ORGANIC LETTERS

2012
Vol. 14, No. 14
3756–3759

Synthesis of Functionalized Cyclohexenone Core of Welwitindolinones via Rhodium-Catalyzed [5 + 1] Cycloaddition

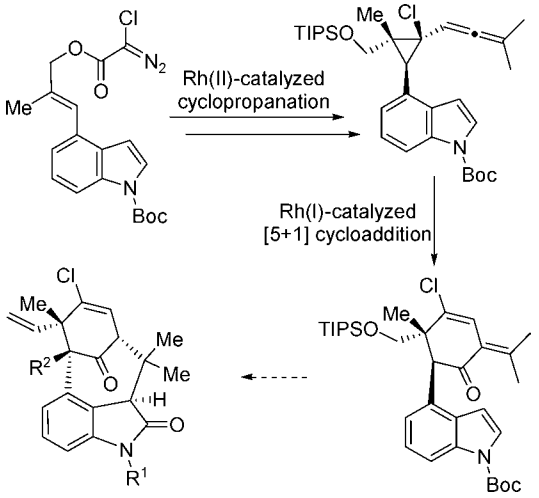
Min Zhang and Weiping Tang*

School of Pharmacy, University of Wisconsin, Madison, Wisconsin 53705, United States

wtang@pharmacy.wisc.edu

Received June 12, 2012

ABSTRACT



The cyclohexenone core of welwitindolinones was synthesized by a Rh(I)-catalyzed [5 + 1]-cycloaddition of an allenylcyclopropane with CO. A pentasubstituted cyclopropane was prepared successfully by a Rh(II)-catalyzed intramolecular cyclopropanation of alkenes with chlorodiazoacetates.

Indole alkaloid welwitindolinones (e.g., **1**–**3**, Scheme 1) and related natural products were isolated from blue-green algae *Hapalosiphon welwitschii* and westiella intricate.[1] *N*-Methylwelwitindolinone C isothiocyanate **1** reversed the drug resistance of cancer cells in the presence of various anticancer drugs, including actinomycin D, colchicine, daunomycin, taxol, and vinblastine.[2] Because of the challenging structures and their interesting biological activity, numerous synthetic efforts have been devoted to the synthesis of welwitindolinone C's[3] and related natural products, such as welwitindolinone A.[4] Recently, research groups of Rawal[5] and Garg[6] independently accomplished elegant syntheses of welwitindolinone C's and their oxidized congeners.

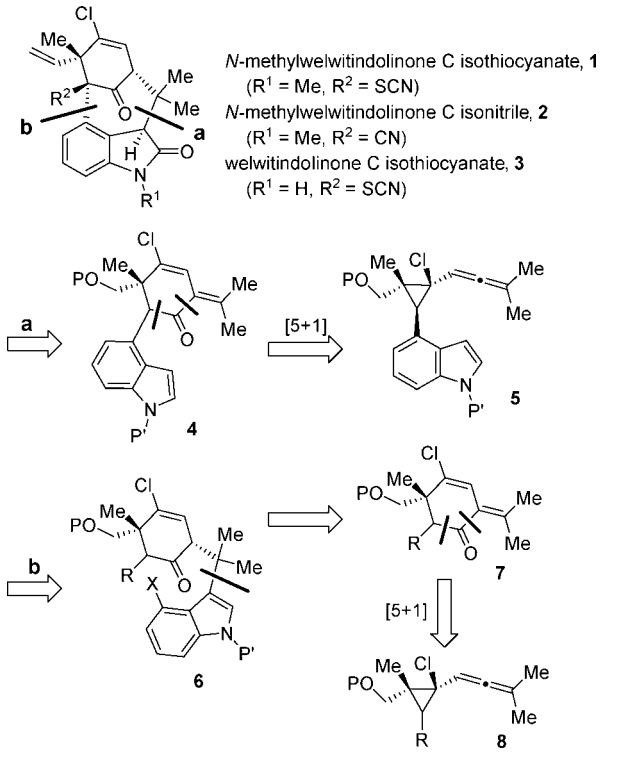
In most previous strategies for welwitindolinone C's, functional groups on the six-membered ring especially the vinyl chloride group were introduced or proposed to be introduced at a late stage, which was often challenging.[7] We envisioned that a Rh-catalyzed [5 + 1] cycloaddition of allenylcyclopropane **5** with CO might afford the fully functionalized cyclohexenone core **4** efficiently. Alternatively, [5 + 1] cycloaddition of allenylcyclopropane **8** may yield cyclohexenone **7**. Closing of the seven-membered ring may be realized by addition to the isopropylidene group in intermediate **4** through strategy **a** or α-arylation of the ketone group in intermediate **6** through strategy **b**.

(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/ol301614v
Published on Web 07/11/2012

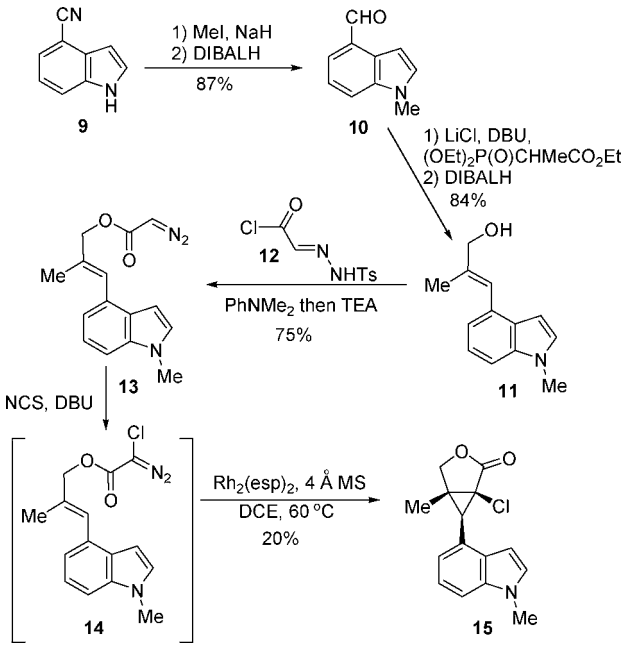
Scheme 1. Proposed Strategies for Welwitindolinones



We recently developed a stereoselective method for the synthesis of highly functionalized cyclohexenones via Rh-catalyzed [5 + 1] cycloaddition of allenylcyclopropanes derived from 1,3-acyloxy migration of propargyl esters.[8,9] We examined the regioselectivity for the cleavage of the cyclopropane ring and found that the C−C bond adjacent to an electron-rich aryl group or away from a quaternary carbon was selectively cleaved.[8,10] This provided the basis for the proposed regioselective [5 + 1] cycloaddition of cyclopropane **5** or **8**.

The synthesis began with the preparation of allylic alcohol **11** from commercially available 4-cyanoindole **9** through a sequence of methylation, reduction, olefination, and reduction (Scheme 2). Esterification and diazo compound formation were achieved in one step using reagent **12**.[11] Chlorination of diazo compound **13** yielded an unstable halodiazoacetate that was directly used in the cyclopropanation reaction. Based on a previous report,[12] Du Bois' $Rh_2(esp)_2$ was an efficient catalyst for mediating intermolecular cyclopropanation of alkenes and halodiazoacetates.[13] We also found that $Rh_2(esp)_2$ was superior to other rhodium catalysts such as $Rh_2(OAc)_4$ for this intramolecular cyclopropanation. The best isolated yield we obtained for product **15**, however, was only about 20%. We suspected that the electron-rich indole ring might interfere with the electrophilic cyclopropanation. Substrates with an electron-withdrawing group on the indole nitrogen were then examined.

Scheme 2. Intramolecular Cyclopropanation of an Alkene Substituted with a *N*-Methyl Indole



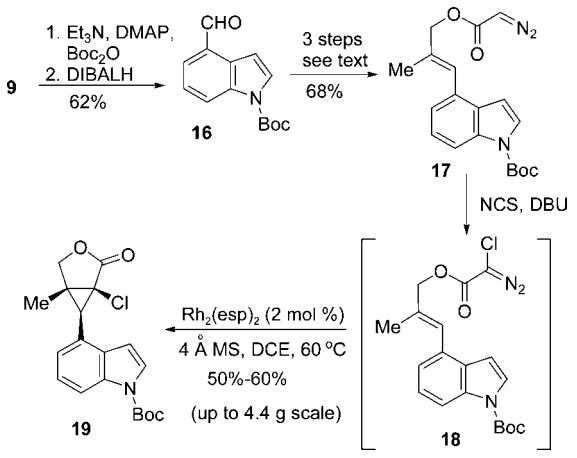
(3) For efforts towards the synthesis of welwitindolinones, see: (a) Konopelski, J. P.; Deng, H. B.; Schiemann, K.; Keane, J. M.; Olmstead, M. M. *Synlett* **1998**, 1105. (b) Wood, J. L.; Holubec, A. A.; Stoltz, B. M.; Weiss, M. M.; Dixon, J. A.; Doan, B. D.; Shamji, M. F.; Chen, J. M.; Heffron, T. 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) Jung, M. E.; Slowinski, F. *Tetrahedron Lett.* **2001**, *42*, 6835. (e) Deng, H. B.; Konopelski, J. P. *Org. Lett.* **2001**, *3*, 3001. (f) Lopez-Alvarado, P.; Garcia-Granda, S.; Alvarez-Rua, C.; Avendano, 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) Lauchli, R.; Shea, K. J. *Org. Lett.* **2006**, *8*, 5287. (l) Xia, J.; Brown, L. E.; Konopelski, J. P. *J. Org. Chem.* **2007**, *72*, 6885. (m) Richter, J. M.; Ishihara, Y.; Masuda, T.; Whitefield, B. W.; Llamas, T.; Pohjakallio, A.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 17938. (n) Boissel, V.; Simpkins, N. S.; Bhalay, G.; Blake, A. J.; Lewis, W. *Chem. Commun.* **2009**, 1398. (o) Boissel, V.; Simpkins, N. S.; Bhalay, G. *Tetrahedron Lett.* **2009**, *50*, 3283. (p) Tian, X.; Huters, A. D.; Douglas, C. J.; Garg, N. K. *Org. Lett.* **2009**, *11*, 2349. (q) Trost, B. M.; Mcdougall, P. J. *Org. Lett.* **2009**, *11*, 3782. (r) Brailsford, J. A.; Lauchli, R.; Shea, K. J. *Org. Lett.* **2009**, *11*, 5330. (s) Freeman, D. B.; Holubec, A. A.; Weiss, M. W.; Dixon, J. A.; Kakefuda, A.; Ohtsuka, M.; Inoue, M.; Vaswani, R. G.; Ohki, H.; Doan, B. D.; Reisman, S. E.; Stoltz, B. M.; Day, J. J.; Tao, R. N.; Dieterich, N. A.; Wood, J. L. *Tetrahedron* **2010**, *66*, 6647. (t) Heidebrecht, R. W.; Gulledge, B.; Martin, S. F. *Org. Lett.* **2010**, *12*, 2492. (u) Ruiz, M.; Lopez-Alvarado, P.; Menendez, J. C. *Org. Biomol. Chem.* **2010**, *8*, 4521.

(4) (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. (c) Baran, P. S.; Maimone, T. J.; Richter, J. M. *Nature* **2007**, *446*, 404. (d) Reisman, S. E.; Ready, J. M.; Weiss, M. M.; Hasuoka, A.; Hirata, M.; Tamaki, K.; Ovaska, T. V.; Smith, C. J.; Wood, J. L. *J. Am. Chem. Soc.* **2008**, *130*, 2087.

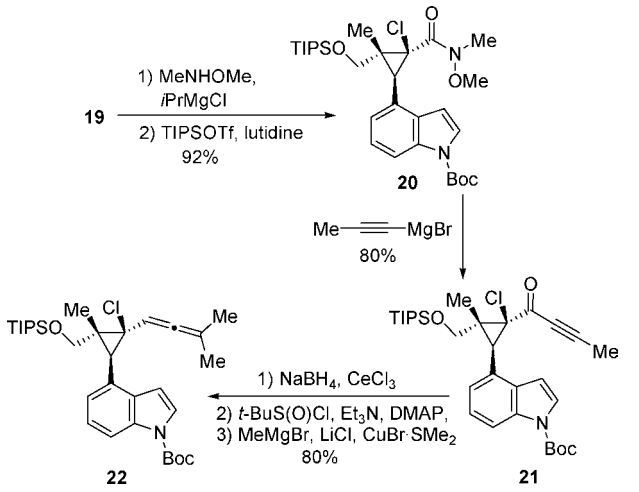
(5) (a) Bhat, V.; Allan, K. M.; Rawal, V. H. *J. Am. Chem. Soc.* **2011**, *133*, 5798. (b) Bhat, V.; Mackay, J. A.; Rawal, V. H. *Org. Lett.* **2011**, *13*, 3214. (c) Bhat, V.; Rawal, V. H. *Chem. Commun.* **2011**, *47*, 9705. (d) Bhat, V.; Mackay, J. A.; Rawal, V. H. *Tetrahedron* **2011**, *67*, 10097. (e) Allan, K. M.; Kobayashi, K.; Rawal, V. H. *J. Am. Chem. Soc.* **2012**, *134*, 1392.

(6) (a) Huters, A. D.; Quasdorf, K. W.; Styduhar, E. D.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, *133*, 15797. (b) Quasdorf, K. W.; Huters, A. D.; Lodewyk, M. W.; Tantillo, D. J.; Garg, N. K. *J. Am. Chem. Soc.* **2012**, *134*, 1396.

Scheme 3. Intramolecular Cyclopropanation of an Alkene Substituted with a *N*-Boc Protected Indole



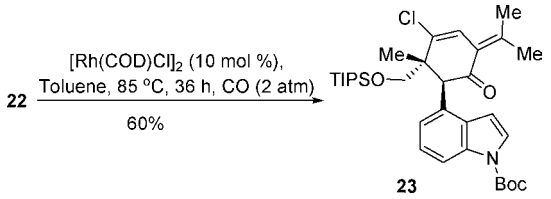
Scheme 4. Preparation of Pentasubstituted Allenylcyclopropane



Boc-protected indole **16** was prepared in two steps from 4-cyanoindole indole **9** (Scheme 3). Diazoacetate **17** could be synthesized according to protocols described in Scheme 2. Chlorination followed by intramolecular cyclopropanation using the $Rh_2(esp)_2$ catalyst afforded bicyclic product **19** in 50−60% yield after two steps starting with 1.2−4.4 g of diazo compound **17**. This represents the first successful example of intramolecular cyclopropanation of alkenes with chlorodiazoaceates, and the reaction could be scaled up to several grams.

Opening of the lactone and protection of the resulting primary alcohol afforded Weinreb amide[14] **20** (Scheme 4). Addition of propynyl magnesium bromide to this amide then yielded ynone **21**, which was reduced to a mixture of two diastereomeric propargyl alcohols. Attempts to prepare allene **22** through an S_N2' reaction led to either decomposition when the leaving group was a mesylate/triflate or no reaction when the leaving was acetate.[15] Eventually, displacement of a sulfoxide leaving group[16] proved to be fruitful and provided the desired allene **22** in 80% yield from ynone **21**.

Scheme 5. Rh-Catalyzed [5 + 1] Cycloaddition of Allenylcyclopropane and CO



With allenylcyclopropane **22** in hand, we then tried the [5 + 1] cycloaddition under different conditions. After screening various solvents (toluene, xylene, DCE, $CHCl_3$, dioxane), catalysts ($[Rh(CO)_2Cl]_2$, $[Rh(COD)_2Cl]_2$, $[RhCl(PPh_3)_3]$, $Ir(CO)_2Cl]_2$), CO pressure (1 atm, 2 atm, and 5 atm), and temperature, we were able to isolate a 60% yield of the desired [5 + 1] cycloaddition product **23** under conditions shown in Scheme 5. The cyclopropane C−C bond adjacent to the indole ring and away from the quaternary carbon was selectively cleaved during the cycloaddition. The relative stereochemistry of the product and the regioselectivity for cleavage of the cyclopropane C−C σ-bond were determined by NOE and HMBC, respectively.[17]

(7) For reviews on strategies and approaches for welwitindolinones, see: (a) Avendano, C.; Menendez, J. C. *Curr. Org. Synth.* **2004**, *1*, 65. (b) Brown, L. E.; Konopelski, J. P. *Org. Prep. Proc. Intl.* **2008**, *40*, 411. (c) Wood, J. L. *Nat. Chem.* **2012**, *4*, 341. (d) Huters, A. D.; Styduhar, E. D.; Garg, N. K. *Angew. Chem., Int. Ed.* **2012**, *51*, 3758.

(8) Shu, D.; Li, X.; Zhang, M.; Robichaux, P. J.; Tang, W. *Angew. Chem., Int. Ed.* **2011**, *50*, 1346.

(9) For selected examples of [5 + 1] cycloaddition of vinyl- and allenylcyclopropanes, see: (a) Taber, D. F.; Kanai, K.; Jiang, Q.; Bui, G. *J. Am. Chem. Soc.* **2000**, *122*, 6807. (b) Kurahashi, T.; De Meijere, A. *Synlett* **2005**, 2619. (c) Iwasawa, N.; Owada, Y.; Matsuo, T. *Chem. Lett.* **1995**, 115. (d) Owada, Y.; Matsuo, T.; Iwasawa, N. *Tetrahedron* **1997**, *53*, 11069. (e) Murakami, M.; Itami, K.; Ubukata, M.; Tsuji, I.; Ito, Y. *J. Org. Chem.* **1998**, *63*, 4. (f) Taber, D. F.; Sheth, R. B.; Tian, W. *J. Org. Chem.* **2009**, *74*, 2433. (g) Jiang, G.-J.; Fu, X.-F.; Li, Q.; Yu, Z.-X. *Org. Lett.* **2012**, *14*, 692.

(10) For a comprehensive review on transition metal mediated reactions involving cyclopropanes, see: Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117.

(11) (a) Blankley, C. J.; Sauter, F. J.; House, H. O. *Org. Synth.* **1969**, *49*, 22. (b) Corey, E. J.; Myers, A. G. *Tetrahedron Lett.* **1984**, *25*, 3559.

(12) (a) Bonge, H. T.; Pintea, B.; Hansen, T. *Org. Biomol. Chem.* **2008**, *6*, 3670. For a computational study of cyclopropanation with halodiazoacetates, see: (b) Bonge, H. T.; Hansen, T. *J. Org. Chem.* **2010**, *75*, 2309.

(13) Espino, C. G.; Fiori, K. W.; Kim, M.; Du Bois, J. *J. Am. Chem. Soc.* **2004**, *126*, 15378.

(14) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.

(15) For selected reviews on the synthesis of allenes, see: (a) Brummond, K. M.; Deforrest, J. E. *Synthesis* **2007**, 795. (b) Yu, S.; Ma, S. *Chem. Commun.* **2011**, *47*, 5384. For selected reviews on transition metal mediated reactions involving allenes, see: (c) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3590. (d) Ma, S. *Chem. Rev.* **2005**, *105*, 2829. (e) Inagaki, F.; Kitagaki, S.; Mukai, C. *Synlett* **2011**, 594. (f) Aubert, C.; Fensterbank, L.; Garcia, P.; Malacria, M.; Simonneau, A. *Chem. Rev.* **2011**, *111*, 1954.

(16) (a) Westmijze, H.; Vermeer, P. *Synthesis* **1979**, 390. (b) Elsevier, C. J.; Vermeer, P. *J. Org. Chem.* **1989**, *54*, 3726.

(17) See Supporting Information for details.

In summary, we have developed an efficient strategy to access the cyclohexenone core of welwitindolinone C's. Highly sterically congested pentasubstituted cyclopropanes were prepared successfully by an intramolecular cyclopropanation of trisubstituted alkenes with chlorodiazoacetates. The [5 + 1] cycloaddition product **23** has a cyclohexenone core with most of the required functionalities for welwitindolinone C's including a quaternary carbon, a vinylchloride group, an indole ring, and a ketone group with an isopropylidene substituent. Efforts to complete the synthesis of welwitindolinone C's and their analogues by installing the second quaternary carbon and closing the seven-membered ring are currently underway in our laboratory,[18] in addition to the study of [5 + 1] cycloaddition of other allenylcyclopropanes.

Acknowledgment. We thank the University of Wisconsin and the NIH (R01 GM088285) for financial support and a Young Investigator Award (to W.T.) from Amgen.

Supporting Information Available. ^{1}H NMR, ^{13}C NMR, IR, HRMS for starting materials and products. This material is available free of charge via the Internet at http://pubs.acs.org.

(18) Initial attempts to close the seven-membered ring by Lewis acid mediated direct cyclization of intermediate **23** were not successful.

The authors declare no competing financial interest.