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A Practical and Efficient Synthesis of the C-16–C-28 Spiroketal Fragment (CD) of the Spongistatins

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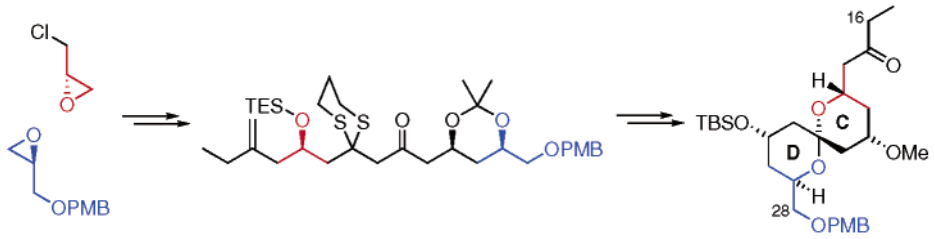
ABSTRACT



A practical and efficient route to the CD spiroketal (C-16–C-28) of the spongistatins is reported. Two stereocenters are introduced from chiral building blocks with the remainder introduced by substrate-controlled transformations. The key β-keto-1,3-dithiane intermediate is generated by a dithiol conjugate addition to an ynone and the 1,3-dithiane unit in the C-ring plays a key role in the spiroketalization and subsequent epimerization. The synthesis requires 24 steps, with a longest linear sequence of 19 steps in an overall yield of 14.5% (for the longest linear sequence).

The spongistatins constitute an important family of architecturally complex marine macrolides that display exceptional antitumor activities against a variety of human cancer cell lines.[1] Isolated independently by Pettit,[2] Kitagawa,[3] and Fusetani[4] in 1993, the spongistatins have attracted significant interest from the synthetic community, resulting in a number of total syntheses.[5]

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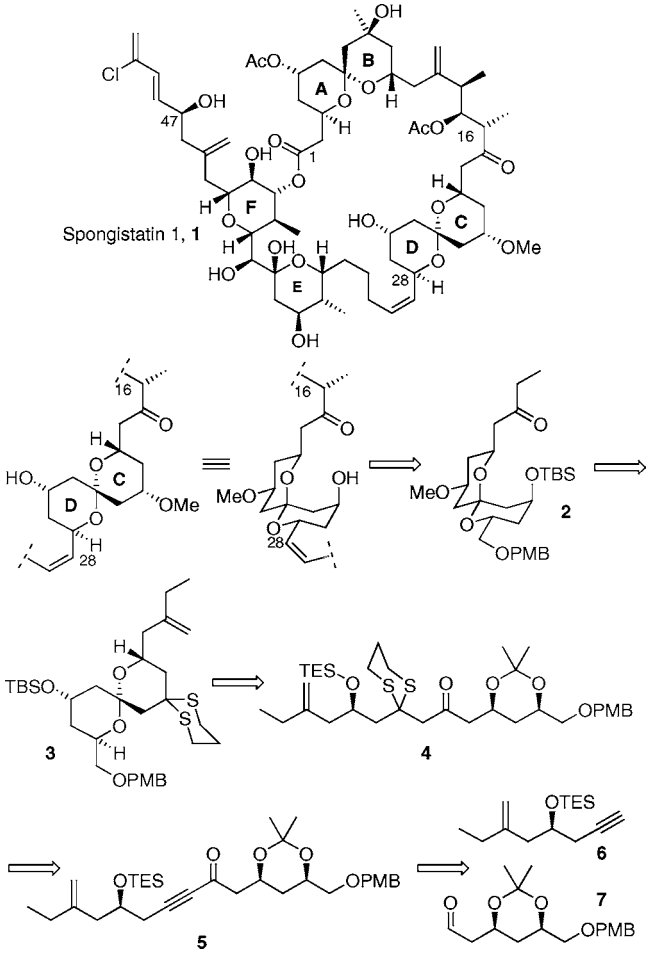
We have previously reported studies toward the assembly of the EF fragment.[6] Here, and in the following communication, we detail our synthesis of the ABCD unit.

A unique feature of the spongistatin family of macrolides is the presence of a partially anomerically stabilized spiroketal (the CD fragment). It is thought that, while lacking the energetically favorable double-anomeric stabilization, the CD spiroketal is stabilized by an intramolecular hydrogen bond between the C25 hydroxyl group and one of the C23 spiroketal oxygen atoms. This postulated interaction has been the inspiration behind many attempts to synthesize this moiety with the desired configuration. Smith observed that Ca^{2+} ions can control an acid-mediated epimerization of the fully anomerically stabilized isomer to the desired partially stabilized CD spiroketal.[5c] Although other methods have been utilized to produce the correct C23 configuration under kinetically controlled conditions, epimerization approaches have been proved in a variety of systems.[7]

Scheme 1. Retrosynthesis for the CD Spiroketal Fragment.

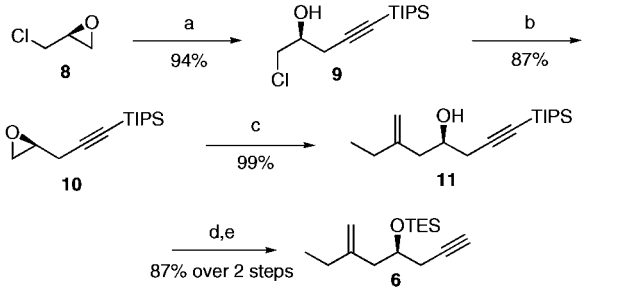


Our retrosynthesis, as others, identified ketone **2** as a key intermediate for the assembly of the ABCD fragment (Scheme 1). Accordingly, **2** could be generated from **3** through a substrate-controlled reduction at a C21 ketone (masked as the 1,3-dithiane in **3**). In turn, **3** could be realized from spirocyclization of the β-keto-1,3-dithiane **4**. We recently reported the facile synthesis of β-keto-1,3-dithianes through a base-mediated conjugate addition of a dithiol to an ynone,[8] and thus, **4** would be readily generated from **5**. Addition of alkyne **6** to aldehyde **7** and subsequent oxidation would form **5**.

A key feature of this approach involved the deployment of the 1,3-dithiane group on the C ring of the spiroketal. It was anticipated that this group would aid the spiroketalization and that the projection of the sulfur atoms may influence the balance between the fully and partially stabilized spiroketal structures.

The synthesis began with the addition of triisopropylsilylacetylene to (*S*)-epichlorohydrin **8** through a modified Hiroa reaction (Scheme 2).[9] It was essential to use BF_3·THF complex, as described by Knight and co-workers, in place of BF_3·Et_2O in order to achieve reproducible results. The resulting chlorohydrin **9** was then converted cleanly to the corresponding epoxide **10** in excellent yield using polymer-supported BEMP as the base. Interestingly, of the wide range of conditions investigated, the use of the polymer-supported base was the only method that did not result in partial β-elimination of the epoxide.[10]

Scheme 2. Synthesis of Alkyne **6**[a]



[a] Conditions: (a) TIPS-CCH, *n*-BuLi, THF, BF_3·THF, −78 °C then (*S*)-epichlorohydrin **8**, THF, −78 °C, 4 h; (b) PS-BEMP (2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine), MeCN, rt, 16 h; (c) 2-butenyl bromide, Mg, Et_2O then 1,4-dioxane, then CuI, −40 → 0 °C; (d) TBAF, THF, rt; (e) TES-Cl, imid, THF, rt.

Epoxide **10** was treated with a 2-butenyl Grignard reagent in the presence of copper(I) iodide[11] and dioxane. The active species in this process is postulated to be bis(2-butenyl)-magnesium and not 2-butenylmagnesium bromide.[12] When

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(10) All new compounds were characterized by ^{1}H NMR, ^{13}C NMR, HRMS, IR, and optical rotation. For details, see the Supporting Information.

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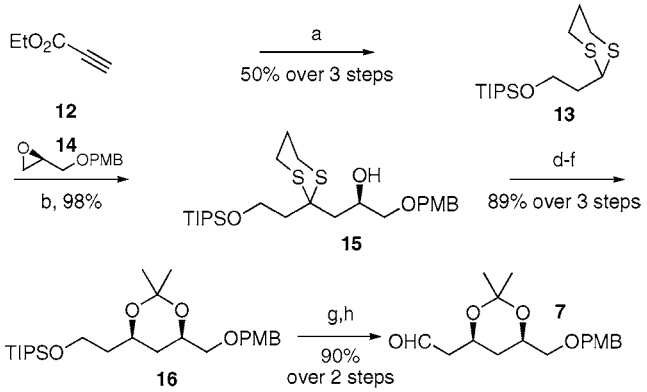
2-butenylmagnesium bromide was used the main product observed was the bromohydrin observed from bromide opening of the epoxide. However, treatment of 2-butenylmagnesium bromide with 1,4-dioxane forms the bis(2-butenyl)magnesium species and precipitates a dioxane−magnesium bromide complex. Addition of catalytic copper(I) iodide followed by the epoxide **10** to this mixture produces cleanly the desired homoallylic alcohol **11** in 99% yield with no trace of the undesired bromohydrin side product. This procedure could find useful application for epoxide opening reactions where halide addition is a problematic side reaction. Treatment of alcohol **11** with TBAF removes the TIPS group, and protection of the hydroxyl as the TES ether generates **6** in good yield over two steps. Fragment **6** is assembled in five steps in 70% overall yield (93% per step) and is readily adapted to a multigram scale.

The synthesis of aldehyde **7** began with the ethoxide-mediated double-conjugate addition of 1,3-propanedithiol to ethyl propiolate **12**,[8] reduction with $LiAlH_4$, and protection of the resulting hydroxyl group as a TIPS ether to form dithiane **13** in 50% yield over three steps (Scheme 3).

Scheme 3. Synthesis of Aldehyde **7**[a]

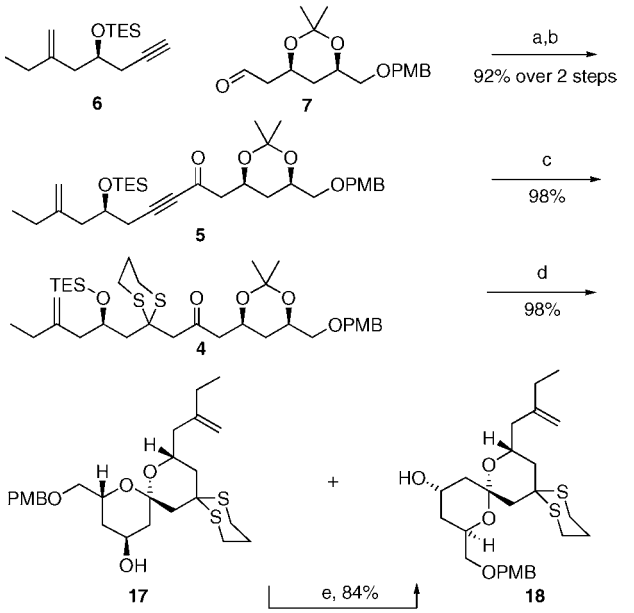


[a] Conditions: (a) (i) $HS(CH_2)_3SH$, NaOEt, EtOH−THF, −10 °C → rt, 16 h, (ii) $LiAlH_4$, THF, 0 °C, 4 h, (iii) TIPSCl, imid, THF, rt, 12 h; (b) *n*-BuLi, THF, rt, 10 min then **14**, THF, −20 → 0 °C, 2 h; (d) I_2, $NaHCO_3$ (aq), MeCN, 0 °C; (e) Et_2BOMe, $NaBH_4$, THF−MeOH, −78 °C, 12 h; (f) $Me_2C(OMe)_2$, Me_2CO, $TsOH·H_2O$, 0 °C; 1 h; (g) TBAF, THF, 2 h; (h) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C then Et_3N, −78 → 0 °C.

Metalation of dithiane **13** with *n*-BuLi at room temperature[13] and interception of the anion with epoxide **14** affords **15** in 98% yield.

Cleavage of the dithiane moiety in **15**,[14] borane-mediated syn-reduction[15] of the resulting ketone, and protection of the corresponding diol as the acetonide derivative generates **16** in 89% over three steps. Importantly, this three-step sequence can be performed on a large scale without need for significant purification until acetonide **16**. Removal of the TIPS group with TBAF liberates the hydroxyl function in 96% yield, and Swern oxidation[16] generates aldehyde **7** in good yield; however, the aldehyde is not stable and must be used immediately.

Scheme 4. Synthesis of Spiroketal **18**[a]



[a] Conditions: (a) *i*-PrMgCl, **6**, THF, 2 h, rt, then **7**, 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) 3.5% $HClO_4$ (aq), 5 equiv of $Ca(ClO_4)_2·4H_2O$, MeCN−CH_2Cl_2, rt, 18 h.

With the key fragments in hand, union of **6** and **7** was investigated (Scheme 4). The anion of acetylene **6** was formed through treatment with *i*-PrMgCl at room temperature followed by addition with the freshly prepared aldehyde **7** to form the propargylic alcohol as a 1:1 mixture of diastereomers in 93% yield. Oxidation with Dess−Martin periodinane[17] affords cleanly the ynone **5**. Dithiol conjugate addition[8] of 1,3-propanedithiol to ynone **5** forms β-keto 1,3-dithiane **4** in excellent yield and generates the required functional pattern for the target molecule. Treatment of the ketone **4** with dilute perchloric acid forms spiroketals **17** and **18** as a 4:1 mixture in favor of the undesired isomer **17**.

Facile equilibration using the conditions adapted from Smith's procedure[5c] allowed the clean conversion of **17** to **18** in 84% yield from **4** after three recycles. Interestingly, the presence of the 1,3-dithiane moiety slows the equilibration process of **17** to **18** and requires 18 h to reach a 2.2:1

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mixture in favor of the desired isomer **18**. Significantly, the two spiroketals are easily separated and the unwanted isomer can be recycled. This feature aids the purification of the two spiroketals such that chromatographic separation is trivial, enabling facile recycling of isomer **17**. In contrast to Smith's examples our calcium mediated spiroketal epimerization does not require the presence of a hydroxyl group at the C17 or C18 position. While in that case[5c] there is certainly an additional stabilizing interaction provided by the hydroxyl group, our system is probably more influenced by the dithiane moiety at C21 and the hydroxyl at C26 (Figure 1).

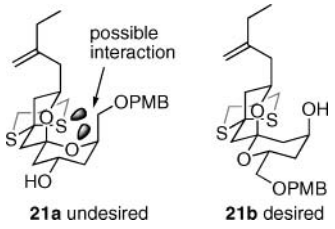


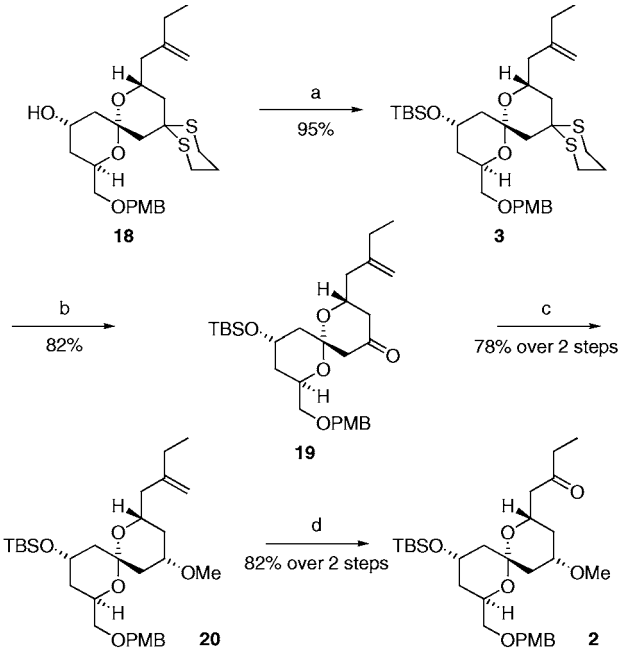
Figure 1. Epimerization of spiroketal **17**.

With the correct CD spiroketal isomer **18** in hand, protection of the C-25 hydroxyl as the TBS ether formed **3** in excellent yield (Scheme 5). Cleavage of the 1,3-dithiane unit caused unexpected problems. Initial attempts to remove the dithiane by a variety of methods led to substantial decomposition and unacceptable mixtures of products. Finally, we found that using the Stork−Zhoa procedure in methanol,[18] to form the dimethyl ketal, followed by treatment with acetic acid in water produced the desired ketone **19** in 82% isolated yield.

Reduction of ketone **19** under modified Luche conditions[19] generated the desired equatorial C-15 alcohol with 17:1 selectivity. Interestingly, use of L-Selectride, as detailed by Crimmins and co-workers for a similar ketone reduction, gave only a 1:1 mixture of isomers.[20] The resulting alcohol was methylated to form **20** in 78% over two steps from ketone **19**. Dihydroxylation of alkene **19** and immediate periodate cleavage formed the desired ketone **2** in 82% yield over two steps. The structure of ketone **2** was confirmed by analysis of the ^{1}H NOSEY spectrum.

In summary, we have developed a practical and efficient synthesis of the CD spiroketal required for our synthesis of the spongipyran natural products. Our synthesis requires the use of two chiral starting materials and thereafter makes use of substrate control to introduce the remaining stereocenters. The synthetic route requires only 24 steps with a longest linear sequence of 19 steps (overall yield of longest linear sequence is 14.5%). In the following paper,[21] we detail our synthesis of the AB spiroketal and the formation of the ABCD fragment.

Scheme 5. Synthesis of Spiroketal **2**[d]



[a] Conditions: (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C; (b) 2 equiv of $PhI(TFA)_2$, MeOH, 0 °C, 30 min then $NaHCO_3$ (aq); AcOH−THF−H_2O, 30 °C, 5 h; (c) (i) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, THF, MeOH, −78 °C, (ii) NaH, MeI, THF, 0 → rt; (d) (cat.) OsO_4, NMO, acetone−H_2O then $NaIO_4$, MeOH−H_2O (2:1) rt, 2 h.

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

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