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Spongistatin Synthetic Studies. Evolution of a Scalable Synthesis for the EF Fragment of (+)-Spongistatin 1 Exploiting a Petasis–Ferrier Union/Rearrangement Tactic

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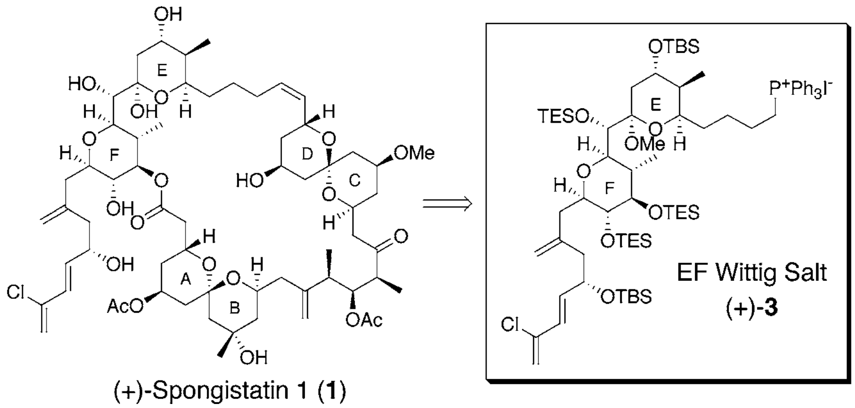
ABSTRACT



(+)-Spongistatin 1 (**1**)

EF Wittig Salt
(+)-**3**

An efficient, stereocontrolled, and scalable second-generation synthesis of (+)-3, an advanced EF subtarget for the total synthesis of (+)-spongistatin 1, has been achieved. Highlights of the strategy include preparation of the F-ring pyran via a Petasis–Ferrier union/rearrangement sequence and installation of the chlorodiene side chain employing a cyanohydrin alkylation. The longest linear sequence, 26 steps, proceeds in 8.3% overall yield.

The spongistatins comprise a unique family of architecturally complex marine macrolides which display extraordinary cytotoxicity.[1] Since their isolation,[2−4] the spongistatins have attracted wide attention among both the chemical and biological communities based on their intriguing structures and potent antitumor activities.[5] The first total syntheses of spongistatin 2 (**2**) by Evans[6] and spongistatin 1 (**1**) by Kishi[7] confirmed the relative and absolute stereochemical assignments proposed by the Kitagawa group[4] (Scheme 1).

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[1] (a) 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. (b) Pettit, G. R. *Pure Appl. Chem.* **1994**, *66*, 2271.

[2] (a) Pettit, G. R.; Cichacz, Z. A.; Gao, F.; Herald, C. L.; Boyd, M. R. *J. Chem. Soc., Chem. Commum.* **1993**, 1166. (b) 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.

[3] Fusetani, N.; Shinoda, K.; Matsunaga, S. *J. Am. Chem. Soc.* **1993**, *115*, 3977.

[4] (a) Kobayashi, M.; Aoki, S.; Sakai, H.; Kawazoe, K.; Kihara, N.; Sasaki, T.; Kitagawa, I. *Tetrahedron Lett.* **1993**, *34*, 2795. (b) Kobayashi, M.; Aoki, S.; Sakai, H.; Kihara, N.; Sasaki, T.; Kitagawa, I. *Chem. Pharm. Bull.* **1993**, *41*, 989.

[5] See refs 8−11 for a list of synthetic studies towards the spongistatins.

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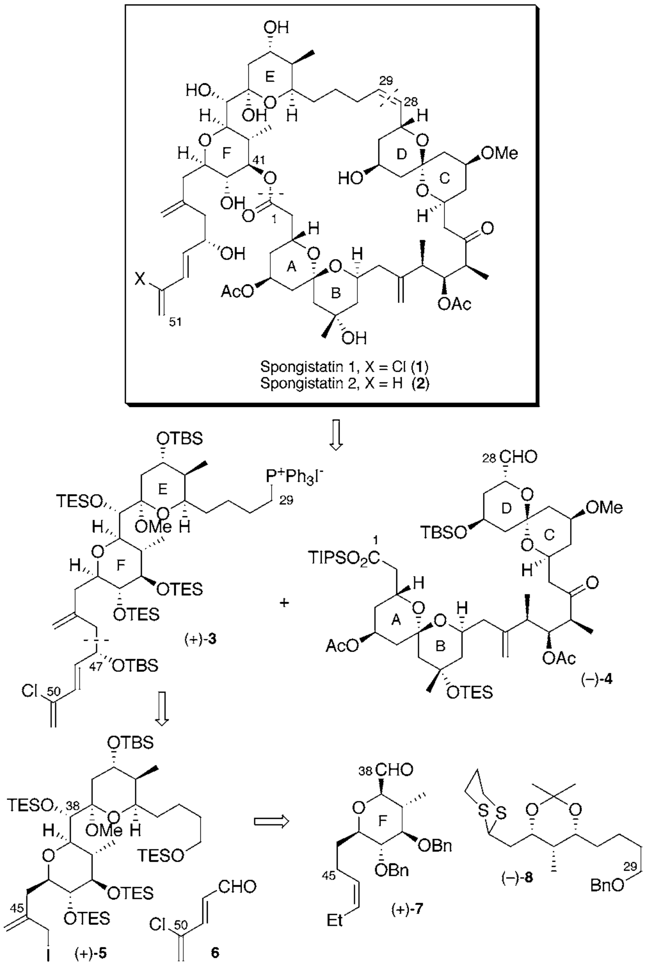
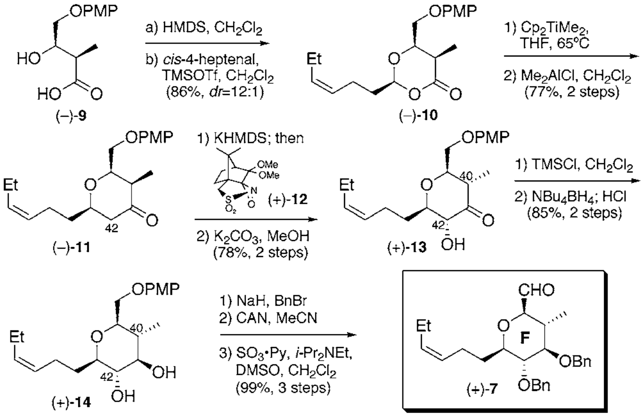
Scheme 1



Subsequent total syntheses now include those from the Smith,[8] Paterson,[9] Crimmins,[10] and Heathcock[11] laboratories.

Structurally, the spongistatins possess a striking array of features, which include two spiroketal moieties, a highly substituted bis-tetrahydropyran unit encased in a 42-membered macrolide framework, 24 stereogenic centers, and a delicate triene side chain.

Scheme 2



Recently, we reported a first-generation synthesis of (+)-spongistatin 1 (**1**)[8b] exploiting an advanced C(29)−C(51) EF Wittig salt. We have since redesigned the EF synthetic strategy with two purposes in mind. First, we sought a preparatively more effective synthesis of the EF fragment by addressing some of the deficiencies encountered in our earlier work. Second, we wished to exploit the modified Petasis−Ferrier union/rearrangement tactic developed in our laboratory to assemble the F-ring tetrahydropyran.[12] With these goals in mind, EF fragment (+)-**3** was envisioned to arise via the stereoselective allylation of bis-pyran iodide (+)-**5** with chlorodiene aldehyde **6** (Scheme 1). Further synthetic analysis of (+)-**5** revealed known dithiane (−)-**8**,[13] which, on the basis of our first-generation synthesis,[8] would be coupled to F-ring aldehyde (+)-**7**, employing chelation control to install the C(38) hydroxyl stereoselectively. F-ring aldehyde (+)-**7**, in turn, would be assembled by way of the Petasis−Ferrier union/rearrangement tactic.

Preparation of F-ring aldehyde (+)-**7** (Scheme 2) began with the TMSOTf-promoted[14] union of bis-silyl β-hydroxy acid (−)-**9**[15] with (4*Z*)-heptenal to afford dioxanone (−)-**10** (86%, dr 12:1).[16] Petasis−Tebbe methylenation (Cp_2TiMe_2)[17] and exposure of the resulting enol ether to Me_2AlCl to trigger the Petasis−Ferrier rearrangement furnished pyranone (−)-**11** as a single isomer[18] in 77% yield (two steps). After considerable experimentation, introduction of the C(42)

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

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

(8) (a) 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. (b) Smith, A. B., III; Zhu, W.; Shirakami, S.; Sfouggatakis, C.; Doughty, V. A.; Bennett, C. S.; Sakamoto, Y. *Org. Lett.* **2003**, *5*, 761.

(9) Paterson, I.; Chen, D. Y.-K.; Coster, M. J.; Acena, 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.

(10) Crimmins, M. T.; Katz, J. D.; Washburn, D. G.; Allwein, S. P.; McAtee, L. F. *J. Am. Chem. Soc.* **2002**, *124*, 5661.

(11) (a) Heathcock, C. H.; Hubbs, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 12836. (b) Heathcock, C. H.; McLaughlin, M.; Medina, J.; Hubbs, J. L.; Wallace, G. A.; Scott, R.; Claffey, M. M.; Hayes, C. J.; Ott, G. R. *J. Am. Chem. Soc.* **2003**, *125*, 12844.

(12) (a) Ferrier, R. J.; Middleton, S. *Chem. Rev.* **1993**, *93*, 2779. (b) Petasis, N. A.; Lu, S.-P. *Tetrahedron Lett.* **1996**, *37*, 141. (c) Smith, A. B., III; Verhoest, P. R.; Minbiole, K. P.; Lim, J. L. *Org. Lett.* **1999**, *1*, 909 and references therein.

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

(14) Seebach, D.; Imwinkelried, R.; Stucky, G. *Helv. Chim. Acta* **1987**, *70*, 448.

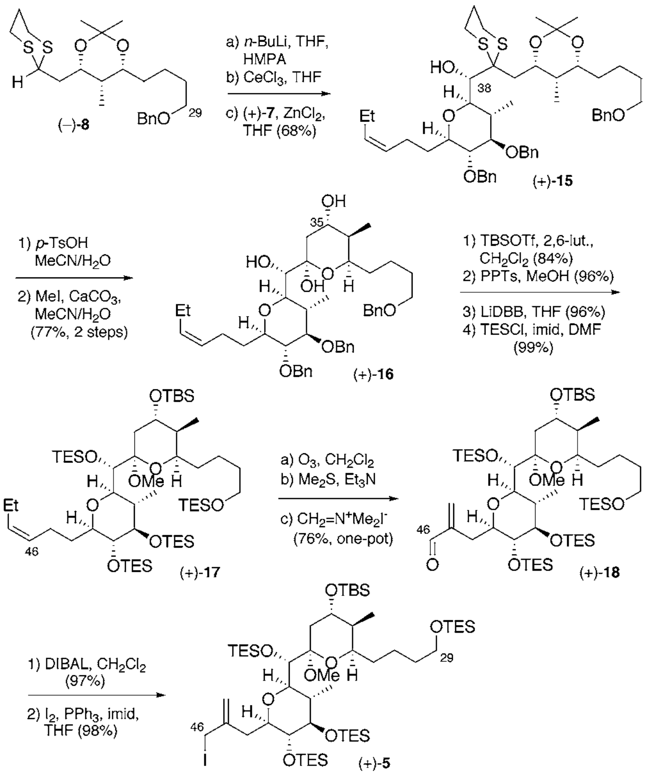
(15) Prepared in two steps exploiting Evans oxazolidinone chemistry; see the Supporting Information.

(16) Upon scale-up, TfOH (~9 mol %) was added, as the reaction does not proceed otherwise, suggesting that adventitious water was more pronounced on small scale thereby generating TfOH in situ.

(17) Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392.

(18) The stereochemistry in (−)-**11** was established on the basis of NOEs observed between the C(39), C(40), and C(43) hydrogens.

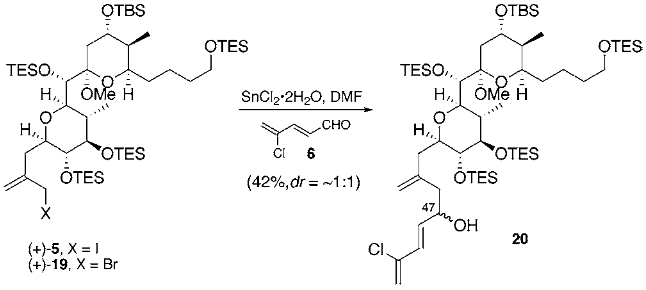
Scheme 3



hydroxyl group was achieved by treatment of the potassium enolate derived from (−)-**11** with oxaziridine (+)-**12**[19] to provide α-hydroxy ketone (+)-**13** in 78% yield after base-promoted epimerization (K_2CO_3, MeOH) of the C(40) methyl substituent. Silylation,[20] selective axial reduction, and an acidic workup to remove the TMS group then furnished diol (+)-**14** in 85% yield (two steps, dr 7:1).[21] Completion of the F-ring aldehyde (+)-**7** was then achieved by formation of the bis-benzyl ether, oxidative removal of the *p*-methoxyphenyl group, and Parikh−Doering[22] oxidation (99%, three steps).

As anticipated, efficient fragment union was achieved via treatment of the cerium anion generated from dithiane (−)-**8** with a premixed solution of aldehyde (+)-**7** and zinc chloride[23] to afford (+)-**15** as a single isomer[24] (68%; Scheme 3). Acidic removal of the acetonide, followed by dethioketalization with in situ formation of the E-ring hemiketal, afforded the EF bis-pyran (+)-**16**. Selective silylation at C(35), formation of the methyl ketal, and reductive debenzylation[25] then led to an intermediate polyol which was protected as the tetra-TES ether to provide (+)-**17** in high yield over the four steps. Partial side-chain introduction began with ozonolysis of alkene (+)-**17** employing a reductive workup, followed without isolation by treatment with Eschenmoser's salt[26] to afford enal (+)-**18**. Completion of allylation precursor (+)-**5** was then achieved by 1,2-reduction of the aldehyde and conversion of the derived alcohol to the allyl iodide.

Scheme 4



Initial attempts to install the chlorodiene moiety focused on a tin-mediated Barbier[27] allylation between iodide (+)-**5** and known chlorodiene aldehyde **6**[8b] (Scheme 4). Precedent for this construction derives from the Paterson group synthesis of spongistatin 1,[9] wherein the boron enolate generated from an EF bis-pyran methyl ketone was coupled to aldehyde **6** to set the C(47) hydroxyl stereochemistry with high selectivity employing substrate control.[28] In an effort to exploit this stereochemical bias, we treated a premixed solution of iodide (+)-**5** [or bromide (+)-**19**] and aldehyde **6** with $SnCl_2 \cdot 2H_2O$ to affect coupling. However, after significant effort, at best we obtained only a 42% yield of **20**, produced as a mixture (∼1:1) of C(47) alcohols. All other conditions (i.e., various metal sources, solvents, and temperatures) proved unsuccessful.

Having exhausted most, if not all options directed at side chain installation via allylation chemistry, we decided to alter our strategy by incorporating the chlorodiene moiety as a nucleophile rather than as an electrophile. To this end, TMS-cyanohydrin **21** (Scheme 5)[29] was prepared and treated with LiHMDS at low temperature, followed by addition of allyl iodide (+)-**5** [or bromide (+)-**19**]. Initial attempts to affect this coupling, however, resulted in cyanohydrin decomposition with recovery of the allyl halide. Subsequent deuterium studies revealed that the anion derived from cyanohydrin **21** is highly unstable, decomposing rapidly at low temperatures.

Suspecting that the instability of the anion derived from cyanohydrin **21** was due to the unsaturation, we prepared

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(19) Davis, F. A.; Kumar, A.; Chen, B.-C. *J. Org. Chem.* **1991**, *56*, 1143.

(20) Silylation at C(42) served to minimize chelation-control in the reduction, which otherwise resulted in poor selectivity.

(21) Watanabe, Y.; Ogasawara, T.; Nakahira, H.; Matsuki, T.; Ozaki, S. *Tetrahedron Lett.* **1988**, *29*, 5359.

(22) Parikh, J. R.; Doering, W. V. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.

(23) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392.

(24) The C(38) stereochemistry was confirmed by Mosher ester analysis; see: Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. (b) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.

(25) Ireland, R. E.; Smith, M. G. *J. Am. Chem. Soc.* **1988**, *110*, 854.

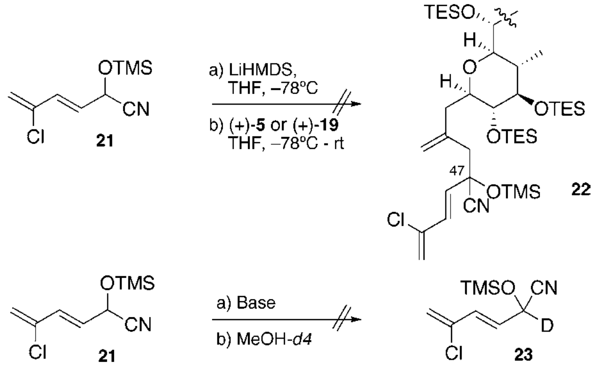
(26) Schreiber, J.; Maag, H.; Hashimoto, N.; Eschenmoser, A. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 330.

(27) Imai, T.; Nishida, S. A. *Synthesis* **1993**, 395.

(28) This is in the 1,5-*syn* sense, opposite to 1,5-*anti* stereoinduction observed for boron aldol reactions of simple *β*-alkoxy ketones, suggesting in this case, the overwhelming contribution from the more remote stereocenters; see ref 9.

(29) Prepared by treatment of **6** with TMSCN and ZnI_2; see: (a) Stork, G.; Maldonado, L. *J. Am. Chem. Soc.* **1971**, *93*, 5286. (b) Evans, D. A.; Truesdale, L. K. *J. Chem. Soc., Chem. Commun.* **1973**, 55.

Scheme 5

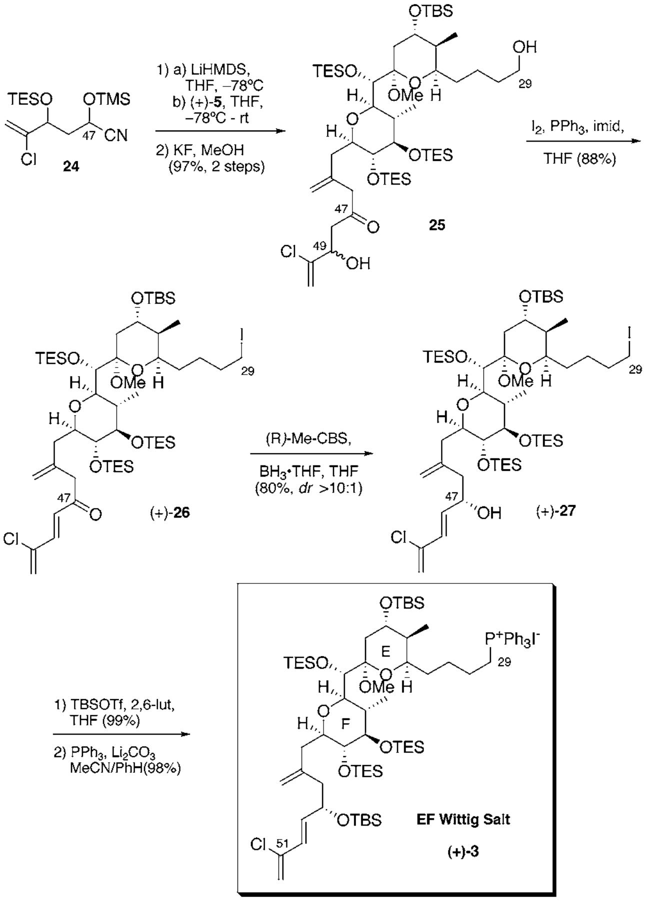


24 (Scheme 6).[30] Pleasingly, modified cyanohydrin **24** underwent clean deprotonation and coupled readily to iodide (+)-**5**. Subsequent hydrolysis of the cyanohydrin moiety (KF, MeOH), accompanied by desilylation at C(29) and C(49), afforded β-hydroxy ketone **25** in high yield (97%, 2 steps), as an inconsequential mixture (∼1:1) of alcohols. Elimination of the C(49) hydroxyl with concomitant formation of the C(29) iodide was then achieved upon treatment of β-hydroxy ketone **25** to iodination under buffered conditions (I_2, PPh_3, imid). Iodoketone (+)-**26** was obtained in 88% yield. Asymmetric reduction employing the Corey protocol[31] then established the C(47) hydroxyl stereogenicity[32] to furnish (+)-**27** in both good yield and with excellent selectivity (80%, dr > 10:1). Notably, this transformation was successfully achieved in the presence of the sensitive chlorodiene moiety, as well as the exomethylene and the primary iodide. Silylation followed by Wittig salt formation completed the synthesis of the fully functionalized C(29)−C(51) EF fragment (+)-**3** for (+)-spongistatin 1.

The synthesis of (+)-**3**, achieved with a longest linear sequence of 26 steps (8.3% overall yield) from β-hydroxy acid (−)-**9**, represents a dramatic improvement in yield compared to our first-generation total synthesis of spongistatin 1 (24 steps, 1.8% overall yield).[8b] Completion of a second-generation synthesis of (+)-spongistatin 1 is now envisioned to be achieved in a fashion similar to our first-generation approach [i.e., Wittig union of (+)-**3** with ABCD (−)-**4**,[33] followed by desilylation, regioselective Yamaguchi cyclization,[6d,34] and global deprotection].

In summary, we have achieved an efficient, stereocontrolled, and most importantly, scalable second-generation synthesis of the advanced EF fragment of (+)-spongistatin 1. The synthesis features construction of the F-ring pyran aldehyde (+)-**7** employing a modified Petasis-Ferrier union/rearrangement sequence developed in our laboratory.[12c] Also noteworthy is the effective installation of the highly sensitive chlorodiene moiety using the cyanohydrin approach. Completion of a second-generation total synthesis of (+)-spongistatin 1 will be disclosed in due course.

Scheme 6



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Supporting Information Available: Spectroscopic and analytical data and selected experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(30) See the Supporting Information for the preparation of **24**.

(31) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986.

(32) The C(47) stereochemistry was confirmed by chemical correlation to an intermediate prepared in our previous synthesis.

(33) The synthesis of (−)-**4** was previously disclosed; see: Smith, A. B., III; Doughty, V. A. D.; Sfouggatakis, C.; Bennett, C. S.; Koyanagi, J.; Takeuchi, M. *Org. Lett.* **2002**, *4*, 783.

(34) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.