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Synthesis of the C1−C23 Fragment of Spirastrellolide A

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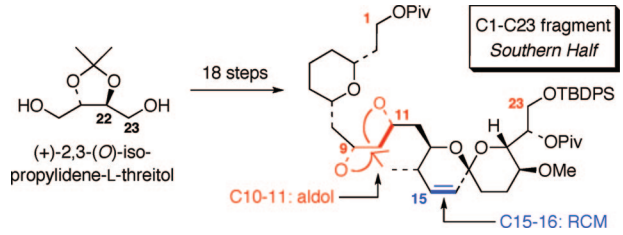
ABSTRACT



Synthesis of the C1−C23 fragment in spirastrellolide A is described, featuring a cyclic acetal-tethered RCM for stereoselective constructions of spiroketal, and a 1,3-*anti* aldol involving methyl ketone enolate and Mukaiyama conditions.

The isolation of (+)-spirastrellolide A, a novel spiroketal-rich macrolide from marine sponge Spirastrellolide coccinea, was reported by Roberge and Andersen et al.[1] In addition to its ability to initiate premature entry into mitosis and untimely mitotic arrest in cells, spirastrellolide A exhibits a potent inhibitory activity against protein phosphatase 2A [IC_{50} = 1 nM] with an excellent selectivity for PP2A over PP1 [ratio of IC_{50} values = 1:50],[1,2] and it does not inhibit PP2C. Its biological activities, therefore, resemble other known Ser/Thr phosphatase inhibitors fostriecin and okadaic acid. Development of protein phosphatase inhibitors has lagged behind interest in kinase inhibitors because of the perceived notion that kinases are more highly regulated and specific.[3] However, there has been a renewed interest in recent years because reversible protein phosphorylation is critical "as the other half" of checkpoints in cell cycles, and protein phosphatases assume an equally important role in regulating cellular signal transductions and should not be ignored. Designing phosphatase inhibitors can lead to new paradigms in developing cancer therapeutics.[3]

As a result, this natural product has attracted an elegant array of synthetic efforts,[4] and most recently, the first total synthesis by Paterson.[5] We became interested in spirastrellolide A when we developed a cyclic acetal tethered RCM as an unconventional approach to the synthesis of spiroketals.[6,7] Consequently, we pursued the synthesis of an epimer [at C22] of the C11−23 fragment to showcase our method.[8]

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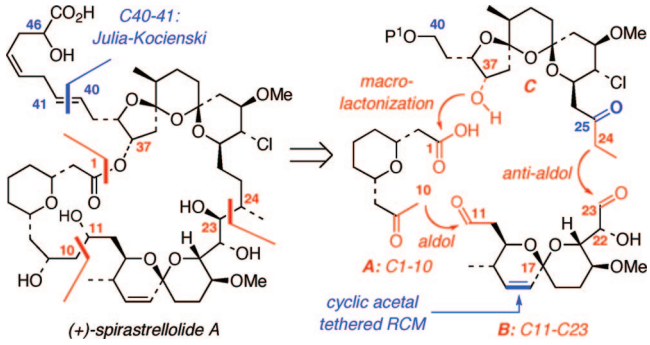
We report here our concise synthesis of the southern half of (+)-spirastrellolide A consisting of the C1−C23 fragment.

Retrosynthetically, while the reconnection at C40−41 will be accomplished by using Julia−Kocienski olefination [also documented by Smith[4j]], the central macrolactone core can be divided into three major fragments: **A**, **B**, and **C** [Scheme 1]. A macrolactonization could link C1 and C37 between

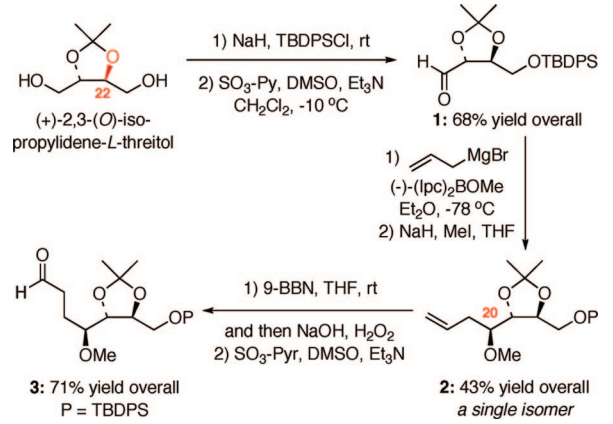
Scheme 1. *Spirastrellolide A*



fragments **A** and **C**. A methyl ketone enolate 1,3-*anti*-aldol reaction will be used to connect fragments **A** and **B** at C10 and C11. While Fürstner[4e] adopts the same disconnection, we independently reported this specific retro-synthetic approach.[9] Another *anti*-aldol would link together fragments **B** and **C** at C23 and C24 but will require the addition of the C25-oxo group. Synthesis of fragment **B** would feature a cyclic acetal tethered RCM.[7]

To prepare the C11−C23 fragment [**B**] with the desired C22-stereocenter, we designed a shorter and more practical route in comparison with our previous effort.[8] We commenced the synthesis of fragment **B** with (+)-2,3-(*O*)-isopropylidene-L-threitol[10] as shown in Scheme 2. Mono-protection of the hydroxyl group with TBDPSCl followed by SO_3-Pyr/DMSO oxidation[11] gave aldehyde **1**[12] in 68% yield. A three-carbon chain extension of aldehyde **1** was accomplished in a four-step sequence featuring Brown's asymmetric allylation,[13] *O*-methylation [to give **2**], 9-BBN

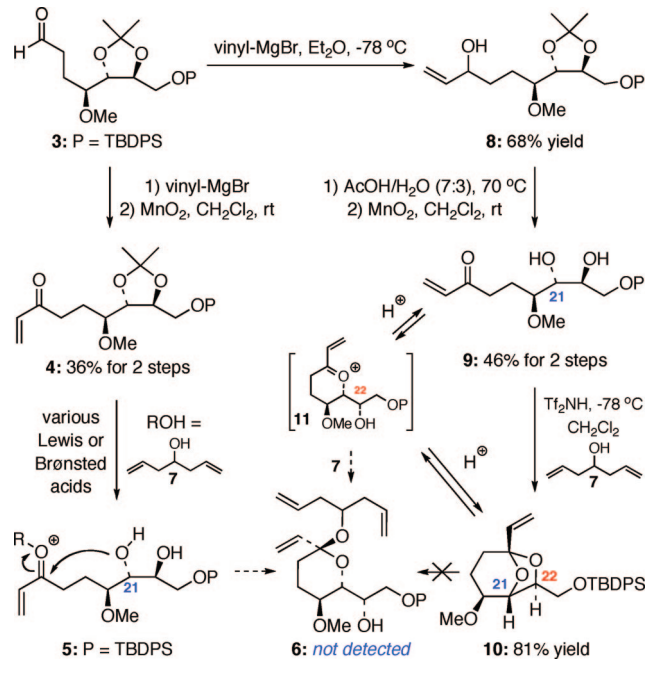
Scheme 2



hydroboration, and SO_3-Pyr/DMSO oxidation that led to methoxy aldehyde **3**. Stereochemistry at C20 was confirmed by using Mosher ester analysis[12] after the asymmetric allylation.

With aldehyde **3** in hand, we explored the possibilities of further shortening of our synthesis. Enone **4** was first prepared from **3** via addition of vinyl magnesium bromide followed by MnO_2 oxidation [Scheme 3]. The idea was to

Scheme 3



condense enone **4** with a homoallyl alcohol such as **7** under Lewis or Brønsted acidic conditions concomitantly with removal of the acetonide group to generate vinyl oxocarbenium ion **5**, which can be trapped internally by the free C21-OH to give vinyl cyclic acetal **6**. However, after screening a range of Lewis and Brønsted acids, we were unable to

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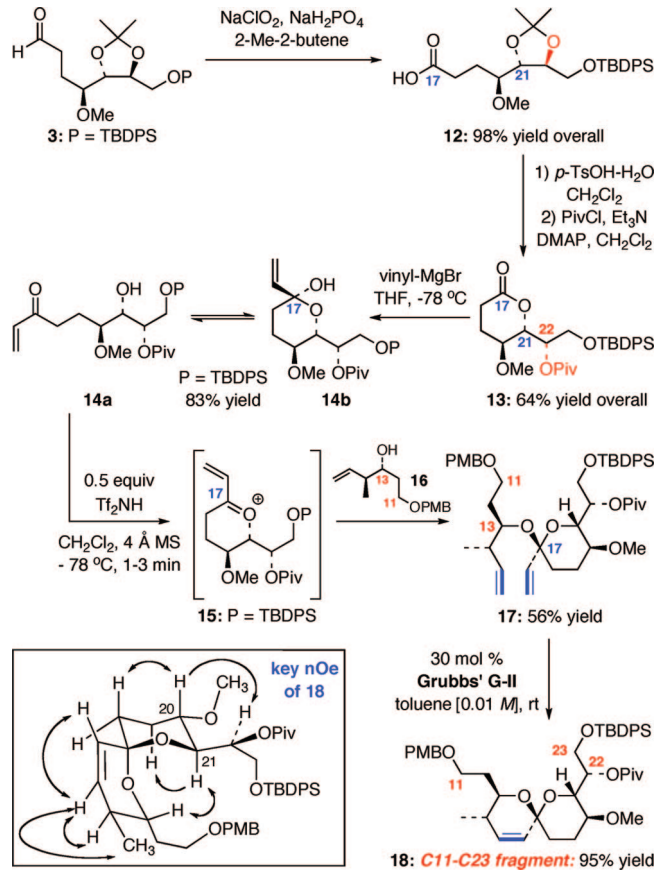
succeed in this transformation.[14] Instead, in most cases, we were able to still recover the starting enone **4**, thereby suggesting that the acetonide protecting group was sufficiently robust under theses conditions to prevent C21-OH from being unveiled for the cyclic acetal formation.

Recognizing that we might have asked too much in an attempt to shorten the synthesis, we removed the acetonide group in allyl alcohol **8** after the addition of vinyl Grignard to aldehyde **3**, and a subsequent MnO_2 oxidation gave enone **9** containing the free diol in 46% overall yields. However, again, attempts to access cyclic acetal **6** from **9** via condensing with homoallyl alcohol **7** failed. From these attempts, we were able to isolate bicyclic acetal **10** with the yield being as high as 81% when using Tf_2NH.[15–17] The formation of **10** is clearly a result of trapping of vinyl oxocarbenium ion **11** by the free C22-OH. Given that **6** and **10** are both derived through **11** and should be reversible, we tried longer reaction time and higher temperature to force **10** toward **6** but were met with decompositions.

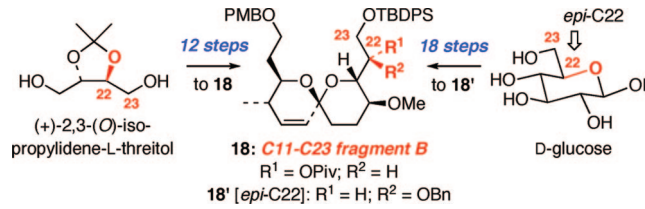
We were able to ultimately succeed in synthesizing the key vinyl cyclic acetal [see **17**] via the route shown in Scheme 4. Lindgren oxidation[18] of aldehyde **3** afforded acid **12**. Removal of the acetonide group led to a selective lactone formation involving only C21-OH, and subsequent capping of C22-OH with PivCl gave lactone **13** in 64% overall yield. The ensuing addition of vinyl magnesium bromide followed by treatment of the resulting lactol mixture **14a/b** with Tf_2NH[8,17] in the presence of alcohol **16**[19] afforded the desired vinyl cyclic acetal **17** in 56% yield.

The key ring-closing metathesis [RCM] of vinyl cyclic acetal **17** furnished the spiroketal in the C11−C23 fragment **18** [or fragment **B**] in 95% yield, using Grubbs' Generation-II Ru-catalyst.[20] Selected NOE experiments of **18** revealed that it possesses the desired relative stereochemistry, and that they closely resemble those reported for the same region in spirastrellolide A.[1] It is noteworthy that the current synthesis of the C11−C23 fragment **18** that commenced with (+)-2,3-(*O*)-isopropylidene-L-threitol is only 12 steps in comparison with the previous route of 18 steps from D-glucose that also led to the wrong stereochemistry at C22 [see **18′**] [Scheme 5].[8]

Scheme 4



Scheme 5



To complete the synthesis of the C1−C23 fragment or *the Southern half*, the C11−C23 fragment **18** was transformed to aldehyde **19** via removal of the PMB protecting group followed by SO_3-Pyr/DMSO oxidation [Scheme 6]. To connect the C10−11 bond, aldehyde **19** was subjected to Mukaiyama aldol conditions[21] employing TMS−enol ether **20** that was derived in situ by using LDA and TMSCl from methyl ketone **21**,[9] which contains the C1−C10 fragment.[9]

(14) Lewis acids screened: BF_3−OEt_2, $TiCl_4$, TMSOTf, $In(OTf)_3$, and $MgBr_2$. Brønsted acids screened: Tf_2NH, *p*-TsOH, TFA, and K-10. Temperature: −20 °C to rt.

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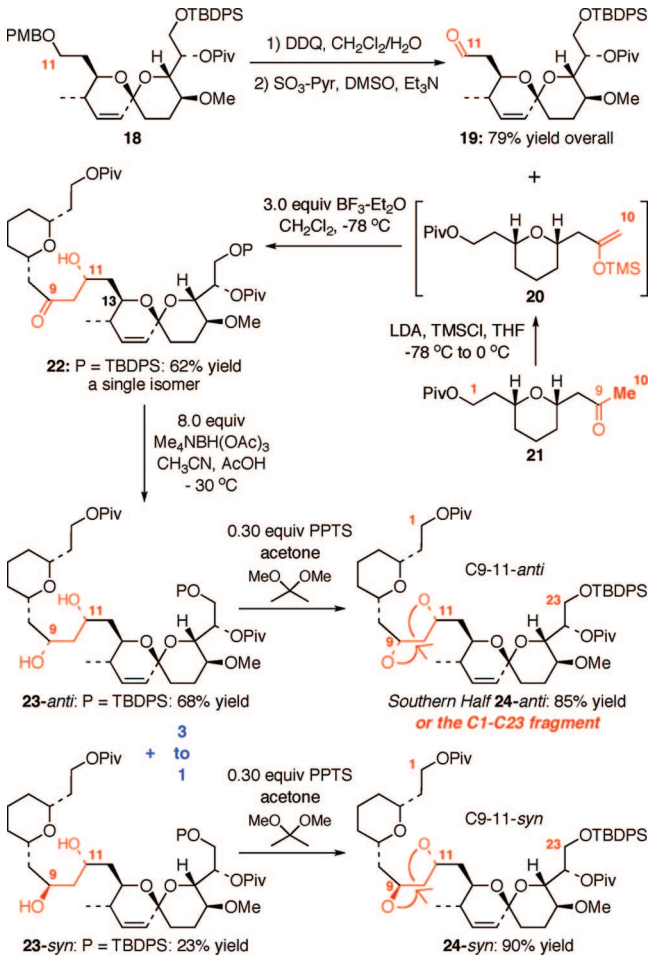
Scheme 6



It was important that TMS−enol ether **20** was first added to aldehyde **19** prior to the addition of a stoichiometric amount of BF_3−Et_2O at −78 °C. The aldol product **22** was obtained as a single isomer in 62% yield with C11−13 relative stereochemistry assigned as *anti* based on Fürstner's related aldol[4e] and our own model studies[9] with both being consistent with Evans's nonchelation 1,3-asymmetric induction model.[22] Directed reduction led to diol **23** with a 3:1 ratio in favor of the C9−11-*anti* isomer. Acetonide formation of both *anti* and *syn* isomers gave the desired southern half **24**-*anti* and **24**-*syn* isomers, respectively. By employing Rychnovsky−Evans's method,[23] we could unambiguously assign the C9−11 relative stereochemistry in both **24**-*anti* and **24**-*syn*.

We have described here our synthesis of the C1−C23 fragment in spirastrellolide A featuring a cyclic acetal-tethered RCM approach to the spiroketal synthesis and a Mukaiyama-methyl ketone 1,3-*anti* aldol. Efforts toward synthesis of the northern half and completing a total synthesis of spirastrellolide A are underway.

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Supporting Information Available: Experimental procedures as well as ^{1}H NMR spectra and characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

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