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Synthesis of the AB Spiroketal Subunit of Spongistatin 1 (Altohyrtin A): The Pyrone Approach

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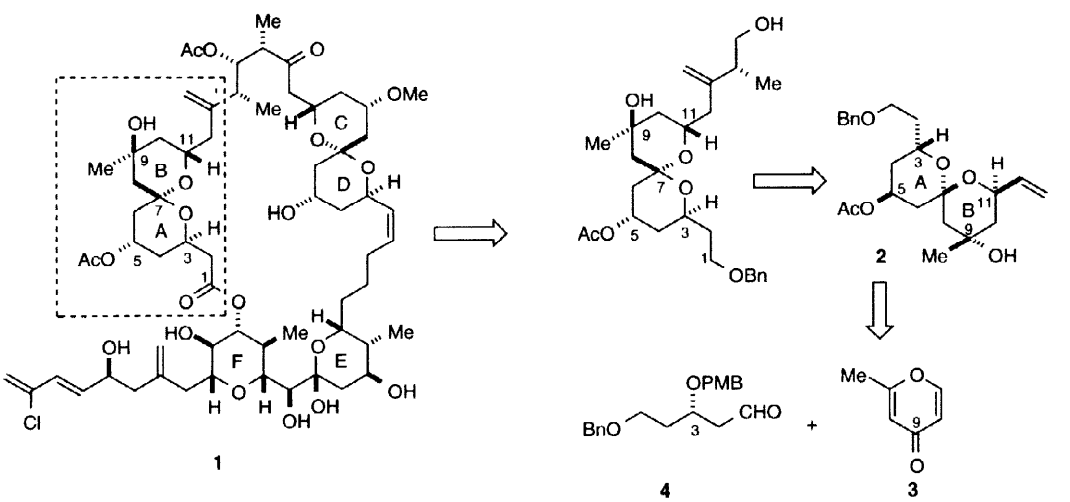
Abstract: The synthesis of the AB spiroketal fragment of spongistatin 1 (altohyrtin A) has been accomplished utilizing the addition of a metalated pyrone to an aldehyde followed by acid catalyzed spirocyclization. A stereoselective copper (I) promoted conjugate addition of vinylmagnesium bromide was used to establish the C11 stereogenic center. © 1998 Elsevier Science Ltd. All rights reserved.

Spongistatin 1 (altohyrtin A) **1** was first isolated by Pettit *et al.*[1] from the marine sponges of the genus *Spongia*. Subsequently, Kitigawa[2] and Fusetani[3] isolated additional examples of this important new class of marine natural products, and it has been shown that spongistatin 1 and altohyrtin A are identical. Spongistatin 1 has been found to be extraordinarily effective against a variety of highly chemoresistant tumor types which comprise the NCI panel of 60 human cancer cell lines.[4] Because of the limited natural supply of spongistatin 1 (altohyrtin A) (400 kg wet weight of *Spongia* sp. provided only 13.8 mg of spongistatin) synthesis may be necessary to provide adequate quantities for further biological studies. Several approaches to the AB spiroketal,[5] CD spiroketal[6] and EF fragments[7] have been reported and recently the first total syntheses of altohyrtin A[8] and C[9] were described. Our studies have focused on the individual construction of three fragments: the C1 - C15 spiroketal (AB rings), the C16 - C28 spiroketal (CD rings) and the C29 -C51 fragment (EF rings). The synthesis of the C1-C13 spiroketal subunit **2** of spongistatin 1, by the utilization of an acid catalyzed cyclization[10] of a substituted γ-pyrone to afford the spiroketal framework is reported here.



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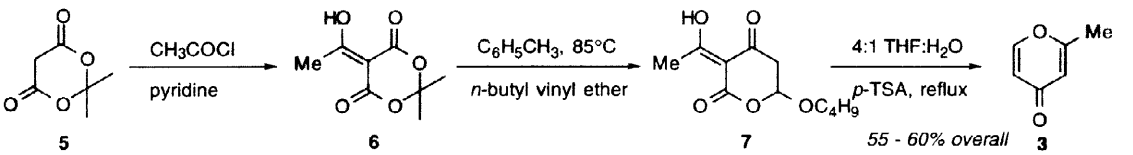
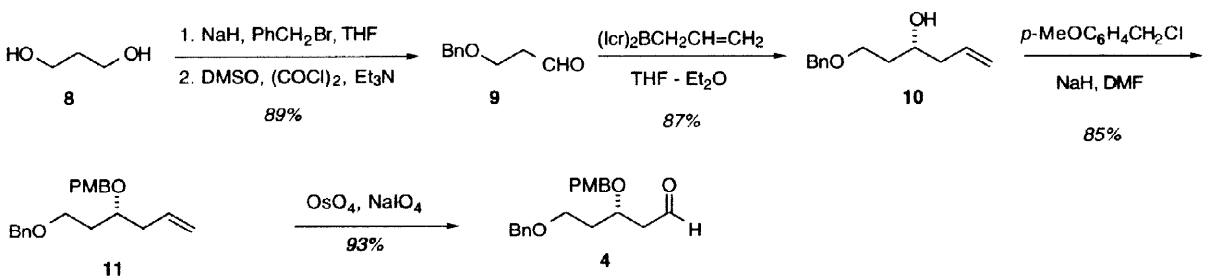
Fundamental to our highly convergent strategy is the metalation of 2-methyl-γ-pyrone **3** and subsequent addition to a β-hydroxy aldehyde **4** to afford a hydroxy pyrone. The 2-methyl-γ-pyrone **3** can be easily synthesized from the acetylation of Meldrum's acid **5** followed by heating in toluene and *n*-butyl vinyl ether at 85°C to yield the pyrandione **7**. Treatment of the pyrandione with catalytic *p*-toluenesulfonic acid in 4:1 THF/H_2O at reflux affords the 2-methyl-γ-pyrone **3**.[11,12]

Scheme 1



The synthesis of the aldehyde **4** began with the protection of 1,3-propanediol **8** as its monobenzyl ether followed by Swern oxidation to afford 89% of the aldehyde **9**. Exposure of aldehyde **9** to Brown's asymmetric allylation procedure[13] produced the homoallylic alcohol **10** in high enantiomeric excess (>95% e.e.). The alcohol **10** was converted to the *p*-methoxybenzyl ether **11** whereupon oxidative cleavage of the alkene gave an excellent yield of the desired aldehyde **4**.

Scheme 2



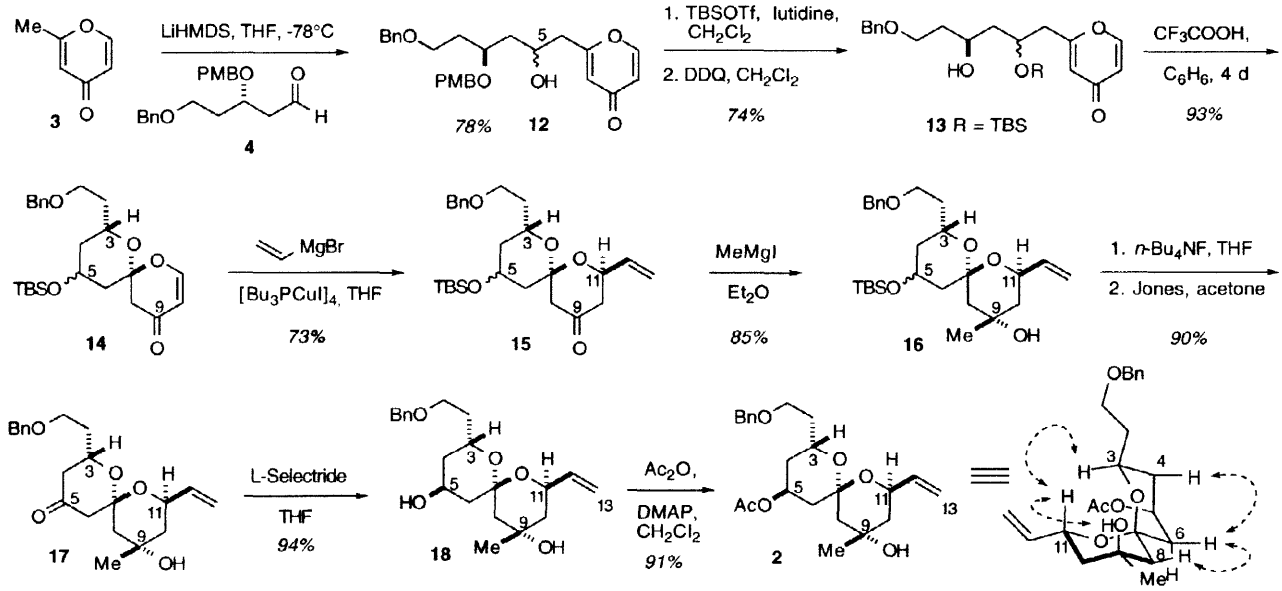
Treatment of pyrone **3** with $LiN(SiMe_3)_2$ followed by addition of the aldehyde **4** afforded the hydroxy pyrone **12** in 78% yield (1:1 diastereomeric mixture; Scheme 3). Protection of the resultant alcohol **12** as a TBS ether and removal of the *p*-methoxybenzyl ether produced the alcohol **13**. Acid catalyzed thermodynamically-controlled spiroketalization yielded the spiroketal **14** plus pyrone **13**. The pyrone was recovered and recycled to provide the spiroketal **14** in 93% yield after two recycles. The spiroenone is presumed to possess the energetically favorable, axial-axial spiroketal based on prior precedent and the NOESY spectrum of **2**.[10,14,15]

Further functionalization of the spiroketal template began with a stereoselective copper (I) catalyzed addition of vinylmagnesium bromide to the spiroenone **14** affording the ketone **15** with >20:1 diastereoselectivity. Based on results in additions to similar spiroenones in the syntheses of milbemycins β_3 and D, it is likely that the C8 benzyloxyethyl group serves to direct the addition to the equatorial face of the enone.[14] Addition of methyl magnesium iodide to the C9 ketone produced exclusively the axial alcohol **16** in 85% yield. Adjustment of the stereochemistry at C5 was accomplished by removal of the C5 TBS ether and oxidation of the alcohol to give the ketone **17**. Finally, stereoselective reduction of the ketone with L-Selectride yielded the axially disposed alcohol **18** which was protected as the acetate **2**.[16] Interactions between the C3 and C11 protons, the

C4 and C6 axial protons, the C11 proton with the C9 OH, and the C6 axial proton with the C8 equatorial proton in the NOESY spectrum of **2** were consistent with those interactions in the NOESY spectrum of spongistatin 1.

Synthesis of the fully functionalized C1 to C13 fragment of spongistatin 1 (altohyrtin A) has been accomplished in 15 steps from 1,3-propanediol **8** and 2-methyl-γ-pyrone **3**. The acid catalyzed cyclization of the hydroxypyrone **13** sets the stage for the stereocontrolled vinylmagnesium bromide addition which establishes the C11 stereocenter. The approach described here is amenable to the preparation of the AB spiroketal fragment in multigram quantities. Further elaboration of the C1 - C13 fragment and its connection to the C16 - C28 fragment are in progress.

Scheme 3



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16. Spectral data for **2**: ^{1}H NMR ($CDCl_3$) δ 1.17 (s, 3H); 1.41 (dd, J = 12.1, 1.4 Hz, H_{10a}); 1.45 (d, J = 13.9 Hz, H_{8a}); 1.51-1.59 (m, 3H); 1.61 (dd, J = 15, 4.1 Hz, H_{6a}); 1.72 (m, 4H); 2.05 (s, 3H); 3.55 (t, J = 5.8 Hz, 2H); 4.19 (m, H_{11a}); 4.36 (m, H_{3a}); 4.49 (d, J = 6 Hz, 2H); 4.55 (s, 1H, OH); 5.00 (m, H_5); 5.05 (dt, J = 8, 2 Hz, H_{13a}); 5.25 (dt, J = 17, 2 Hz, 1H); 5.80 (ddd, J = 17, 10, 4 Hz, 1H); 7.25-7.35 (m, 5H).