Studies toward the synthesis of spirastrellolide A. Preparation of a C31-C47 model.

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In memory of Professor Harry Wasserman, a gentleman and a scholar.

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ABSTRACT

The synthesis of a C31-C47 model of spirastrellolide A is reported. Key steps include an iron catalyzed cross coupling reaction to incorporate the linear side chain as a single unit, and the carbonyl ene reaction of an exocyclic enol ether to prepare the 5,6-spiroketal. A trans-ketalization from 5,6- to 6,6-spiroketal frameworks is used to facilitate stereochemical assignment.

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Spirastrellolide A is an antimitotic polyketide that shows potent and selective inhibition of protein phosphatase 2A ($IC_{50} = 1$ nM) and causes premature entry of cells into mitosis (Figure 1).¹ This 38 membered macrocycle contains both 6,6- and 5,6,6-spiroketal units, a cis-2,6-disubstituted tetrahydropyran, and a multitude of additional functionality. The acyclic side chain, appended at C38, contains a skipped diene and terminates in an α -hydroxy carboxylic acid. The complex architecture and interesting biological profile of this and other spirastrellolides² have captured the attention of the organic chemistry community. Total syntheses of spirastrellolide A and F methyl esters have appeared,³ as have a number of reports describing the preparation of spirastrellolide fragments.⁴

Our interest in the preparation of spirastrellolide A and related compounds led us to consider methods by which to append the linear side chain. Considering the sensitive functionality contained within this unit, we wanted to explore the limits of

methodology that would allow direct incorporation of this substructure in a single transformation. Toward this end we initiated studies aimed at the synthesis of the C31-C47 spirastrellolide model **2** that contained both the linear side chain and a truncated version of the bis-spiroketal that is found in the natural product. Retrosynthetically, we anticipated incorporation of the side chain via a cross coupling reaction between a suitably functionalized vinyl halide **3** and a spiroketal **4** that contained an exocyclic methylene (Scheme 2). In turn, preparation of the spiroketal **4** was envisaged from an exocyclic enol ether **6** via a carbonyl ene reaction⁵ and subsequent spirocyclization. Access to the vinyl halide **3** was expected from the corresponding aldehyde **5** that is readily available from (*S*)-malic acid.

Figure 1.

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Synthesis of the requisite spiroketal commenced with the carbonyl ene reaction of the exocyclic enol ether **6** with ethyl glyoxylate (Scheme 2).⁵ The resulting dihydropyran **7** was treated with aqueous HCl to give the corresponding spiroketals as a 2:1 mixture of diastereomers **8a** and **8b** that differ in stereochemistry at C37 (spirastrellolide numbering).⁶ From here, the individual spiroketals were separated and converted to the corresponding exocyclic enol ethers **9a** and **9b** by protection of the secondary alcohol followed by treatment with the Petasis reagent.⁷

Scheme 2.

At this point it remained to determine the relative stereochemistry at C37 in each diastereomer, **10a** and **10b**. While a direct comparison of coupling constants in the five membered ring was not useful in this regard, we anticipated that conversion of the 5,6-spiroketals to the corresponding 6,6-derivatives would allow us to distinguish the two compounds. Thus, hydroboration of the exocyclic enol ethers **10** followed by an oxidative workup gave the corresponding primary alcohols **11** (Scheme 3). We anticipated that hydroboration of the exocyclic enol ethers would occur opposite the C37 silyloxy substituent to give products **11a** and **11b** in which the hydroxymethyl and silyloxy groups are *cis*. From here, deprotection of the secondary alcohols followed by equilibration of the diols **12a** and **12b** under thermodynamic conditions provided spiroketals **13a** and **13b** that were then converted to the corresponding bis-acetates. As expected, each of the 6,6-spiroketals prepared as described above displayed a unique coupling pattern that allowed determination of the relative stereochemistry of the acetoxy groups in spiroketals **14a** and **14b**, and by extension, the relative stereochemistry at C37 in the exocyclic enol ethers **10a** and **10b** (Scheme 4). Thus, spiroketal **14a**, prepared from exocyclic enol ether **10a** showed a large-large and large-small coupling patterns for H_a and $H_{a'}$ respectively, and large-large-small coupling patterns for both H_b and H_c ; a pattern

consistent with a diequatorial disposition of the two acetoxy groups. At the same time, spiroketal **14b**, prepared from exocyclic enol ether **10b**, showed large-small coupling constants for both H_a and $H_{a'}$, and small-small-small coupling patterns for both H_b and H_c .⁸ This coupling pattern is consistent with the acetoxy groups being diaxial. By extension, exocyclic enol ether **10a** was determined to have an alpha silyloxy group, whereas that in exocyclic enol ether **10b** was determined to be beta.

Scheme 3.

This data also supports our premise that hydroboration of the exocyclic enol ethers **10** would occur opposite the silyloxy group at C37 (*cf.* Scheme 2). Had hydroboration occurred from the same face as the C37 substituent, the resulting 6,6-spiroketals, **15a** and **15b**, would each show one small-small-small and one large-small-small coupling pattern for protons adjacent to the acetoxy substituents. Signals corresponding to these patterns were not observed.

With the requisite exocyclic enol ether **10a** in hand, preparation of the vinyl halide component commenced from (S)-malic acid **16** (Scheme 5).⁹ Thus, this substrate was converted to the dioxolane derivative **17** according to the procedure of Seebach.¹⁰ Under these conditions the acetal was isolated as a single diastereomer. Selective reduction of the carboxylic acid followed by direct oxidation of the resulting alcohol provided aldehyde **19** in 63% yield over two steps. Attempts to purify the intermediate alcohol **18** by silica gel chromatography were complicated by facile translactonization.¹¹ Best results were obtained when this compound was used directly from the borane reduction without further purification.

Treatment of the aldehyde **19** with the known Wittig reagent provided the skipped ene-yne **21** in 55% yield. Central to the success of this transformation was the use of a polar additive,

Scheme 4.

N,N'-dimethylethyleneurea (DMEU), to enhance solubility of the phosphonium salt **20**.¹² Cleavage of the trimethylsilyl group gave the terminal acetylene **22**, which unfortunately did not provide the vinyl iodide **23** when treated sequentially with Cp_2ZrHCl and iodine. Conversion of a skipped enyne to the corresponding vinyl iodide by this process is known on a more hindered system.¹³

Scheme 5.

Preparation of the desired vinyl iodide **23** was ultimately realized, albeit in modest yield, upon treatment of the aldehyde **19** with a modified Wittig reagent in which the requisite functionality was already intact (Scheme 6). Formation of the corresponding phosphonium salt **25** was readily achieved upon treatment of the known alkyl iodide **24**¹⁴ with PPh_3 in refluxing ethanol.

Scheme 6.

With the preparation of all key components, studies were initiated to couple the exocyclic enol ether **10a** with vinyl iodide **23** using the *B*-alkyl Suzuki reaction (Scheme 7).¹⁴ Use of the more base stable ester **26**, available in two steps from the corresponding 1,3-dioxolane derivative **23**, was also evaluated. Unfortunately, despite extensive experimentation, we were unable to identify conditions to effect this transformation by *B*-alkyl Suzuki. Nor were we able to effect a coupling reaction between the exocyclic enol ether **10a** and even simple vinyl or aryl halides.

As such, we turned our attention to an alternate coupling protocol. Cahiez had recently reported an iron-catalyzed method for the alkylation of alkenyl magnesium derivatives.¹⁶ Despite the potential complication of generating a Grignard reagent in the presence of a skipped diene and other reactive functionality (*cf.* **23**), we were encouraged to find that the alkyl iodide **28**, prepared in one step from the corresponding alcohol **11a**, underwent smooth reaction with isopropenyl magnesium bromide to give the coupled product **29** (Scheme 8).

Scheme 7.

Scheme 8.

In order to facilitate incorporation of the spirastrellolide side chain, a modified vinyl iodide **30** that did not contain a terminal ester function was prepared (Scheme 9). Thus, (*S*)-malic acid was converted by a known sequence of reactions to the ester **31**,¹⁷ that was then subjected to a reduction/oxidation to give the aldehyde **32**.¹⁸ Subsequent Wittig reaction with the ylide derived from the phosphonium salt **25** provided the desired compound **30** in 53% yield as a single stereoisomer.

Scheme 9.

From here, generation of the coupled product was achieved by conversion of the (*S*)-vinyl iodide **30** to the corresponding Grignard reagent, followed by addition of the ($\pm$)-alkyl halide **28** and catalytic $\text{Fe}(\text{acac})_3$. By this method, the spiroketal **33** that contains the full spirastrellolide side chain was obtained in 57% yield as a 1:1 mixture of diastereomers (Scheme 10).

Scheme 10.

In conclusion, we have demonstrated the use of an iron-catalyzed coupling protocol to effect the preparation of a C28-C47 model of spirastrellolide A. Formation of the key C38-C39 linkage was achieved from a functionalized 5,6-spiroketal and a vinyl halide that comprised part of a sensitive skipped diene moiety. Generation of the 5,6-spiroketal unit was achieved by the carbonyl ene reaction of an exocyclic enol ether, followed by spirocyclization. This application demonstrates the utility of the carbonyl ene methodology developed previously in our lab for the preparation of complex substructures. Determination of relative stereochemistry in the resulting spiroketal subunit was realized by a facile trans-ketalization from 5,6 to 6,6-spiroketal systems. Further studies toward the synthesis of spirastrellolide A are currently ongoing and will be reported in due course.

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Supplementary data

Supplementary data (experimental procedures, characterization data, copies of ^1H and ^{13}C NMR spectra) associated with this article can be found in the online version at <http://xxx>.

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