An approach to the welwistatin core via a diazoketone rearrangement-ring expansion strategy

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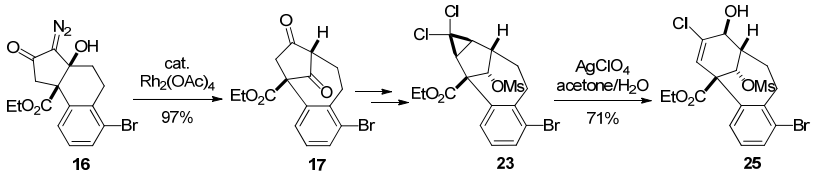
Supporting Information Placeholder



ABSTRACT: The rhodium-catalyzed decomposition of fused bicyclic α-diazo-β-hydroxyketone **16** and rearrangement to **17** is featured in an approach to the bridged bicyclic core of welwistatin. The bicyclic [4.3.1] core of **25** is furnished from a subsequent cyclopropanation to generate **23**, followed by its ring expansion.

The welwitindolinones are a family of indole alkaloids first isolated from the cyanobacteria *Hapalosiphon welwtschii* and *Westiella intricata* by Moore and coworkers in 1994 (Figure 1).[1] Except for welwitindolinone A, all members of the other subclasses possess a bicyclo[4.3.1]decane core. Probably the most well-known congener is welwistatin (**1**), a member of the welwitindolinones C, because of its potent anti-MDR activity, effective at a concentration of 10^{-7} M, a dose 30-fold lower than its IC_{50} values and 20-100 fold more potent than the reference MDR-reversing agent, verapamil.[2]

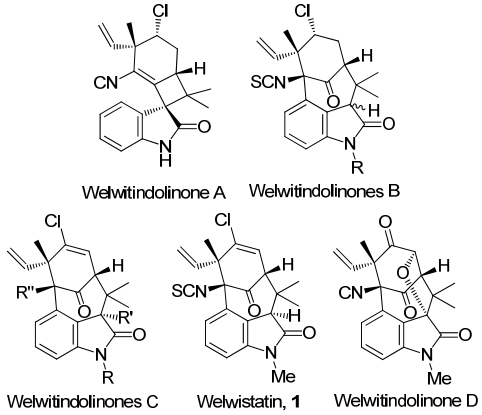
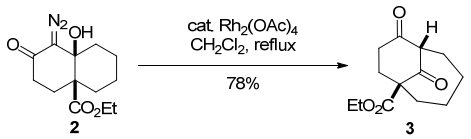


Figure 1. Welwitindolinone family of alkaloids

Due to its fascinating molecular architecture and impressive bioactivity, welwistatin has been a coveted target that has attracted many synthetic efforts.[3] To date, there are three total syntheses, completed by Rawal's group and Garg's group in 2012,[4,5] and Hatakeyama in 2015,[6] a formal total synthesis by Martin,[7] as well as numerous approaches and studies to construct the bridged bicyclic framework of this natural product.[8]

We have reported a strategy to construct bridged bicyclic ketones via a rhodium-catalyzed decomposition and rearrangement of readily accessible fused bicyclic α-diazo-β-hydroxyketones.[9] Not only is a range of bicyclo[m.n.1]alkanediones accessible by this reaction, the products are well-decorated for further applications in synthesis. To continue our studies on the scope, limitations and applications of this reaction, the rhodium (II) catalyzed decomposition of bicyclic α-diazo-β-hydroxyketones was explored as a key step in the synthesis of the bicyclo[4.3.1]decane framework of welwistatin, **1**.

Scheme 1. Rhodium-catalyzed rearrangement of 2

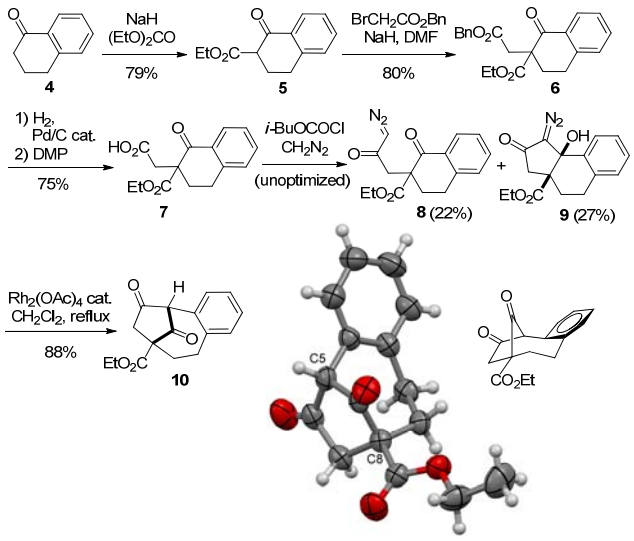


Our previous work has shown that **3** having a bicyclo[4.3.1]decanone framework can be obtained from the rhodium-catalyzed decomposition and rearrangement of diazoketone **2** (Scheme 1).[9] Notably, the welwistatin bicyclic core is fused to an aromatic backbone, which could alter the conformation, as well as the stereoelectronics of the ring systems and

the migratory aptitudes of the bonds as well. Therefore, the diazoketone rearrangement was first studied in the context of an aromatic platform.

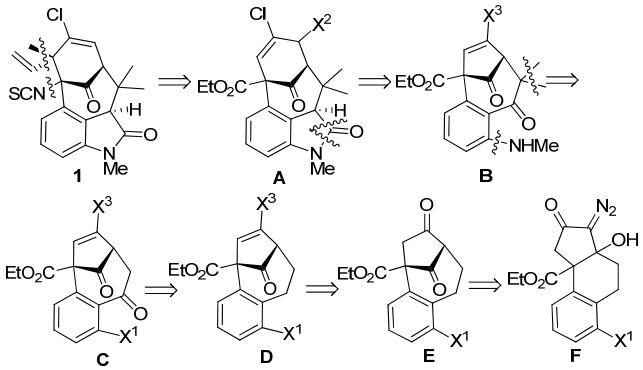
We designed, then synthesized arylated diazoketone **9** as shown in Scheme 2. Commercially-available α-tetralone **4** was ethoxycarbonylated under standard conditions in 79% yield. Alkylation with benzyl 2-bromoacetate generated diester **6**. Subsequently, hydrogenolysis was employed to selectively deesterify the benzyl ester in the presence of the ethyl ester. However, the aryl ketone was also concomitantly reduced under these conditions. Therefore, the product mixture obtained after hydrogenation was treated with Dess-Martin periodinane to afford ketoacid **7** over two steps in 75% overall yield**.** Activation and treatment with diazomethane generated diazoketone **8,** some of which already underwent cyclization under the basic reaction conditions to provide **9**. Treatment with a catalytic amount of $Rh_2(OAc)_4$ in refluxing dichloromethane resulted in carbene formation and rearrangement leading to bridged bicyclic **10** in excellent yield, whose X-ray crystal structure was also obtained.

Scheme 2. Synthesis and rearrangement of 9



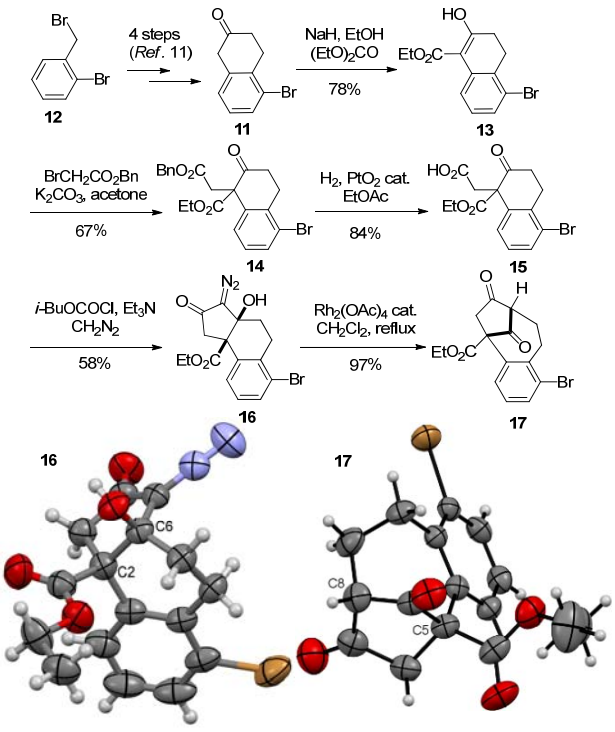
With this result in hand, we applied this approach as a strategy towards the bicyclo[4.3.1]decanone core of welwistatin as shown in Scheme 3. The late stage conversion of a bridgehead carbonyl to an isocyanate is precedented in the synthesis by Rawal,[4] and the substituents on the cyclohexene moiety could be installed by an S_N2' displacement or a conjugate addition, retroanalyzing **1** back to **A**. The three carbon bridge bearing the vinylic chloride could be obtained from a dichlorocyclopropanation-ring expansion from bicyclic [4.2.1] alkene**.** A stepwise assembly of the oxindole as in Funk's approach retroanalyzes **A** back to aniline **B**.[8h] The aniline could be derived from a haloarene by a Buchwald-Hartwig amination,[10] and the dimethyl substituents could be installed by α-alkylation of the carbonyl group of **C**, which is a benzylic oxidation product of **D** after functional group manipulations that convert the carbonyl group to a double bond in the two carbon bridge. Functional group interconversions gives key intermediate **E**, which can be derived from the rearrangement of the carbene derived from bicyclic [4.3.0] α–diazo-β-hydroxyketone **F,** a reaction we have reported previously.[9]

Scheme 3. Retrosynthetic analysis of 1



Although **11** is commercially available from specialty chemical suppliers, it was prepared from dibromotoluene **12** following the route published by Johnston (Scheme 4).[11] β-Tetralone **11** was then ethoxycarbonylated and alkylated, as in the synthesis of **6**. In this case, alkylation provided a somewhat lower yield of the desired diester **14**, due to a competitive O-alkylation side reaction. Hydrogenolysis was uneventful to yield acid **15** which was activated and treated with diazomethane. Cyclization occurred concomitantly with diazoketone formation and provided **16.** Its X-ray crystal structure was obtained and affirmed its *cis*-fused relative stereochemistry. Treatment of fused bicyclic α-diazo-β-hydroxyketone **16** generated bridged bicyclic dione **17** in 97% yield, whose X-ray crystal structure confirmed its bicyclo[4.2.1]nonane framework.

Scheme 4. Synthesis and rearrangement of 16



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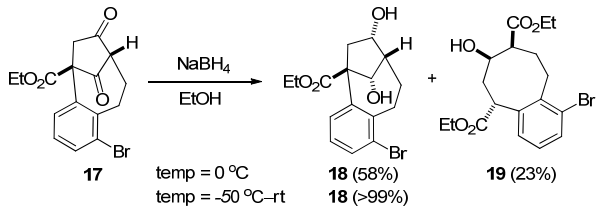
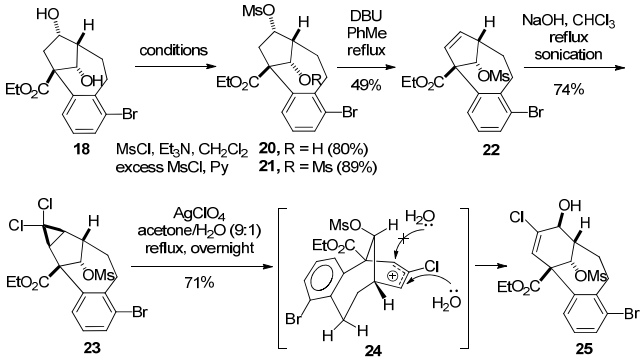
Our manipulations of dione **17** quickly revealed that it was labile to bases or nucleophiles which can initiate retro-Dieckmann reactions to relieve the ring strain. For example, when dione **17** was reduced, in addition to diol **18**, retro-Dieckmann product **19** was also obtained (Scheme 5), whose structure was determined by X-ray crystallographic analysis (see SI). However, by decreasing the temperature, and ensuring an excess of $NaBH_4$ to reduce both carbonyl groups, diol **18** could be obtained quantitatively.

Scheme 5. Reduction of dione 17



Attempted direct dehydration of diol **18** using Martin's sulfurane or Burgess reagent were not successful.[12,13] Towards activating diol **18** for elimination, mono-mesylation provided **20** selectively (Scheme 6), but treatment of **20** with DBU to induce elimination led to products derived from a retro-aldol reaction instead. However, diol **18** could be bis-mesylated to give **21**, where based-induced elimination generated alkene **22** in acceptable yield.

Scheme 6. Synthesis of 25 with [4.3.1] bicyclic core

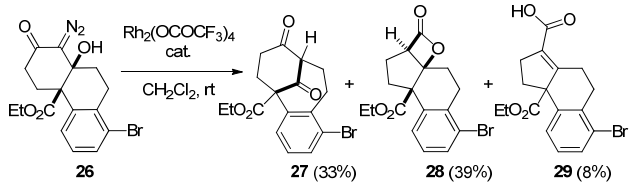


As **22** corresponds to synthon **D** in our retrosynthetic plan (Scheme 3), the next transformation to be tackled would be the installation of the indole. However, we wanted to establish that the bicyclo[4.3.1]decane core of the natural product could indeed be secured from **22**, and so we explored the ring-expansion next.

Dichlorocyclopropanation of **22** turned out to be challenging and the outcomes were unsatisfactory under many sets of conditions tried, including phase-transfer catalysis.[14] Finally, it was achieved under Regen's conditions, using $NaOH/CHCl_3$ with heating and sonication, to provide cyclopropane **23** in good yield (Scheme 6).[15] NOE studies of **23** indicated that cyclopropanation occurred on the less hindered face, *syn* with respect to the one carbon bridge. Silver-promoted electrocyclic ring opening afforded the desired bicyclo[4.3.1]decene **25** incorporating the vinylic chloride functional group. The allyl cation intermediate **24** could have been quenched at either electrophilic site, but apparently, water attack at the site distal from the ethoxycarbonyl group, and on the less hindered face, to generate **25** as a β-alcohol and as the most advanced intermediate to date.

An alternative and more direct entry to a simpler, bicyclo[4.3.1]decane framework could be envisioned via the rhodium-catalyzed rearrangement of fused bicyclic α-diazo-β-hydroxyketone **26** (Scheme 7), which could be prepared in 3 steps from **13** (see SI). This approach was also explored. However, upon treatment of **26** with rhodium, the expected bridged [4.3.1] bicyclic decane **27** was obtained in only 33% yield as one of the products. The others were ring-contracted compounds **28** and **29** derived from a Wolff rearrangement of the rhodium carbene,[16] which remained as a significant or even predominant pathway in the reaction of **26** over a range of conditions tried (see SI). This result was surprising because the rhodium-catalyzed reaction of **2** proceeded smoothly to give **3** having the [4.3.1] bicyclic decane framework, and the successful rhodium-catalyzed rearrangement of **16** to **17** showed that the bromoaryl group did not perturb the electronics of the migrating bonds adversely. Rhodium carbenes undergoing Wolff rearrangements are not very common,[17] and Wolff rearrangements have not been observed in any of our previous studies on the rhodium-catalyzed decomposition of α-diazo-β-hydroxyketones.[9] More work will be needed to elucidate the mechanistic details of this outcome, but we surmise that the peculiar behaviour of this [4.4.0] bicyclic diazoketone **26** could be due to its altered conformation, being fused with the aromatic ring.

Scheme 7. Reaction of 26



In summary, the synthesis of the bicyclo[4.3.1]decane core of welwistatin furnished with a vinylic chloride functional group, has been successfully accomplished by a diazoketone rearrangement and ring expansion strategy. The rhodium catalysed decomposition of fused bicyclic α-diazo-β-hydroxyketone **16** highlighted the use of this rearrangement for the synthesis of bridged bicyclic natural products. We will report our progress in the synthesis of welwistatin in due course.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Experimental procedures, analytical data and ^{1}H, ^{13}C NMR spectra for all new compounds (PDF)
X-ray data for compounds **10**, **16**, **17**, **19** (cif)

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Author Contributions

†Author responsible for x-ray crystallographic analysis.

Notes

The authors declare no competing financial interest.

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REFERENCES

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. Smith, C. D.; Zilfou, J. T.; Stratmann, K.; Patterson, G. M. L.; Moore, R. E. *Mol. Pharmacol*. **1995**, *47*, 241.

3. (a) Avendano, C.; Menendez, J. C. *Curr. Org. Synth.* **2004**, *1*, 65. (b) Brown, L. E.; Konopelski, J. P. *Org. Prep. Proc. Int.* **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.

4. (a) Bhat, V.; Allan, K. M.; Rawal, V. H. *J. Am. Chem. Soc.* **2011**, *133*, 5798. (b) Bhat, V.; Rawal, V. H. *Chem. Commun.* **2011**, *47*, 9705. (c) Allan, K. M.; Kobayashi, K.; Rawal, V. H. *J. Am. Chem. Soc.* **2012**, *134*, 1392.

5. (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. (c) Weires, N. A.; Styduhar, E. D.; Baker, E. L.; Garg, N. K. *J. Am. Chem. Soc.* **2014**, *136*, 14710.

6. Komine, K.; Nomura, Y.; Ishihara, J.; Hatakeyama, S. *Org. Lett.* **2015**, *17*, 3918.

7. (a) Fu, T.-h.; McElroy, W. T.; Shamszad, M.; Martin, S. F. *Org. Lett.* **2012**, *14*, 3834. (b) Fu, T.-h.; McElroy, W. T.; Shamszad, M.; Heidebrecht, R. W., Jr.; Gulledge, B.; Martin, S. F. *Tetrahedron* **2013**, *69*, 5588.

8. (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) Deng, H.; Konopelski, J. P. *Org. Lett.* **2001**, *3*, 3001. (d) Jung, M. E.; Slowinski, F. *Tetrahedron Lett.* **2001**, *42*, 6835. (e) Lopez-Alvarado, P.; García-Granda, S.; Alvarez-Rua, C.; Avendano, C. *Eur. J. Org. Chem.* **2002**, 1702. (f) MacKay, J. A.; Bishop, R. L.; Rawal, V. H. *Org. Lett.* **2005**, 7, 3421. (g) Baudoux, J.; Blake, A. J.; Simpkins, N. S. *Org. Lett.* **2005**, 7, 4087. (h) Greshock, T. J.; Funk, R. L. *Org. Lett.* **2006**, 8, 2643. (i) Lauchli, R.; Shea, K. J. *Org. Lett.* **2006**, 8, 5287. (j) Xia, J.; Brown, L. E.; Konopelski, J. P. *J. Org. Chem.* **2007**, *72*, 6885. (k) Richter, J. M.; Ishihara, Y.; Masuda, T.; Whitefield, B. W.; Llamas, T. S.; Pohjakallio, A.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 17938. (l) Boissel, V.; Simpkins, N. S.; Bhalay, G.; Blake, A. J.; Lewis, W. *Chem. Commun.* **2009**, 1398. (m) Boissel, V.; Simpkins, N. S.; Bhalay, G. *Tetrahedron Lett.* **2009**, *50*, 3283. (n) Tian, X.; Huters, A. D.; Douglas, C. J.; Garg, N. K. *Org. Lett.* **2009**, *11*, 2349. (o) Trost, B. M.; McDougall, P. J. *Org. Lett.* **2009**, *11*, 3782. (p) Brailsford, J. A.; Lauchli, R.; Shea, K. J. *Org. Lett.* **2009**, *11*, 5330. (q) 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. (r) Heidebrecht, R. W.; Gulledge, B.; Martin, S. F. *Org. Lett.* **2010**, *12*, 2492. (s) Ruiz, M.; Lopez-Alvarado, P.; Menendez, J. C. *Org. Biomol. Chem.* **2010**, *8*, 4521. (t) Bhat, V.; MacKay, J. A.; Rawal, V. H. *Org. Lett.* **2011**, *13*, 3214. (u) Bhat, V.; MacKay, J. A.; Rawal, V. H. *Tetrahedron* **2011**, *67*, 10097. (v) Zheng, M.; Tang, W. *Org. Lett.* **2012**, *14*, 3756.

9. Li, Z.; Lam, S. M.; Ip, I.; Wong W.T.; Chiu, P. *Org. Lett.* **2017**, *19*, 0000.

10. (a) Guran, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **1995**, *34*, 1348. (b) Louie, J.; Hartwig, J. F.; *Tetrahedron Lett.* **1995**, *36*, 3609.

11. Chandra, A.; Viswanathan, R.; Johnston, J. N. *Org. Lett.* **2007**, *9*, 5027.

12. Arhart, R. J.; Martin J. C. *J. Am. Chem. Soc.* **1972**, *94*, 5003.

13. (a) Atkins, G. M.; Burgess, E. M. *J. Am. Chem. Soc.* **1968**, *90*, 4744. (b) Burgess, E. M.; Penton, H. R.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26.

14. Parham, W. E.; Schweizer, E. E.; Mierzwa, S. A. *Org. Synth.* **1961**, *41*, 76.

15. Regens, S. L.; Singh, A. *J. Org. Chem.* **1982**, *47*, 1587.

16. (a) Gill, G. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Pattenden, G., Eds.; Pergamon Press: New York, 1991; Vol. 3, pp 887. (b) Kirmse, W. *Eur. J. Org. Chem*. **2002**, 2193.

17. (a) Taylor, E. C.; Davies, H. M. L. *Tetrahedron Lett.* **1983**, *24*, 5453. (b) Pirrung, M. C.; Morehead, A. T. Jr. *J. Am. Chem. Soc.* **1994**, *116*, 8991. (c) Yong, K.; Salim, M.; Capretta, A. *J. Org. Chem.* **1998**, *63*, 9828. (d) Lee, Y. R.; Suk, J. Y.; Kim, B. S. *Tetrahedron Lett.* **1999**, *40*, 8219. (e) Marsden, S. P.; Pang, W. K. *J. Chem. Soc. Chem. Commun.* **1999**, 1199. (f) Lawlor, M. D.; Lee, T. W.; Danheiser, R. L. *J. Org. Chem.* **2000**, *65*, 4375 (g) Lee, D. J.; Kim, K.; Park, Y. J. *Org. Lett.* **2002**, *4*, 873. (h) Gerstenberger, B. S.; Lin, J.; Mimieux, Y. S.; Brown, L. E.; Oliver, A. G.; Konopelski, J. P. *Org. Lett.* **2008**, *10*, 369.