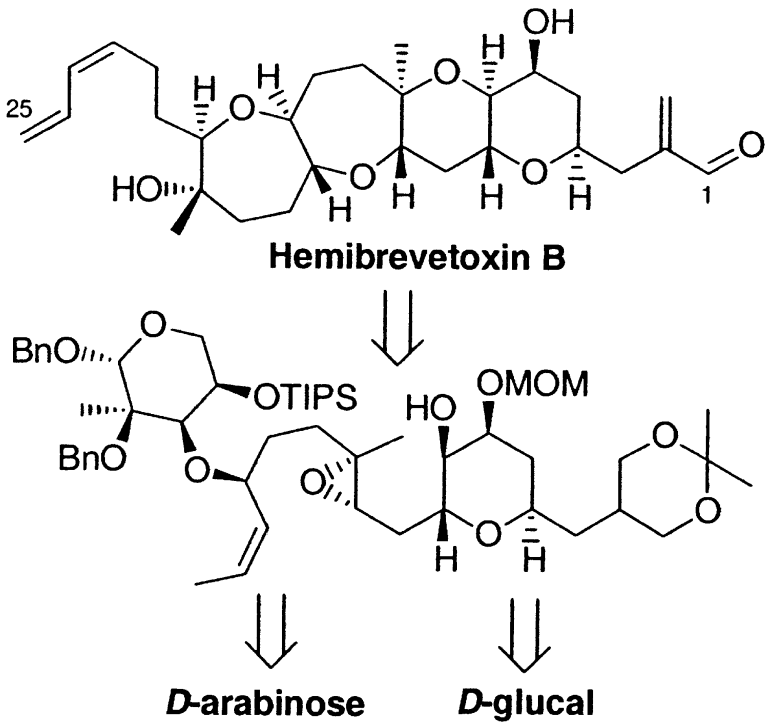
Communication

A Convergent Total Synthesis of Hemibrevetoxin B

Armen Zakarian, Alexandre Batch, and Robert A. Holton

J. Am. Chem. Soc., **2003**, 125 (26), 7822-7824• DOI: 10.1021/ja029225v • Publication Date (Web): 06 June 2003



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 13 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
COMMUNICATIONS

Published on Web 06/06/2003

A Convergent Total Synthesis of Hemibrevetoxin B

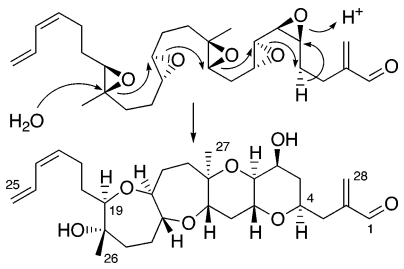
Armen Zakarian, Alexandre Batch, and Robert A. Holton*

Department Of Chemistry, Florida State University, Tallahassee, Florida 32306

Received November 5, 2002; E-mail: holton@chem.fsu.edu

Hemibrevetoxin B (Scheme 1) belongs to a structurally unique family of marine neurotoxins isolated from the dinoflagellate *Gymnodinium breve*.[1] Other members of the group, such as the ciguatoxins and brevetoxins A and B, are potent ichthyotoxins that bind to receptor site 5 of voltage-dependent sodium channels and cause membrane depolarization in neurons at nanomolar concentrations.[2] These compounds possess an impressive molecular architecture incorporating a *trans*-fused cyclic polyether framework with ring sizes ranging from five to nine and a plethora of chiral centers. Three total and three formal total syntheses of hemibrevitoxin B, all utilizing a linear strategy, have been reported.[3]

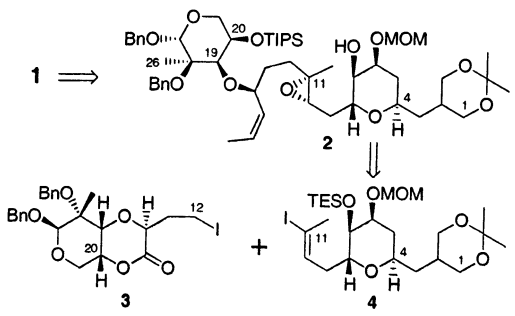
Scheme 1



A cascade epoxy alcohol cyclization has been proposed for the biosynthesis of the polyether toxins (Scheme 1).[1] In this Communication we report the first *convergent* total synthesis of hemibrevetoxin B utilizing a biomimetic epoxy alcohol cyclization as the key step.

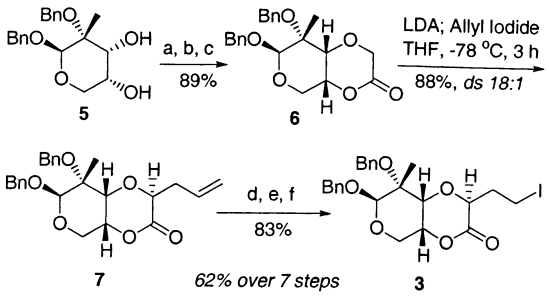
On the basis of extensive model studies,[4] we envisioned that the B and C rings of hemibrevetoxin B could be formed by a biomimetic cyclization of **2**, initiated by electrophilic attack on the double bond and proceeding via a bicyclic epoxonium ion (Scheme 2). A precursor of **2** could be formed by the union of two fragments of roughly equal size and complexity, iodide **3** representing the C12−C21 fragment and vinyl iodide **4** representing the C1−C11 fragment.

Scheme 2



The synthesis of **3** began with diol **5**, which was prepared from benzyl β-D-arabinopyranoside in 90% overall yield by a modification of Ireland's protocol (Scheme 3).[5] Allylation of lactone **6**, prepared from **5** in three steps and 89% yield, afforded **7** (83%) and its diastereomer (5%). Oxidative cleavage of the double bond, reduction, and conversion of the resultant primary alcohol to iodide **3** proceeded in 83% yield. By this route, fragment **3** was obtained in 12 steps and 56% overall yield from benzyl β-D-arabinopyranoside.

Scheme 3 [a]



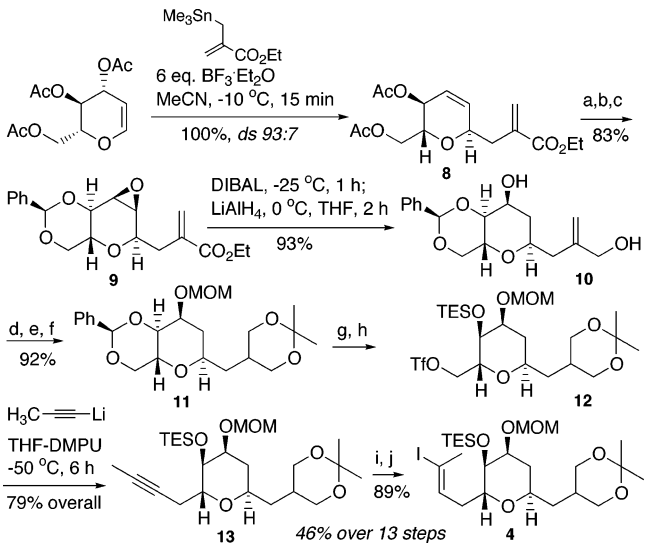
[a] Conditions: (a) *n*-Bu_2SnO; TrBr, TBAI, PhMe, 8 h; (b) NaH, $BrCH_2CO_2Bu$-*t*, DME, 80 °C, 5 h; (c) 0.1 equiv of CSA, PhH, 80 °C, 20 h; (d) 0.07 equiv of OsO_4, 5 equiv of $NaIO_4$, $NaHCO_3$, *t*-BuOH−H_2O-Et_2O, rt, 3 h; (e) $NaBH_3CN$, THF−AcOH (9:1), rt, 20 min; (f) Ph_3P, I_2, 2,6-lutidine, CH_2Cl_2, rt, 2 h.

The synthesis of fragment **4** commenced with BF_3-promoted *C*-allylation of tri-*O*-acetyl-D-glucal[6] with ethyl 2-trimethylstannylacrylate,[7] which afforded **8** (93%) and the C4 epimer of **8** (7%) (Scheme 4). Acetate hydrolysis, epoxidation and protection of the diol produced benzylidene acetal **9** in 83% overall yield. One-pot reduction of the epoxide and conjugated ester groups in **9** gave diol **10** in 93% yield. Hydroboration−oxidation and selective protection of the triol afforded acetonide **11** (92%), which was converted to **13** in 79% yield via triflate **12**.[8] Hydrozirconation−iodination[9] of **13** gave a mixture of regioisomers in low yield. Silylcupration[10] proceeded smoothly, but iododesilylation gave stereoisomeric mixtures in several different solvents, presumably due to solvent participation.[11] However, in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP),[12] a polar solvent with low nucleophilicity, iododesilylation of the vinylsilane with NIS proceeded with complete retention, giving **4** in 89% yield from **13**. Thus, the synthesis of **4** from tri-*O*-acetyl-D-glucal required 13 steps and proceeded in 46% overall yield.

The coupling of the two fragments was accomplished by Pd(dppf)Cl_2-catalyzed reaction of organozinc iodide **14** with vinyl iodide **4** (Scheme 5).[13] When the preparation of **14** was carried out via metal−iodine exchange between primary iodide **3** and diethylzinc employing palladium or Mn/Cu mixed metal catalysis,[14] the yield of **15** was low and variable (~30−50%), and significant quantities of the ethyl-coupled byproduct were obtained. However, when alkylzinc iodide **14** was prepared using Rieke active zinc,[15] alkene **15** was reproducibly obtained in 76% yield at 86% conversion.

10.1021/ja029225v CCC: $25.00

Scheme 4 [a]



[a] Conditions: (a) 0.05 equiv of MeONa, MeOH, 0 °C to rt, 2 h; (b) MCPBA, $NaHCO_3$, CH_2Cl_2, rt, 80 h; (c) $PhCH(OMe)_2$, cat. CSA, MeCN, reflux, 2 h; (d) BH_3·DMS, THF, rt, 3 h; 30% H_2O_2, pH 7 phosphate buffer, 25 °C, 12 h; (e) 0.05 equiv of CSA, $Me_2C(OMe)_2$−Me_2CO, 25 °C, 1 h; (f) MOMCl, *i*-Pr_2NEt−CH_2Cl_2 (1:1), 25 °C, 12 h; (g) Li, NH_3, THF, −78 °C, 1 h; (h) Tf_2O, 2,6-lutidine, −78 °C, 0.5 h; TESOTf, CH_2Cl_2, 0 °C, 0.5 h; (i) $(MePh_2Si)_2Cu(CN)Li_2$, THF-Et_2O (1:1), −78 to −40 °C, 4 h; (j) NIS, $(CF_3)_2CHOH$, 0 °C, 90 s.

Hydrolysis of lactone **15** gave a hydroxy acid which underwent diastereoselective iodolactonization, providing **16** (75%) along with its diastereomer (11%). Protection of the hydroxyl group and methanolysis provided the C10−C11 epoxide **17**, having the desired stereochemistry, in 95% yield. Conversion of **17** to the cascade cyclization substrate **2** was then carried out by reduction of the ester, oxidation to the aldehyde, Wittig olefination and, finally, selective removal of the triethylsilyl protecting group, in 83% overall yield.

This cyclization substrate was designed so that the cyclization could be initiated by electrophilic attack on the olefin, and its *Z* configuration was chosen with the hope that facial selectivity in the electrophilic addition would be controlled by allylic 1,3-strain.[16] This approach seemed particularly attractive because the double bond can react with a number of electrophiles without interference from the epoxide and hydroxyl groups.

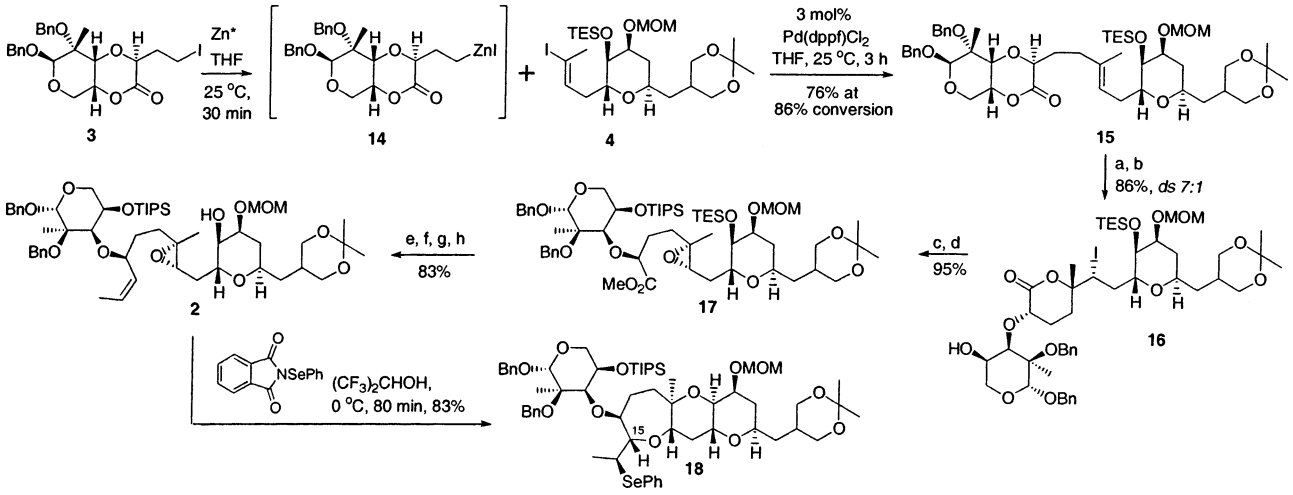
A major challenge in the application of tandem epoxy alcohol cyclizations to the synthesis of *trans*-fused polycyclic ethers is the known preference of epoxides to undergo intramolecular openings in a 5-*exo*, rather than a 6-*endo*, fashion.[17] This issue was recently addressed by Houk et al. through ab initio calculations for proton-catalyzed 5-*exo* and 6-*endo* epoxy alcohol cyclizations.[18] They inferred that 6-*endo* cyclizations have a looser, S_N1-type transition state. Therefore, we proposed that the regioselectivity of the intramolecular epoxide opening could be shifted in the 6-*endo* direction by the proper choice of highly polar solvent, and HFIP proved to be an excellent selection.

In the event, using HFIP as solvent, **2** underwent a smooth cyclization in the 6-*endo* mode upon treatment with a variety of electrophiles. The optimum conditions involved treatment of **2** in HFIP solution with *N*-(phenylseleno)phthalimide at 0 °C to give **18** as a single diastereomer in 83% yield. Thus, two ether rings of hemibrevetoxin B were assembled in a single synthetic operation. In a control experiment, no reaction was observed when a solution of **2** in HFIP was stirred at 0 °C for 1.5 h.

The completion of the synthesis is depicted in Scheme 6. Oxidation−elimination of the selenide gave olefin **19** in 91% yield, but removal of the benzyl protecting groups on the pyranose ring in **19** proved troublesome due to the sensitivity of the allylic ether. Ultimately, the deprotection was achieved (78%) by inverse addition of lithium in ammonia to a THF solution of **19**. Lactol **20** underwent olefination and deprotection to give triol **21** (88%), and its efficient (85%) ring closure to triol **22** was achieved using the second-generation ruthenium-based olefin metathesis catalyst.[19] The C20−C25 side chain was constructed by cleavage of the diol, olefination of the resulting aldehyde, reduction of the double bonds, protection of the tertiary hydroxyl as the TMS ether, and reduction of the amide to give aldehyde **23** in 79% overall yield. Peterson olefination of **23** using the (*E*)-γ-silylallylboronate reagent[20] gave **24** (78%) along with 5% of the *E* isomer. Finally, removal of the acetonide and TMS groups of **24**, mono-tosylation of the triol, oxidation, and final MOM ether cleavage with $LiBF_4$ in aqueous acetonitrile[21] delivered **1** in 69% overall yield.

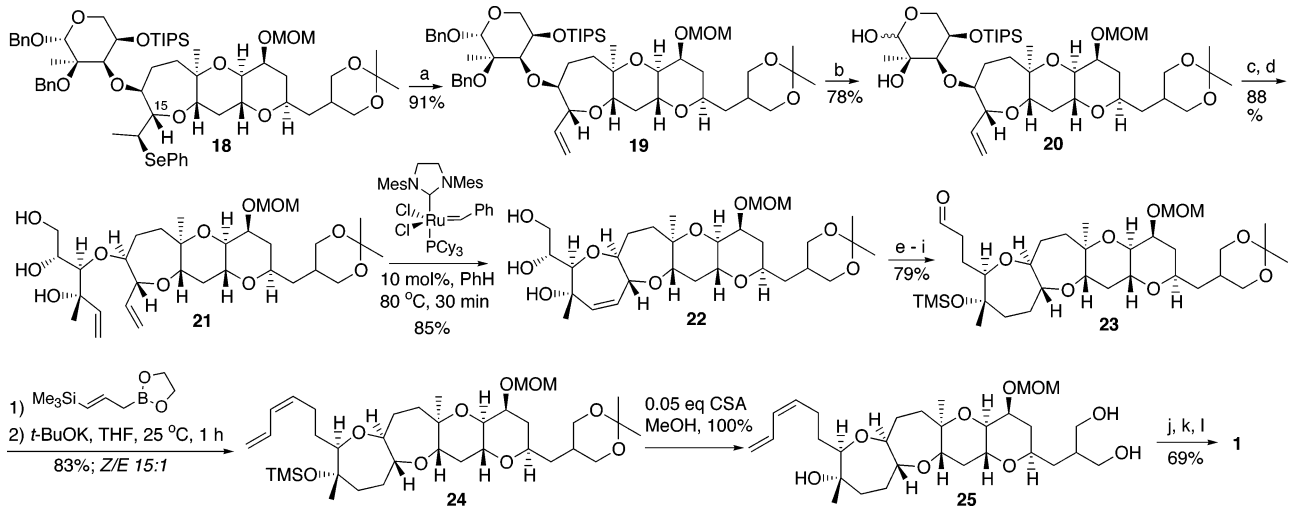
The synthetic material had physical data (^1H, ^{13}C, IR, $[\alpha]_D$, elemental analysis) identical with those reported for the natural product.[1b] Thus, the convergent synthesis of hemibrevetoxin B was accomplished in 39 steps and ca. 4% overall yield in the longest linear sequence from tri-*O*-acetyl-D-glucal.

Scheme 5 [a]



[a] Conditions: (a) LiOH, THF−H_2O (2:1), 0 °C, 20 min; (b) NIS, 2,6-lutidine, CH_2Cl_2, −10 °C, 3 h; (c) TIPSOTf, 2,6-lutidine, *t*-BuOAc, −10 °C, 15 min; (d) 1.1 equiv of MeONa/MeOH, CH_2Cl_2, −35 °C, 1 h; (e) $LiAlH_4$, THF, −78 °C, 1 h; (f) $(COCl)_2$−DMSO, *i*-Pr_2NEt, −78 to 0 °C, 30 min; (g) $Ph_3PEt^+Br^-$, NaHMDS, THF−DMPU (3:2), rt, 2 h; (h) 6 M aqueous HF−Py−MeCN, rt, 8 h.

Scheme 6 [a]



[a] Conditions: (a) 30% aqueous H_2O_2, THF, reflux, 1 h; (b) Li, NH_3, 3 equiv of ethyl allyl ether, THF, −78 °C; (c) Me_3SiCH_2MgCl, THF, reflux, 1 h; (d) *t*-BuOK, THF, 25 °C, 30 min; TBAF, 25 °C, 30 min; (e) $NaIO_4$, Et_2O−*t*-BuOH−H_2O, (5:1:1), rt, 10 min; (f) $(EtO)_2P(O)CH_2C(O)N(Me)OMe$, NaH, THF, 30 min; (g) H_2, 20% $Pd(OH)_2$/C, EtOAc, rt, 15 h; (h) TMSCl, Et_3N, CH_2Cl_2, rt, 12 h; (i) DIBAL, THF, −78 °C, 1 h; (j) *n*-Bu_2SnO; TsCl, TBAI, CH_2Cl_2, 0 °C, 2 h; (k) $(COCl)_2$, DMSO, −78 °C; Et_3N, rt, 0.5 h; (l) $LiBF_4$, 4% aqueous MeCN, reflux, 2 h.

In conclusion, a biomimetic cascade epoxy alcohol cyclization has been successfully implemented in the total synthesis of a *trans*-fused polycyclic ether toxin, allowing for development of the first convergent approach to hemibrevetoxin B.

Acknowledgment. We thank the FSU Research Foundation and donors to the FSU Foundation for financial support of this work.

Supporting Information Available: Selected experimental procedures and physical data for the synthetic intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Lin, Y.; Risk, M.; Ray, S. M.; Van Engen, D.; Clardy, J.; Golic, J.; James, J. C.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 6773. (b) Prasad, A. V. K.; Shimizu, Y. *J. Am. Chem. Soc.* **1989**, *111*, 6476.
(2) (a) Rein, K. S.; Baden, D. G.; Gawley, R. E. *J. Org. Chem.* **1994**, *59*, 2101. (b) Rein, K. S.; Lynn, B.; Baden, D. G.; Gawley, R. E. *J. Org. Chem.* **1994**, *59*, 2107.
(3) (a) Nicolaou, K. C.; Reddy, K. R.; Skokotas, G.; Sato, F.; Xiao, X.-Y.; Hwang, C.-K. *J. Am. Chem. Soc.* **1993**, *115*, 3558. (b) Kadota, I.; Yamamoto, Y. *J. Org. Chem.* **1998**, *63*, 6597. (c) Morimoto, M.; Matsukura, H.; Nakata, T. *Tetrahedron Lett.* **1996**, *37*, 6365. (d) Mori, Y.; Yaegassi, K.; Furukawa, H. *J. Org. Chem.* **1998**, *63*, 6200. (e) Rainier, J.; Allwein, S. P.; Cox, J. M. *J. Org. Chem.* **2001**, *66*, 1380. (f) Holland, J. M.; Lewis, M.; Nelson, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4082.
(4) (a) Kim, H.-B. Ph.D. Dissertation. Florida State University, 1989. (b) Zakarian, A. Ph.D. Dissertation. Florida State University, 2001. See also: (c) Tokiwano, T.; Fujiwara, K.; Murai, A. *Synlett* **2000**, 335. (d) McDonald, F. A.; Wang, X.; Do, B.; Hardcastle, K. I. *Org. Lett.* **2000**, *2*, 2917.
(5) Ireland, R. E.; Courtney, L.; Fitzsimmons, B. J. *J. Org. Chem.* **1983**, *48*, 5186.
(6) Danishefsky, S.; Kerwin, J. F. *J. Org. Chem.* **1982**, *47*, 3803.
(7) Fouquet, E.; Gabriel, A.; Maillard, B.; Pereyre, M. *Bull. Soc. Chim. Fr.* **1995**, *95*, 590.
(8) Mori, Y.; Yaegassi, K.; Furukawa, H. *J. Am. Chem. Soc.* **1996**, *118*, 8158. Kotsuki, H.; Kadota, I.; Masamitsu, O. *Tetrahedron Lett.* **1990**, *31*, 4609.
(9) Hart, D. W.; Blackburn, T. F.; Schwartz, J. *J. Am. Chem. Soc.* **1975**, *97*, 679.
(10) (a) Holton, R. A.; Zakarian, A., submitted for publication. (b) Fleming, I.; Newton, T. W., Roessler, F. *J. Chem. Soc., Perkin Trans. 1* **1981**, *1*, 2527.
(11) Stamos, D. P.; Taylor, A. G.; Kishi, Y. *Tetrahedron Lett.* **1996**, *37*, 4609.
(12) (a) pK_a 9.3: Middleton, W. J.; Lindsey, R. V. *J. Am. Chem. Soc.* **1964**, *86*, 4948. (b) Purcell, K. F.; Stikeleather, J. A.; Brunk, S. D. *J. Am. Chem. Soc.* **1969**, *91*, 4019. (c) Trahanovsky, W. S.; Doyle M. P. *Tetrahedron Lett.* 1968, 2155. Sunko, D. E.; Szele, I. *Tetrahedron Lett.* **1972**, 3617. (d) Schadt, F. L.; Schleyer, P. v. R.; Bentley T. W. *Tetrahedron Lett.* **1974**, 2335.
(13) Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 158. Negishi E.; Okukado, N.; King A. O.; VanHorn, D. E.; Spiegel, B. I *J. Am. Chem. Soc.* **1978**, *100*, 2254.
(14) (a) Stadtmuller, H.; Lentz, R.; Tucker, C. E.; Studemann, T.; Dorner, W.; Knochel, P. *J. Am. Chem. Soc.* **1993**, *115*, 7027. (b) Klement, I.; Knochel, P.; Chau, K.; Cahiez, G. *Tetrahedron Lett.* **1994**, *35*, 1177.
(15) Zhu, L.; Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* **1991**, *56*, 1445.
(16) Johnson, F. *Chem. Rev.* **1968**, *68*, 375. For a recent review on A1,3-strain, see: Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841−60.
(17) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734. Also, see: Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5330. Nicolaou, K. C.; Hwang, C.-K.; Duggan, M. E.; Nugiel, D. A.; Abe, Y.; Reddy, K. B.; DeFrees, S. A.; Reddy, D. R.; Awartani, R. A.; Conley, S. R.; Rutjes, F. P. J. T.; Theodorakis, E. A. *J. Am. Chem. Soc.* **1995**, *117*, 10227.
(18) Na, J.; Houk, K. N.; Shevin, C. G.; Janda, K. D.; Lerner, R. A. *J. Am. Chem. Soc.* **1993**, *115*, 8453. 6-exo vs 7-endo: Na, J.; Houk, K. N. *J. Am. Chem. Soc.* **1996**, *118*, 9204.
(19) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. Org. Lett. **1999**, *1*, 953. The classic Grubbs' catalyst was unreactive.
(20) Wuts, P. G. H.; Jung, Y.-W. *J. Org. Chem.* **1986**, *51*, 635.
(21) Lipshutz, B. H.; Pegram, J.; Money, M. C. **Tetrahedron Lett. 1981**, *22*, 4603. Lipshutz, B. H.; Harvey, P. F. **Synth. Commun. 1982**, *12*, 267. Ireland, R. E.; Varney, M. D. *J. Org. Chem.* **1986**, *51*, 635.

JA029225V