Asymmetric Total Synthesis of Spongistatins 1 and 2

ARTICLE *in* JOURNAL OF THE AMERICAN CHEMICAL SOCIETY · JUNE 2002

Impact Factor: 12.11 · DOI: 10.1021/ja0262683 · Source: PubMed

5 AUTHORS, INCLUDING:

David G Washburn
GlaxoSmithKline plc.
10 PUBLICATIONS **202** CITATIONS
SEE PROFILE

Shawn Allwein
Teva Pharmaceutical Industries Ltd.
20 PUBLICATIONS **555** CITATIONS
SEE PROFILE

J|A|C|S
COMMUNICATIONS

Published on Web 04/26/2002

Asymmetric Total Synthesis of Spongistatins 1 and 2

Michael T. Crimmins,* Jason D. Katz, David G. Washburn, Shawn P. Allwein, and Laura F. McAtee

Department of Chemistry, Venable and Kenan Laboratories of Chemistry, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599-3290

Received March 21, 2002

In 1993 Pettit,[1] Kitagawa,[2] and Fusetani[3] independently identified members of a new class of potent antitumor agents that were named the spongistatins, altohyrtins, and cinachyrolides. The spongistatins (altohyrtins) elicit extraordinary (subnanomolar) growth inhibition of a variety of chemoresistant tumor types included in the NCI panel of 60 human cancer cell lines. Human melanoma and lung, brain, and colon cancers were particularly susceptible to spongistatin 1, whose activity correlates well with the class of microtubule interactive antimitotics.[4] The remarkable biological profile and the extremely limited supply of this class sparked intense synthetic efforts toward their synthesis. The proposed structures of the three subclasses featured six pyran rings: AB and CD spiroketal fragments as well as an E ring hemiketal and a highly substituted F ring tetrahydropyran, all embedded in a 42-membered macrolide. The conflicting absolute configurations, which were based on extensive spectroscopic analysis, remained unresolved until the Kitigawa assignment[2] was confirmed by the first synthesis of spongistatin 2 (altohyrtin C) by Evans[5] and spongistatin 1 (altohyrtin A) by Kishi.[6] Synthesis of spongistatin 2 by Smith[7] and spongistatin 1 by Paterson[8] followed these initial publications. Additional reports of syntheses of various fragments have also been reported from other laboratories[9] (Figure 1).

We previously reported approaches to the AB[10] and CD[11] spiroketals as well as the fully elaborated EF segment.[12] We disclose here the elaboration of the AB spiroketal, a modification of the approach to the EF segment, and the details of the efficient confluence of the individual fragments. An important consideration in our strategic plan was the ability to efficiently assemble four major fragments (the C1−C15 AB fragment **2**, the C16−C28 CD fragment **3**, the C29−C43 EF fragment **4**, and the C44−C51 side chain **5**) at a very advanced stage of the synthesis with minimal functional group interconversion. Thus, we chose to incorporate each individual fragment with its native functionality (or as nearly as possible) and selected the fully elaborated CD fragment **3** as the nexus about which to assemble the subunits.

An efficient synthesis of the C1−C13 portion **6** (Scheme 1) of the AB fragment **2** through the aldol union of a metalated pyrone with a β-alkoxyaldehyde followed by acid-catalyzed cyclization to prepare the diaxial AB spiroketal core has been disclosed.[10] Completion of the AB fragment **2** required the elaboration of the C12−C15 side chain including introduction of the C14 stereogenic center. The side chain at C11 was extended through the application of our asymmetric aldol procedure that utilizes chlorotitanium enolates of oxazolidinethiones.[13] Thus, hydroboration of the alkene **6** with 9-BBN under ultrasonic irradiation,[14] followed by Swern oxidation of the resultant alcohol gave the aldehyde **7**. Asymmetric aldol addition of the chlorotitanium enolate of *N*-propionyl-(*S*)-4-benzyloxazolidine-2-thione to aldehyde **7** provided the alcohol **8** (96:4 d.r.) after reductive removal of the auxiliary. Selective

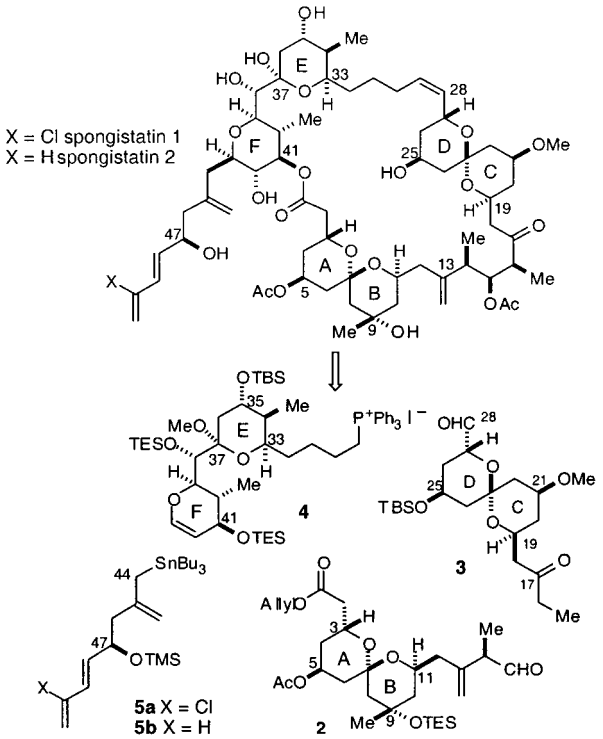


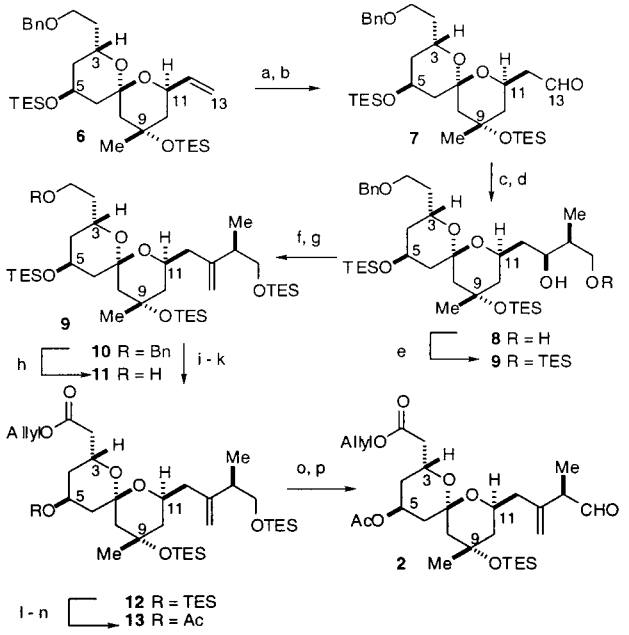
Figure 1. Retrosynthesis for the spongistatins.

protection of the primary alcohol as its TES ether furnished the secondary alcohol **9**. Oxidation of the C13 hydroxyl was succeeded by Wittig olefination of the resulting ketone to incorporate the C13 alkene in 86% yield. The C1 benzyl ether of alkene **10** was reductively cleaved to deliver alcohol **11**, which was subjected to a two-stage oxidation to the carboxylic acid. The carboxylic acid was esterified under standard Mitsunobu conditions[15] to generate the allyl ester **12**. The allyl ester was chosen to allow hydrolysis of the ester under very mild conditions immediately prior to the macrolactonization. Any concern regarding the sensitivity of the C50 vinyl chloride to the conditions required to remove the allyl ester [Pd(0)] were alleviated during the construction of the C44−C51 side chain.[12] The C5 TES ether was transformed in three high-yield steps to the C5 acetate **13**. The AB spiroketal **2** was completed by selective hydrolysis of the C15 silyl ether and careful oxidation of the alcohol under Dess−Martin[16] conditions immediately prior to use in the ensuing aldol reaction.

The synthesis of the C29−C43 fragment **4** was completed as shown in Scheme 2. Our previous approach to the EF fragment was modified to accommodate protecting-group alterations for successful implementation of the final assembly strategy. Methyl ketone **14** was synthesized through an analogous sequence to our previous route[12] with the exception of the use of a triethylsilyl ether rather than a TBS ether at C41. Enolization of the methyl ketone

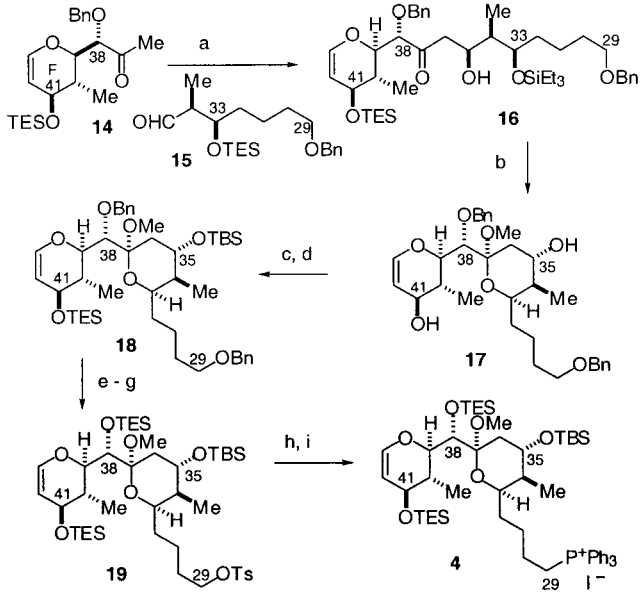
* To whom correspondence should be addressed. E-mail: crimmins@email.unc.edu.

Scheme 1: Synthesis of the C1−C15 AB Fragment[a]



[a] a) 9-BBN, THF, ultrasound; then H_2O_2, NaOH, 92%; b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 88%; c) *N*-propionyl-(*S*)-4-benzyloxazolidine-2-thione, $TiCl_4$, (−)-sparteine, CH_2Cl_2; d) $LiBH_4$, MeOH, 74%, 2 steps; 96:4 d.r.; e) TESCl, imidazole, CH_2Cl_2, 94%; f) *n*-Pr_4NRuO_4, NMO, CH_2Cl_2, 95%; g) Ph_3PCH_3Br, *n*-BuLi, 90%; h) LDBB, THF, 84%; i) Dess−Martin periodinane, CH_2Cl_2; j) $NaClO_2$, *t*-BuOH, 2-methyl-2-butene, pH 5 buffer; k) CH_2═$CHCH_2OH$, DEAD, Ph_3P, THF, 96% (3 steps); l) HF-pyr, pyridine, CH_3CN; m) TESCl, imidazole, CH_2Cl_2, 92% (2 steps); n) Ac_2O, CH_2Cl_2, 96%; o) HF−pyr, pyridine, CH_3CN; p) Dess−Martin periodinane, pyridine, CH_2Cl_2, 84% (2 steps).

Scheme 2: Synthesis of the C29−C43 EF Fragment[a]



[a] a) Cy_2BCl, Et_3N, pentane; 93% (>98:2 d.r.); b) PPTS, 3:1 CH_2Cl_2:MeOH, 72% c) TESCl, imidazole, CH_2Cl_2; d) TBSCl, $KN(SiMe_3)_2$, THF, −78 °C, 93% (2 steps); e) LDBB, THF; f) TsCl, Et_3N, DMAP; g) Et_3SiCl, imidazole, CH_2Cl_2, 76% (3 steps); h) NaI, acetone; i) Ph_3P, CH_3CN, C_6H_6, Li_2CO_3, 85% (2 steps).

14 with Cy_2BCl and Et_3N in pentane followed by addition of aldehyde **15**[12] led to the isolation of a single diastereomeric aldol adduct **16**. The α and *β* oxygen substituents of the methyl ketone apparently act in synergy to direct the highly selective aldol process.[12] Exposure of **16** to PPTS in 3:1 dichloromethane:methanol produced the ketal **17**, which was then advanced to the silyl ether **18** by sequential protection of the C41 and C35 hydroxyls.[9a] The C29 and C38 benzyl ethers were reductively cleaved by the action of LDDB, the C29 alcohol was selectively tosylated, and the C38 hydroxyl was protected as its TES ether **19**. Finally, the tosylate was converted to the phosphonium salt **4** via the C29 iodide.

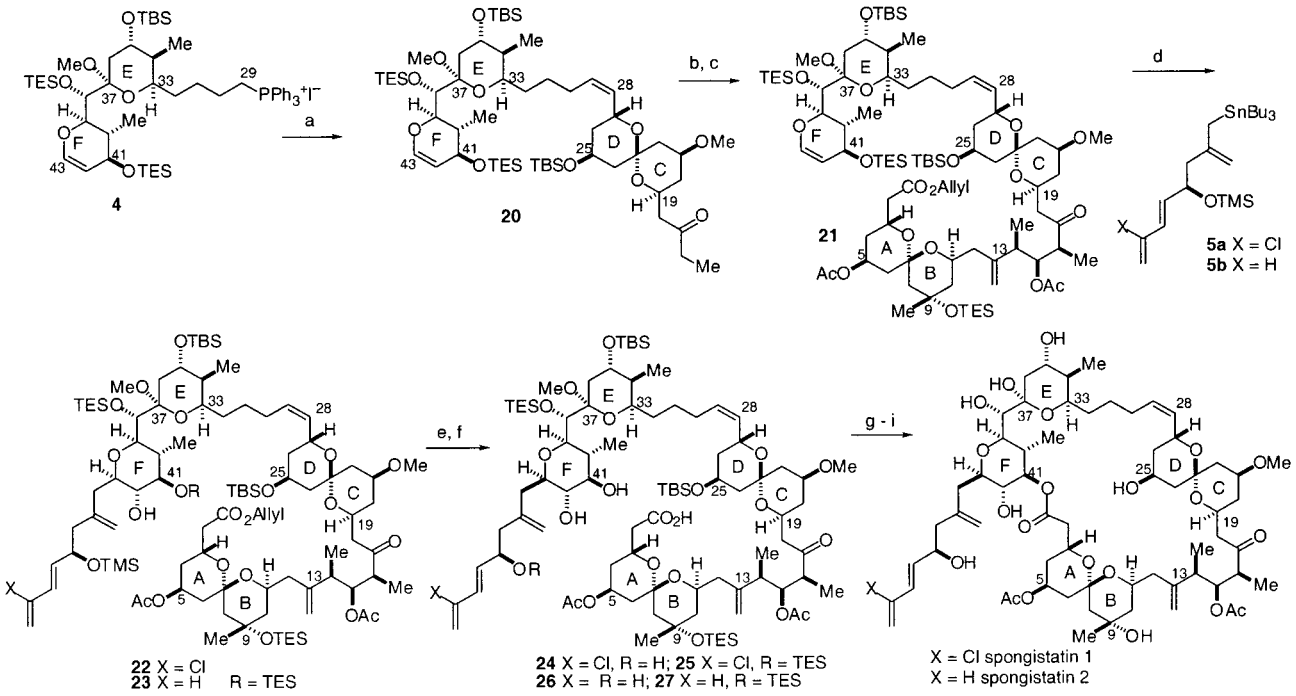
Having established viable approaches to the four key subunits in sufficient quantities, the final assault on their assembly to the spongipyrans was advanced as illustrated in Scheme 3. The critical issue of minimal refunctionalization during the assembly was addressed by using the CD fragment **3**, as the aldehyde at C28 and the ketone at C17, as the foundation of the assemblage. Thus, the four fragments were connected in their required final oxidation states in just four synthetic steps. The C28−C29 olefin was constructed in a remarkably efficient manner through the 1:1 stoichiometric combination of the CD aldehyde **3** and the ylide derived from EF phosphonium salt **4** by the metalation of the phosphonium salt with MeLi−LiBr.[17] The alkene **20** was obtained as a single detectable diastereomer in 86% yield. The resultant ethyl ketone was immediately treated with Cy_2BCl and Et_3N followed by addition of the AB aldehyde **2** to furnish the *anti* aldol product **21** with good selectivity (65%, 6:1 d.r.) after acylation of the C15 hydroxyl.[5,7,8]

The C44−C51 side chains, X = Cl and X = H for spongistatins **1** and **2**, respectively, were attached through the Evans protocol.[5,18] Exposure of the enol ether **21** to excess dimethyldioxirane led to exclusive epoxidation of the C42−C43 enol ether with no detectable oxidation of any other alkenes. Direct exposure of the epoxide to allyl stannanes **5a**[12] and **5b** in the presence of Bu_3SnOTf independently led to the fully elaborated spongistatin 1 and 2 seco esters **22** and **23**. It is noteworthy that the chlorodiene unit of spongistatin 1 can be introduced through this method.

With the fully elaborated spongistatin framework in place, the task of closing the macrolide and completing the synthesis was addressed. The allyl ester was removed with $(Ph_3P)_4Pd$ in the presence of morpholine[19] with no evidence of damage to the fragile chlorodiene moiety. The C41 and C47 silyl ethers were selectively removed with buffered HF−pyridine to access the seco acids **24** and **26**. Attempted macrolactonization of the seco acids **24** and **26** under the Yamaguchi[20] and Keck[21] protocols led to complex mixtures of products, which included acylation of the C47 hydroxyl by 2,4,6-trichlorobenzoyl chloride. Exposure of seco acid **24** to DCC, DMAP, and DMAP-HCl produced a 3:1 mixture of the C41 and C42 macrolides. It thus appeared that to improve the selectivity of the macrolactonization, the C47 hydroxyl needed to be rendered unreactive.[5] To that end, when the spongistatin 2 precursor **26** was treated with excess Et_3SiCl and imidazole, the selective protection of the C47 hydroxyl was achieved without event, as previously reported in the Evans synthesis.[5] However, attempts to execute the same transformation on the spongistatin 1 precursor **24** led to partial hydrolysis of the C37 methyl ketal, presumably due to the presence of the mildly acidic imidazole hydrochloride. Fortunately, addition of Et_3N to the reaction mixture suppressed the ketal hydrolysis, and the synthesis was advanced to the hydroxy acids **25** and **27**. The regioselective macrocyclic lactonization[5−8] was subsequently performed without difficulty through the Yamaguchi protocol,[20] and final removal of all the remaining protecting groups by treatment with 5% HF in acetonitrile produced synthetic spongistatin 1 and spongistatin 2, both identical in all respects {by ^1H, ^{13}C, IR, $[\alpha]^D_{25}$ and MS} to previously reported data.[1,2,5,8]

In summary, the synthesis of both spongistatin 1 and spongistatin 2 have been achieved from an advanced common intermediate. The efficient assembly strategy, which centers on the CD fragment as

Scheme 3: Final Fragment Assembly[a]



[a] a) MeLi−LiBr, THF, −78 °C, then aldehyde **3**, 86%; b) Cy_2BCl, Et_3N, pentane, −78 °C aldehyde **2**; c) Ac_2O, Et_3N, DMAP, CH_2Cl_2, (6:1 d.r., 60% isolated major diastereomer, 2 steps); d) dimethyldioxirane, acetone, 0 °C, then *n*-Bu_3SnOTf, CH_2Cl_2, −78 °C, X = Cl, 70% (X = H, 74%); e) $Pd(Ph_3P)_4$, morpholine, 85%(94%); f) HF−pyr, pyridine, 79%(78%); g) TESCl, imidazole, CH_2Cl_2, 94%(87%); h) 2,4,6-trichlorobenzoyl chloride, *i*-Pr_2NEt, DMAP, $PhCH_3$, 55%(60%); i) 5% HF, CH_3CN, H_2O, 45%(50%).

the foundation for the final assembly, avoids the need for refunctionalization of the late-stage, complex intermediates.

Acknowledgment. This work was supported by a research grant (CA63572) and a postdoctoral fellowship (GM20817 for S.P.A.) from the National Institutes of Health.

Supporting Information Available: ^1H spectra of synthetic spongistatin 1 and spongistatin 2 (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Pettit, G. R.; Cichacz, Z. A.; Gao, F.; Herald, C. L.; Boyd, M. R.; Schmidt, J. M.; Hooper, J. N. A. *J. Org. Chem.* **1993**, *58*, 1302. Pettit, G. R.; Cichacz, Z. A.; Gao, F.; Herald, C. L.; Boyd, M. R. *J. Chem. Soc., Chem. Commun.* **1993**, 1166. Pettit, G. R.; Herald, C. L.; Cichacz, Z. A.; Gao, F.; Schmidt, J. M.; Boyd, M. R.; Christie, N. D.; Boettner, F. E. *J. Chem. Soc., Chem. Commun.* **1993**, 1805. Pettit, G. R.; Herald, C. L.; Cichacz, Z. A.; Gao, F.; Boyd, M. R.; Christie, N. D.; Schmidt, J. M. *Nat. Prod. Lett.* **1993**, *3*, 239. Pettit, G. R.; Cichacz, Z. A.; Herald, C. L.; Gao, F.; Boyd, M. R.; Hamel, E.; Bai, R. *J. Chem. Soc., Chem. Commun.* **1994**, 1605. Bai, R.; Cichacz, Z. A.; Herald, C. L.; Pettit, G. R.; Hamel, E. *Mol. Pharmacol.* **1993**, *44*, 757. Pettit, R. K.; McAllister, S. C.; Pettit, G. R.; Herald, C. L.; Johnson, J. M.; Cichacz, Z. A.; Hamel, E. *Int. J. Antimicrob. Agents* **1998**, *9*, 147. Bai, R.; Taylor, G. F.; Cichacz, Z. A.; Herald, C. L.; Pettit, G. R.; Hamel, E. *Biochemistry* **1995**, *34*, 9714.

(2) Kobayashi, M.; Aoki, S.; Sakai, H.; Kawazoe, K.; Kihara, N.; Sasaki, T.; Kitagawa, I. *Tetrahedron Lett.* **1993**, *34*, 2795. Kobayashi, M.; Aoki, S.; Kitagawa, I. *Tetrahedron Lett.* **1994**, *35*, 1243. Kobayashi, M.; Aoki, S.; Sakai, H.; Kihara, N.; Sasaki, T.; Kitagawa, I. *Chem. Pharm. Bull.* **1993**, *41*, 989. Kobayashi, M.; Aoki, S.; Gato, I.; Kitagawa, I. *Chem. Pharm. Bull.* **1996**, *44*, 2412.

(3) Fusetani, N.; Shinoda, K.; Matsunoga, S. *J. Am. Chem. Soc.* **1993**, *115*, 3977.

(4) Pettit, G. R. *J. Nat. Prod.* **1996**, *59*, 812.

(5) Evans, D. A.; Trotter, W.; Coleman, P. J.; Côté, B.; Dias, L. C.; Rajapakse, H. A.; Tyler, A. N. *Tetrahedron* **1999**, *55*, 8671. Evans, D. A.; Coleman, P. J.; Dias, L. C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2738. Evans, D. A.; Trotter, B. W.; Côté, B.; Coleman, P. J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2741. Evans, D. A.; Trotter, B. W.; Côté, B.; Coleman, P. J.; Dias, L. C.; Tyler, A. N. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2744.

(6) Guo, J.; Duffy, K. J.; Stevens, K. L.; Dalko, P. I.; Roth, R. M.; Hayward, M. M.; Kishi, Y. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 187. Hayward, M. M.; Roth, R. M.; Duffy, K. J.; Dalko, P. I.; Stevens, K. L.; Guo, J.; Kishi, Y. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 192.

(7) Smith, Amos B., III; Doughty, V. A.; Lin, Q.; Zhuang, L.; McBriar, M. D.; Boldi, A. M.; Moser, W. H.; Murase, N.; Nakayama, K.; Sobukawa, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 191. Smith, Amos B., III.; Lin, Q.; Doughty, V. A.; Zhuang, L.; McBriar, M. D.; Kerns, J. K. Brook, C. S.; Murase, N.; Nakayama, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 196. Smith, Amos B., III; Doughty, V. A.; Sfouggatakis, C.; Bennett, C. S.; Koyanagi, J.; Takeuchi, M. *Org. Lett.* **2002**, *4*, 783.

(8) Paterson, I.; Chen, D. Y.-K.; Coster, M. J.; Aceña, J. L.; Bach, J.; Gibson, K. R.; Keown, L. E.; Oballa. R. M.; Trieselmann, T.; Wallace, D. J.; Hodgson, A. P.; Norcross, R. D. *Angew. Chem., Int. Ed.* **2001**, *40*, 4055.

(9) For leading references to synthetic approaches from other laboratories see: Wallace, G. A.; Scott, R. W.; Heathcock, C. H.; *J. Org. Chem.* **2000**, *65*, 4145. Zuev, D.; Paquette, L. A.; *Org. Lett.* **2000**, *2*, 679. Terauchi, T.; Nakata, M. *Tetrahedron Lett.* **1998**, *39*, 3795. Lemaire-Audoire, S.; Vogel, P. *Tetrahedron Lett.* **1998**, *39*, 1345. Lemaire-Audoire, S.; Vogel, P. *J. Org. Chem.* **2000**, *65*, 3346. Zemribo, R.; Mead, K. T. *Tetrahedron Lett.* **1998**, *39*, 3895. Fernandez-Megia, E.; Gourlaouen, N.; Ley, S. V.; Rowlands, G. J. *Synlett* **1998**, 991. Micalizio, G. C.; Pinchuk, A. N.; Roush, W. R. *J. Org. Chem.* **2000**, *65*, 8730. Anderson, J. C.; McDermott, B. P. *Tetrahedron Lett.* **1999**, *40*, 7135. Samadi, M.; Munoz-Letelier, C.; Poigny, S.; Guyot, M. *Tetrahedron Lett.* **2000**, *41*, 3349. Terauchi, T.; Terauchi, T.; Sato, I.; Tsukada, T.; Kanoh, N.; Nakata, M. *Tetrahedron Lett.* **2000**, *41*, 2649. Kary, P. D.; Roberts, S. M.; *Tetrahedron Asymmetry* **1999**, *10*, 217. Kim, H.; Hoffmann, M. R. *Eur. J. Org. Chem.* **2000**, 2195. Barrett, A. G. M.; Braddock, D. C.; de Koning, P. D.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **2000**, *65*, 375

(10) Crimmins, M. T.; Washburn, D. G. *Tetrahedron Lett.* **1998**, *39*, 7487

(11) Crimmins, M. T.; Katz, J. D. *Org. Lett.* **2000**, *2*, 957.

(12) Crimmins, M. T.; Katz, J. D.; Captain, L. F.; Tabet, E. A.; Kirincich, S. J. *Org. Lett.* **2001**, *3*, 949.

(13) Crimmins, M. T.; King, B. W.; Tabet, E. A., Chaudhary, K. *J. Org. Chem.* **2001**, *65*, 894. Crimmins, M. T. Chaudhary, K. *Org. Lett.* **2000**, *2*, 775. Crimmins, M. T.; King, B. W.; Tabet, E. A. *J. Am. Chem. Soc.* **1997**, *119*, 7883.

(14) Brown, H. C.; Racherla, U. S. *Tetrahedron Lett.* **1985**, *26*, 2187.

(15) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017.

(16) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4156. Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899. Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

(17) Crimmins, M. T.; Al-awar, R. S.; Vallin, I. M.; O'Mahony, R.; Hollis, W. G., Jr.; Bankaitis-Davis, D. M.; Lever, J. G. *J. Am. Chem. Soc.* **1996**, *119*, 7513.

(18) Evans, D. A.; Trotter, B. W., Coté, B. *Tetrahedron Lett.* **1998**, *39*, 1709.

(19) Friedrich-Bochnitshek, S.; Waldmann, H.; Kunz, H. *J. Org. Chem.* **1989**, *54*, 751.

(20) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989. Hikota, M.; Tone, H.; Horita, K.; Yonemitsu, O. *J. Org. Chem.* **1990**, *55*, 7−9.

(21) Boden, E. P.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394.

JA0262683