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Synthesis of the C(2)–C(13) Fragment (The A–B Spiroketal Unit) of Spongistatin 1 (Altohyrtin A): Use of a Common Intermediate for the Synthesis of Both Spongistatin Spiroketals

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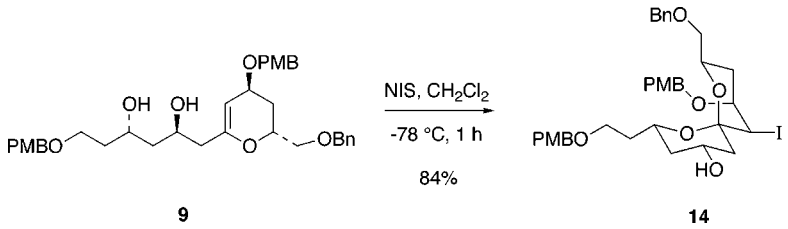
ABSTRACT



9 **14**

A convergent synthesis of 14 corresponding to the A–B spiroketal core of spongistatin 1 has been accomplished via an iodo-spiroketalization reaction of glycal 9, which was synthesized in three steps from a late-stage intermediate used in our synthesis of the C–D spiroketal fragment of spongistatin 1. Elaboration of 14 to the A–B spiroketal 15 was accomplished in three steps.

The spongistatins are a unique class of marine polyether macrolactone metabolites that were isolated in 1993.[1−6] This class of compounds has demonstrated excellent antimitotic activity against numerous cancer cell lines. Due to their complex structural features, limited availability, and potent cytotoxicity, these compounds have generated considerable interest from synthetic chemists.[7] Total syntheses of two members from this class of compounds have been reported.[8−12]

We have previously described syntheses of the E−F bispyran[13] and the C−D spiroketal,[14] and here we describe a synthesis of the other major structural fragment, the A−B spiroketal (**15**). Our synthesis of **15** constitutes a second example of the iodo-spiroketalization methodology used in our synthesis of the C−D spiroketal and, moreover, utilizes a late-stage intermediate from that work. The ability to utilize

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common intermediates of such complex structures is critical in efforts to synthesize sufficient quantities of the natural product for more detailed biological evaluation. To maximize efficiency, bifurcation along the synthetic pathway should occur at as late a stage as possible.

Upon examination of the two spiroketal units in spongistatin 1, we realized the opportunity that exists for accessing both units by using the same precursor for the A and D rings (Figure 1). Disconnection of the spiroketal centers leads to

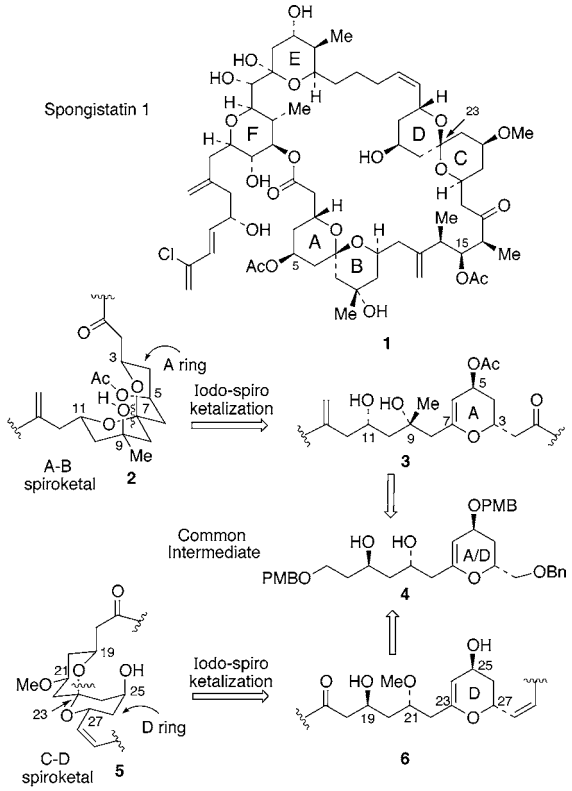

Figure 1. Identification of a Common Intermediate for the A−B and C−D Spiroketals.

similarly substituted glycal precursors such as **3** and **6**. The divergence between the spiroketal precursors lies at the two hydroxyl centers (e.g., C(11) and C(9) in **3**, and C(19) and C(21) in **6**) on the appended alkyl side chain. To utilize **4**, an intermediate from our C−D spiroketal synthesis, as an intermediate in the synthesis of the A−B spiroketal, inversion of the stereochemistry at C(11) and installation of the tertiary alcohol at C(9) would be needed.

On the basis of previous work in construction of the A−B spiroketal,[15−19] we planned to install the C(9) tertiary alcohol via methyl Grignard addition to a ketone such as **7** (Figure

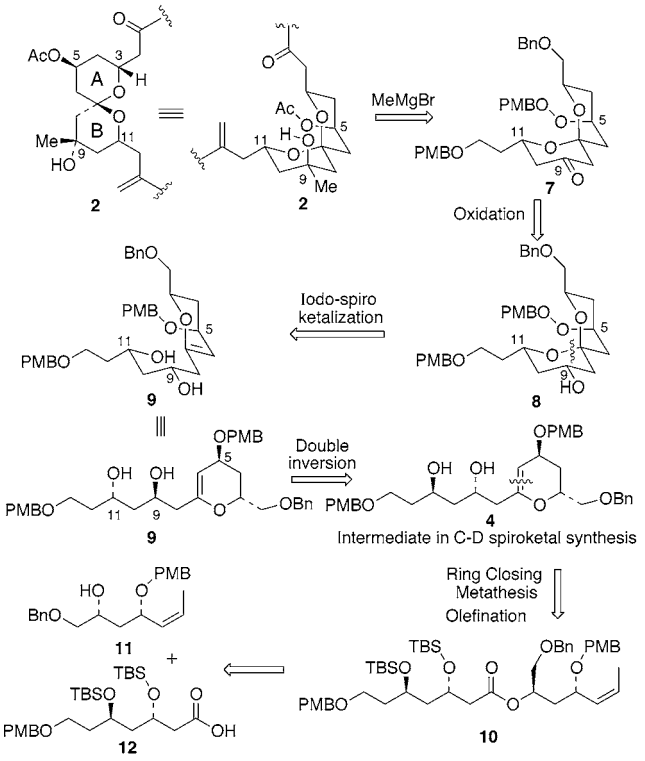

Figure 2. Retrosynthetic Analysis of the A−B Spiroketal.

2). Ketone **7** could in turn be derived from alcohol **8** or its C(9) epimer. Although the stereochemistry at C(9) of **8** is arbitrary, we chose to target the configuration shown in **8** to minimize 1,3-diaxial interactions during cyclization leading to the spiroketal. There are two possible bond disconnections that could be made to utilize our intramolecular iodo-spiroketalization strategy.[14] Based on similar glycal substructures identified earlier (see **3** and **6**), disconnection of the B ring leads to **9**, which contains the structural features common to both the A and D rings of the spongistatin spiroketals. Glycal **9** may be derived from **4** by inversion of configuration at C(9) and C(11). Glycal **4** is derived from ester **10** via an olefination−ring-closing metathesis sequence.[14] Ester **10**, in turn, is derived from alcohol **11** and carboxylic acid **12**, the preparation of which was described in our synthesis of the C−D spiroketal.[14]

Initially, we explored the Mitsonobu reaction (PPh_3, DEAD, *p*-nitrobenzoic acid[20]) to effect the double inversion of **4**, but only mixtures of monoacetylated (monoinverted) products were obtained. Consequently, we chose to adopt a two-step procedure for this key transformation (Scheme 1). Treatment of diol **4** with methanesulfonyl chloride and Et_3N in CH_2Cl_2 provided the bismesylate, which was used directly in the subsequent reaction. Displacement of the mesylates with cesium acetate[21−23] in toluene at 80 °C for 24 h provided

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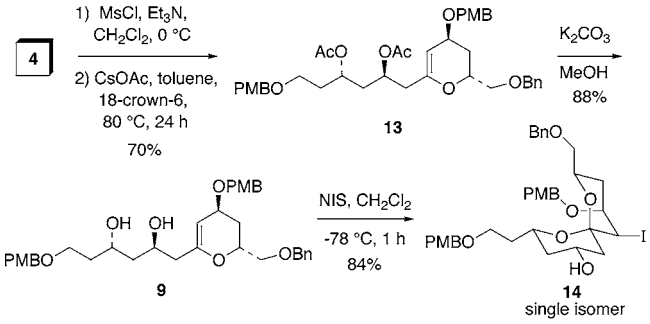
Scheme 1. Synthesis of the A−B Spiroketal Core



the bisacetate **13** in 70% yield over two steps. Deprotection of the acetates under basic conditions (K_2CO_3, MeOH) provided the diol **9** in 88% yield.

The stage was now set for application of the intramolecular iodo-spiroketalization reaction, this time targeting spiroketal **14** possessing two stabilizing anomeric effects. Treatment of diol **9** with NIS in CH_2Cl_2 at −78 °C provided the spiroketal **14** as a single isomer (84%). Diagnostic ^{1}H NMR NOE enhancements were observed between H(11)−H(9) and H(11)−H(3) in **14** (Figure 3). These ^{1}H NMR NOE experiments confirmed the stereochemistry of **14** and also established that we had indeed inverted both of the hydroxyl centers in the conversion of **4** to **13**. Additional enhancements were observed between H(6)−H(5) and H(6)−H(8)ax that helped to confirm the stereochemistry of **14**.

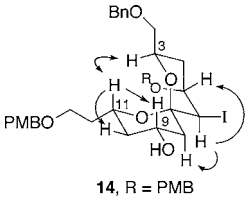
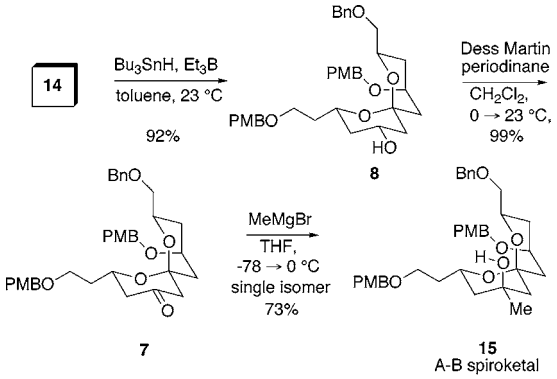


Figure 3. Diagnostic NOEs for **14**.

Final elaboration of **14** to the A−B spiroketal **15** began with the reductive dehalogenation of **14** with tributyltin hydride and triethylborane,[24] which provided **8** (92%) (Scheme 2). Oxidation of **8** with the Dess Martin periodinane[25] afforded the ketone **7** in almost quantitative yield (99%). Finally, addition of MeMgBr to ketone **7** provided the A−B spiroketal **15** as a single isomer (73%). The configuration of **15** was confirmed on the basis of several ^{1}H NMR NOE enhancements (Figure 4).[12]

Scheme 2. Completion of the A−B Spiroketal



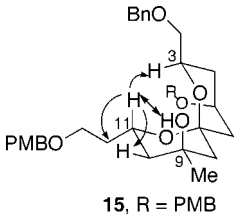


Figure 4. Diagnostic NOEs for A−B Spiroketal **15**.

In summary, we have achieved a highly convergent, stereocontrolled synthesis of the A−B spiroketal fragment **15** of spongistatin 1. This synthesis proceeds in seven steps from a late-stage intermediate **4** from our synthesis of the C−D spiroketal. Further studies directed toward the completion of the C(1)−C(28) fragment of spongistatin 1 will be reported in due course.

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Supporting Information Available: Experimental procedures and spectral data for compounds **7**−**9** and **13**−**15** and stereochemical assignments for **14** and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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