ORGANIC LETTERS

2012
Vol. 14, No. 16
4082–4085

A Macrocyclic β-Iodoallenolate Intermediate Is Key: Synthesis of the ABD Core of Phomactin A

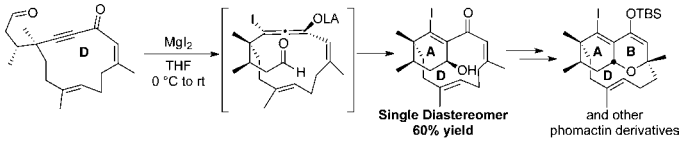
Jennifer Ciesielski, Kevin Cariou, and Alison J. Frontier*

Department of Chemistry, University of Rochester, Rochester, New York 14627, United States

frontier@chem.rochester.edu

Received June 21, 2012

ABSTRACT



An enantioselective strategy for the synthesis of phomactin natural products is described. The Lewis acid triggered cyclization of a β-iodoallenolate embedded in a 12-membered macrocycle was used to obtain a highly functionalized bicyclo[9.3.1]pentadecane in good yield and high diastereoselectivity. This iodoenone contains the substituents of the AD ring system of the phomactin family of natural products, appropriate for further functionalization. Synthesis of the oxadecalin core of phomactin A from the AD iodoenone intermediate was achieved. In this unusual strategy, rings A and B are both fashioned within a macrocyclic precursor.

The phomactin natural products (Figure 1) were isolated from *Phoma* sp. [SANK 11486], a marine fungus that grows on the shell of a crab *Chinoecetes opilioi*, off the coast of Fukui prefecture, Japan.[1]

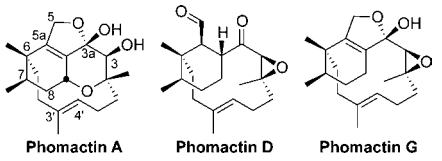


Figure 1. Phomactins A, D, and G.

Interestingly, the phomactins were found to be platelet-activating factor (1-*O*-alkyl-2(*R*)-(acetylglyceryl)-3-phosphorylcholine, PAF) antagonists, inducing platelet aggregation and inhibiting the binding of platelet-activating factor to its receptor.[2,3] PAF is a highly potent phospholipid, and it is thought to be involved in a number of inflammatory and respiratory diseases.[2] Phomactin A is the most structurally intricate member of the family and has thus triggered a variety of creative synthetic strategies

(1) (a) For the isolation of phomactin A, see: Sugano, M.; Sato, A.; Iijima, Y.; Oshima, T.; Furuya, K.; Kuwano, H.; Hata, T.; Hanzawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 5463. (b) For the isolation of phomactins B, B1, B2, and D, see: Sugano, M.; Sato, A.; Iijima, Y.; Furuya, K.; Haruyama, H.; Yoda, K.; Hata, T. *J. Org. Chem.* **1994**, *59*, 564. (c) For the isolation of phomactins E, F, and G, see: Sugano, M.; Sato, A.; Iijima, Y.; Furuya, K.; Kuwano, H.; Hata, T. *J. Antibiot.* **1995**, *48*, 1188. (d) For the isolation of phomactin C, see: Chu, M.; Patel, M. G.; Gullo, V. P.; Truumees, I.; Puar, M. S. *J. Org. Chem.* **1992**, *57*, 5817.

(2) (a) Braquit, P.; Touqui, L.; Shen, T. Y.; Vargaftig, B. B. *Pharm. Rev.* **1987**, *39*, 97. (b) Cooper, K.; Parry, M. *J. Ann. Rep. Med. Chem.* **1989**, *24*, 81.

(3) Phomactin A induced platelet aggregation (IC_{50} = 10 μM) and inhibited the binding of platelet-activating factor to its receptor (IC_{50} = 2.3 μM) (see ref 1a).

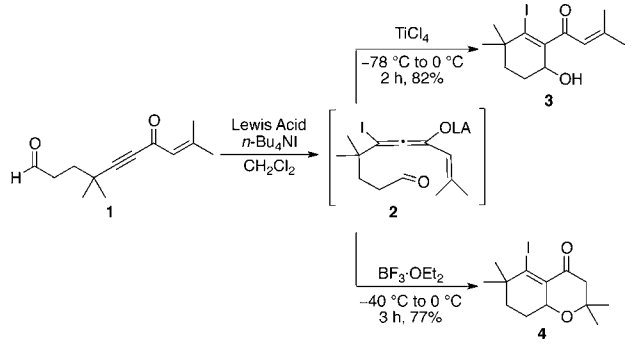
(4) For recent reviews on total syntheses and approaches to the phomactins, see: (a) Goldring, W. P. D.; Pattenden, G. *Acc. Chem. Res.* **2006**, *39*, 354. (b) Cole, K. P.; Hsung, R. P. *ChemTracts* **2003**, *16*, 811. For total syntheses of phomactin A, see: (c) Goldring, W. P. D.; Pattenden, G. *Chem. Commun.* **2002**, 1736. (d) Tang, Y.; Cole, K. P.; Buchanan, G. S.; Li, G.; Hsung, R. P. *Org. Lett.* **2009**, *11*, 1591. (e) Buchanan, G. S.; Cole, K. P.; Tang, Y; Hsung, R. P. *J. Org. Chem.* **2011**, *76*, 7027. (d) Buchanan, G. S.; Cole, K. P.; Li, G.; Tang, Y; You, L.; Hsung, R. P. *Tetrahedron* **2011**, *67*, 10105. (g) Mohr, P. J.; Halcomb, R. L. *J. Am. Chem. Soc.* **2003**, *125*, 1712. For approaches to phomactin A, see: (h) Seth, P. P.; Totah, N. I. *Org. Lett.* **2000**, *2*, 2507. (i) Teng, D.; Wang, B.; Augatis, A. J.; Totah, N. I. *Tetrahedron Lett.* **2007**, *48*, 4605. (j) Chemler, S. R.; Iserloh, U.; Danishefsky, S. J. *Org. Lett.* **2001**, *3*, 2949. (k) Mi, B.; Maleczka, R. E. *Org. Lett.* **2001**, *3*, 1491. (l) Shapland, P. D. P.; Thomas, E. J. *Tetrahedron* **2009**, *65*, 4201 and references cited therein. (m) Schwartz, K. D.; White, J. D. *Org. Lett.* **2011**, *13*, 248. (n) Huang, S.; Du, G.; Lee, C. *J. Org. Chem.* **2011**, *76*, 6534. (o) You, L. F.; Hsung, R. P.; Bedermann, A. A.; Kurdyumov, A. V.; Tang, Y.; Buchanan, G. S.; Cole, K. P. *Adv. Synth. Catal.* **2008**, *350*, 2885.

10.1021/ol3017116
Published on Web 08/02/2012

over the past decade.[4] It is characterized by a tetracyclic framework comprised of a bicyclo[9.3.1]pentadecane core, six stereocenters (three of which are quaternary), a reduced furanochroman, and an oxadecalin.

Our synthetic approach was focused on building the oxadecalin core of phomactin A from a macrocyclic precursor. To achieve this task, we intended to employ a β-iodoallenolate cyclization recently developed in our laboratory.[5] As shown in Scheme 1, 1,4-addition of iodide to alkynone **1** generates β-iodoallenolate intermediate **2**, which can be selectively converted into either cyclohexenyl alcohol **3** or oxadecalin **4**, depending on the Lewis acid.[6,7] In this communication we describe the execution of this transformation within a carefully crafted 12-membered macrocycle, as a strategy for the synthesis of the framework of members of the phomactin family, including the tricyclic core of phomactin A.

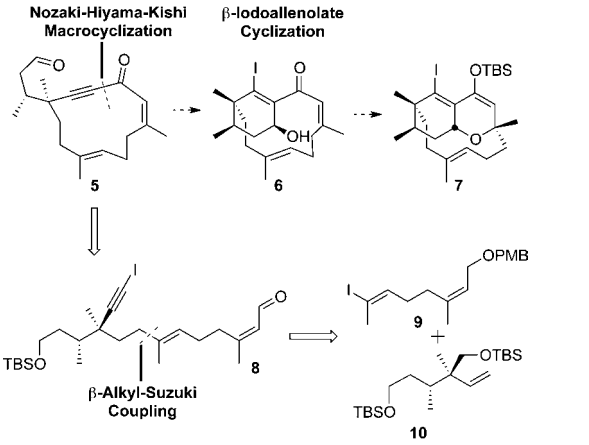
Scheme 1. β-Iodoallenolate Cyclization



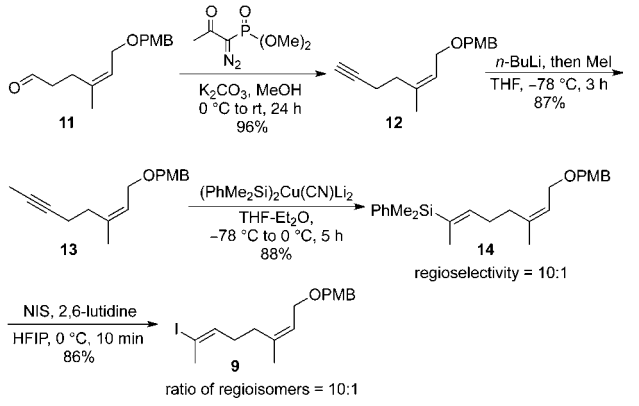
The synthetic strategy is centered on cyclization of macrocycle **5** to produce target alcohol **6**, which contains not only the framework of the phomactins but also a vinyl iodide moiety that could act as a versatile linchpin (Scheme 2). An oxy-Michael ring closure of cyclohexenyl alcohol **6** would then give tricycle **7**, containing the ABD ring system of phomactin A. Macrocycle **5** could come from a Nozaki–Hiyama–Kishi reaction with linear precursor **8**, which, in a convergent manner, would come from the β-alkyl Suzuki coupling of vinyl iodide **9** and olefin **10**.

The synthesis of the vinyl iodide **9** commenced with known nerol derived aldehyde **11** (Scheme 3).[8] Then, using

Scheme 2. Synthetic Strategy



Scheme 3. Synthesis of Vinyl Iodide **9**



the Ohira–Bestmann[9] modification of the Seyferth–Gilbert homologation,[10] aldehyde **11** was transformed into terminal alkyne **12**. Alkylation with methyl iodide followed by regioselective silylcupration afforded vinyl silane **14** in high yield.[11] Iododesilylation of vinyl silane **14** was achieved using the conditions developed by Zakarian (*N*-iodosuccinimide (NIS), 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), and 2,6-lutidine).[12] Thus, the desired vinyl iodide **9** was generated in four steps and 63% overall yield from aldehyde **11**.

The key challenge for the synthesis of olefin **10** was the diastereoselective installation of the C7 tertiary center adjacent to the C6 all-carbon quaternary center (Figure 1). To achieve this, we relied on the enantioselective

(5) Ciesielski, J.; Canterbury, D. P.; Frontier, A. J. *Org. Lett.* **2009**, *11*, 4374.

(6) For the formation of β-iodoallenolate intermediates from alkynones and alkynyl esters and their subsequent intermolecular addition to aldehydes, see: (a) Taniguchi, M.; Hino, T.; Kishi, Y. *Tetrahedron Lett.* **1986**, *27*, 4767. (b) Deng, G. H.; Hu, H.; Wei, H. X.; Paré, P. W. *Helv. Chim. Acta* **2003**, *86*, 3510. (c) Lee, S. I.; Hwang, G. S.; Ryu, D. H. *Synlett* **2007**, 59. (d) Wei, H. X.; Gao, J. J.; Li, G. G.; Paré, P. W. *Tetrahedron Lett.* **2002**, *43*, 5677. (e) Wei, H. X.; Hu, J. L.; Purkiss, D. W.; Paré, P. W. *Tetrahedron Lett.* **2003**, *44*, 949.

(7) For the use of β-iodoallenolate intermediates in total synthesis, see: (a) Lee, S. I.; Hwang, G. S.; Shin, S. C.; Lee, T. G.; Jo, R. H.; Ryu, D. H. *Org. Lett.* **2007**, *9*, 5087. (b) Sloman, D. L.; Bacon, J. W.; Porco, J. A. *J. Am. Chem. Soc.* **2011**, *133*, 9952.

(8) Kanada, R. M.; Itoh, D.; Nagai, M.; Niijima, J.; Asai, N.; Mizui, Y.; Abe, S.; Kotake, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 4350.

(9) (a) Ohira, S. *Synth. Commun.* **1989**, *19*, 561. (b) Mueller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521.

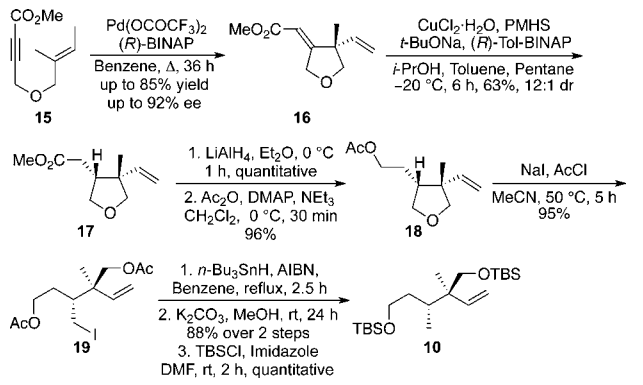
(10) (a) Seyferth, D.; Hilbert, P.; Marmor, R. S. *J. Am. Chem. Soc.* **1967**, *89*, 4811. (b) Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1979**, *44*, 4997.

(11) (a) Fleming, I.; Newton, T. W.; Roessler, F. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2527. (b) Nakamura, E.; Mori, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 3751. (c) Fleming, I.; Newton, T. W. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1805. (d) Barbero, A.; Pulido, F. J. *Acc. Chem. Res.* **2004**, *37*, 817.

(12) Ilardi, E. A.; Stivala, C. E.; Zakarian, A. *Org. Lett.* **2008**, *10*, 1727.

palladium-catalyzed cycloisomerization protocol developed by Mikami.[13] Accordingly, enyne **15** was converted into compound **16**, with excellent yield and enantioselectivity (Scheme 4). Then, conjugate reduction of the α,β-unsaturated ester was accomplished by using Buchwald's procedure to afford compound **17** in 63% yield as a 12:1 mixture of diastereomers.[14] The ester was then reduced and protected as an acetate, and the absolute and relative configuration of compound **18** was confirmed by X-ray crystallography of the corresponding *p*-nitrobenzoate derivative.[15] Regioselective opening of the tetrahydrofuran moiety using NaI and AcCl gave rise to iodide **19**.[16] The selectivity can be attributed to iodide attack at the least hindered, more reactive allylic carbon, which is expected to be more favorable than attack at the neopentylic carbon. Radical reduction of the alkyl iodide with *n*-Bu_3SnH and subsequent cleavage of the acetates with K_2CO_3 in methanol provided the diol. Finally, protection of both alcohols with *tert*-butyldimethylchlorosilane (TBSCl) gave the desired olefin **10** in 43% overall yield over eight steps.

Scheme 4. Synthesis of Olefin **10**



Coupling of **9** and **10** was accomplished by hydroboration of olefin **10** with 9-borabicyclo[3.3.1] nonane (9-BBN) followed by *in situ* β-alkyl Suzuki coupling[17] with vinyl iodide **9** to furnish compound **20** in good yield (Scheme 5). Desilylation of the coupling product followed by selective monoprotection of the primary alcohol with TBSCl gave neopentylic alcohol **21**. Oxidation with pyridinium chlorochromate (PCC) and subsequent homologation with the Ohira–Bestmann reagent produced alkyne **22**. Then, the *p*-methoxybenzyl ether was oxidatively cleaved with DDQ, and the terminal alkyne was iodinated with NIS in the presence of silver nitrate. Finally, oxidation with the Dess-Martin periodinane (DMP) gave macrocyclization precursor **8**.

Iodoalkyne **8** was cyclized to afford the corresponding macrocycle *via* an intramolecular Nozaki–Hiyama–Kishi Cr(II)/Ni(II) coupling (Scheme 5).[18] Oxidation of the resulting alcohol with MnO_2 gave the desired ketone **23** in a 3.6:1.0 ratio of *Z* and *E* isomers.[19] Fortunately, these isomers were easily separable *via* flash chromatography. After separation of the *E*- and *Z*-isomers, the *Z*-isomer was desilylated using a HF–pyridine solution in tetrahydrofuran. Oxidation of the primary alcohol with the Ley–Griffith reagent[20] afforded aldehyde **5** in just four steps from iodoalkyne **8**.

Next, we examined the β-iodoallenolate cyclization with aldehyde **5** (Scheme 6). The first attempts with the conditions previously reported ($BF_3 \cdot OEt_2$ and $TiCl_4$; Scheme 1) failed to provide the corresponding oxadecalin or even the cyclohexenyl alcohol. These conditions gave either complex mixtures or degradation, indicating that these conditions were too harsh. So, we turned our attention to MgI_2, a milder Lewis acid.[6e,7b,21] β-Iodoallenolate **24** was then generated in the presence of MgI_2 and cyclized smoothly to afford cyclohexenyl alcohol **6**, in a 60% yield as a single diastereomer. The relative stereochemistry of the alcohol was assigned by NOE analysis.[22]

Cyclohexenyl alcohol **6** could serve as an intermediate for the synthesis of multiple members of the phomactin family (Figure 1). This versatility is a notable feature of our synthetic approach to the phomactins. In this study, we focused on generating the tricyclic core of phomactin A.

Mitsunobu inversion of the alcohol with *p*-nitrobenzoic acid using diethyl azocarboxylate (DEAD) and triphenylphosphine generated compound **26**, whose structure was assigned by X-ray crystallography (Scheme 7). Removal of the *p*-nitrobenzoate ester followed by treatment of cyclohexenyl alcohol **25** with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) and 2,6-lutidine in toluene triggered an oxy-Michael addition, producing tricycle **7**. This oxadecalin derivative possesses all the stereogenic centers of the A, B, and D rings of phomactin A and was assembled using a highly diastereoselective synthetic strategy.

(13) Hatano, M.; Terada, M.; Mikami, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 249.

(14) Hughes, G.; Kimura, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11253.

(15) See Supporting Information for further details and the X-ray structure.

(16) Oku, A.; Harada, T.; Kita, K. *Tetrahedron Lett.* **1982**, *23*, 681.

(17) For a comprehensive review on this reaction, see: Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544.

(18) (a) Elliott, M. R.; Dhimane, A. L.; Hamon, L.; Malacria, M. *Eur. J. Org. Chem.* **2000**, 155. (b) For a comprehensive review of this reaction, see: Fürstner, A. *Chem. Rev.* **1999**, *99*, 991. (c) For a review on the asymmetric version of this reaction, see: Hargaden, G. C.; Guiry, P. J. *Adv. Synth. Catal.* **2007**, *349*, 2407.

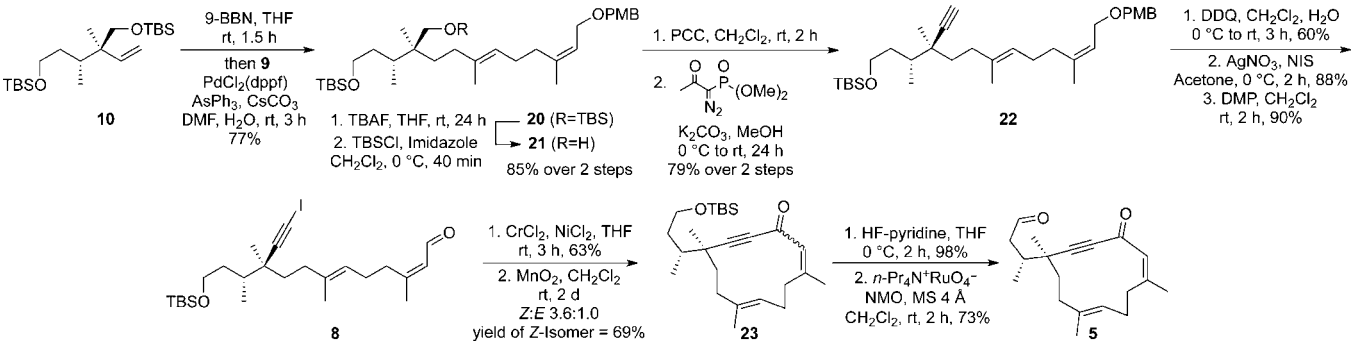
(19) *E*/*Z* isomerization has been observed during the oxidation of allylic alcohols to α,β-unsaturated ketones with MnO_2: (a) Xiao, S.; Prestwich, G. D. *Synth. Commun.* **1990**, *20*, 3125. (b) Tojo, G.; Fernandez, M. I. *Oxidation of Alcohols to Aldehydes and Ketones: A Guide to Current Common Practice*; Springer: New York, 2006; p 308. However, isomerization during the Nozaki–Hiyama–Kishi coupling cannot be ruled out.

(20) Ley, S.; Norman, J.; Griffith, W.; Marsden, S.; Jung, M. E. *Synthesis* **1994**, 639.

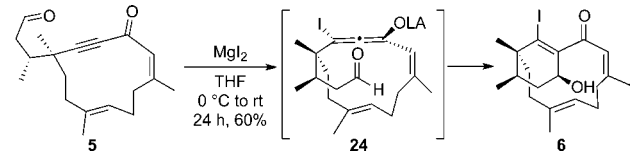
(21) For examples of MgI_2 used in a β-iodoallenolate reaction, see: (a) Wei, H.; Chen, D.; Xu, X.; Li, G.; Paré, P. W. *Tetrahedron: Asymmetry* **2003**, *14*, 971. (b) Sharma, V.; McLaughlin, M. L. *J. Comb. Chem.* **2010**, *12*, 327. (c) Wei, H.; Hu, J.; Jasoni, R. L.; Li, G.; Paré, P. W. *Helv. Chim. Acta* **2004**, *87*, 2359.

(22) See Supporting Information for NOE data and details concerning the structure assignment of compound **6**.

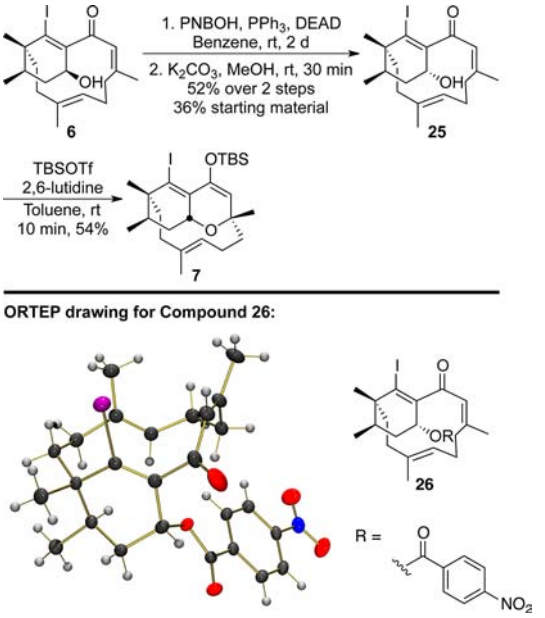
Scheme 5. Synthesis of Macrocycle **5**



Scheme 6. β-Iodoallenolate Cyclization with Macrocycle **5**



Scheme 7. Synthesis of the Core of Phomactin A



In summary, we have developed a novel enantioselective approach to the central core of the phomactins and synthesized the ABD ring system of phomactin A. The strategy features the efficient cyclization of a β-iodoallenolate intermediate, generating the AD ring system of the phomactin skeleton within a 12-membered macrocycle.

Acknowledgment. We are grateful to the Lavoisier Program for a postdoctoral fellowship (K.C.) and the National Institute of Health (NIGMS R01 GM079364) for funding this work. We are also grateful to Dr. Alice Bergmann (University of Buffalo) and Dr. Furong Sun (University of Illinois, Urbana–Champaign) for carrying out high-resolution mass spectroscopy and to Dr. William Brennessel (University of Rochester) for solving structures by X-ray crystallography. The authors thank Dr. Daniel Canterbury (University of Rochester) and Dr. David Lebœuf (University of Rochester) for helpful discussions.

Supporting Information Available. Experimental procedures, characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.