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Synthesis of the C-1–C-28 ABCD Unit of Spongistatin 1

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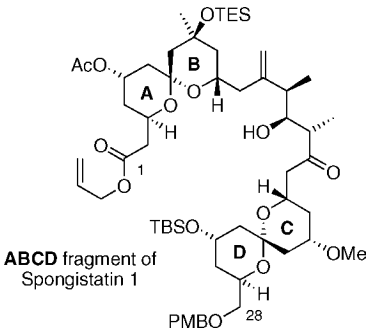
ABSTRACT



The synthesis of the C-1–C-28 ABCD fragment of spongistatin is described. Anti-selective boron-mediated aldol coupling of a CD spiroketal ketone fragment to an AB spiroketal aldehyde unit forms the desired C1–C28 advanced intermediate. Other features include the double conjugate addition of a dithiol to an ynone to generate the key β-keto-dithiane unit required for the synthesis of the AB spiroketal fragment.

Isolated independently by Pettit, Kitagawa, and Fusetani in 1993,[1] the spongistatins have attracted significant interest from the synthetic community which has resulted in a number of total syntheses.[2] These natural products are an important family of architecturally complex marine macrolides that display exceptional antitumor activities against a variety of human cancer cell lines.[3]

We have previously reported studies toward the assembly of the EF fragment[4] and here and in the preceding paper[1] we detail our synthesis of the ABCD unit.

We recognized the efficacy of the anti-selective aldol coupling, demonstrated by Evans,[2a,b] Paterson,[2d] and more recently Smith[2c] and Crimmins,[2e] to join the AB and CD units together to form the basis of fragment **2** in their total syntheses. Accordingly, we envisaged that AB aldehyde **4** and CD ketone **5** would be suitable coupling partners for this transformation (Scheme 1). Our synthesis of the CD spiroketal **5** is reported in the previous paper,[1] and the AB spiroketal **4** can be realized using a similar strategy. Spiroketalization precursor **6** can be formed using a dithiol conjugate addition methodology from ynone **7**.[5] In turn, this can be assembled from alkyne **8** and aldehyde **9**.

Our synthesis of alkyne **8** began with trityl protection of (*S*)-Roche's ester followed by reduction with $LiAlH_4$ and oxidation using Swern conditions[6] to form the aldehyde (Scheme 2). Immediate treatment with propane-1,3-dithiol and boron trifluoride−Et_2O complex forms dithiane **11** after protection of the resulting hydroxyl group as its TBS ether. Lithiation of the dithiane[7] and treatment of the anion with (*S*)-epichlorohydrin furnishes an epoxide which undergoes subsequent reaction with TIPS-acetylene under modified Hiroa conditions to form dithiane **12** in good yield.[8] Iodine mediated dithiane cleavage[9] and TES protection of the hydroxyl forms ketone **13** in 96% over two steps. Methylenation of ketone **13** proved to be a challenging transformation. After much experimentation, treatment of ketone **13** with the Petasis reagent[10] in toluene at 120 °C for 3 h proved to be the optimal reaction, generating alkene **14** in 71% yield.

(1) See the references in the preceding paper: Gaunt, M.J.; Hook. D. F.; Tanner, H. R.; Ley, S. V. *Org. Lett.* **2003**, *5*, 4815.

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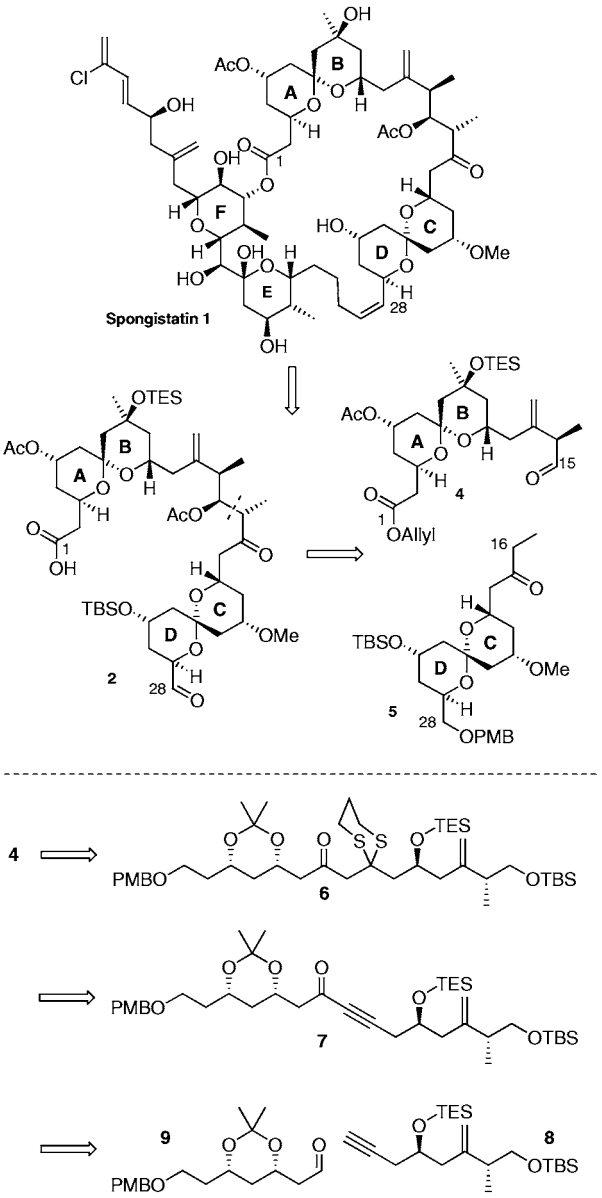
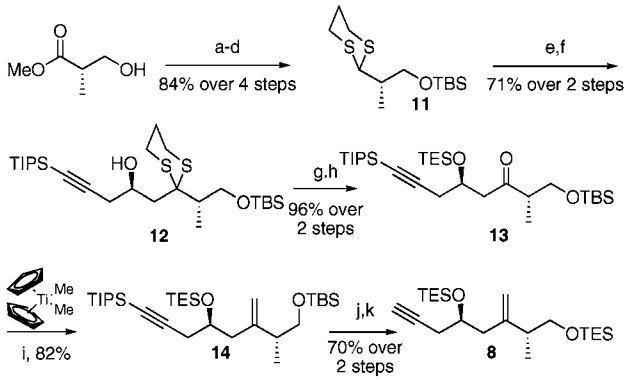
Scheme 1. Retrosynthesis for the ABCD Fragment of Spongistatin **1**



Scheme 2. Synthesis of Alkyne **8**



[a] Conditions: (a) TrCl, pyr, CH_2Cl_2, 16 h, rt; (b) (i) $LiAlH_4$, THF, 0 °C, 2 h, (ii) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C then DIPEA −78 → 0 °C; (c) $HS(CH_2)_3SH$, $BF_3{\cdot}Et_2O$, THF, −78 °C, 4 h; (d) TBS-Cl, THF, imid, 2 h, rt; (e) *n*-BuLi, THF, rt, 10 min then (*S*)-epichlorohydrin, THF, −20 °C → rt, 16 h; (f) (i) *n*-BuLi, THF, −78 °C, 1 h, (ii) $BF_3{\cdot}$THF, −78 °C, 1 h, (iii) epoxide, THF, −78 °C, 1.5 h; (g) I_2, MeCN, $NaHCO_3$, 0 °C; (h) TES-Cl, THF, imid, 2 h, rt; (i) Petasis reagent, microwave;[12] (j) TBAF, THF, rt, 4 h; (k) TES-Cl, THF, imid, 2 h, rt.

Interestingly, the reaction proved to be much more efficient when carried out under microwave heating, forming the alkene **14** after 10 min in an improved 82% yield.[11] The TIPS-protected acetylene was essential for the success of this reaction; however, it was not possible to remove this group in the presence of the other silicon functionality. Therefore, global deprotection and reprotection as the bis-TES ether afforded the desired alkyne **8**.

The synthesis of aldehyde **9** began with dithiane **15**.[8] This dithiane is also common to the synthesis of the CD fragment (Scheme 3). Lithiation of dithiane **15**[8] and interception of the anion with epoxide **16** forms **17** in 91% yield. Cleavage of the dithiane group with iodine- and borane-mediated syn-

(2) Evans, D. A.; Trotter, B. W.; Coleman, P. J.; Cote, B.; Dias, L. C.; Rajapaske, 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.; Cote, B.; Coleman, P. J. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 2741. Evans, D. A.; Trotter, B. W.; Cote, B.; Coleman, P. J.; Dias, L. C.; Tyler, A. N. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 2744. (b) 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. 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. (c) 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.; Sobukawa, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 196. Smith, A. B., III; Doughty, V. A.; Sfouggatakis, C.; Bennett, C. S.; Koyanagi, J.; Takeuchi, M. *Org. Lett.* **2002**, *4*, 783. (d) 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. (e) Crimmins, M. T.; Katz, J. D.; Washburn, D. G.; Allwein, S. P.; McAtee, L. F. *J. Am. Chem. Soc*. **2002**, *124*, 5661. (f) 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. For other ABCD syntheses, see: Terauchi, T.; Terauchi, T.; Sato, I.; Shoji, W.; Tsukada, T.; Tsumoda, T.; Kanoh, N.; Nakata, M. *Tetrahedron Lett*. **2003**, *44*, 7741. Zuev, D.; Paquette, L. A. *Org. Lett*. **2000**, *2*, 679 for ABCD fragment syntheses.

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(7) Ide, M.; Nakata, M *Bull. Chem. Soc. Jpn*., **1999**, *72*, 2491.

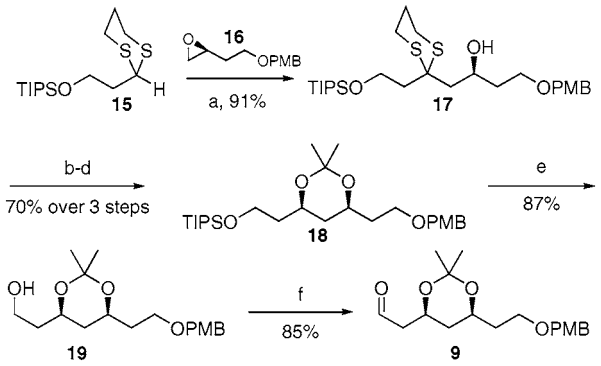
(8) Evans, A. B.; Knight, D. W. *Tetrahedron Lett*. **2001**, *42*, 6947.

(9) Based on Russell, G. A.; Ochrymowycz, L. A. *J. Org. Chem*. **1969**, *34*, 3618.

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

(11) **Microwave-Accelerated Petasis Olefination.** The Petasis reagent (3.6 mL of a 0.2 M solution in toluene) was added to ketone **13** (250 mg, 0.45 mmol) and the ionic liquid 1-ethyl-3-methylimidazoline hexafluorophosphate (40 mg), and the reaction was stirred at 160 °C for 10 min in a Personal Chemistry Emrys Liberator Microwave. A fully automated coherent synthesis system microwave machine was used. This was supplied by Personal Chemistry, Hamnesplanaden 5, 75319, Uppsala, Sweden, www.personalchemistry.com. Further studies on a microwave-accelerated Petasis olefination will be published in due course.

Scheme 3. Synthesis of Aldehyde **9**[a]

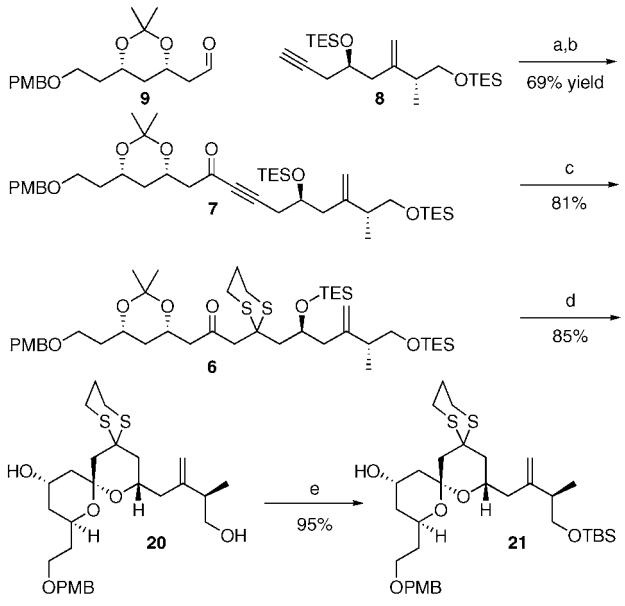


[a] Conditions. (a) *n*-BuLi, THF, rt, 10 min then **16**, THF, −20 → 0 °C, 2 h; (b) I_2, $NaHCO_3$(aq), MeCN, 0 °C; (c) Et_2BOMe, $NaBH_4$, THF−MeOH, −78 °C, 12 h; (d) $MeC_2(OMe)_2$, PPTS, CH_2Cl_2, 1 h; (e) TBAF, THF, 2 h; (f) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C then Et_3N, −78 → 0 °C.

reduction[12] forms a diol that can be protected as its acetonide derivative to form **18**. Removal of the TIPS group with TBAF and oxidation using Swern conditions[6] forms aldehyde **9** in good yield. It is important to note that aldehyde **9** was used immediately in the coupling with alkyne **8**.

The key union was achieved by addition of the acetylide anion of alkyne **8** to aldehyde **9** and subsequent oxidation with Dess−Martin periodinane[13] to form ynone **7** in 69% yield (Scheme 4). We have previously reported the ethoxide-mediated addition of dithiols to ynones to form β-keto-

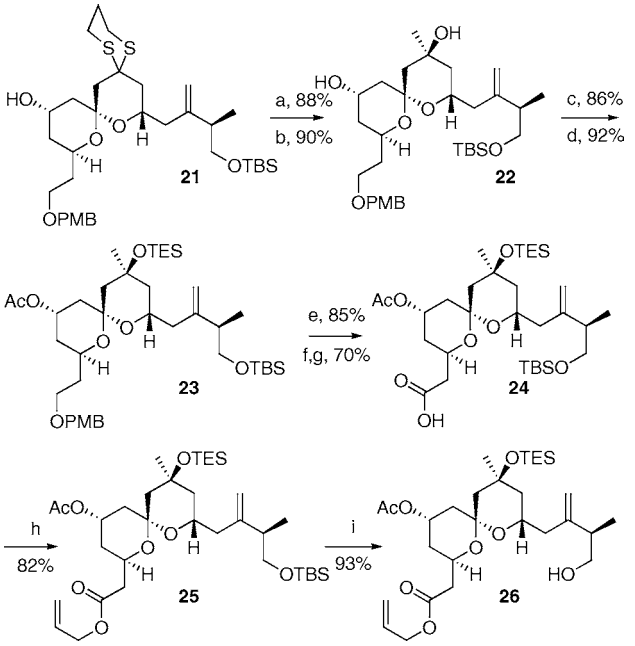
Scheme 4. Synthesis of Spiroketal **21**[a]



[a] Conditions: (a) *i*-PrMgCl, **8**, THF, 2 h, rt, then **9**, THF, −20 °C, 1 h; (b) Dess−Martin periodinane, CH_2Cl_2, rt, 1 h; (c) $HS(CH_2)_3SH$, NaOMe, MeOH−CH_2Cl_2, −10 °C → rt, 16 h; (d) 10% $HClO_4$(aq), MeCN−CH_2Cl_2, rt, 30 min; (e) TBSCl, imid, THF, 16 h, rt.

dithianes.[8] Accordingly, base-mediated conjugate addition of 1,3-propanedithiol to ynone **7** formed the β-ketodithiane **6** in 81% yield. Spiroketalization, effected by treatment with $HClO_4$, formed **20** in good yield as a single diastereisomer. It is interesting to note that in the presence of the 1,3-dithiane unit cyclization cleanly produces the spiroketal; however, when the corresponding 1,3-dione is present the cyclization was capricious.

Scheme 5. Completion of the AB Spiroketal **26**[a]

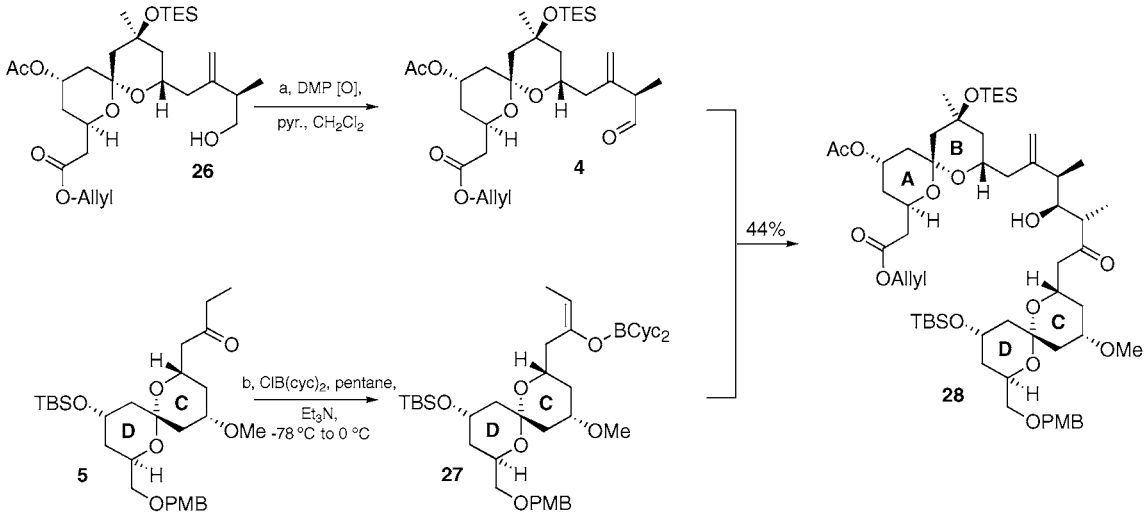


[a] Conditions. (a) I_2, $NaHCO_3$(aq), MeCN, 0 °C, 1 h; (b) MeLi, $CeCl_3$, THF, −78 °C, 1 h; (c) Ac_2O, pyr, DMAP, CH_2Cl_2, rt, 40 h; (d) TESOTf, 2,6-lutidine, −78 → 0°C, 1 h; (e) DDQ, pH 7 buffer, CH_2Cl_2, 4 h, rt; (f) Dess−Martin periodinane, 30 min, pyr, CH_2Cl_2 rt, 3 h; (g) $NaClO_2$, *t*-BuOH, 2-Me-2-butene, pH 7 buffer, rt, 3 h; (h) allyl bromide, Cs_2CO_3, THF, rt, 16 h; HF·pyr, pyr, THF, rt, 16 h.

With the core of the AB spiroketal in hand, we began the functionalization that would lead to the desired aldol coupling unit (Scheme 5). Elaboration of spiroketal **21** began with our favored iodine-mediated cleavage of the dithiane unit[12] to form the corresponding ketone in excellent yield. Addition of MeLi in the presence of anhydrous cerium(III) chloride formed the tertiary alcohol as a single diastereomer (>20:1). Selective acetylation of the secondary alcohol and TES protection of the tertiary hydroxyl group formed **23** in 79% yield over two steps. Removal of the PMB group and two-step oxidation using Dess−Martin and Pinnick conditions formed the acid that was converted to the corresponding allyl ester **25** using allyl bromide and cesium carbonate. HF·pyridine complex selectively removes the primary TBS group to generate the desired spiroketal **26**. The synthesis of the

(12) Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155.
(13) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4383.

Scheme 6. Completion of ABCD Fragment



AB spiroketal fragment requires a total of 36 steps from commercially available starting materials with a longest linear sequence of 26 steps.

With the key fragments prepared we attempted the aldol union of the CD ketone **5** and AB aldehyde **4** (Scheme 6). Dess−Martin oxidation of AB alcohol **26** afforded the aldehyde **4** that was used immediately. Treatment of ketone **5** with dicyclohexylboron chloride formed the *E*-enol borinate **27** and following reaction with aldehyde **4** formed the anti-aldol product **28** as a 8:1 mixture of diastereomers (44% yield of desired diastereoisomer). Acetylation and removal of the PMB ether proceeded without note to form ABCD fragment **2**.

To this point, the total number of steps required to form the ABCD fragment is 64 with a longest linear sequence of 34 (based on the AB fragment **4**).

In summary, we have completed a synthesis of the ABCD fragment of spongistatin 1. A key aspect of this route is the generation and use of a β-keto dithiane unit to introduce the required orthogonal dione functionality. We are currently optimizing the AB spiroketal synthesis in order to develop a more efficient route to the advanced ABCD intermediate, and these results will be reported in due course.

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Supporting Information Available: Experimental data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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