the kinetic lithium enolate, which was carboxylated using the Mander reagent[8] to afford **14** in 96% yield.[9]

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(3) For a review on studies toward **1** and related structures, see: Avendaño, C.; Menéndez, J. C. *Curr. Org. Synth.* **2004**, *1*, 65.

(4) (a) Konopelski, J. P.; Deng, H. B.; Schiemann, K.; Keane, J. M.; Olmstead, M. M. *Synlett* **1998**, 1105. (b) Deng, H.; Konopelski, J. P. *Org. Lett.* **2001**, *3*, 3001. (c) 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. (d) 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. (e) Kaoudi, T.; Quiclet-Sire, B.; Seguin, S.; Zard, S. Z. *Angew. Chem., Int. Ed.* **2000**, *39*, 731. (f) Jung, M. E.; Slowinski, F. *Tetrahedron Lett.* **2001**, *42*, 6835. (g) López-Alvarado, P.; García-Granda, S.; Álvarez-Rúa, C.; Avendaño, C. *Eur. J. Org. Chem.* **2002**, 1702.

(5) For recent reviews on Pd-catalyzed enolate arylation, see: (a) Lloyd-Jones, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 953. (b) Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 211. (c) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234.

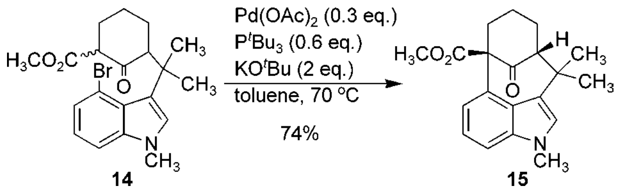
(6) For examples of intramolecular Pd-catalyzed enolate arylations, see: (a) Ciufolini, M. A.; Qi, H. B.; Browne, M. E. *J. Org. Chem.* **1988**, *53*, 4149. (b) Muratake, H.; Hayakawa, A.; Natsume, M. *Tetrahedron Lett.* **1997**, *38*, 7577. (c) Muratake, H.; Natsume, M. *Tetrahedron Lett.* **1997**, *38*, 7581. (d) Muratake, H.; Nakai, H. *Tetrahedron Lett.* **1999**, *40*, 2355. (e) Muratake, H.; Natsume, M.; Nakai, H. *Tetrahedron* **2004**, *60*, 11783. (f) Shaughnessy, K. H.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1998**, *63*, 6546. (g) Lee, S.; Hartwig, J. F. *J. Org. Chem.* **2001**, *66*, 3402. (h) Honda, T.; Namiki, H.; Satoh, F. *Org. Lett.* **2001**, *3*, 631. (i) Gaertzen, O.; Buchwald, S. L. *J. Org. Chem.* **2002**, *67*, 465. (j) Zhang, T. Y.; Zhang, H. B. *Tetrahedron Lett.* **2002**, *43*, 1363. For examples of intramolecular Pd-catalyzed vinylations, see: (k) Piers, E.; Marais, P. C. *J. Org. Chem.* **1990**, *55*, 3454. (l) Piers, E.; Renaud, J. *J. Org. Chem.* **1993**, *58*, 11. (m) Solé, D.; Peidro, E.; Bonjoch, J. *Org. Lett.* **2000**, *2*, 2225. (n) Yu, J. M.; Wang, T.; Liu, X. X.; Deschamps, J.; Flippen-Anderson, J.; Liao, X. B.; Cook, J. M. *J. Org. Chem.* **2003**, *68*, 7565. For an example from our lab of a Pd-catalyzed phenolate arylation, see: (o) Hennings, D. D.; Iwasa, S.; Rawal, V. H. *J. Org. Chem.* **1997**, *62*, 2.

(7) (a) Chan, T. H.; Paterson, I.; Pinsonnault, J. *Tetrahedron Lett.* **1977**, *18*, 4183. (b) Reetz, M. T.; Maier, W. F. *Angew. Chem.* **1978**, *90*, 50. (c) Reetz, M. T.; Schwellnus, K. *Tetrahedron Lett.* **1978**, *19*, 1455. (d) Muratake, H.; Natsume, M. *Tetrahedron* **1990**, *46*, 6331. (e) Sakagami, M.; Muratake, H.; Natsume, M. *Chem. Pharm. Bull.* **1994**, *42*, 1393.

(8) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425.

With ketoester **14** in hand, the key intramolecular Pd-catalyzed enolate arylation was examined next (Scheme 3).

Scheme 3



A variety of experimental conditions were screened, including different bases, solvents, and Pd sources, in an effort to optimize the reaction.[10] The highest yield was obtained using Pd(OAc)$_2$/P^{t}Bu$_3$ (0.3:0.6 equiv) in the presence of KO^{t}Bu (2 equiv) in toluene at 70 °C. The best results were obtained when palladium acetate, the ligand, and the base were premixed at room temperature, followed by the addition of a solution of **14**. The reaction proceeded quickly (less than 4 h) and afforded the product (**15**) as a crystalline solid in 74% yield. While the ^{1}H NMR and ^{13}C NMR spectra of **15** were consistent with the assigned structure, definitive proof of the structure was ultimately secured through X-ray crystallography, which clearly confirmed the presence of the desired bicyclo[4.3.1]decane ring system (Figure 1).

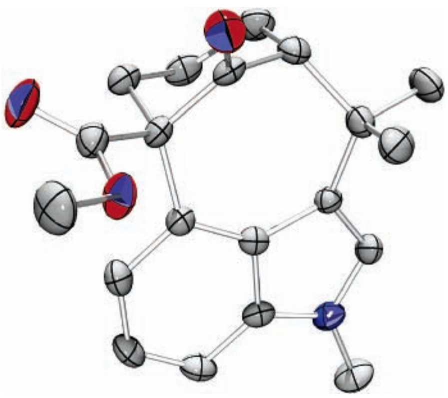
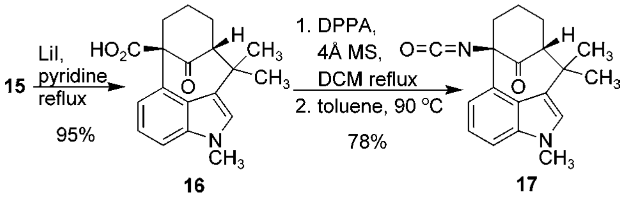


Figure 1. ORTEP of compound **15**.

What remained to be established through these studies was the feasibility of installing a nitrogen on the bridgehead (C11) carbon. The plan was to perform the Curtius rearrangement of the acyl azide derived from ester **15** in the presence of an alcohol and thus generate a carbamate that could be deprotected to reveal a functionalizable amine. In preparation for acyl azide formation, conditions for the hydrolysis of ester **15** were examined. To our surprise, **15** proved to be quite resistant toward basic hydrolysis, affording the acid in low conversions and yields, even under forcing conditions.[11] The low reactivity of ester **15** to basic hydrolysis can be understood by considering the structural constraints in the molecule. Inspection of the X-ray crystal structure of **15** shows that the conformation of the bicyclic ring system forces the ester to occupy a position where both faces of the carbonyl are inaccessible to hydrolytic attack (Figure 1). The top face is blocked by the ketone carbonyl group, the bottom by the indole C5 carbon. For this reason, we decided to employ nucleophilic dealkylation conditions to remove the methyl group.[12] Refluxing the ester in pyridine with an excess of LiI cleanly afforded the desired acid **16** in 95% yield, with no evidence of the decarboxylation product (Scheme 4).

Scheme 4



Keto acid **16** was treated with diphenylphosphoryl azide (DPPA), triethylamine, and 4-methoxy benzyl alcohol in refluxing THF, with the expectation that the intermediate isocyanate would be intercepted by the benzylic alcohol.[13] Remarkably, even after the reaction mixture was heated for 24 h, the major product of the reaction was the isocyanate. With a view toward optimizing the isocyanate formation, the Curtius rearrangement was performed in the absence of an alcohol and provided the desired isocyanate **17** in a 78% isolated yield.

The success of the arylation reaction followed by a Curtius rearrangement to form the bridgehead isocyanate lays the groundwork for our synthetic plan toward *N*-methylwelwitindolinone C isothiocyanate (**1**) and presents an attractive method for rapidly building up the highly complex welwitindolinone skeleton in a convergent manner. The model structure is conveniently synthesized in 10 steps from 4-bromoindole and contains the majority of the structural complexity of **1**. Additionally, this route highlights the power of the Pd-catalyzed enolate arylation reaction, which should prove useful in other alkaloid synthesis problems. While new challenges will likely await us in the synthesis of welwitindolinone **1**, we expect this strategy to be amenable to assembling the core of the natural product.

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(9) Although the carbomethoxylation proceeded cleanly; the product proved elusive to rigorous purification, most likely due to facile enolization and epimerization of the β-ketoester functionality.

(10) See Supporting Information.

(11) Refluxing in MeOH/H$_2$O with 60 equiv of LiOH for 22 h gave incomplete conversion and partial decomposition of the product.

(12) McMurry, J. *Org. React.* **1976**, *24*, 187.

(13) Shioiri, T.; Yamada, S.; Ninomiya, K. *J. Am. Chem. Soc.* **1972**, *94*, 6203.

Acknowledgment. We thank Professor Chong Zheng (Northern Illinois University) for solving the X-ray crystal structure of **15**. We thank the National Cancer Institute of the NIH (CA101438) for financial support. J.A.M gratefully acknowledges postdoctoral fellowship support (#PF-04-016-01-CDD) from the American Cancer Society.

Supporting Information Available: Experimental procedures and spectral data for all new compounds and crystallographic data for **15**. This material is available free of charge via the Internet at http://pubs.acs.org. Crystallographic data for the structural analysis of **15** has also been deposited with the Cambridge Crystallographic Data Centre (CCDC 271206). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

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