Organic LETTERS

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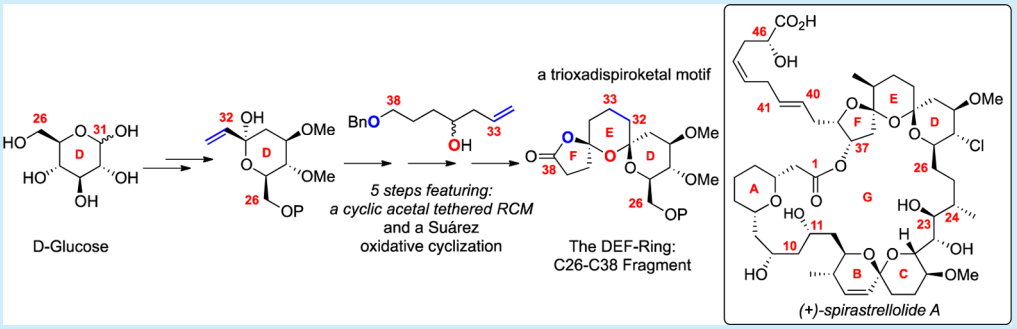
An Approach toward Constructing the Trioxadispiroketal Core in the DEF-Ring of (+)-Spirastrellolide A

Yi-Biao Wu,[†] Yu Tang,*[,†] Guo-Ying Luo,[†] Yang Chen,[†] and Richard P. Hsung*[,‡]

[†]School of Pharmaceutical Science and Technology, Key Laboratory for Modern Drug Delivery & High-Efficiency, Collaborative Innovation Center of Chemical Science and Engineering, Tianjin University, Tianjin, 300072 P. R. China

[‡]Division of Pharmaceutical Sciences, School of Pharmacy, and Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53705 United States

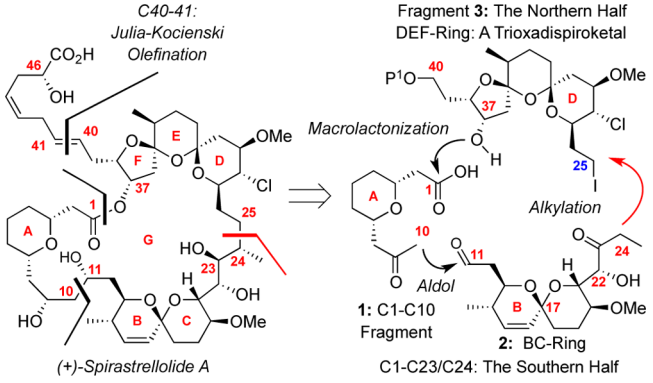
Supporting Information



ABSTRACT: A concise and stereoselective synthesis of the trioxadispiroketal motif that embodies the DEF-ring of the marine macrolide (+)-spirastrellolide A is described. The synthetic approach features a sequence of cyclic acetal tethered ring-closing metathesis and Suárez oxidative cyclization, thereby constituting a viable strategy for constructing the Northern Half.

The spirastrellolides are a family of structurally unprecedented marine macrolides that are protein phosphatase inhibitors, thereby representing valuable lead compounds for developing new anticancer therapeutics.[1,2] (+)-Spirastrellolide A was first isolated from the Caribbean sponge *Spirastrella coccinea* off the coast of Dominica (see Scheme 1),[3a] and this was followed by six structurally related congeners (spirastrellolide B−-G) and their respective methyl ester derivatives.[3c,d] (+)-Spirastrellolide A exhibits an impressive inhibitory activity against protein PP2A (IC_{50} ca. 1 nm) with an excellent selectivity for PP2A over PP1 (~50:1), while showing no inhibition of PP2C.[4] Such a biological profile resembles other well-known Ser/Thr phosphatase inhibitors, fostriecin and okadaic acid.[5] Despite lagging behind the development of cancer therapeutics based on kinase inhibitors because of the perceived notion that kinases are more highly regulated and specific, there has been a renewed interest in protein phosphatase inhibitors in recent years.[1,2,6] Phosphatases work in concert with kinases to maintain the all too critical reversibility in protein phosphorylations. Consequently, they signify "the other half" of checkpoints in cell cycles and assume an equally important role in regulating cellular signal transductions and should not be ignored.

Scheme 1. Our Synthetic Plan for (+)-Spirastrellolide A



To date, there have been many papers describing elegant synthetic efforts toward these natural products[7−11] including two monumental total syntheses by Paterson[10] and Fürstner.[11]

Our[12] long-standing synthetic strategy toward (+)-spirastrellolides has featured cyclic acetal-tethered transformations for constructing spiroketals.[13,14] Specifically, the use of cyclic acetal-tethered ring-closing metathesis (RCM)[15,16] has allowed us to complete a synthesis of the BC-ring (see **2**)[12] and ultimately the assembly of the entire Southern Half or the C1−C23 fragment through connection with A-ring via Mukaiyama antialdol (see **1**).[12b−e] On the other hand, fragment **3**, or the Northern Half, contains a challenging trioxadispiroketal motif that embodies the DEF-ring. Nevertheless, we want to showcase our cyclic acetal-

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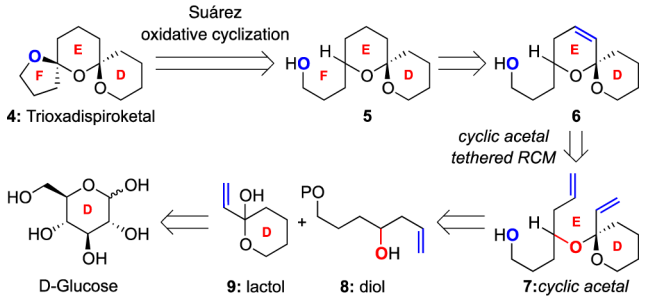
tethered RCM method in a synthesis of the Northern Half of (+)-spirastrellolide A. We report here an approach toward the trioxadispiroketal core of the DEF-ring that would employ a sequence of cyclic acetal tethered RCM along with the Suárez oxidative cyclization.[17−19]

A general design of our approach is shown in Scheme 2. We intend to build the trioxadispiroketal core **4** through use of

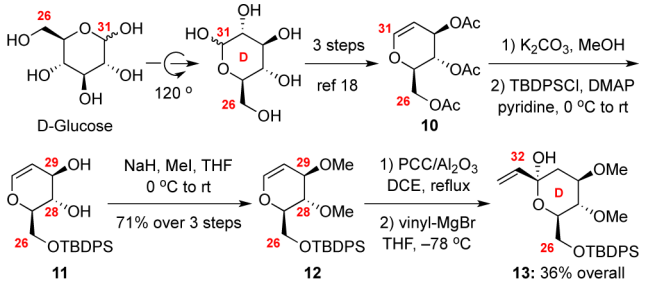
Scheme 2. Approach to DEF-Ring



Suárez oxidative cyclization of spiroketal **5** to close the F-ring and adoption of the RCM of cyclic acetal **7** to construct the DE-ring. Cyclic acetal **7** should be readily accessible from diol **8** and lactol **9**. While we could use simpler lactols and diols such as shown with **8** and **9** to quickly establish the concept of a DEF-ring construction involving cyclic acetal tethered RCM, we chose D-glucose as the starting point because it contains the stereochemical information that could be translated to that in the D-ring.

Our synthesis commenced with D-glucose, which was converted into tri-*O*-acetyl-D-glucal **10** using known procedures (Scheme 3).[20] After standard deacetylation was followed by

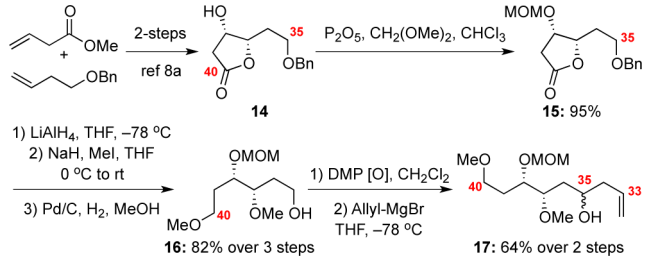
Scheme 3. D-Ring Synthesis from D-Glucose



monoprotection at C26, diol **11** could be obtained and was further protected as methyl ethers using NaH and MeI (see **12**).[21] PCC-oxidation of **12** would give the corresponding lactone,[22] which was converted to the key lactol intermediate **13** upon exposure to excess vinyl magnesium bromide. Lactol **13** exists in equilibrium with its ring-opened ketone form at room temperature. It is noteworthy that while it is capped as a simple methyl ether here, it is known that the C29-OH group can be selectively protected.[23] From this would emerge the possibility of converting the unprotected C28-OH into the desired chloride in the D-ring of spirastrellolide A.

With lactol **13** in hand, we proceeded to prepare the alcohol needed for the cyclic acetal formation. As shown in Scheme 4, we selected Paterson's lactone **14**[24] because we had hoped to bring in as many side-chain (C39−C46) carbons and stereochemical elements as possible. A sequence of protection, LAH reduction, methyl ether formation, and standard debenzylation would

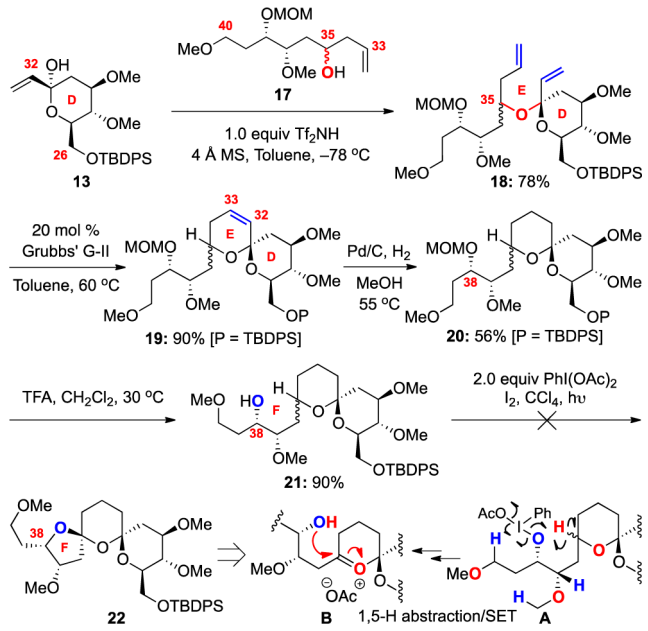
Scheme 4. Synthesis of C33−C40 Fragment 17



afford protected tetraol **16**. Subsequent oxidation and allylation using allylmagnesium bromide would give the homoallylic alcohol **17** as a mixture of diastereomers. It is noteworthy that diastereomeric control of the allylation is not critical because any stereochemical information at C35 will be lost during the oxidative cyclization.

In the presence of 1.0 equiv of Tf_2NH,[25,26] cyclic acetal formation proceeded smoothly to afford **18** in 78% yield (Scheme 5). RCM using Grubbs' Gen-II catalyst[27] took place in

Scheme 5. Attempted Cyclic Acetal Tethered RCM−Suárez Oxidative Cyclization Sequence



high yield to give the desired DE-ring spiroketal **19**. Hydrogenation and removal of the MOM group at C38 led to alcohol **21** being ready for Suárez oxidative cyclization. However, we could not carry out this transformation using the Suárez modified conditions, which involve $PhI(OAc)_2$ and irradiation with a LED lamp.[18] Although we are not sure at this point what the reasons are, we do observe one product that consistently appears in modest yield. Unfortunately, we could not assign its structure unambiguously using available spectroscopic data, and neither is it crystalline. However, this unassigned product is most likely associated with competing hydrogen abstractions as shown in **A** with half arrows shown for the desired 1,5-hydrogen abstraction for the red hydrogen atom and blue hydrogen atoms being the possible competing ones.

With this assumptive analysis of possible byproduct in mind, we decided to simplify the alcohol piece because using the more elaborate fragment **17** might have been a detriment for the

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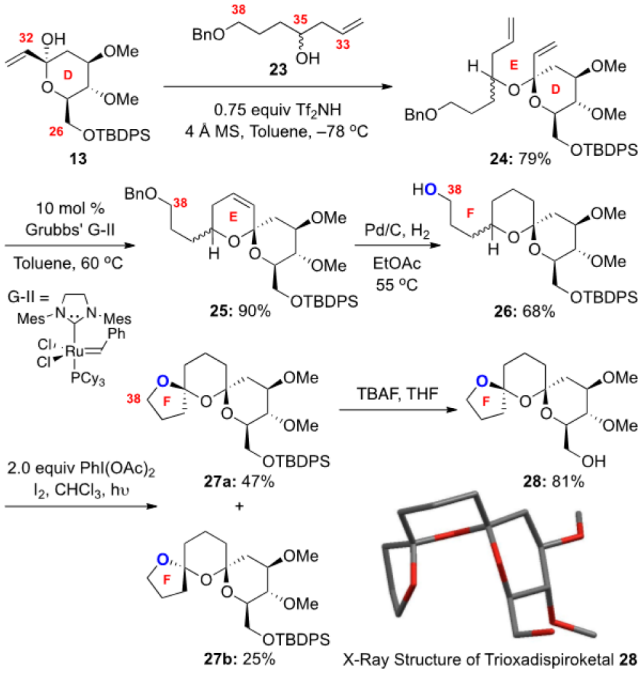
cyclization. As shown in Scheme 6, monoprotected diol **23**, which could be accessed quickly from 1,4-butanediol, was used

Scheme 6. Successful Trioxadispiroketal Construction

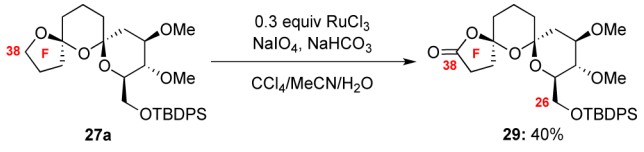


for the cyclic acetal formation. The ensuing RCM of **24** with Grubbs' Gen-II catalyst led to the DE-ring spiroketal **25** in 90% yield. Hydrogenation of the E-ring olefin concomitant with debenzylation gave the free alcohol **26**. Under the Suárez modified conditions, the Suárez oxidative cyclization indeed took place to afford trioxadispiroketals **27a** and **27b** as two separable diastereomers in 72% combined yield.

The major isomer **27a** was treated with TBAF, and the resulting free alcohol **28** was crystalline, which allowed us to obtain a single-crystal X-ray structure to confirm the structural integrity and relative stereochemistry of this trioxadispiroketal. It is noteworthy that although trioxadispiroketals **27a** and **27b** are readily separable, when using $CDCl_3$ that was not treated with base such as K_2CO_3, equilibration occurred to give an isomeric mixture with a 1:1.5 ratio (slightly in favor of **27b**) starting from either pure **27a** or **27b**. This equilibration outcome implies that the modest ratio in favor of the major trioxadispiroketal **27a** is actually kinetic.

Consequently, to render this strategy amenable for constructing the actual DEF-ring, the OH group at C37 and chain extension at C38 must be introduced after the oxidative cyclization. Fortuitously, we quickly found that trioxadispiroketal **27a** could be oxidized to its corresponding lactone **29** in 40% yield using catalytic $RuCl_3$ (Scheme 7).[28] This transformation provides the possibility of installing the C37-OH group and extending toward C46 using this approach.

Scheme 7. Ru(III)-Oxidation of the F-Ring



In summary, we have developed here a concise and stereoselective approach toward the trioxadispiroketal motif in DEF-ring of the marine macrolide (+)-spirastrellolide A. This synthetic approach features a sequence of cyclic acetal tethered ring-closing metathesis and Suárez oxidative cyclization and employs the readily available and inexpensive D-glucose for the D-ring synthesis. It constitutes a viable strategy for constructing the Northern Half. These efforts are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures as well as NMR spectra, characterizations, and X-ray structural files (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: yutang@tju.edu.cn.
*E-mail: rhsung@wisc.edu.

Notes

The authors declare no competing financial interest.

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