An Approach to the Total Synthesis of Welwistatin
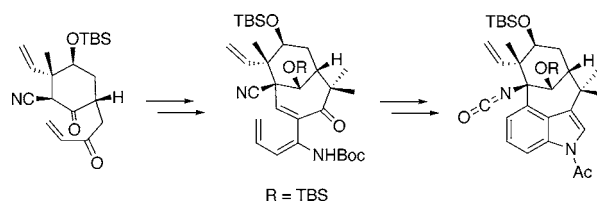
Thomas J. Greshock and Raymond L. Funk*

Department of Chemistry, Pennsylvania State University, University Park, Pennsylvania 16802

rlf@chem.psu.edu

ABSTRACT

R = TBS

An approach to the total synthesis of the antimicrotubule agent welwistatin is described. Key transformations include (1) a 7-endo intramolecular conjugate addition reaction of enone 6 to deliver the strained bicyclo[4.3.1]decanone 5; (2) a 6π electrocyclic ring closure of trienecarbamate 16 followed by oxidation to afford protected aniline 17; and (3) an intramolecular cyclization of acetic acid derivative 18 to give rise to indole 19.

The welwitindolinones[1] are a fascinating family of indole alkaloids isolated from blue-green algae. Welwitindolinone C isothiocyanate (welwistatin) is one of the major alkaloids isolated from both *Hapalosiphon welwitschii* and *Westiella intricate*,[1a] and the structure of the *N*-methyl congener was secured by X-ray crystallographic analysis (Scheme 1). Moreover, it has been hypothesized that all of these welwitindolinones arise from welwitindolinone A via epoxidation of the alkene moiety and subsequent cyclization at C(4).[1a] It was originally believed that welwistatin reversed P-glycoprotein-mediated multiple drug resistance (MDR).[2a] However, it was later shown that welwistatin is a cytotoxin itself and inhibits the proliferation of SK-OV-3 and A-10 cells (IC$_{50}$, 72 and 900 nM, respectively) and, more importantly, arrests P-glycoprotein-overexpressing MCF-7/AdR cells (IC$_{50}$, 130 nM) in the G2 mitotic phase.[2b] Moreover, immunofluorescence studies of tubulin organization revealed that welwistatin causes dose-dependent disr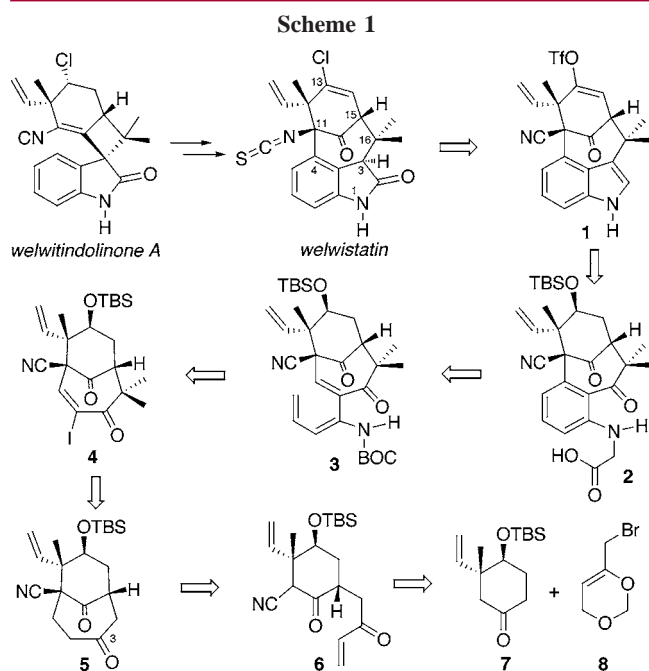uption of microtubules in intact cells. Additional experimentation suggested that welwistatin does not bind to either the colchicine or taxol sites.[2b] Thus, this compound represents a new antimicrotubule agent that may be useful for the treatment of drug-resistant tumors.

The unprecedented ring system, the sensitive vinyl chloride and bridgehead isothiocyanate functionalities, the vicinal quaternary centers, and the C(16) *gem*-dimethyl substituent conspire to make the synthesis of welwistatin an especially challenging problem. Several synthetic approaches have been described, and all of them have in common the elaboration of the complete ring system from an appropriately substituted indole or oxindole.[3,4] We present a conceptually distinct strategy for the total synthesis of welwistatin that (1) permits the immediate incorporation of the C(12), C(15) relative

(1) (a) Stratmann, K.; Moore, R. E.; Bonjouklian, R.; Deeter, J. B.; Patterson, G.; 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. *J. Nat. Prod.* **1999**, *62*, 569.

(2) (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.

(3) For approaches to the welwitindolinones, see: (a) Konopelski, J. P.; Deng, H.; Schiemann, 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.; Quiclet-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. *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) For a review: Avendano, C.; Menéndez, J. C. *Curr. Org. Synth.* **2004**, *1*, 65.

Scheme 1

Scheme 2

through either a chair or boat conformer would be less preferred because of a developing 1,3-diaxial interaction with the silyloxy substituent or a flagpole–flagpole interaction with the methyl group, respectively.[8] The resulting alkylation product then would be converted to a β-ketonitrile and heated to effect retrocycloaddition to enone **6**, the substrate for the intramolecular Michael addition leading to diketone **5**.

Our synthesis commenced with the preparation of the known ketone **7**, easily available from 3-methylanisole either as the racemate or in optically pure form (Scheme 2).[9] As
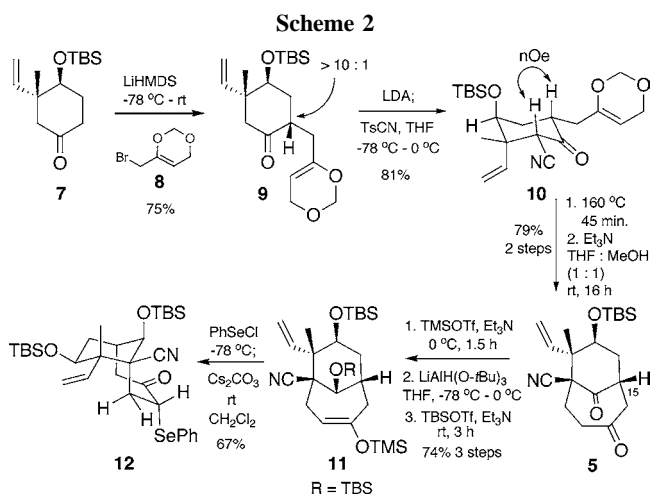
stereochemistry beginning with an easily accessible substituted cyclohexanone; (2) addresses the early-stage construction of the strained bridged bicyclic substructure using our 1,3-dioxin-based methodology;[5] and (3) subsequently elaborates the indole/oxindole ring system by exploiting our newly developed annelation sequence.[6]

Our retrosynthetic analysis is outlined in Scheme 1. Indole **1** possesses a fully intact ring system and is suitably functionalized for the introduction of the vinyl chloride, bridgehead isothiocyanate, and oxindole functionalities from the respective vinyl triflate,[7] bridgehead nitrile, and indole[3d,e] moieties. Indole **1** was envisaged to arise from α-iodoenone **4** through extension of our newly developed indole annelation sequence.[6] Thus, electrocyclic ring closure of trienecarbamate **3** and a carbonyl condensation reaction involving the α-anilinoacid **2** were the expected key bond-forming steps. It seemed likely that the C(3) carbonyl group of diketone **5** could be chemo- and regioselectively enolized to sequentially install the vinyl iodide functionality and thence the *gem*-dimethyl group. We had previously prepared bicyclo[4.3.1]-decan-3,10-diones related to dione **5** using halide **8** as a bromomethyl vinyl ketone equivalent.[5] In this specific application, it was hoped that the kinetic enolate of ketone **7** would undergo axial alkylation from the α-face through a chair conformer possessing equatorial vinyl and silyloxy substituents. Alkylation of the enolate from the β-face

expected, alkylation of the enolate derived from ketone **7** with allylic bromide **8** proceeded diastereoselectively to deliver ketone **9**. The tentative stereochemical assignment was confirmed upon cyanation of its regioselective enolate with *p*-toluenesulfonyl cyanide to afford β-ketonitrile **10** whose coupling constants for the diagnostic ^{1}H NMR resonances, as well as NOE observations, were consistent with the assigned structure. It should be noted that all attempts to prepare the analogous β-ketoester were uniformly unsuccessful and instead led to the isolation of the O-acylated product. With the correct C(12)–C(15) relative stereochemistry now in place, we turned to completion of the bridged bicyclic structure. Thus, thermolysis of dioxin **10** effected a retrocycloaddition to afford enone **6** (Scheme 1). Treatment of enone **6** with Et$_3$N in THF/MeOH effected a smooth 7-endo intramolecular conjugate addition reaction to deliver the desired bicyclo[4.3.1]decanone **5** with no indication of competing epimerization at C(15).

With the fully substituted bridged bicyclic ring system in hand, we directed our attention toward the preparation of the α-haloenone (**4**, Scheme 1) required for the indole annelation sequence. Concurrent investigations indicated that the bridgehead carbonyl of enone **4** would prove to be

(4) For total syntheses of welwitindolinone A, see: (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.

(5) Greshock, T. J.; Funk, R. L. *J. Am. Chem. Soc.* **2002**, *124*, 754.

(6) Greshock, T. J.; Funk, R. L. *J. Am. Chem. Soc.* **2006**, *128*, 4946.

(7) For treatment of the corresponding vinyl stannane with CuCl$_2$, see: (a) Takeda, T.; Kanamori, F.; Matususita, H.; Fujiwara, T. *Tetrahedron Lett.* **1991**, *32*, 6563. (b) Madec, D.; Férézou, J. P. *Tetrahedron Lett.* **1997**, *38*, 6661.
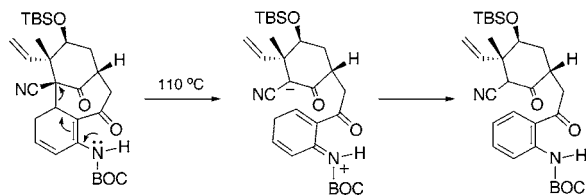
(8) This analysis is substantiated by several examples of highly diastereoselective C(6) alkylations of related 3,3,4-trisubstituted cyclohexan-1-ones. See: (a) Fredrich, P.; Bohlmann, F. *Tetrahedron* **1988**, *44*, 1369. (b) Tomioka, K.; Masumi, F.; Yamashita, T.; Koga, K. *Tetrahedron* **1989**, *45*, 643. (c) Kato, M.; Kosugi, H.; Ichiyanagi, T.; Yamabe, O. *J. Chem. Soc., Perkin Trans. 1* **1999**, 783.

(9) Frejd, T.; Polla, M. *Tetrahedron* **1991**, *47*, 5883.

troublesome, in particular, during the anticipated electrocyclic ring closure of triene carbamate **3**.[10] Accordingly, ketone **5** (Scheme 2) was regioselectively converted to a silyl enol ether, the problematic bridgehead ketone then was reduced stereoselectively (9:1) with LiAlH(O-*t*Bu)$_3$, and the resulting alcohol was protected with TBSOTf to afford the more robust bicyclic compound **11**. Because attempts to α-iodinate the enone obtained from Saegusa oxidation [Pd(OAc)$_2$] of silyl enol ether **11** were unsuccessful, we turned to alternative strategies for the preparation of an α-haloenone. It was eventually discovered that the selenide **12**, obtained by treatment of silyl enol ether **11** with PhSeCl followed by brief thermodynamic equilibration of the resulting diastereomeric α-phenylselenoketones (4:1; **12**:epi) with Cs$_2$CO$_3$, was a viable precursor to **13**.
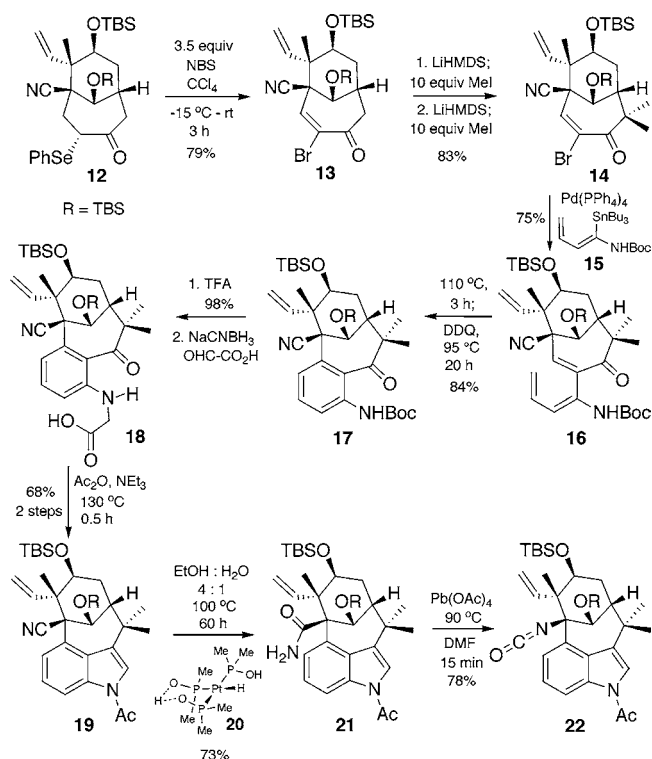
Indeed, we were pleased to find that subjection of selenide **12** to excess NBS in CCl$_4$ cleanly provided the desired α-bromoenone **13** (Scheme 3).[11] It is of interest to note that the epimeric selenide afforded only *des*-bromo **13** when subjected to these reaction conditions. Following introduction of the *gem*-dimethyl group by sequential enolate methylations, we turned to the Stille coupling of α-bromoenone **14** with α-stannyl enecarbamate **15**[6] to prepare the key electrocyclization precursor, amidotriene **16**. We were gratified to discover that, upon heating in toluene (110 °C, 3 h), triene **16** now underwent an uneventful ring closure to afford a cyclohexadiene that was oxidized in situ with DDQ to furnish the protected aniline **17**. Removal of the BOC group of carbamate **17** with TFA and reductive amination of the resultant aniline with glyoxylic acid provided acid **18**. Closure to *N*-acetylindole **19** was then effected using the conditions employed in our methodological studies and constitutes the sterically most demanding example of this transformation that we have examined. Although we plan to introduce the bridgehead nitrogen at a later stage in our projected total synthesis, we thought it would be prudent to document the feasibility of this Hofmann-rearrangement-based transformation in such a congested environment. To

Scheme 3

that end, we found that hydrolysis of the encumbered nitrile could be accomplished with the remarkable Parkins catalyst **20**[12] to secure the bridgehead amide **21**. It was equally pleasing to discover that the Baumgarten variant[13] of the Hofmann rearrangement was successful when amide **21** was subjected to Pb(OAc)$_4$ in DMF at 90 °C, thereby providing the most advanced welwistatin total synthesis intermediate, isocyanate **22**, reported to date. Thus, it is hoped that indole **19** is well functionalized for the intensive functional group manipulation phase of our total synthesis endeavor. These studies are underway and will be disclosed in due course.

Supporting Information Available: Spectroscopic data and experimental details for the preparation of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(10) In previous studies, we had found that the product of the electrocyclic ring closure of the *des*-methyl analogue of trienecarbamate **3** was thermally unstable and underwent a concomitant vinylogous retro-Mannich reaction as shown below. This result no doubt reflects the strain (and synthetic challenge) imposed by the encumbered C(12) quaternary carbon. Indeed, the electrocyclic rearrangements of model systems lacking substituents at this position proceeded uneventfully.

(11) This fortuitous transformation most likely proceeds through the α-phenylselenyl α-haloketone. For the halogenation of an α-phenylselenyl ketone, see: Tsuda, Y.; Hosoi, S. *Chem. Pharm. Bull.* **1985**, *33*, 1745.

(12) (a) Ghaffar, T.; Parkins, A. W. *Tetrahedron Lett.* **1995**, *36*, 8657. (b) Ghaffar, T.; Parkins, A. W. *J. Mol. Catal. A* **2000**, *160*, 249. (c) For another application of this catalyst in an equally complex setting, see: Herzon, S. B.; Myers, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 5342.

(13) (a) Baumgarten, H. E.; Staklis, A. *J. Am. Chem. Soc.* **1965**, *87*, 1141. (b) Baumgarten, H. E.; Smith, H. L.; Staklis, A. *J. Org. Chem.* **1975**, *40*, 3554.