ORGANIC LETTERS

2003
Vol. 5, No. 5
761−764

Total Synthesis of (+)-Spongistatin 1. An Effective Second-Generation Construction of an Advanced EF Wittig Salt, Fragment Union, and Final Elaboration

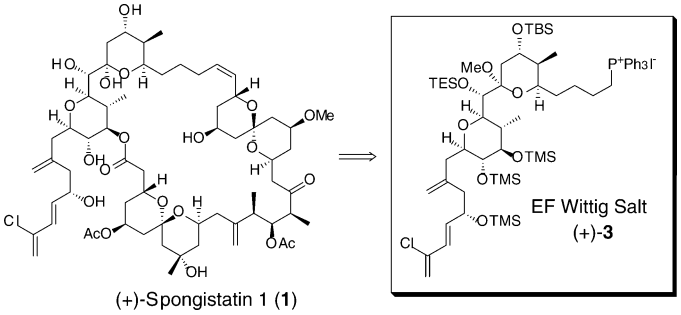
Amos B. Smith, III,* Wenyu Zhu, Shohei Shirakami, Chris Sfouggatakis, Victoria A. Doughty, Clay S. Bennett, and Yasuharu Sakamoto

Department of Chemistry, Monell Chemical Senses Center, and Laboratory for Research on the Structure of Matter, University of Pennsylvania, Philadelphia, Pennsylvania 19104

smithab@sas.upenn.edu

Received January 8, 2003

ABSTRACT



A stereocontrolled, total synthesis of (+)-spongistatin 1 (1) has been achieved. Union of a second-generation EF Wittig salt (+)-3 with the advanced ABCD aldehyde (–)-4, followed by regioselective macrolactonization and global deprotection afforded (+)-spongistatin 1 (1). The longest linear sequence, 29 steps, proceeded in 0.5% overall yield.

The spongistatins (aka altohyrtins) comprise an architecturally unique family of macrolides that display extraordinary cytotoxicity against several highly chemo-resistant tumor cell lines.[1] Since their independent isolation by three research groups,[2−4] the spongistatins have been the focus of considerable attention in both the chemical and biological communities, based on their intriguing structures and potent antitumor activities.[5−11] The relative and absolute stereochemistries, first deduced by Kitagawa,[4] were confirmed via the total synthesis of spongistatin 2 (**2**) by Evans[5] and spongistatin 1 (**1**) by Kishi[6] (Scheme 1). More recently, we,[7] Paterson,[8] and

(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.

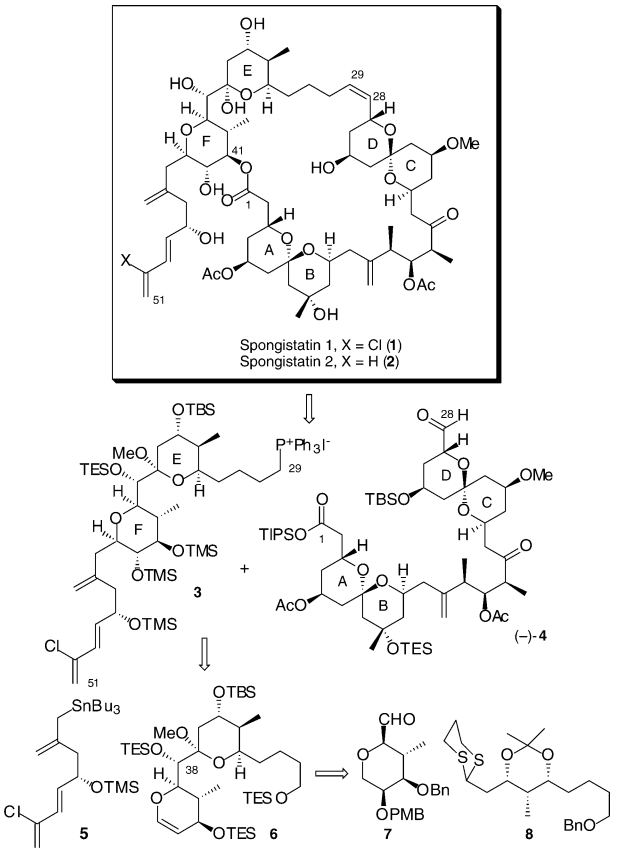
(4) (a) Kobayashi, M.; Aoki, S.; Sakai, H.; Kawazoe, K.; Kihara, N.; Sasaki, T.; Kitagawa, I. *Tetrahedron Lett*. **1993**, *34*, 2795. (b) Kobayashi, M.; Aoki, S.; Sakai, H.; Kihara, N.; Sasaki, T.; Kitagawa, I. *Chem. Pharm. Bull*. **1993**, *41*, 989.

(5) (a) Evans, D. A.; Coleman, P. J.; Dias, L. C. *Angew. Chem., Int. Ed. Engl*. **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.

(6) (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.

10.1021/ol034037a CCC: $25.00
Published on Web 02/05/2003

Scheme 1

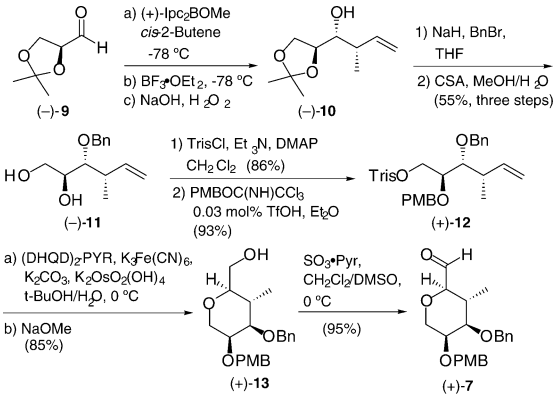


Crimmins[9] have also achieved successful total syntheses in this area.

The spongistatins possess a striking array of structural features, including a 42-membered macrolactone incorporating two spiroketals, a hemiketal, and a tetrahydropyran, which is subtended by a highly unsaturated side chain. Having recently achieved a preparatively useful synthesis of the advanced ABCD fragment (−)-**4**,[12] we turned to a second-generation synthesis of the C(29)−C(51) EF Wittig salt (+)-**3**. Our strategy called for three subunits **5**, **7**, and **8**. On the basis of our first-generation syntheses, we envisioned a chelation-controlled addition of known dithiane **8**[11] to F-ring aldehyde **7**, followed by removal of the acetonide and dithiane with in situ hemiketalization would provide the EF bis-pyran **6** with the requisite C(38) stereogenicity. Installation of the chlorodiene side chain would next take advantage of the Evans tactic involving addition of a fully elaborated allylstannane **5** to a C(42)−C(43) epoxide. Completion of the synthesis of **1** would then entail TMS protection of the C(41, 42, and 47) hydroxyls, generation of the Wittig phosphonium salt, union with the advanced ABCD fragment (−)-**4**,[12] regioselective macrolactonization, and global deprotection.

Preparation of the requisite F-ring aldehyde **7** (Scheme 2) began with a Brown asymmetric crotylboration[13] of aldehyde (−)-**9**[14] to furnish homoallylic alcohol (−)-**10**; the diastereoselectivity was excellent (>20:1). Subsequent benzylation and acidic removal of the acetonide generated diol (−)-**11**; the overall yield for the three steps was 55%. Selective sulfonation of the primary hydroxyl with 2,4,6-triisopropylbenzenesulfonyl chloride (TrisCl), followed by protection of the secondary hydroxyl as the PMB ether[15] afforded alkene (+)-**12**. Sharpless asymmetric dihydroxylation[16] then led to an intermediate diol, which upon treatment with NaOMe achieved ring closure to afford tetrahydropyran (+)-**13** in 85% yield (dr, 6:1). Parikh−Doering[17] oxidation completed construction of the C(38)−C(43) tetrahydropyran (+)-**7**.

Scheme 2



As anticipated, efficient fragment union was achieved in a highly stereocontrolled fashion (>20:1; 51% yield; Scheme 3) via treatment of the cerium anion generated from dithiane (−)-**8** with a premixed solution of aldehyde (+)-**7** and zinc chloride.[18] Acidic removal of the acetonide (CSA, MeOH/H_2O, 86%) in (+)-**14**, followed by dithiane removal employing the conditions of Fujita[19] [$Hg(ClO_4)_2$, $CaCO_3$, CH_3CN/H_2O, 95%], with concomitant hemiketal formation then afforded (+)-**15** possessing the E and F rings. Selective protection of the sterically more accessible C(35) hydroxyl

(7) (a) 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. (b) 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.

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

(10) For synthetic approaches to the spongistatins, see refs 5−9 and references therein.

(11) 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.

(12) Smith, A. B. III; Doughty, V. A.; Sfouggatakis, C.; Bennett, C. S.; Koyanagi, J.; Takeuchi, M. *Org. Lett*. **2002**, *4*, 783.

(13) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc*. **1986**, *108*, 5919.

(14) Hubschwerlen, C. *Synthesis* **1986**, 962.

(15) Nakajima, N.; Horita, K.; Abe, R.; Yonemitsu, O. *Tetrahedron Lett*. **1988**, *29*, 4139.

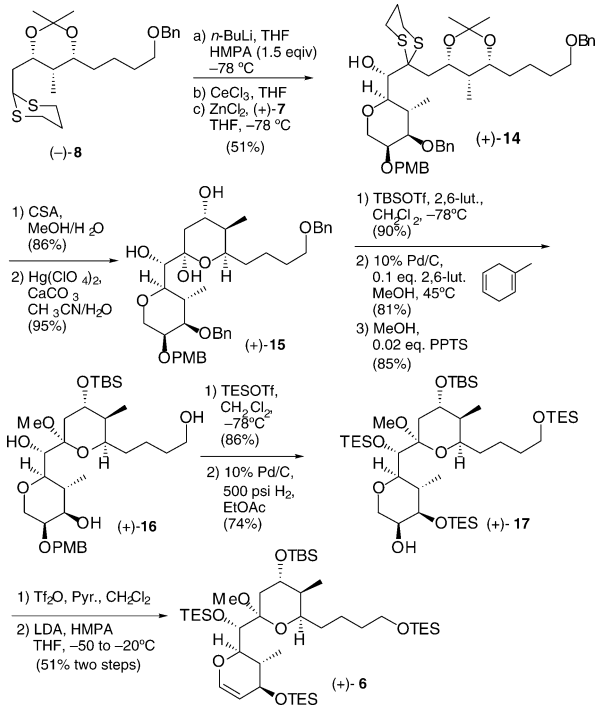
(16) Crispino, G. A.; Jeong, K.-S.; Kolb, H. C.; Wang, Z.-M.; Xu, D.; Sharpless, K. B. *J. Org. Chem*. **1993**, *58*, 3785.

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

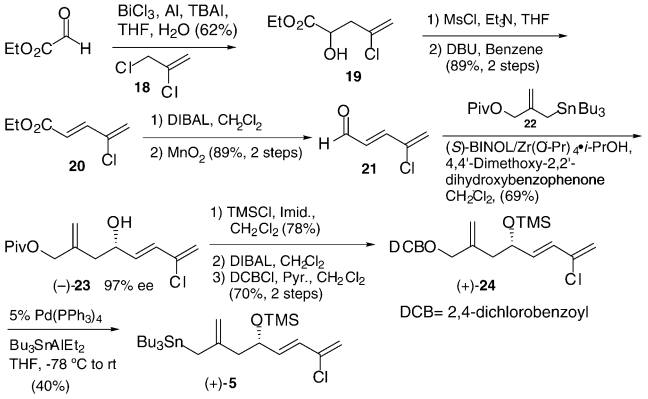
(18) The use of cerium chloride serves to suppress enolization; see: Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc*. **1989**, *111*, 4392.

(19) Fujita, E.; Nagao, Y.; Kaneko, K. *Chem. Pharm. Bull*. **1978**, *26*, 3743.

Scheme 3



Scheme 4

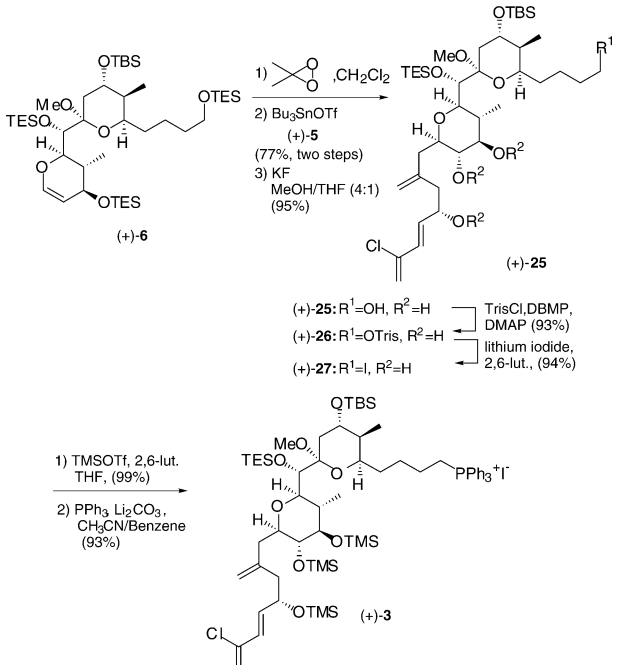


(TBSOTf, 2,6-lutidine, 90%) next provided an intermediate TBS ether. Removal of the C(29) and C(41) benzyl ethers in the presence of a PMB group, as now required, proved difficult. Precedent for such chemoselectivity has been observed by Hirota[20] for phenolic hydroxyls, using a Pd/C-pyridine catalyst. In our case this protocol resulted in no reaction. We reasoned that the pyridine may compete with the benzyl group for access to the active palladium surface, and thus a bulkier pyridine derivative might be more appropriate. Pleasingly, clean debenzylation was achieved in the presence of the C(42) PMB group via transfer hydrogenation, using 2,6-lutidine as an additive. Methanolysis of the intermediate triol then afforded methyl ketal (+)-**16** in high yield for the two steps. Exhaustive silylation (TESOTf, CH_2Cl_2, 86%), followed by medium-pressure hydrogenolysis (500 psi) removed the PMB group to furnish alcohol (+)-**17**. Enol ether (+)-**6** was then generated in two steps via triflation (Tf_2O, Pyr.) and elimination (LDA) of triflic acid.

For the required allylstannane side chain (+)-**5** (Scheme 4), our departing point entailed coupling commercially available allyl chloride **18** with ethyl glyoxalate in the presence of catalytic $BiCl_3$ (0.12 equiv); ester **19** was obtained in 62% yield.[21] Mesylation (MsCl, Et_3N) of the hydroxyl group, followed by elimination (DBU) of methanesulfonic acid then provided the α,β-unsaturated ester **20** (89%, two steps). Reduction with DIBAL next led to an intermediate alcohol that upon oxidation yielded aldehyde **21** in 89% yield (two steps). Initial attempts to couple **21** with stannane **22** using the Keck protocol[22] resulted in high enantioselectivity (98% ee), albeit the yields were at best modest (ca. 33%). Application of a bis-zirconium catalyst[23] led to a marked improvement in yield (69%), furnishing homoallylic alcohol (−)-**23** with similar enantioselectivity (97% ee). Silylation (TMSCl, imid., 78%), followed by removal of the pivaloate moiety (DIBAL) and installation of the 2,4-dichlorobenzoate (DCBCl, Pyr., 70%, two steps) then afforded (+)-**24**. Completion of the fully functionalized allyl stannane side chain (+)-**5** was achieved by exposure of (+)-**24** to $Pd(PPh_3)_4$ and $Bu_3SnAlEt_2$.[24] Importantly, the chlorodiene moiety was not compromised under the palladium conditions.

Side chain installation proceeded readily via the Evans precedent (Scheme 5);[5] specifically, epoxidation of bis-pyran (+)-**6** with dimethyldioxirane in methylene chloride, followed in turn by treatment with allylstannane (+)-**5** in the presence of Bu_3SnOTf and then KF (MeOH/THF) provided (+)-**25** as a single isomer in good yield (73%; 3 steps).

Scheme 5

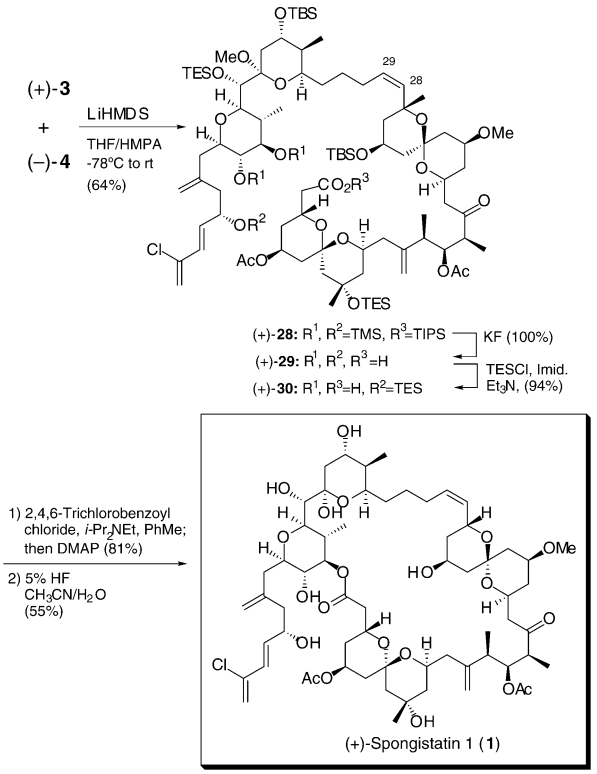


(20) Sajiki, H.; Kuno, H.; Hirota, K. *Tetrahedron Lett.* **1997**, *38*, 399.
(21) Wada, M.; Ohki, H.; Abiba, K. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1738.

Selective sulfonation of the primary hydroxyl group with TrisCl (2,6-di-^{t}Bu-4-methylpyridine, DMAP, 93%) next furnished (+)-**26**. Interestingly, use of the less hindered bases such as Et_3N or Hünig's base resulted in lower yields of the primary sulfonate, in conjunction with hydrolysis of the C(37) methyl ketal. Conversion of (+)-**26** to the iodide (LiI, 2,6-lutidine, 94%), protection of the three secondary hydroxyls (TMSOTf, 2,6-lutidine, 99%), and reaction with PPh_3 (Li_2CO_3, 93%) then completed assembly of the EF Wittig salt (+)-**3**. The synthesis of the fully functionalized EF fragment was thus achieved employing 24 steps in the longest linear sequence, with an overall yield of 1.8%.

For (+)-spongistatin 1 (**1**), fragment assembly was achieved via Wittig coupling of (+)-**3** with advanced aldehyde (−)-**4**[12] to provide (+)-**28** in 64% yield, employing a modification of the conditions reported by Paterson (Scheme 6).[8]

Scheme 6



After removal of the TMS and TIPS groups (KF, MeOH/THF, quant.), selective protection[5,9] of the C(47) hydroxyl (TESCl, imid., Et_3N, 94%) provided (+)-**30**. Regioselective macrolactonization[5−9] then led to the desired 42-membered macrolide as the sole product in high yield (81%). Global deprotection[7] employing dilute aqueous HF completed the total synthesis of (+)-spongistatin 1 (**1**), which was identical in all respects (500 MHz ^{1}H, 125 MHz ^{13}C NMR, HRMS, IR and chiroptic properties) to the literature data.[1,8]

In conclusion, we have achieved an effective, second-generation stereocontrolled total synthesis of (+)-spongistatin 1 (**1**), highlighted by a highly selective dithiane addition to F-pyran aldehyde (+)-**7**, the construction of allylstannane (+)-**5**, and the efficient union of fragments. The synthesis proceeded in 29 steps for the longest linear sequence (based on the EF subunit), with an overall yield of 0.5%. Importantly, the linear sequence for our second-generation synthesis [18 steps shorter than our previously reported formal synthesis of spongistatin 1 (**1**)][7a] is highly competitive with the other published approaches.

Acknowledgment. Financial support was provided by the NIH (NCI) through grant CA-70329, by Postdoctoral Fellowships from the Uehara Memorial Foundation and the JSPS for research abroad (2002) to S.S., and by a Royal Society Fulbright Fellowship to V.A.D.

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.

OL034037A

(22) (a) Keck, G. E.; Tarbet, K. H.; Graci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467. (b) Brückner, R.; Weigand, S. *Chem. Eur. J.* **1996**, *2*, 1077.

(23) (a) Hanawa, H.; Kii, S.; Asao, N.; Maruoka, K. *Tetrahedron Lett.* **2000**, *41*, 5543. (b) Kii, S.; Maruoka, K. *Tetrahedron Lett.* **2001**, *42*, 1935.

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