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

Matthew J. Gaunt, Alan S. Jessiman, Paolo Orsini, Huw R. Tanner, David F. Hook, and Steven V. Ley*

Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, UK
svl1000@cam.ac.uk

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ABSTRACT

The synthesis of the C1−C28 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 fragment4 and here and in the preceding paper1 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 Smith2c 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 LiAlH4 and oxidation using Swern conditions6 to form the aldehyde (Scheme 2). Immediate treatment with propane-1,3-dithiol and boron trifluoride-ether complex forms dithiane 11 after protection of the resulting hydroxyl group as its TBS ether. Lithiation of the dithiane7 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 cleavage9 and TES protection of the hydroxyl forms ketone 13 in 96% over two steps. Methyl enation of ketone 13 proved to be a challenging transformation. After much experimentation, treatment of ketone 13 with the Petasis reagent10 in toluene at 120 °C for 3 h proved to be the optimal reaction, generating alkene 14 in 71% yield.

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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 \(15\).\(^{5}\) This dithiane is also common to the synthesis of the CD fragment (Scheme 3). Ligation of dithiane \(15\) and interception of the anion with epoxide \(16\) forms \(17\) in 91% yield. Cleavage of the dithiane group with iodic- and borane-mediated syn-

\[\text{Conditions: (a) } \text{TrCl, pyr, CH}_2\text{Cl}_2, 16 \text{ h, rt; (b) } \text{LiAlH}_4, \text{THF, } 0^\circ\text{C, 2 h; (c) } (\text{COCl})_2, \text{DMSO, CH}_2\text{Cl}_2, -78^\circ\text{C then DPEA} \text{ -78 } \rightarrow 0^\circ\text{C; (c) HS(CH}_2)_2\text{SH, BF}_3\text{-EtO, THF, } -78^\circ\text{C, 4 h; (d) } \text{TBS-Cl, THF, imid, 2 h, rt; (e) } n\text{-BuLi, THF, } -78^\circ\text{C, 1 h, (i) } \text{BF}_3\text{-THF, } -78^\circ\text{C, 1 h, (ii) } \text{epoxide, THF, } -78^\circ\text{C, 1.5 h; (g) } \text{MeCN, NaHCO}_3, 0^\circ\text{C; (h) } \text{TES-Cl, THF, imid, 2 h, rt; (i) } \text{Petas reagent, microwave; (j) } \text{TBAF, THF, rt, 4 h; (k) } \text{TES-Cl, THF, imid, 2 h, rt.}\]

\[\text{TIPS-protected acetylene was essential for the success of this reaction; however, it was not possible to remove this group in the presence of the other silicon functionality. Therefore, global deprotection and reprotection as the bis-TES ether afforded the desired alkyne.}\]
reduction\textsuperscript{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\textsuperscript{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\textsuperscript{13} to form ynone 7 in 69\% yield (Scheme 4). We have previously reported the ethoxide-mediated addition of dithiols to ynones to form \( \beta \)-ketodithianes.\textsuperscript{8} Accordingly, base-mediated conjugate addition of 1,3-propanedihitol to ynone 7 formed the \( \beta \)-ketodithiane 6 in 81\% yield. Spiroketalization, effected by treatment with HClO\textsubscript{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.

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\textsuperscript{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, Cs\textsubscript{2}CO\textsubscript{3}, THF, rt, 16 h; HF-pyr, pyr, THF, rt, 16 h.

\textsuperscript{12} Conditions. (a) \( \eta \)-BuLi, THF, rt, 10 min then 16, THF, \(-20 \degree C, 2\) h; (b) I\textsubscript{2}, NaHCO\textsubscript{3}(aq), MeCN, 0 \degree C; (c) Et\textsubscript{2}BOMe, NaBH\textsubscript{4}, THF–MeOH, \(-78 \degree C, 12\) h; (d) MeC\textsubscript{2}(OMe)\textsubscript{2}, PPTS, CH\textsubscript{2}Cl\textsubscript{2}, 1 h; (e) TBAF, THF, 2 h; (f) (COCl)\textsubscript{2}, DMSO, CH\textsubscript{2}Cl\textsubscript{2}, \(-78 \degree C\) then Et\textsubscript{3}N, \(-78 \degree C, 0\) \degree C.

\textsuperscript{13} Conditions. (a) I\textsubscript{2}, NaHCO\textsubscript{3}(aq), MeCN, 0 \degree C; (b) MeLi, CeCl\textsubscript{3}, THF, \(-78 \degree C, 1\) h; (c) Ac\textsubscript{2}O, pyr, DMAP, CH\textsubscript{2}Cl\textsubscript{2}, rt, 40 h; (d) TESOTI, 2,6-lutidine, \(-78 \rightarrow 0\degree C, 1\) h; (e) DDQ, pH 7 buffer, CH\textsubscript{2}Cl\textsubscript{2}, 4 h, rt; (f) Dess–Martin periodinane, 30 min, pyr, CH\textsubscript{2}Cl\textsubscript{2}, rt, 3 h; (g) NaClO\textsubscript{2}, t-BuOH, 2-Me-2-butene, pH 7 buffer, rt, 3 h; (h) allyl bromide, Cs\textsubscript{2}CO\textsubscript{3}, THF, rt, 16 h; HF-pyr, pyr, THF, rt, 16 h.


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.