ORGANIC LETTERS

2003
Vol. 5, No. 10
1617−1620

Synthetic Studies on Borrelidin: Enantioselective Synthesis of the C1–C12 Fragment

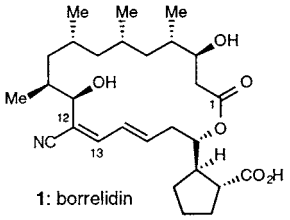
Binh G. Vong, Sunny Abraham, Alan X. Xiang, and Emmanuel A. Theodorakis*

Department of Chemistry and Biochemistry, University of California, San Diego, 9500 Gilman Drive, La Jolla, California 92093-0358

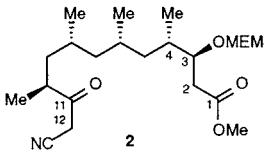
etheodor@chem.ucsd.edu

Received February 11, 2003

ABSTRACT



1: borrelidin

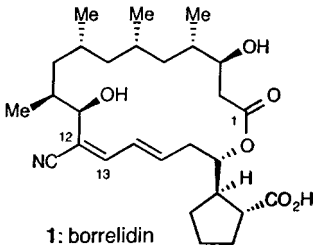


2

An efficient, enantioselective synthesis of the C1–C12 fragment 2 of borrelidin is presented. Construction of the "skipped" polymethylene chain of 2 was accomplished by iteration of Myers' alkylation, while formation of the C3 stereocenter was achieved by Roush's asymmetric allylboration methodology.

First isolated from *Streptomyces rochei* in 1949,[1] borrelidin (**1**, Figure 1) is a macrolide antibiotic with a unique chemical structure and exciting medicinal attributes.[2] Initial studies indicated that **1** exhibits a broad antiviral and antibacterial profile[3] that may arise by inhibiting the enzymatic activity of threonyl-tRNA synthetase.[4] In fact, borrelidin was so named because of its specific cytotoxicity against *Borrelia*,[1] the spirochete of relapsing fever.[5] Recently, **1** was also found to display antiangiogenic[6] and antimitotic properties.[7] The latter may be due to inhibition of cyclin-dependent kinase (CDK), a mode of action not previously manifested by any other macrolide antibiotics.[8]

From a chemical point of view, borrelidin is an atypical 18-membered macrolide distinguished by a 1,3,5,7-"skipped" methylene chain (C4−C10), a cyclopentane carboxylic acid fragment, and a conjugated cyanodiene unit.[9,10] The latter motif is unprecedented in natural products structures and may play an important role in the biological mode of action of



1: borrelidin

Figure 1. Chemical structure of borrelidin.

(1) Berger, J.; Jampolsky, L. M.; Goldberg, M. W. *Arch. Biochem.* **1949**, *22*, 476−478. For subsequent isolations of **1** from related *Streptomyces* strains, see: Singh, S. K.; Gurusiddaiah, S.; Whalen, J. W. *Antimicrob. Agents Chemother.* **1985**, *27*, 239−245. Maher, H.; Evans, R. H. *J. Antibiot.* **1987**, *40*, 1455−1456.

(2) Buck, M.; Farr, A. C.; Schnitzer, R. J. *Trans. N. Y. Acad. Sci., Ser. 2* **1949**, *11*, 207−209. Grunberg, E.; Eldrige, D.; Soo-hoo, G.; Kelly, D. R. *Trans. N. Y. Acad. Sci., Ser. 2* **1949**, *11*, 210−212.

(3) Lumb, M.; Macey, P. E.; Spyvee J.; Whitmarsh, J. M.; Wright, R. D. *Nature* **1965**, *206*, 263−265. Dickinson, L.; Griffiths, A. J.; Mason, C. G.; Mills, R. F. N. *Nature* **1965**, *206*, 265−268. Schüz, T. C.; Zähner, H. *Microbiol. Lett.* **1993**, *114*, 41−46.

(4) Cantt, J. S.; Bennett, C. A.; Arfin, S. M. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 5367−5370. Hirakawa, T.; Morinaga, H.; Watanabe, K. *Agr. Biol. Chem.* **1974**, *38*, 85−89. Paetz, W.; Nass, G. *Eur. J. Biochem.* **1973**, *35*, 331−337. Nass, G.; Poralla, K.; Zähner, H. *Naturwissensh.* **1971**, *58*, 603−610. Poralla, K.; Zähner, H. *Arch. Microbiol.* **1968**, *61*, 143−153. For a review on threonyl-tRNA synthetase, see: Friest, W.; Gauss, D. H. *Biol. Chem., Hoppe-Seyler* **1995**, *376*, 213−224.

10.1021/ol034243i CCC: $25.00
Published on Web 04/10/2003

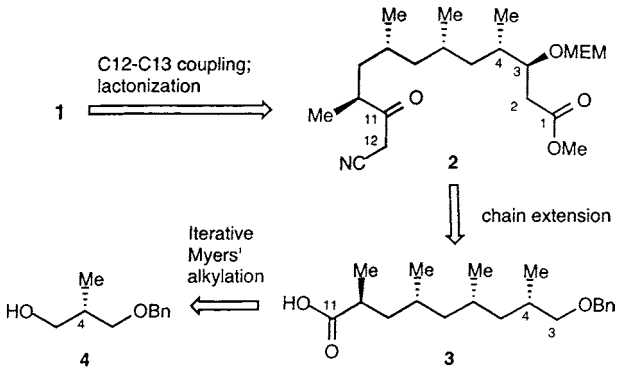


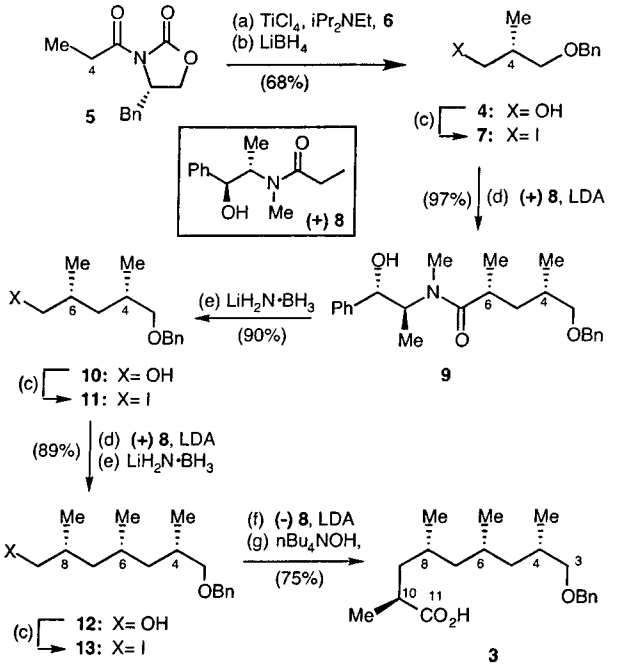
Figure 2. Retrosynthetic analysis of borrelidin.

this natural product. The combination of unusual chemical architecture and diverse biological profile has prompted the development of synthetic routes toward borrelidin[11] that have recently culminated to the first total synthesis of **1** by Morken and collaborators.[12] In continuation of our synthetic effort,[13] we present herein an enantioselective synthesis of the C1−C12 fragment (**2**) of borrelidin.

A plausible scenario for the synthesis of **1** could rely upon the union of two fragments across the macrolactone functionality and the C12−C13 double bond. On the basis of this approach, ketonitrile **2**, carrying six of the nine total stereocenters of borrelidin, was selected as a key synthetic intermediate (Figure 2). Further disconnection across the C11−C12 bond and C2−C3 bond of **2** results in fragment **3**, which is highlighted by the presence of the skipped methylene motif.[14] Among the different strategies for construction of this type of scaffold,[15] the most applicable to our case appeared to be Myers' alkylation.[16,17] This iterative approach could ensure the construction of the chiral centers with a high degree of enantio- and diastereoselectivity.[18] On the basis of these considerations, compound **4** was projected to be the starting material for our synthetic effort (Figure 2).

Our synthesis of the C1−C12 fragment of borrelidin is delineated in Schemes 1 and 3 and departs from readily available oxazolidinone **5**.[19] Stereoselective alkylation of **5**

Scheme 1. Synthesis of Fragment **3** via Myers' Iterative Alkylation Process[a]



[a] Reagents and conditions: (a) 1.1 equiv of $TiCl_4$, 1.1 equiv of iPr_2EtN, 2.0 equiv of $BnOCH_2Cl$ (**6**), CH_2Cl_2, 0 °C, 6 h, 85%; (b) 2.2 equiv of $LiBH_4$, 2.2 equiv of H_2O, THF, 0 °C, 1 h, 80%; (c) 1.2 equiv of PPh_3, 1.35 equiv of I_2, 1.5 equiv of imid, 2 h, 0 °C, 96% for **7**, 95% for **11**, 97% for **13**; (d) 2.1 equiv of (+) **8**, 4.0 equiv of LDA, 12 equiv of LiCl, THF, 0 °C, 18 h, 97%; (e) 4.0 equiv of $LiH_2N{\cdot}BH_3$, −78 to 0 °C, 3 h, 90% for **10**, 95% for **12**; (f) 2.1 equiv of (−) **8**, 4.0 equiv of LDA, 12.2 equiv of LiCl, THF, 0 °C, 18 h, 89%; (g) 5.0 equiv of nBu_4NOH, tBuOH/H_2O 3/1, reflux, 24 h, 84%.

(5) Montgomery, R. R.; Palmarozza, R. E.; Beck, D. S.; Ngo, E.; Joiner, K. A.; Malawista, S. E. *Inflammation* **2000**, *24*, 277−288. Montgomery, R. R.; Nathanson, M. H.; Malawista, S. E. *J. Immunol.* **1993**, *150*, 909−915.

(6) Wakabayashi, T.; Kageyama, R.; Naruse, N.; Tsukahara, N.; Funahashi, Y.; Kitoh K.; Watanabe Y. *J. Antibiot.* **1997**, *50*, 671−676.

(7) Tsunchiya, E.; Yukawa, M.; Miyakawa, T.; Kimura, K.; Takahashi, H. *J. Antibiot.* **2001**, *54*, 1, 84−90. Poralla, K. In *Mechanism of Action of Antimicrobial and Antitumor Agents*; Corcoran, J. W., Hahn, F. E., Eds.; Springer: Berlin, 1975; pp 365−388.

(8) Tsuchiya, E.; Yukawa, M.; Miyakawa, T.; Kimura, K.; Takahashi, H. *J. Antibiot.* **2001**, *54*, 84−90.

(9) Anderton, K.; Rickards, R. W. *Nature* **1965**, *498*, 269. Kuo, M. S.; Yurek, D. A.; Kloosterman, D. A. *J. Antibiot.* **1989**, *42*, 1006−1007. Keller-Schierlein, W. *Experientia* **1966**, *22*, 355−359. Keller-Schierlein, W. *Helv. Chim. Acta* **1967**, *50*, 731−753.

(10) The structure and absolute stereochemistry of **1** have been determined from a single-crystal X-ray analysis. See: Anderson, B. F.; Herlt, A. J.; Rickards, R. W.; Robertson, G. B. *Aust. J. Chem.* **1989**, *42*, 717−730.

(11) Haddad, N.; Grishko, M.; Brik, A. *Tetrahedron Lett.* **1997**, *38*, 6075−6078. Haddad, N.; Brik., A.; Grishko, M. *Tetrahedron Lett.* **1997**, *38*, 6079−6082. Zhao, C.-X.; Duffey, M. O.; Taylor, S. J.; Morken, J. P. *Org. Lett.* **2001**, *3*, 1829−1831.

(12) Duffey, M. O.; LeTiran, A.; Morken, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 1458−1459.

(13) Xiang, A. X. Dissertation Thesis, University of California, San Diego, 2000.

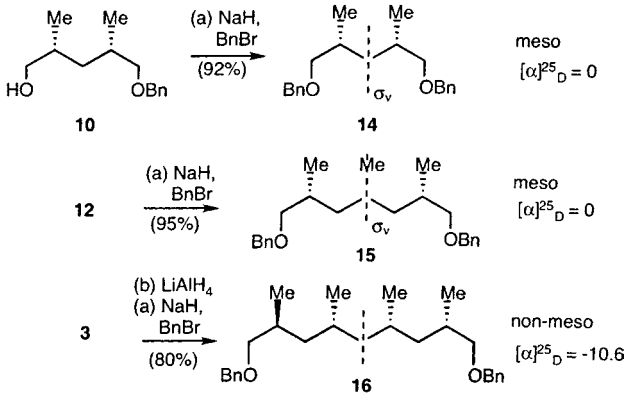
(14) The skipped methylene motif constitutes a common structural element in many natural products of polyketide origins including ionomycin, rapamycin, and related macrolides. For a recent monograph on macrolides, see: *Macrolide Antibiotics Chemistry, Biology, and Practice*, 2nd ed.; Omura, S., Ed.; Academic Press: London, 2002; pp 1−637.

(15) For selected examples of related syntheses, see: Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737−1742. Evans, D. A.; Dow, R. L.; Shih, T. L.; Takacs, J. M.; Zahler, R. *J. Am. Chem. Soc.* **1990**, *112*, 5290−5312. Calter, M. A.; Liao, W.; Struss, J. A. *J. Org. Chem.* **2001**, *66*, 7500−7504. Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1996**, *37*, 1081−1084. Birkbeck, A. A.; Enders, D. *Tetrahedron Lett.* **1998**, *39*, 7823−7826. Oppolzer, W.; Moretti, R.; Thomi, S. *Tetrahedron Lett.* **1989**, *30*, 5603−5606. Masamune, S.; Abiko, A.; Moriya, O.; Filla, S. A., *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 793−795. Hanessian, S.; Murray, P. J. *Can. J. Chem.* **1986**, *64*, 2231−2234.

(16) Myers, A. G.; Yang, B. H.; Chen, H.; Gleason, J. L. *J. Am. Chem. Soc.* **1994**, *116*, 9361−9362. Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496−6511.

(17) Use of other chiral auxiliaries in conjunction with β-branched iodides are low yielding due to the reduced reactivity of the electrophile. This, however, is not an issue for the pseudoephedrine-based alkylation reported by Myers and collaborators (ref 16). See also: Myers, A. G.; Yang, B. H.; Chen, H.; Kopecky, D. J. *Synlett* **1997**, 457−459.

Scheme 2. Confirmation of Stereochemistry of Alkylation via Symmetry Elements[a]



[a] Reagents and conditions: (a) 1.4 equiv of NaH, 1.3 equiv of BnBr, 0.1 equiv of TBAI, THF, 0 °C, 3 h, 92% for **14**, 95% for **15**, 96% for **16**; (b) 5.0 equiv of LAH, Et_2O, 10 h, 84%.

with benzyl chloromethyl ether (**6**) followed by reductive cleavage of the chiral auxiliary with $LiBH_4$ afforded alcohol **4**, containing the C4 methyl group, in 68% yield (Scheme 1). Treatment of **4** with triphenylphosphine, iodine, and imidazole produced iodide **7** (96% yield)[20] and set the stage for the installation of the second methyl group (C6 center). To this end, alkylation of the enolate of (+)-pseudoephedrine propionamide **8** with β-branched iodide **7** afforded the 1,3-*syn*-alkylated substrate **9**. Reduction of amide **9** with lithium amidotrihydroborate (LAB) gave rise to alcohol **10** in 90% yield as a single diastereomer (>95% de), as evidenced by ^1H and ^{13}C NMR studies. Unequivocal proof for the stereochemistry of **10** was obtained by alkylation of the hydroxyl group with benzyl bromide (Scheme 2). Such a maneuver produced benzyl ether **14** that was expected to be a meso structure based on the anticipated alkylation outcome. Indeed, both the symmetry displayed in ^1H and ^{13}C NMR data and the absence of specific rotation for **14** demonstrated unambiguously that the two methyl groups are syn to each other.

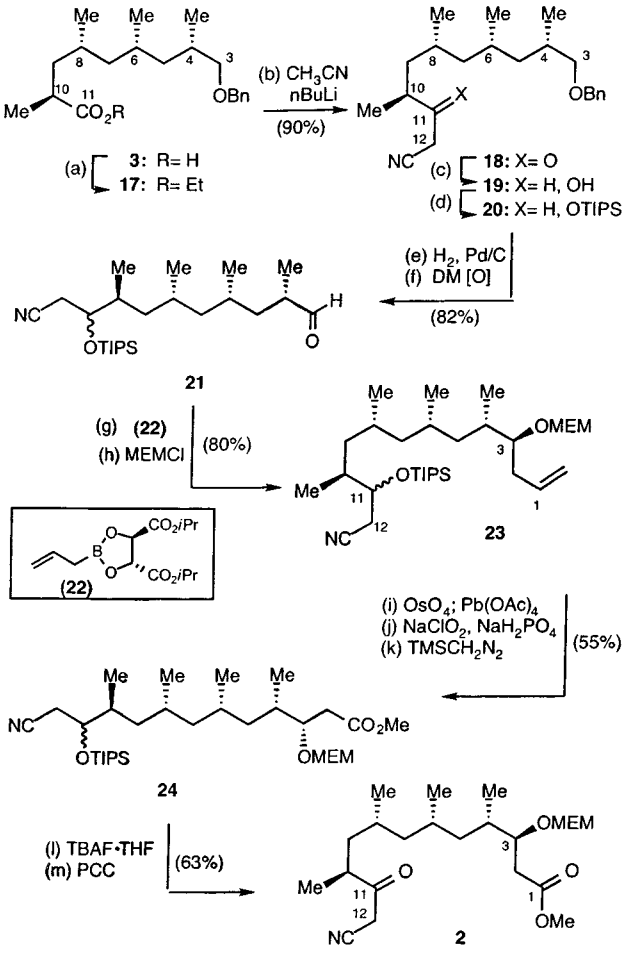
Conversion of alcohol **10** to the corresponding iodide **11** provided the appropriate electrophile for a second round of alkylation. Along this line, quenching of the lithium enolate of (+)-**8** with **11** produced, after reduction with LAB, the homologated alcohol **12** (89% over two steps). The syn,-syn-relationship of the C4, C6, and C8 methyl groups was again examined following benzylation of alcohol **12** (Scheme 2). The newly produced benzyl ether **15** was proved to be a meso structure on the basis of the absence of specific rotation.

(18) For selected applications of Myers' alkylation in natural products synthesis, see: Sudau, A.; Munch, W.; Bats, J. W.; Nubbemeyer, U. *Eur. J. Org. Chem.* **2002**, *19*, 3315−3325. Myers, A. G.; Siu, M.; Ren, F. *J. Am. Chem. Soc.* **2002**, *124*, 4230−4232. Bode, J. W.; Carreira, E. M. *J. Org. Chem.* **2001**, *66*, 6410−6424. Kopecky, D. J.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2001**, *123*, 8420−8421. Keck, G. E.; Knutson, C. E.; Wiles, S. A. *Org. Lett.* **2001**, *3*, 707−710. Snider, B. B.; Song, F. *Org. Lett.* **2001**, *3*, 1817−1820.

(19) Ireland, R. E.; Thaisrivongs, S.; Dussault, P. H. *J. Am. Chem. Soc.* **1988**, *110*, 5768−5779.

(20) Garegg, P. J.; Samuelson, B. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2866−2870. See also ref 17.

Scheme 3. Synthesis of the Fragment **2** of Borrelidin[a]



[a] Reagents and conditions: (a) 1.2 equiv of EtOH, 1.4 equiv of DCC, 0.1 equiv of DMAP, CH_2Cl_2, 2 h, 25 °C, 95%; (b) 2.0 equiv of CH_3CN, 2.0 equiv of *n*BuLi, THF, −78 °C, 1 h, 90%; (c) 1.2 equiv of $NaBH_4$, MeOH, 1 h, 96%; (d) 1.5 equiv of TIPSCl, 2.0 equiv of 2,6-lutidine, 0.1 equiv of DMAP, CH_2Cl_2, 6 h, 25 °C, 94%; (e) H_2, 0.1 equiv of Pd/C (10%), 60 psi, 12 h, THF, 89% (+5% SM recovered); (f) 1.5 equiv of Dess−Martin reagent, 2.0 equiv of pyridine, CH_2Cl_2, 1 h, 0 °C, 92%; (g) 1.4 equiv of **22**, toluene, 4 Å MS, −78 °C, 1 h, 87%; (h) 5.0 equiv of MEMCl, 8.0 equiv of *i*PrNEt$_2$, 92%; (i) cat. OsO_4, 2.0 equiv of NMO, *t*BuOH/THF/H_2O 10/3/1, 6 h; then 1.5 equiv of $Pb(OAc)_4$, CH_2Cl_2, 0 °C 10 min, 74%; (j) 3.0 equiv of $NaClO_2$, 3.0 equiv of NaH_2PO_4, 3.0 equiv of 2-methyl-2-butene, *t*BuOH/H_2O 2/1, 0.5 h, 81%; (k) 1.6 equiv of $TMSCH_2N_2$, MeOH/CH_3CN 1/1, 20 min, 91%; (l) 1.5 equiv of TBAF·THF, THF, 2 h, 84%; (m) 3.0 equiv of PCC, CH_2Cl_2, 12 h, 75%.

Installation of the C10 methyl group with the desired stereochemistry required use of the unnatural enantiomer of pseudoephedrine derivative (−) **8** as the chiral auxiliary. Iteration of the alkylation sequence was accomplished by initially converting alcohol **12** to the corresponding iodide **13** (97%). Subsequent treatment of **13** with the lithium enolate of (−) **8** followed by hydrolysis of resulting homologated amide with excess tetra-*n*-butylammonium hydroxide produced carboxylic acid **3** in 75% yield (over two steps). As with the previous alkylations, compound **3** was reduced to the corresponding alcohol and transformed

to the benzyl ether **16** (Scheme 2). As predicted, this compound exhibited a specific rotation, indicating that it was not a meso structure. This, in turn, confirmed the anti,syn,-syn,syn orientation of the four methyl stereocenters.

Elaboration of carboxylic acid **3** to ketonitrile **2** is shown in Scheme 3. Esterification of acid **3** with ethanol and DCC afforded ethyl ester **17** that upon alkylation with the lithium salt of acetonitrile produced β-ketonitrile **18** in 86% yield. Since this functionality was found to be incompatible with subsequent synthetic manipulations, it was reduced to the corresponding secondary alcohol and subsequently protected with TIPS chloride. This maneuver afforded silyl ether **20** in 90% yield as a 1.3:1 mixture of stereoisomers at the C11 center. This product was carried forth as a mixture since the hydroxyl group was projected eventually to be reoxidized to the desired ketone.

Exposure of benzyl ether **20** to hydrogenation produced the corresponding alcohol, which after treatment with Dess−Martin periodinane gave rise to aldehyde **21** (82% over two steps). Concerned with potential epimerization of the C4 center, we treated aldehyde **21** immediately after extraction with allyl boronate **22** using Roush's asymmetric allylboration conditions.[21] The resulting homoallylic alcohol was then protected with MEMCl to afford ether **23** in 80% overall yield as a single diastereomer at the C3 center.

Transformation of compound **23** to methyl ester **24** was achieved by a sequence of three steps that included (1) a one-pot dihydroxylation and oxidative cleavage of the terminal alkene followed by (2) oxidation of the resulting aldehyde to the carboxylic acid and (3) esterification with TMS-diazomethane. This manipulation produced methyl ester **24** in 63% yield. Exposure of **24** to TBAF as a fluoride source and oxidization of the newly generated secondary alcohol gave rise to β-ketonitrile **2** representing the fully functionalized C1−C12 fragment of borrelidin.

In conclusion, we have presented herein an efficient and enantioselective synthesis of the C1−C12 fragment of borrelidin (**1**). Highlights of our strategy include the construction of the skipped polymethylene segment of **1** by iteration of Myers' alkylation methodology and the formation of the C3 stereocenter using Roush's allylboration reaction. Both methods proceeded in high yield with exceptional stereocontrol. Extension of the above strategy to a total synthesis of borrelidin and structural activity investigation is currently underway in our laboratories.

Acknowledgment. Financial support from the NIH (CA 086079) is gratefully acknowledged. We also thank the Department of Education for a GAANN Fellowship to B.G.V. and Professor M. S. VanNieuwenhze (UCSD) for helpful discussions.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds **2**−**4**, **7**, and **10**−**18** and selected experimental procedures for compounds **7**, **9**, **10**, **3**, and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL034243I

(21) Hoong, L. K.; Palmer, M. A.; Park, J. C.; Roush, W. R. *J. Org. Chem.* **1990**, *55* 4109−4117. Hoong, L. K.; Palmer, M. A.; Park, J. C.; Palkowitz, A. D.; Roush, W. R. *J. Org. Chem.* **1990**, *55*, 4117−4126.