

A Synthesis of the Welwistatin Core<sup>§</sup>

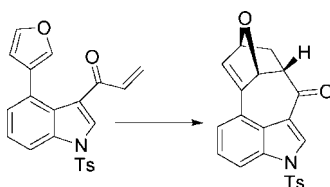
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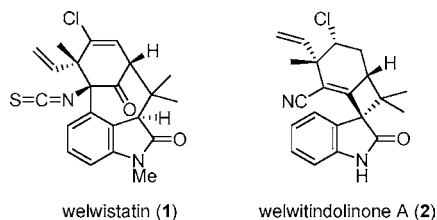
Received August 22, 2006

## ABSTRACT



An approach to the core structure of the microtubule-targeting agent welwistatin is described. The approach utilizes the type 2 intramolecular Diels–Alder reaction, with indole serving as the tether between diene and dienophile, to form the natural product's characteristic bicyclo[4.3.1]decane skeleton.

Despite the success of microtubule-targeting agents paclitaxel, vinblastine, and colchicine as cancer therapeutics, the effectiveness of these treatments is diminished in many instances by multiple drug resistance (MDR).<sup>1</sup> The mechanism of MDR is thought to be overexpression of P-glycoprotein, which acts as a drug efflux pump. The antimicrotubule agent welwistatin has shown the unique characteristic of maintaining its antimicrotubule properties in laboratory cell lines, even when those cell lines had MDR and overexpressed P-glycoprotein. This enhanced cytotoxic action demonstrates that welwistatin may be effective as an anticancer drug.



Welwistatin is an alkaloid isolated from blue-green algae, along with several related compounds.<sup>2</sup> Though welwitin-

dolinone A has been synthesized by impressive efforts of two groups, no members of the welwistatin structural class have yielded to total synthesis to date.<sup>3</sup> Recently, several core structure syntheses have been disclosed, emphasizing the significant interest in synthesizing this challenging molecule.<sup>4</sup> The complex architecture of welwistatin comprises 4 stereocenters, 3 quaternary carbons including 2 which are vicinal, a sensitive vinyl chloride, and an imbedded bicyclo[4.3.1] ring system. We hypothesized that this bicyclo[4.3.1] system could be accessed through a type 2 intramolecular Diels–Alder (T2IMDA) cyclization by using the indole framework to tether the diene and dienophile (Scheme

(2) (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.

(3) (a) Baran, P. S.; Richter, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 15394. (b) Reisman, S. E.; Ready, J. M.; Hasuoka, A.; Smith, C. J.; Wood, J. L. *J. Am. Chem. Soc.* **2006**, *128*, 1448.

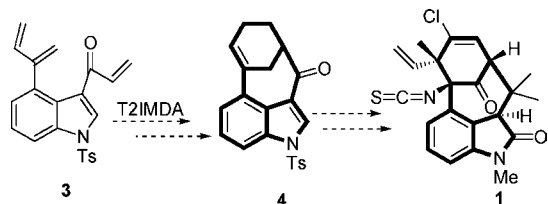
(4) (a) Konopelski, J. P.; Deng, H.; Scheimann, K.; Keane, J. M.; Olmstead, M. M. *Synlett* **1998**, 1105. (b) Wood, J. L.; Holubec, A. A.; Stoltz, B. M.; Weiss, M. M.; Dixon, J. A.; Doan, B. D.; Shamji, M. F.; Chen, J. M.; Heffron, T. P. *J. Am. Chem. Soc.* **1999**, *121*, 6326. (c) Kaoudi, T.; Quietlet-Sire, B.; Seguin, S.; Zard, S. Z. *Angew. Chem., Int. Ed.* **2000**, *39*, 731. (d) Konopelski, J. P.; Deng, H. *Org. Lett.* **2001**, *3*, 3001. (e) Jung, M. E.; Slowinski, F. *Tetrahedron Lett.* **2001**, *42*, 6835. (f) López-Alvarado, P.; García-Granda, S.; Álvarez-Rúa, C.; Avendaño, C. *Eur. J. Org. Chem.* **2002**, 1702. (g) 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. (h) MacKay, J. A.; Bishop, R. L.; Rawal, V. H. *Org. Lett.* **2005**, *7*, 3421. (i) Baudoux, J.; Blake, A. J.; Simpkins, N. S. *Org. Lett.* **2005**, *7*, 4087. (j) Greshock, T. J.; Funk, R. L. *Org. Lett.* **2006**, *8*, 2643. (k) For a review, see: Avendaño, C.; Menéndez, J. C. *Curr. Org. Synth.* **2004**, *1*, 65.

<sup>§</sup> Dedicated to the memory of the late Dr. Vinayak Kane.

(1) (a) Smith, C. D.; Zilfou, J. T.; Stratmann, K.; Patterson, G.; Moore, R. E. *Mol. Pharm.* **1995**, *47*, 241. (b) Zhang, X.; Smith, C. D. *Mol. Pharm.* **1996**, *49*, 288. (c) Jordan, M. A.; Wilson, L. *Nature Rev. Cancer* **2004**, *4*, 253.

1).<sup>5</sup> Our interest is to develop a concise entry to the

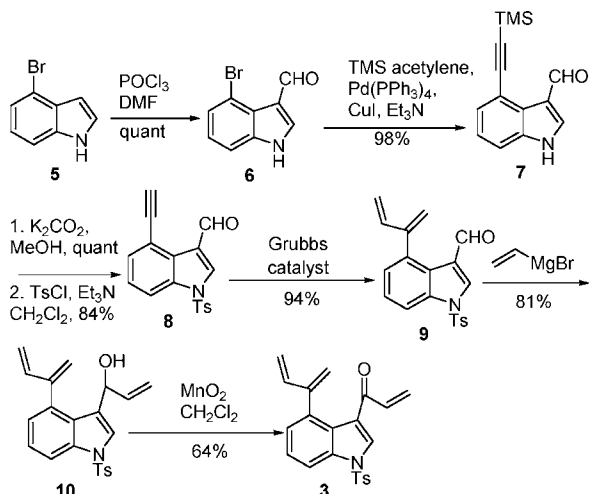
**Scheme 1.** The T2IMDA Strategy for Constructing the Welwistatin Core



welwistatin core structure, and investigate the potential of the indole group as a tether in the T2IMDA and its effects on stereochemistry and reactivity on the cycloaddition step.

To establish the feasibility of this approach, we targeted the parent 1,3-butadiene and unsubstituted enone as the Diels–Alder components to access the core structure of welwistatin. Our synthetic route began with 4-bromoindole.<sup>6</sup>

**Scheme 2.** Synthesis of the Diels–Alder Precursor

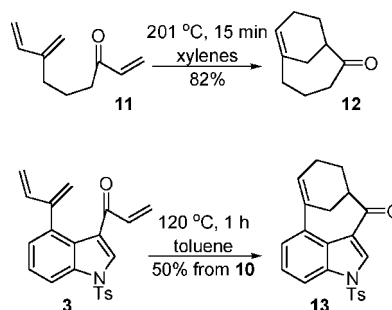


Vilsmeier–Hack formylation of this compound gave a quantitative yield of aldehyde **6**.<sup>7</sup> A Sonagashira coupling was used to install the TMS-protected acetylene at the 4-position of the indole. Deprotection of the acetylene proceeded cleanly, and the indole nitrogen was protected at this stage with tosyl chloride. Tosyl protection of the indole was found to be necessary for the subsequent metathesis step, as this protecting group improved the toluene solubility of the compound. The ene–yne metathesis in toluene was subsequently accomplished in 94% yield by using Grubbs

second generation catalyst at 80 °C under a balloon filled with ethylene.<sup>8</sup>

The *N*-tosyl protecting group was also critical for the following step, the addition of vinylmagnesium bromide to aldehyde **9** to form the allylic alcohol **10**. With the *N*-methyl group, the allylic alcohol rapidly decomposed.<sup>9</sup> Tosyl protection disfavored carbocation formation, and permitted isolation of the allylic alcohol **10** in 81% yield. MnO<sub>2</sub> was used to oxidize the allylic alcohol to the corresponding vinyl ketone **3**, the T2IMDA cyclization precursor. The indole group had not previously been incorporated as part of the tether in the T2IMDA reaction. It was anticipated, however, that this group could reduce the conformational freedom of the Diels–Alder precursor, resulting in milder conditions for the cycloaddition. Previous experience had shown that a simple C4-alkyl chain tether required a temperature of 200 °C for 15 min to induce cyclization to the bicyclo[4.3.1] cycloadduct (Scheme 3).<sup>10</sup>

**Scheme 3.** A Comparison of the Reactivities of T2IMDA Precursors



Our attempt at the T2IMDA reaction was conducted at 120 °C. Gratifyingly, the reaction was complete after 1 h at this temperature, and the product was isolated in 50% yield overall from **10**. Connectivity in the cycloadduct was established by 2D NMR experiments. Mass spectrometry revealed the monomeric nature of the product, eliminating the possibility that a bimolecular cycloaddition between two indole molecules had occurred. These data confirmed the synthesis of the welwistatin core.

Following the success of the indole moiety as a tether in the T2IMDA cyclization in forming the welwistatin core structure, we endeavored to introduce functionality at key positions. One possibility was the use of furan as the diene. Though furan has been used as a diene in many Diels–Alder reactions, the need to overcome its aromatic stabilization usually limits its use in cycloadditions.<sup>11</sup> Strategies to increase the reactivity of furan have included high pressure, the introduction of heteroatoms at the 1-position, and tethering

(5) Bear, B. R.; Sparks, S. M.; Shea, K. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 820.

(6) Moyer, M. P.; Shiurba, J. F.; Rapoport, H. *J. Org. Chem.* **1986**, *51*, 5106.

(7) Somei, M.; Kizu, K.; Kunitomo, M.; Yamada, F. *Chem. Pharm. Bull.* **1985**, *33*, 3696.

(8) (a) Tonogaki, K.; Mori, M. *Tetrahedron Lett.* **2002**, *43*, 2235. (b) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317.

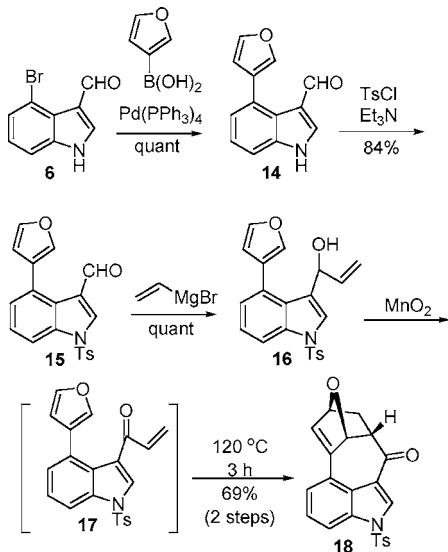
(9) Similar results were observed previously: Bannasar, M. L.; Zulaica, E.; Tummers, S. *Tetrahedron Lett.* **2004**, *45*, 6283.

(10) Shea, K. J.; Wise, S. *Tetrahedron Lett.* **1979**, *20*, 1011.

(11) Kappe, C. O.; Murphree, S. S.; Padwa, A. *Tetrahedron* **1997**, *53*, 14179.

the dienophile to the 1-position for type 1 intramolecular Diels–Alder reactions. To the best of our knowledge, no examples of T2IMDA cyclizations with furan dienes have been reported. Installing furan as the diene began with

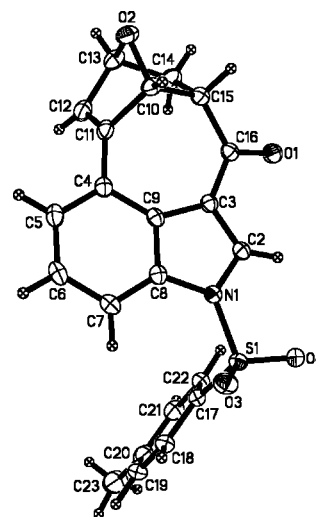
**Scheme 4.** The Furan Diene to Access a Functionalized Core of Welwistatin



aldehyde **6**. Suzuki coupling with 3-furan boronic acid gave 4-furylindole **14** quantitatively. Protection of the indole to tosylate and addition of vinyl magnesium bromide to give the allylic alcohol **16** proceeded as in the unfunctionalized diene case. Oxidation with  $\text{MnO}_2$  gave the cyclization precursor, which was immediately dissolved in toluene and heated to 120 °C. This relatively low temperature for the cycloaddition was deemed necessary to disfavor retrocycloaddition. Surprisingly, cycloadduct **18** was obtained after 3 h in 69% yield. The cycloadduct proved to be stable indefinitely at ambient temperature, and its structure was confirmed through X-ray crystallography.

Cycloadduct **18** incorporates oxygen at both ketone and vinyl chloride positions in the natural product, and thus

opening the oxo bridge can allow for elaboration to these functionalities in a synthesis of welwistatin. In summary, a



**Figure 1.** ORTEP of cycloadduct **18**.

3,4-substituted indole has served as a tether in the T2IMDA cyclization to form the core structure of welwistatin. The unfunctionalized core was accessed in 8 steps from 4-bromoindole. The unprecedented use of furan as a diene in the T2IMDA reaction provided an appropriately functionalized welwistatin core from 4-bromoindole in 6 steps. Elaboration of this core is underway.

**Acknowledgment.** This research was supported by the National Institutes of Health. We are grateful to Dr. Joseph W. Ziller (UCI) for X-ray crystallographic work, Dr. Phil Dennison (UCI) for NMR expertise, and Dr. John Greeves (UCI) for mass spectral data. R.L. thanks the National Institutes of Health for a predoctoral fellowship.

**Supporting Information Available:** Experimental details and spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL0620747