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An Aldol Approach to the Synthesis of the EF Fragment of Spongistatin 1

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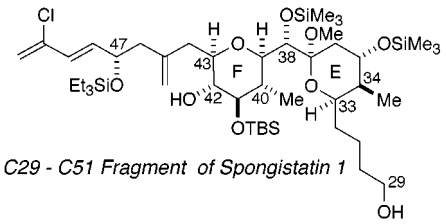
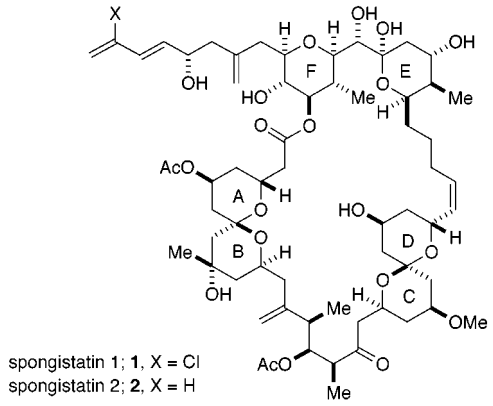
ABSTRACT



C29 - C51 Fragment of Spongistatin 1

A synthesis of the C29−C51 fragment of spongistatin 1, containing the E and F rings, has been completed. The approach relies on four diastereoselective aldol additions and an asymmetric glycolate alkylation to establish eight of the eleven stereogenic centers. The intact chlorodiene side chain was appended by a Lewis acid catalyzed addition of an allylstannane to an epoxy enol ether.

Spongistatin 1 was isolated from the marine sponge *Spongia* sp. in 1993 by Pettit.[1] Subsequently Pettit,[2] Kitagawa,[3] and Fusetani[4] have discovered additional members of this class of potent antitumor agents. The spongistatins (altohyrtins) have been found to be extraordinarily effective against a variety of chemoresistant tumor types, which comprise the NCI panel of 60 human cancer cell lines. Human melanoma, lung, brain, and colon cancers were found to be especially sensitive to spongistatin 1. The activity of the spongistatins correlates well with the class of microtubule interactive antimitotics.[5] The unique structures, the unprecedented biological activity, and the limited supply of the spongistatins have prompted substantial effort toward their total synthesis.[6−19] Several laboratories have reported progress toward the synthesis of the spongistatins, and three independent total syntheses have been documented. The total syntheses by Evans[20] and Kishi[21] served to confirm the structures of spongistatin 2 (altohyrtin C, **2**) and spongistatin 1 (altohyrtin A, **1**), respectively, and a recent report from the Smith group



spongistatin 1; **1**, X = Cl
spongistatin 2; **2**, X = H

Figure 1. Structures of spongistatins 1 and 2.

(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.
(2) Pettit, G. R.; Cichacz, Z. A.; Herald, C. L.; Gao, F.; Boyd, M. R.; Schmidt, J. M.; Hamel, E.; Bai, R. *J. Chem. Soc., Chem. Commun.* **1994**, 1605.
(3) 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.
(4) Fusetani, N.; Shinoda, K.; Matsunoga, S. *J. Am. Chem. Soc.* **1993**, *115*, 3977.
(5) Pettit, G. R. *J. Nat. Prod.* **1996**, *59*, 812.

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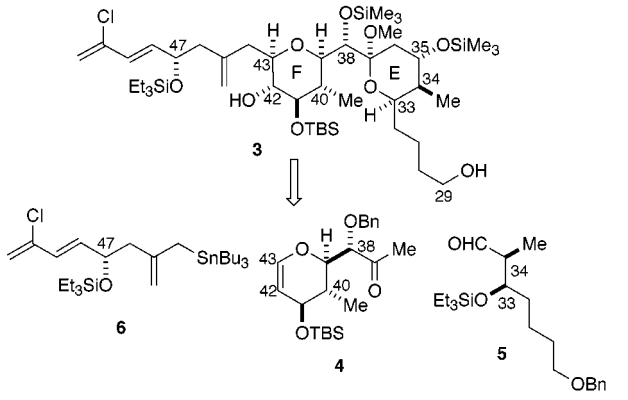
described the most recent synthesis of spongistatin 2, as well as a formal synthesis of spongistatin 1.[22]

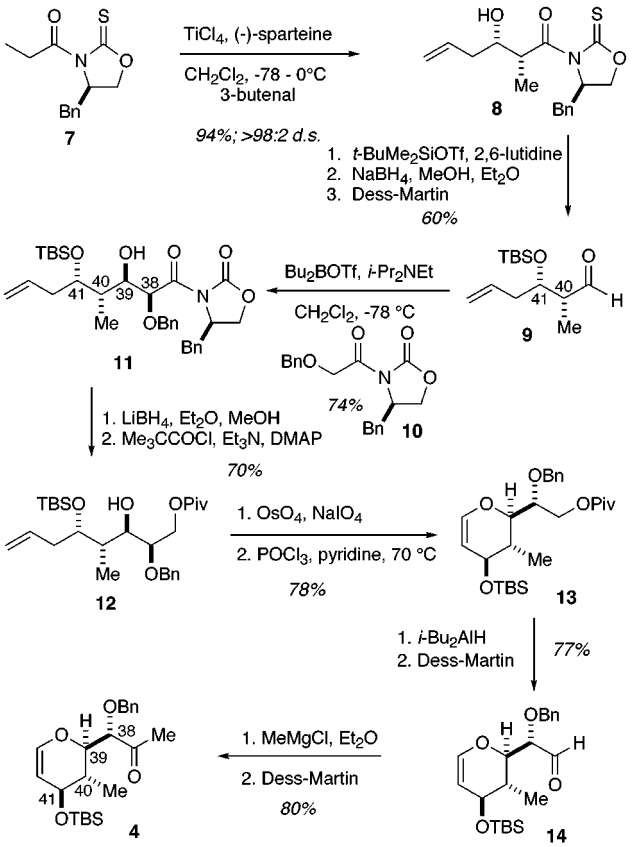
Our strategy for the synthesis of the C29−C51 fragment containing the E and F pyran rings focused on the assembly of the three subunits **4**, **5**, and **6**. It was envisioned that an F ring methyl ketone **4** might undergo a diastereoselective aldol addition to *syn* β-silyloxy aldehyde **5** to establish the C35 stereogenic center. Subsequently, the entire chlorodiene side chain would be attached through the addition of allylstannane **6** to a C42−C43 epoxide, as executed by Evans with the deschloro derivative.[20] The synthesis of the F ring

Scheme 1



methyl ketone **4** was accomplished as illustrated in Scheme 2. The C40−C41 stereocenters and the C38−C39 stereocenters were introduced by two sequential aldol additions.

Scheme 2



By using our recently developed modification of the Evans aldol,[23] exposure of *N*-propionyloxazolidinethione **7** to titanium tetrachloride and (−)-sparteine followed by the addition of 3-butenal,[24] *syn* aldol adduct **8** was produced in 94% yield in >98:2 diastereoselectivity.[25] The hydroxyl was protected as its TBS ether, the auxiliary was reductively

(6) Smith, A. B., III; Zhuang, L.; Brook, C. S.; Boldi, A.; McBriar, M. D.; Moser, W. H.; Murase, N.; Nakayama, K.; Verhoest, P. R.; Lin, Q. *Tetrahedron Lett.* **1997**, *38*, 8667. Smith, A. B., III; Zhuang, L.; Brook, C. S.; Lin, Q.; Moser, W. H.; Trout, R. E. L.; Boldi, A. *Tetrahedron Lett.* **1997**, *38*, 8671. Smith, A. B., III; Lin, Q.; Nakayama, K.; Boldi, A.; Brook, C. S.; McBriar, M. D.; Moser, W. H.; Sobukawa, M.; Zhuang, L. *Tetrahedron Lett.* **1997**, *38*, 8675.

(7) Claffey, M. M.; Heathcock, C. H. *J. Org. Chem.* **1996**, *61*, 7646. Hayes, C. J.; Heathcock, C. H. *J. Org. Chem.* **1997**, *62*, 2678. Claffey, M. M.; Hayes, C. J.; Heathcock, C. H. *J. Org. Chem.* **1999**, *64*, 8267. Wallace, G. A.; Scott, R. W.; Heathcock, C. H. *J. Org. Chem.* **2000**, *65*, 4145.

(8) Paterson, I.; Oballa, R. M.; Norcross, R. D. *Tetrahedron Lett.* **1996**, *37*, 8581. Paterson, I.; Oballa, R. M. *Tetrahedron Lett.* **1997**, *38*, 8241. Paterson, I.; Keown, L. E. *Tetrahedron Lett.* **1997**, *38*, 5727. Paterson, I.; Wallace, D. J.; Gibson, K. R. *Tetrahedron Lett.* **1997**, *38*, 8911. Paterson, I.; Wallace, D. J.; Oballa, R. M. *Tetrahedron Lett.* **1998**, *39*, 8548.

(9) Paquette, L. A.; Zuev, D. *Tetrahedron Lett.* **1997**, *38*, 5115. Paquette, L. A.; Braun, A. *Tetrahedron Lett.* **1997**, *38*, 5119.

(10) Hermitage, S. A.; Roberts, S. M. *Tetrahedron Lett.* **1998**, *39*, 3563. Hermitage, S. A.; Roberts, S. M.; Watson, D. J. *Tetrahedron Lett.* **1998**, *39*, 3567. Kary, P. D.; Roberts, S. M.; Watson, D. J. *Tetrahedron: Asymmetry* **1999**, *10*, 213. Kary, P. D.; Roberts, S. M. *Tetrahedron: Asymmetry* **1999**, *10*, 217.

(11) Crimmins, M. T.; Washburn, D. G. *Tetrahedron Lett.* **1998**, *39*, 7487. Crimmins, M. T.; Katz, J. D. *Org. Lett.* **2000**, *2*, 957.

(12) Terauchi, T.; Nakata, M. *Tetrahedron Lett.* **1998**, *39*, 3795.

(13) Lemaire-Audoire, S.; Vogel, P. *Tetrahedron Lett.* **1998**, *39*, 1345. Lemaire-Audoire, S.; Vogel, P. *J. Org. Chem.* **2000**, *65*, 3346.

(14) Zemribo, R.; Mead, K. T. *Tetrahedron Lett.* **1998**, *39*, 3895.

(15) Fernandez-Megia, E.; Gourlaouen, N.; Ley, S. V.; Rowlands, G. J. *Synlett* **1998**, 991.

(16) Micalizio, G. C.; Roush, W. R. *Tetrahedron Lett.* **1999**, *40*, 3351. Micalizio, G. C.; Pinchuk, A. N.; Roush, W. R. *J. Org. Chem.* **2000**, *65*, 8730.

(17) Anderson, J. C.; McDermott, B. P. *Tetrahedron Lett.* **1999**, *40*, 7135.

(18) Samadi, M.; Munoz-Letelier, C.; Poigny, S.; Guyot, M. *Tetrahedron Lett.* **2000**, *41*, 3349.

(19) Terauchi, T.; Terauchi, T.; Sato, I.; Tsukada, T.; Kanoh, N.; Nakata, M. *Tetrahedron Lett.* **2000**, *41*, 2649.

(20) 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.

(21) 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.

(22) Smith, A. 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, A. 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.

(23) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *65*, 894. Crimmins, M. T.; King, B. W.; Tabet, E. A. *J. Am. Chem. Soc.* **1997**, *119*, 7883−7884.

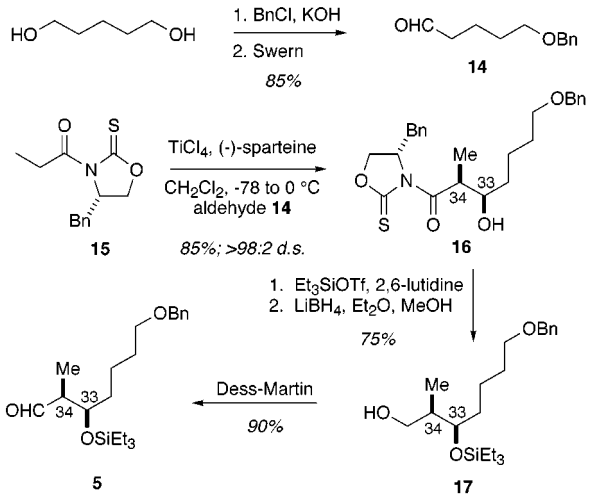
(24) Crimmins, M. T.; Kirincich, S. J.; Wells, A. J.; Choy, A. L. *Synth. Commun.* **1998**, *28*, 3675. Crimmins, M. T.; Choy, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 5663.

(25) All new compounds were characterized by ^{1}H and ^{13}C NMR, IR, and optical rotation. Yields are for isolated, chromatographically purified products.

removed with $LiBH_4$, and the resulting primary alcohol was oxidized to the aldehyde with the Dess−Martin periodinane[26] to provide the aldehyde **9** in preparation for the second aldol addition. Treatment of the aldehyde **9** with the dibutylboryl enolate derived from **10**, followed by oxidative workup of the aldolate under carefully controlled conditions,[27] provided the aldol adduct **11** in 74% yield as a single observable diastereomer. Initial attempts to close the pyran ring by oxidative cleavage of alkene **11** to the corresponding aldehyde with subsequent cyclodehydration to the enol ether met with poor results. We attributed this to participation by the oxazolidinone acyl group during the dehydration step. To avoid this problem, the oxazolidinone was reductively removed and the primary alcohol was selectively protected as the pivalate to provide alkene **12** in 70% overall yield. Oxidative cleavage of the alkene followed by dehydration of the resultant hemiketal with phosphorus oxychloride[20] cleanly delivered the enol ether **13**. Reduction of the pivalate unmasked the primary alcohol, which was oxidized to aldehyde **14**. Without purification, aldehyde **14** was exposed to methylmagnesium chloride in ether.[28] The mixture of diastereomeric secondary alcohols was then oxidized with the Dess−Martin periodinane[26] to provide the desired methyl ketone **4** in 80% yield.

The C29−C35 aldehyde **5** was prepared as illustrated in Scheme 3. Once again, we took advantage of the titanium

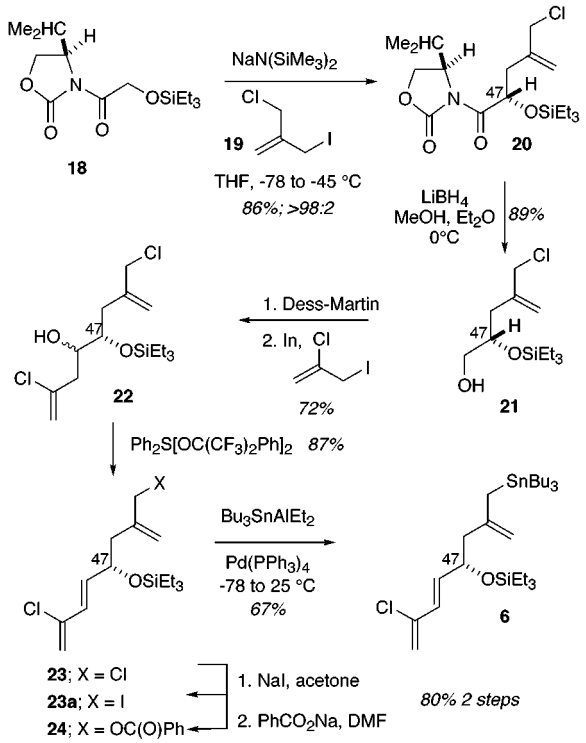
Scheme 3



tetrachloride-(−)-sparteine mediated aldol addition.[23] Exposure of aldehyde **14**, readily available from 1,5-pentanediol, to the chlorotitanium enolate of *N*-acyloxazolidinethione **15** resulted in a highly selective aldol reaction to give **16** in 85% yield (>98:2 diastereoselectivity). The alcohol was protected as its TES ether, and the auxiliary was reductively removed to give the primary alcohol **17**. Finally, the alcohol was oxidized to the aldehyde under Dess−Martin conditions[26] (immediately prior to the ensuing aldol reaction) to afford the required aldehyde **5**.

Synthesis of the third and final subunit, allyl stannane **6**, proved to be a difficult undertaking. A number of possible approaches to the allylstannane **6** were investigated but were generally thwarted as a result of the sensitivity of the chlorodiene unit to strongly basic reagents. Ultimately, the successful strategy outlined in Scheme 4 was developed. The

Scheme 4



C47 stereocenter was established through an asymmetric glycolate alkylation recently reported from our laboratory.[29] Alkylation of the sodium enolate of *N*-acyloxazolidinone **18** with the allyl iodide **19** delivered allylic chloride **20** in 86% yield (>98:2 diastereoselectivity). Careful reduction of the oxazolidinone with lithium borohydride avoided both reduction of the carbon−chlorine bond and transfer of the silyl ether producing alcohol **21** in good yield. Oxidation of the alcohol to the aldehyde was followed immediately by addition of the allylindium species generated from 2-chloro-3-iodopropene.[21,30] The resultant mixture of alcohols **22** was exposed to the Martin sulfurane[21,31] to effect dehydration to the chlorodiene **23**. Attempts to displace the allylic chloride with Bu_3SnLi failed to deliver the allylstannane. Use of other allylic leaving groups also met with extensive decomposition when they were treated with basic reagents. We then turned

(26) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4156.
(27) Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001.
(28) 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**, *118*, 7513.
(29) Crimmins, M. T.; Emmitte,; K. A., Katz, J. D. *Org. Lett.* **2000**, *2*, 2165.
(30) Yi, X.-H.; Meng, Y.; Li, C.-J. *Tetrahedron Lett.* **1997**, *38*, 4731.
(31) Arhart, R. J.; Martin, J. C. *J. Am. Chem. Soc.* **1972**, *94*, 5003.

to milder methods for allylic substitution reactions. It was hoped that Trost's conditions[32] for Pd(0)-mediated substitution might effect the desired transformation. To that end, the allyl chloride was converted to the allylic benzoate **24**. Exposure of the benzoate to $Pd(PPh_3)_4$ and $Bu_3SnAlEt_2$ provided the allylstannane **6** without destruction of the chlorodiene functionality.

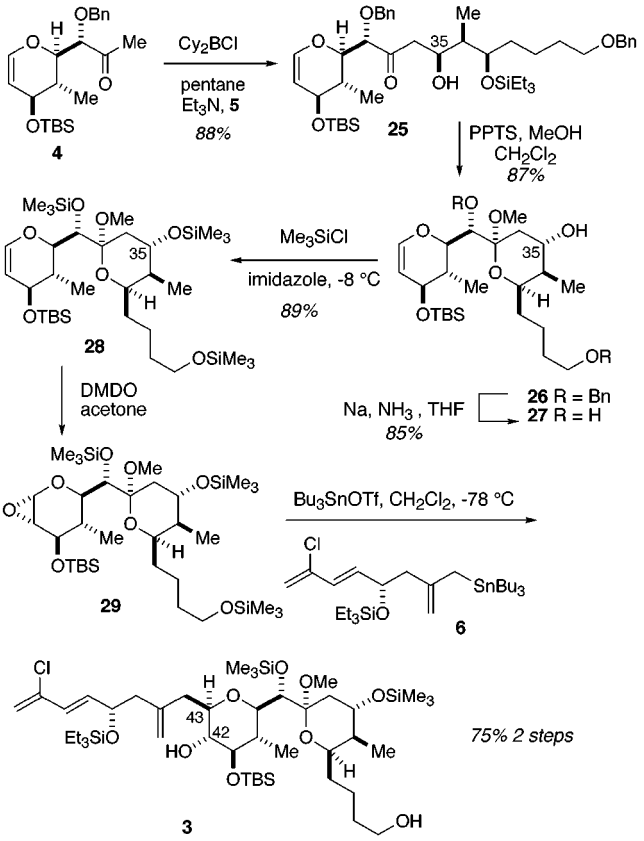
With the three required subunits in hand, it remained to assemble them into the desired EF fragment of spongistatin 1. Because of our experience with the sensitivity of the chlorodiene unit, we decided to explore the aldol reaction between the methyl ketone **4** and the aldehyde **5** prior to installation of the chlorodiene unit.

While analogous aldol reactions to establish the C35 center have been reported to result in low diastereoselectivity,[7,13,15,16] all but one of these reports utilized the lithium enolate of the methyl ketone or the silyl enol ether in a Mukaiyama-type aldol. A single report of the use of a boron enolate of an analogous methyl ketone had been noted. Ley had executed a similar aldol addition, albeit in low yield and with the chiral dialkyl boron chloride [(−)-$(Ipc)_2BCl$].[15] Evans[33] has demonstrated that boron enolates of β-alkoxy methyl ketones give 1,5 *anti* selectivity in aldol additions in contrast to the 1,5 *syn* selectivity of the corresponding ethyl ketones. A twist-boat conformation was proposed for the transition state of the methyl ketone aldol, while a chair conformation was invoked to rationalize the reaction for the ethyl ketone. In addition, Paterson[34] has noted 1,4 *syn* selectivity in the aldol reaction of boron enolates of α-alkoxy ethyl ketones. If α-alkoxy ketones behave as the β-alkoxy ketones, a reversal in selectivity should be observed when switching from ethyl to methyl ketones. Therefore, in ketone **4**, both the α-alkoxy and the β-alkoxy groups should direct the aldol addition in the same sense producing a 1,4 *anti*, 1,5 *anti* orientation—the required stereochemistry for C35 in spongistatin 1.

Enolization of the methyl ketone **4** with $(C_6H_{11})_2BCl$ and Et_3N in pentane followed by addition of aldehyde **5** led to the isolation of a single diastereomeric aldol adduct **25** (Scheme 5). Since the sense of diastereoselection could not be readily determined immediately after the aldol addition, the aldol adduct **25** was exposed to MeOH, PPTS to cleave the triethylsilyl ether and effect closure of the E ring pyran unit to the mixed ketal **26**. The coupling constants of the 500 MHz ^1H NMR and NOESY spectra of ketal **26** corroborated the assignment of the C35 stereocenter.

Completion of the intact EF fragment was achieved by first removal of the C29 and C38 benzyl ethers to give triol

Scheme 5



27. Protection of the C29, C35, and C38 hydroxyls as trimethylsilyl ethers produced **28**. Enol ether **28** was exposed to dimethyldioxirane to afford the epoxide **29**, which was treated immediately with allylstannane **6** and Bu_3SnOTf according to the conditions described by Evans.[20] A single diastereomeric product **3** was obtained from the reaction. The product contained both the intact chlorodiene unit and the C35 and C38 TMS ethers.

The synthesis of the fully elaborated EF fragment of spongistatin 1 was completed in 19 linear steps in approximately 7% overall yield. The approach is highly convergent and proceeds with high levels of stereocontrol throughout. The highly selective assembly of the methyl ketone **4** and aldehyde **5**, as well as the demonstration that the chlorodiene side chain can be incorporated as a single unit using the Evans allylstannane approach, are noteworthy. Current efforts are directed toward assembly of the EF fragment with the AB and CD subunits.[11]

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(32) Trost, B. M.; Herndon, J. W. *J. Am. Chem. Soc.* **1984**, *106*, 6835. Plé, P. A.; Hamon, A.; Jones, G. *Tetrahedron* **1997**, *53*, 3395.

(33) Evans, D. A.; Coleman, P. J.; Côté, B. *J. Org. Chem.* **1997**, *62*, 788.

(34) Paterson, I.; Wallace, D. J.; Velázquez, S. M. *Tetrahedron Lett.* **1994**, *35*, 9083. Paterson, I.; Wallace, D. J. *Tetrahedron Lett.* **1994**, *35*, 9087.