Asymmetric Total Synthesis of Spongistatins 1 and 2
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In 1993 Pettit, Kitagawa, and Fusetani independently identified members of a new class of potent antitumor agents that were named the spongistatins, altohyrtins, and cinachyrophiles.1 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 and lung, brain, and colon cancers were particularly susceptible to spongistatin 1, whose activity correlates well with the class of microtubule interactive antimitotics.2 The remarkable biological profile and the extremely limited supply of this class sparked intense synthetic efforts toward their synthesis. The proposed structures of the three subclasses featured six pyran rings: AB and CD spiroketal fragments as well as a E ring hemiketal and a highly substituted F ring tetrahydropyran, all embedded in a 42-membered macrolide.

The conflicting absolute configurations, which were based on extensive spectroscopic analysis, remained unresolved until the Kitigawa assignment2 was confirmed by the first synthesis of spongistatin 2 (altohyrtin C) by Evans3 and spongistatin 1 (altohyrtin A) by Kishi.4 Synthesis of spongistatin 2 by Smith5 and spongistatin 1 by Paterson6 followed these initial publications. Additional reports of syntheses of various fragments have also been reported from other laboratories7 (Figure 1).

We previously reported approaches to the AB10 and CD11 spiroketalts as well as the fully elaborated EF segment.12 We disclose here the elaboration of the AB spiroketal, a modification of the approach to the EF segment, and the details of the efficient confluence of the individual fragments. An important consideration in our strategic plan was the ability to efficiently assemble four major fragments (the C1–C15 AB fragment 2, the C16–C28 CD fragment 3, the C29–C43 EF fragment 4, and the C44–C51 side chain 5) at a very advanced stage of the synthesis with minimal functional group interconversion. Thus, we chose to incorporate each individual fragment with its native functionality (or as nearly as possible) and selected the fully elaborated CD fragment 3 as the nexus about which to assemble the subunits.

An efficient synthesis of the C1–C13 portion 6 (Scheme 1) of the AB fragment 2 through the aldol union of a metalated pyrone with a β-alkoxyaldehyde followed by acid-catalyzed cyclization to prepare the diaxial AB spiroketal core has been disclosed.10 Completion of the AB fragment 2 required the elaboration of the C12–C15 side chain including introduction of the C14 stereogenic center. The side chain at C11 was extended through the application of our asymmetric aldol procedure that utilizes chlorotitanium enolates of oxazolidinethiones.13 Thus, hydroboration of the alkene 6 with 9-BBN under ultrasonic irradiation,14 followed by Swern oxidation of the resultant alcohol gave the aldehyde 7. Asymmetric aldol addition of the chlorotitanium enolate of N-propionyl-l-(S)-4-benzoyloxazolidine-2-thione to aldehyde 7 provided the alcohol 8 (96:4 d.r.) after reductive removal of the auxiliary. Selective protection of the primary alcohol as its TES ether furnished the secondary alcohol 9. Oxidation of the C13 hydroxyl was succeeded by Wittig olefination of the resulting ketone to incorporate the C13 alkene in 86% yield. The C1 benzyl ether of alkene 10 was reductively cleaved to deliver alcohol 11, which was subjected to a two-stage oxidation to the carboxylic acid. The carboxylic acid was esterified under standard Mitsunobu conditions15 to generate the allyl ester 12. The allyl ester was chosen to allow hydrolysis of the ester under very mild conditions immediately prior to the macrolactonization. Any concern regarding the sensitivity of the C50 vinyl chloride to the conditions required to remove the allyl ester [Pd(0)] were alleviated during the construction of the C44–C51 side chain.12 The C5 TES ether was transformed in three high-yield steps to the C5 acetate 13. The AB spiroketal 2 was completed by selective hydrolysis of the C15 silyl ether and careful oxidation of the alcohol under Dess–Martin16 conditions immediately prior to use in the ensuing aldol reaction.

The synthesis of the C29–C43 fragment 4 was completed as shown in Scheme 2. Our previous approach to the EF fragment was modified to accommodate protecting-group alterations for successful implementation of the final assembly strategy. Methyl ketone 14 was synthesized through an analogous sequence to our previous route12 with the exception of the use of a triethylsilyl ether rather than a TBS ether at C41. Enolization of the methyl ketone...
produced the ketal 17, which was then advanced to the silyl ether 18 by sequential protection of the C41 and C35 hydroxyls.5,16 The C29 and C38 benzyl ethers were reductively cleaved by the action of LDDBB, the C29 alcohol was selectively tosylated, and the C38 hydroxyl was protected as its TES ether 19. Finally, the tosylate was converted to the phosphonium salt 4 via the C29 iodide.

Having established viable approaches to the four key subunits in sufficient quantities, the final assault on their assembly to the spongipyrans was advanced as illustrated in Scheme 3. The critical issue of minimal functionalization during the assembly was addressed by using the CD fragment 3, as the aldehyde at C28 and the ketone at C17, as the foundation of the assembly. Thus, the four fragments were connected in their required final oxidation states in just four synthetic steps. The C28–C29 olefin was constructed in a remarkably efficient manner through the 1:1 stoichiometric combination of the CD aldehyde 3 and the ylide derived from EF phosphonium salt 4 by the metalation of the phosphonium salt with MeLi–LiBr.17 The alkene 20 was obtained as a single detectable diastereomer in 86% yield. The resultant ethyl ketone was immediately treated with Cy2BCl and Et3N followed by addition of the AB aldehyde 2 to furnish the anti atidol product 21 with good selectivity (65%, 6:1 d.r.) after acylation of the C15 hydroxyl.5,7,8

The C44–C51 side chains, X = Cl and X = H for spongistatins 1 and 2, respectively, were attached through the Evans protocol.5,18 Exposure of the enol ether 21 to excess dimethylhydroxide led to exclusive epoxidation of the C42–C43 enol ether with no detectable oxidation of any other alkenes. Direct exposure of the epoxide to allyl stannanes 5a and 5b in the presence of Bu3SnOEt independently led to the fully elaborated spongistatin 1 and 2 seco esters 22 and 23. It is noteworthy that the chlorodiene unit of spongistatin 1 can be introduced through this method.

With the fully elaborated spongistatin framework in place, the task of closing the macrocycle and completing the synthesis was addressed. The allyl ester was removed with (Ph3P)4Pd in the presence of morpholine19 with no evidence of damage to the fragile chlorodiene moiety. The C41 and C47 silyl ethers were selectively removed with buffered HF–pyridine to access the seco acids 24 and 26. Attempted macrolactonization of the seco acids 24 and 26 under the Yamaguchi20 and Keck21 protocols led to complex mixtures of products, which included acylation of the C47 hydroxyl by 2,4,6-trichlorobenzoyl chloride. Exposure of seco acid 24 to DCC, DMAP, and DMAP-HCl produced a 3:1 mixture of the C41 and C42 macrodilides. It thus appeared that to improve the selectivity of the macrolactonization, the C47 hydroxyl needed to be rendered unreactive.5 To that end, when the spongistatin 2 precursor 26 was treated with excess Et3SiCl and imidazole, the selective protection of the C47 hydroxyl was achieved without event, as previously reported in the Evans synthesis.5 However, attempts to execute the same transformation on the spongistatin 1 precursor 24 led to partial hydrolysis of the C37 methyl ketal, presumably due to the presence of the mildly acidic imidazole hydrochloride. Fortunately, addition of Et3N to the reaction mixture suppressed the ketal hydrolysis, and the synthesis was advanced to the hydroxy acids 25 and 27. The regioselective macrocyclic lactonization was subsequently performed without difficulty through the Yamaguchi protocol,20 and final removal of all the remaining protecting groups by treatment with 5% HF in acetonitrile produced synthetic spongistatin 1 and spongistatin 2, both identical in all respects [by 1H, 13C, IR, (α)D25 and MS] to previously reported data.1,2,5,8

In summary, the synthesis of both spongistatin 1 and spongistatin 2 have been achieved from an advanced common intermediate. The efficient assembly strategy, which centers on the CD fragment as
the foundation for the final assembly, avoids the need for refunctionalization of the late-stage, complex intermediates.

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Supporting Information Available: 1H spectra of synthetic spongistatin 1 and spongistatin 2 (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References


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