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Enantio- and Diastereoselective Allylmetalations: An Easy and Efficient Access to the AB Spiroketal of Spongistatin

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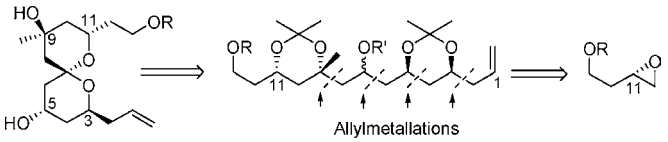
ABSTRACT



A unique combination of highly enantio- and diastereoselective allylmetalations and a one-pot "desacetalization/spiroketalization" have been employed to synthesize the AB spiroketal fragment (C1−C13) of spongistatin in 15 steps and in excellent diastereoselectivity.

In 1993, the isolation of several series of macrolides from the marine sponges of the genus *Spongia* such as spongistatins, cinachyrolides, and altohyrtins was reported by Pettit et al. (Figure 1). These compounds exhibit extremely potent antitumor activity.[1−7] The spongistatins (altohyrtins) elicit extraordinary (subnanomolar) growth inhibition of a variety of chemoresistant tumor types included in the NCI panel of 60 human cancer cell lines. Human melanoma, lung, brain, and colon cancers were particularly sensitive to spongistatin 1, whose activity correlates well with the class of microtubule interactive antimitotics. This remarkable biological profile and the extremely limited supply of these compounds (400 kg wet weight of *Spongia* sp. provided only 13.8 mg of spongistatin) have sparked intense synthetic efforts and there has been enormous interest in the pharmacology and structure of these compounds.

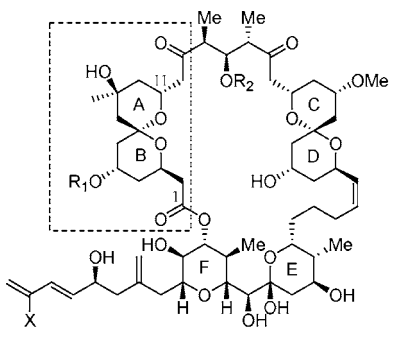


Figure 1. Spongistatin family.

Seven total syntheses[8] and a number of syntheses of key substructures[9,10] have been reported. The syntheses of altohyrtin C (identical with spongistatin 2) and altohyrtin A (spongistatin 1) have served to confirm their structure (Figure 1).[5] Partial syntheses have focused on the synthesis of the

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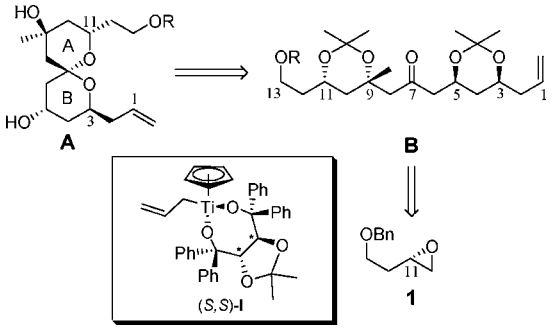
AB and CD spiroketals and on the EF tetrahydropyran moieties.[10]

Here, we would like to report the synthesis of the AB spiroketal **A**, which was planned from ketone **B** (Scheme 1). It was envisaged that the stereogenic center at C11 will

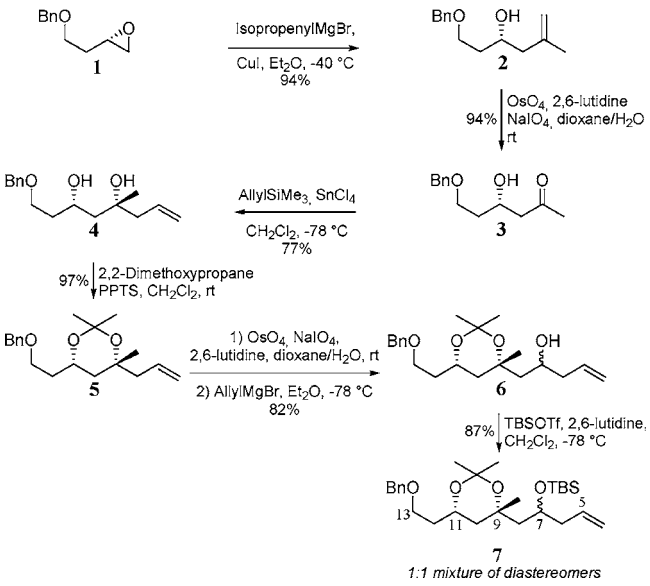
Scheme 1



be issued from the ring opening of the optically active epoxide **1** and the C3 and C9 stereogenic centers will be controlled by using a diastereoselective addition of an allylmetal respectively on a β-hydroxy aldehyde and a β-hydroxy ketone. Furthermore, the use of an enantioselective allyltitanation was envisaged to establish the C5 stereogenic center.

The synthesis of the AB ring of spongistatin began with the opening of the known epoxide **1**[11] with isopropenylmagnesium bromide in the presence of CuI (THF, −40 °C) to afford the homoallylic alcohol **2** in 94% yield (Scheme 2). To control the stereogenic center at C9, compound **2** was

Scheme 2



converted to the corresponding ketone **3** in 94% yield by oxidative cleavage (OsO_4, $NaIO_4$, 2,6-lutidine, dioxane/H_2O).[12] At this stage, the stereospecific introduction of the C9 stereocenter was attempted by using an allylstannane synthesized from trimethylallylsilane. When ketone **3** and trimethylallylsilane were combined by using a number of different Lewis acids, addition protocols, and precomplexation protocols, only one set of conditions, i.e., a premixed solution of trimethylallylsilane and $SnCl_4$ in CH_2Cl_2 at −78 °C, was found to produce the desired alcohol **4** in good yield (77%) and with excellent diastereoselectivity (dr > 99:1) in favor of the *syn* isomer. The stereochemical assignment was achieved by examination of the ^1H and ^{13}C NMR spectra[13] of ketal **5**, obtained from **4** by treatment with 2,2-dimethoxypropane, in the presence of PPTS (0.1 equiv) in CH_2Cl_2 at room temperature. Elaboration of the C5−C13 fragment was achieved in a two-step sequence. After oxidative cleavage of the olefin **5** (OsO_4, $NaIO_4$, 2,6-lutidine, dioxane/H_2O), the resulting aldehyde was treated with allylmagnesium bromide (Et_2O, −78 °C) to provide the desired alcohol **6** as a 1/1 inseparable mixture of diastereomers

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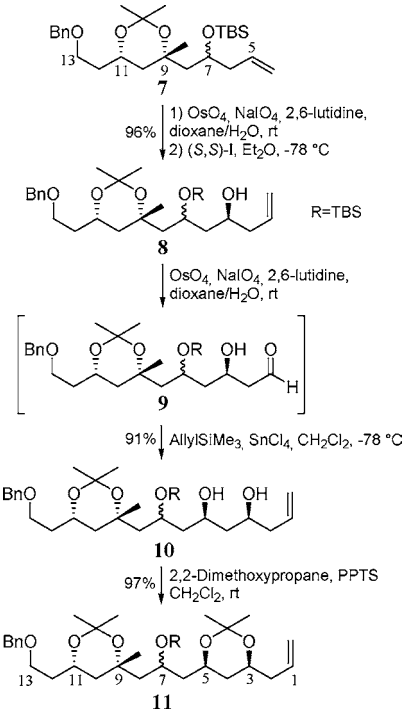
obtained in 82% yield. We have to point out that the hydroxy group at C7 will be the precursor of a ketone, necessary to build up the spiroketal and, in consequence, the control of the stereogenic center is not necessary. After silylation of the hydroxy group at C7 (TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C), the fully protected triol **7** was isolated in 87% yield (Scheme 2).

The transformation of the C5−C13 fragment **7** into the C1−C13 fragment **11** utilized an enantioselective allyltitanation and a diastereoselective allylmetalation of a *β*-hydroxy aldehyde (Scheme 3).

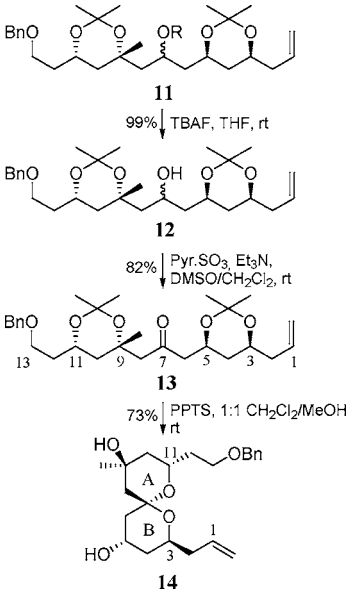
Scheme 3



At first, an oxidative cleavage of the olefin in **7** (OsO_4, $NaIO_4$, 2,6-lutidine, dioxane/H_2O) led to the corresponding aldehyde, which was not purified but directly treated with the highly enantioface selective allyltitanium complex (*S*,*S*)-**I**[14] (Scheme 1) to produce the desired homoallylic alcohol **8** with a good diastereoselectivity (96%, dr > 98:2) (Scheme 3). By using a similar strategy to the one employed to transform ketone **3** into *syn*-1,3-diol **4**, compound **8** was converted into diol **10** by first performing an oxidative cleavage yielding aldehyde **9**, and then a treatment of crude **9** with a premixed solution of trimethylallylsilane and $SnCl_4$ in CH_2Cl_2 at −78 °C produced *syn*-diol **10** in high yield and excellent diastereoselectivity (91% yield, dr > 99:1). Protection of **10** (2,2-dimethoxypropane, PPTS, CH_2Cl_2) led to the bisacetonide **11** (97% yield). Examination of the ^{13}C NMR spectra of **11** showed a signal at 98.33 ppm, demonstrating the *syn* relationship for the hydroxy groups at C3 and C5.[13]

The precursor of the spiroketal, ketone **13**, was synthesized in two steps from **11** (Scheme 4). Deprotection of the hydroxy group at C7 (TBAF, THF) afforded the free alcohol **12**, which was oxidized by using Pyr·SO_3 (TEA, DMSO/CH_2Cl_2) to provide ketone **13** in 81% overall yield over two steps as a single isomer. It is worth noting that other oxidants such as PCC, IBX, or Dess−Martin periodinane led to the decomposition of **12**. Acidic treatment of **13** with a catalytic amount of PPTS in a 1:1 mixture of CH_2Cl_2/MeOH at room temperature led to a one-pot process (i.e., deprotection−spiroketalization) to furnish the desired thermodynamic AB spiroketal **14** in 73% yield (Scheme 4). Extensive NMR studies (^1H NMR, ^{13}C NMR, NOESY) and comparison with Crimmins' similar spiroketal[10a] showed that compound **14** is in full agreement with the structure of the C1−C13 AB spiroketal ring system of spongistatin.

Scheme 4



The synthesis of the AB spiroketal fragment of spongistatin has been achieved in 15 steps with an overall yield of 24% and with excellent diastereoselectivity starting from known (*S*)-2-(2-benzyloxyethyl)oxirane and by using a unique combination of highly enantioselective and diastereoselective allylmetalations.

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Supporting Information Available: Experimental procedures and full analytical data (including ^1H and ^{13}C spectra). This material is available free of charge via the Internet at http://pubs.acs.org.

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