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Synthesis of the Spirastrellolide A, B/C Spiroketal: Enabling Solutions for Problematic Au(I)-Catalyzed Spiroketalizations

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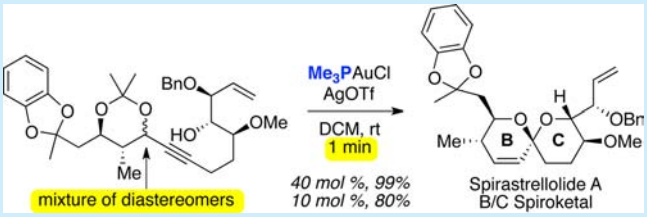
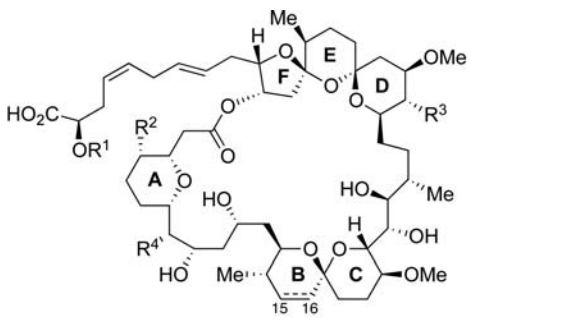
Supporting Information

ABSTRACT: A synthesis of the spirastrellolide A, B/C-ring monounsaturated spiroketal is reported. The key step relies on a Au-catalyzed spiroketalization of a propargyl triol employing an acetonide as a regioselectivity regulator. Through observation and analysis, a set of conditions has been developed that facilitates the use of a mixture of diastereomeric substrates, obviating the need to control the stereochemistry of the propargyl stereocenter and enabling a convenient retrosynthetic disconnection. The key reaction proceeds in 80% yield in 1 min at ambient temperature with the Me_3PAuCl/AgOTf catalyst system. These conditions should be widely applicable for new synthetic endeavors as they appear to overcome all issues with the Au-catalyzed spiroketalization.



The Spirastrellolide natural products were first isolated from the marine sponge *Spirastrella coccinea* by Andersen and co-workers in 2003.[1] The family consists of several congeners named spirastrellolides A–G (**1**–**7**) that display potent biological activity. Spirastrellolide A methyl ester was reported as a novel antimitotic agent (IC_{50} 100 ng/mL)[1a] and was later shown to selectively inhibit protein phosphatase 2A (PP2A); (IC_{50} = 1 nM).[1b] In 2004, the revised structure of spirastrellolide A appeared and is the basis for the assignment of the stereochemistry of spirastrellolides A–G (Figure 1).[1b] The absolute configuration was later determined in 2007.[1c] Due to the potent biological activity and interesting and complex molecular architecture, the spirastrellolides have attracted the attention of the synthetic community with four total syntheses[2] and numerous approaches having been reported to date.[3]



Spirastrellolide A	**1**	$R^1 = R^2 = R^4 = H$,	$R^3 = Cl$,	Δ(C15-C16) = ✓
Spirastrellolide B	**2**	$R^1 = R^2 = R^3 = R^4 = H$,		Δ(C15-C16) = X
Spirastrellolide C	**3**	$R^1 = R^2 = R^3 = H$,	$R^4 = OH$,	Δ(C15-C16) = X
Spirastrellolide D	**4**	$R^1 = R^4 = H$,	$R^2 = R^3 = Cl$,	Δ(C15-C16) = ✓
Spirastrellolide E	**5**	$R^1 = R^2 = R^3 = R^4 = H$,		Δ(C15-C16) = ✓
Spirastrellolide F	**6**	$R^1 = R^2 = R^4 = H$,	$R^3 = Cl$,	Δ(C15-C16) = X
Spirastrellolide G	**7**	$R^1 = Me$,	$R^2 = R^4 = H$,	$R^3 = Cl$, Δ(C15-C16) = ✓

Figure 1. Structures of spirastrellolides A–G.

Our interest in these natural products stems from the densely functionalized macrolide core of the molecules, consisting of saturated oxygen heterocycles. As part of a program aimed at developing new Au-catalyzed methods for dehydrative transformations of unsaturated alcohols, we initiated method development studies for the formation of the requisite heterocycles.[4] We felt that it was important to address the B/C-ring system as an unsaturated spiroketal is also found in okadaic acid,[5] another potent phosphatase inhibitor, and thus became interested in spirastrellolides A, D, E, and G. As can be seen in Scheme 1, spirastrellolide A lends itself to disconnection into the fragments containing tetrahydropyran, unsaturated spiroketal, and bispiroketal motifs. Our initial report demonstrated the use of Au catalysis for the formation of tetrahydropyrans, and we reported an A-ring synthon in racemic form that has now been prepared enantioselectively.[4a] To complete the southern hemisphere, a B/C-ring unsaturated spiroketal was necessary, but application of our Au-catalyzed propargyl triol method[4b] proved to be problematic. Fortunately, we were able to gain an understanding of the underlying problems, and this led to the development of a mechanistic rationale and eventually to a good solution to the spiroketalization problem. Herein we report an efficient synthesis of the B/C-ring fragment and describe the important details necessary for successful spiroketalization.

As shown above, retrosynthetic analysis suggested that the B/C-ring spiroketal **8** should be available by spiroketalization of an alkyne precursor **9**. This approach distinguishes itself from more traditional spiroketalization methods as oxygenation at spiroketal

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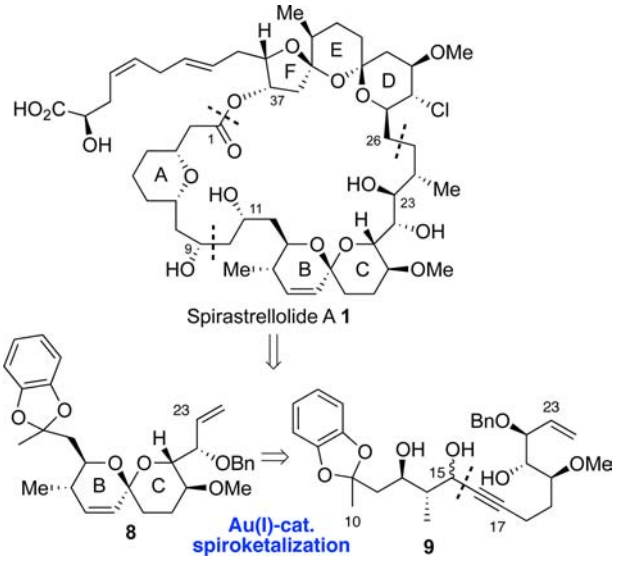
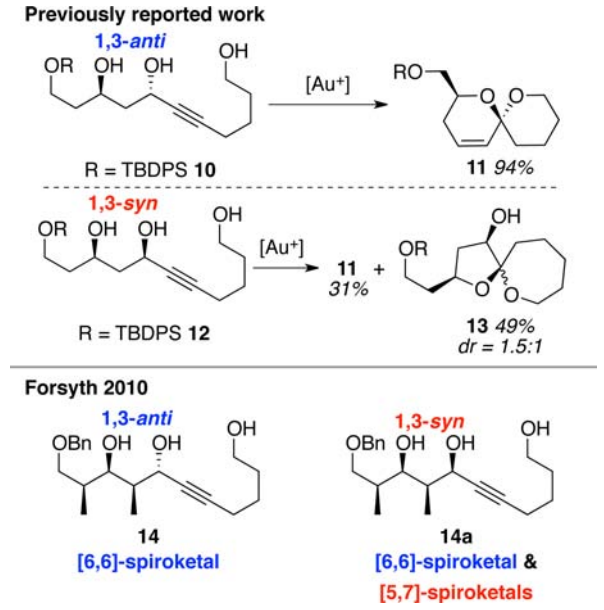
Scheme 1. Retrosynthetic Analysis of Spirastrellolide A



C17 is introduced via addition to the alkyne C17 and the $\Delta_{15,16}$ olefin is produced by elimination of the C15 hydroxyl group. At the outset, it was thought that the C15 hydroxyl group stereochemistry in **9** should be inconsequential, but this was somewhat in question. As seen in Scheme 2, the relative

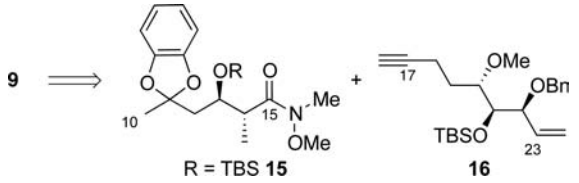
Scheme 2. Problematic 1,3-*syn*-Diols for Spiroketalization



stereochemistry of the indicated diols had a pronounced effect on the spiroketalization with the 1,3-*anti*-diols **10** and **14** smoothly providing the [6,6]-spiroketals (1,7-dioxaspiro[5.5]undecanes) in high yields and the 1,3-*syn*-diols providing mixtures of [6,6]- and [5,7]-spiroketals with virtually no selectivity.[6]

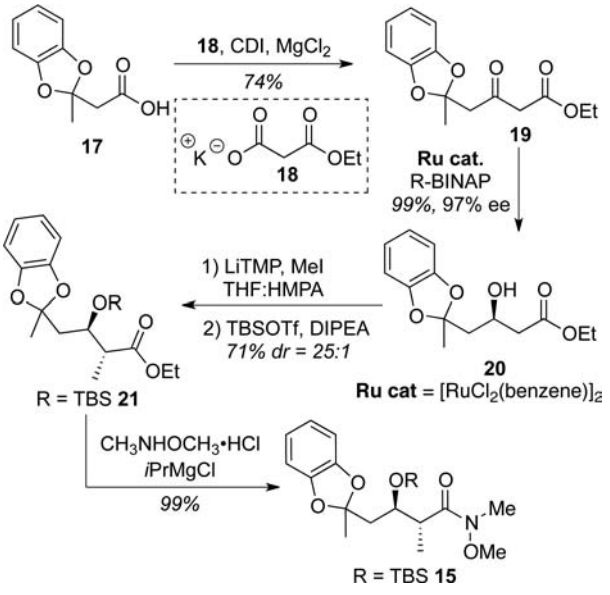
These data suggested that it may be important to control the C15 stereochemistry, but the effect of the C14 methyl group was unknown. This would later be borne out here (vide infra) and also by Smith and co-workers.[7] In anticipation of these stereochemical consequences, triol **9** would be prepared by selective ketone reduction if necessary, and thus Weinreb amide **15** and alkyne **16** were selected as synthetic intermediates (Scheme 3).

Scheme 3. Retrosynthetic Analysis of Spiroketalization Precursor 9



The synthesis of Weinreb amide **15** (Scheme 4) began with known acid **17**,[8] forming the monoprotected β-ketoester **19** by

Scheme 4. Synthesis of Amide Fragment 15



coupling with **18**.[9] The C13 stereochemistry was set in 97% ee by Noyori reduction[9] and the methyl group introduced by alkylation[10] to provide **21** in 25:1 dr after TBS protection. The ester was then smoothly converted to the Weinreb amide **15** in nearly quantitative yield.

Synthesis of the alkyne **16** commenced from *O*-allyl L-arabinose **22**,[11] which contains the C20−22 stereotriad required for spirastrellolide A, and proved to be a convenient starting material (Scheme 5). This required chain extension at both termini, which would be accomplished by Wittig olefination and epoxide opening. In the event, selective formation of the six-membered ketal and benzyl protection of the remaining hydroxyl group were accomplished, forming **23** in 99% yield. Deallylation and Wittig olefination then provided the olefin **24**.[12] Addition of the alkyne moiety proved to be slightly more difficult. To achieve this, the acetonide was first cleaved and the resulting primary alcohol selectively activated as the tosylate. At this stage, extensive efforts to form the epoxide and protect the ensuing C21 alcohol failed, resulting in decomposition. The C20,21 alcohols needed to be differentiated as C20 bears a methyl ether in the natural product and the C21 hydroxyl group is required for the Au-catalyzed cyclization. It was found that the C20 alcohol could be selectively protected, but all attempts to then protect the C21 alcohol provided unsatisfactory results. To overcome this issue,

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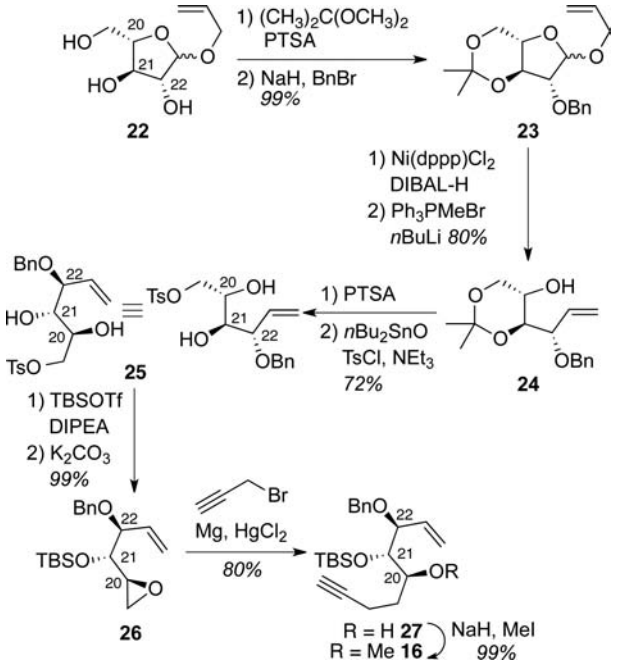
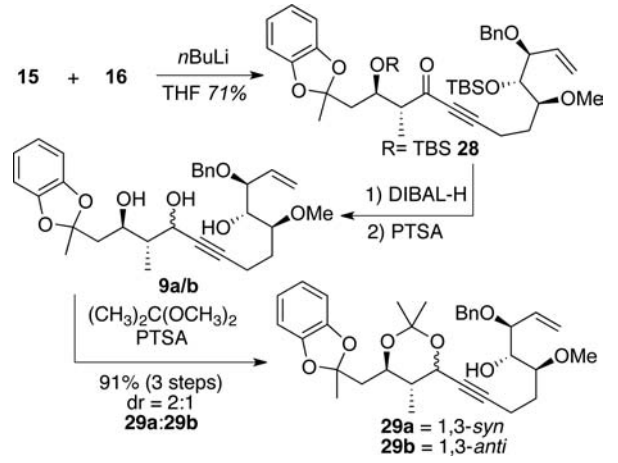
Scheme 5. Synthesis of Alkyne Fragment 16



the C20 alcohol was protected as the TBS ether, and a silyl migration/epoxide formation sequence then nicely afforded epoxide **26**. To complete the synthesis of **16**, the epoxide was opened with a propargyl Grignard reagent prepared with catalytic $HgCl_2$ as an initiator,[13] and the C20 methyl ether formed with NaH and MeI.

Union of the two fragments was accomplished in 71% yield by acetylide addition to the Weinreb amide to give the ketone **28** (Scheme 6). At this stage, it was decided to do a simple DIBAL-H

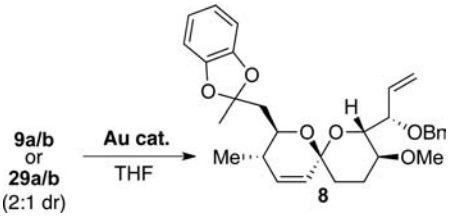
Scheme 6. Synthesis of Spiroketalization Substrates



reduction and explore the key spiroketal formation[4b] on a 2:1 mixture of diastereomers **9a**,**b** thus obtained, with the goal of overcoming the requirement for a specific diastereomer. The material was also converted to the acetonides **29a**,**b**, initially to determine the relative stereochemistry[14] and later for preparative purposes. Conversion of the ketone **28** to the acetonides **29a**,**b** proceeded in 91% yield over three steps.

With a source of triols **9a**,**b** in hand, Au-catalyzed spiroketalization was attempted. While the reaction proceeded using the Echavarren catalyst (Table 1, entry 1), unfortunately, the yield was low (50% isolated yield) and it appeared that one

Table 1. Au(I) Spiroketalization Studies



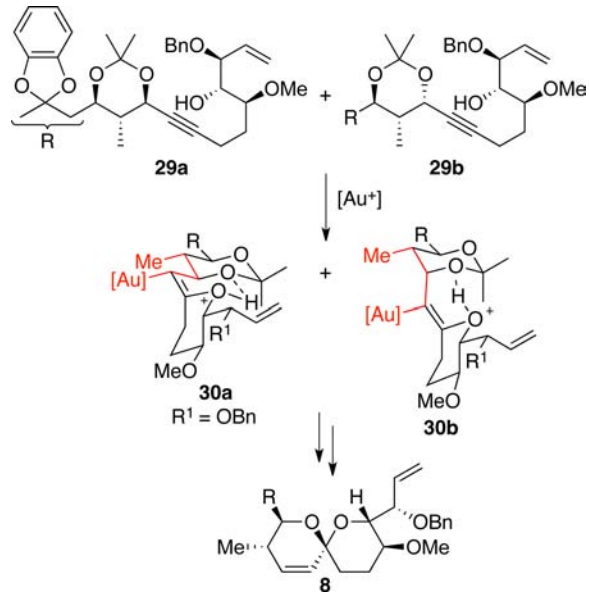
entry	alkyne	catalyst system	yield[a]
1	**9a/b**	JohnPhos Au(MeCN)SbF_6	50%
2	**9a/b**	AuCl	50%
3	**29a/b**	AuCl	decomp
4	**29a/b**	JohnPhos Au(MeCN)SbF_6	50%

[a]Mixtures of **8** and [5,7]-spiroketals were observed.

diastereomer rapidly provided the product while the other sluggishly reacted and formed a mixture of **8** and [5,7]-spiroketals. Use of simple AuCl provided the same results (entry 2). During our work on this system, Smith reported the same observation and nicely determined that the 1,3-*anti*-diastereomer was the one that was smoothly cyclizing in his system.[7] Forsyth provided a mechanistic rationale for this phenomenon that was based on steric effects,[6] and we recently reported a method to overcome this issue using AuCl as catalyst with acetonide substrates such as **29a**,**b**.[15] Unfortunately, employing the optimized conditions (entry 3) only resulted in decomposition. In an attempt to overcome this, the less Lewis acidic Echavarren catalyst was employed (entry 4) and the isolated yield improved to 50%, but this was still deemed unacceptable.

At this stage, it was hypothesized that the diastereomers **29a** and **29b** follow similar reaction pathways (Scheme 7). The process must begin with an initial *anti*-alkoxyauration to provide **30a** and **30b**, respectively. Examination of these σ-gold

Scheme 7. Analysis of 1,3-*syn*- and 1,3-*anti*-Diols in Au-Catalyzed Spiroketalization



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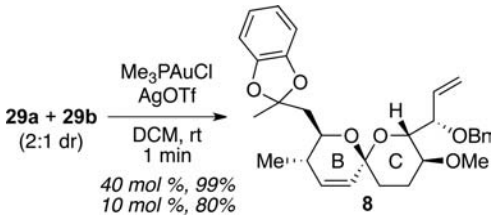
complexes reveals a *syn*-pentane interaction in the intermediate **30a**, resulting from the C13,15-*syn*-diastereomer **29a**, while such an interaction would be greatly diminished in **30b**, which results from the C13,15-*anti*-diastereomer **29b**. This was intriguing as it may explain the reactivity problem of the *anti* diastereomers such as **29b**.[4,6,7] To complete the transformation, what is needed is an *anti*-elimination of the σ-gold complex to release acetone and reveal the second hydroxyl group for cyclization. In both **30a** and **30b**, the proper *anti*-periplanar orientation required for this elimination is achieved, and the leaving group is likely further activated by hydrogen bonding, as was reported for similar reactions on THP systems.[16]

This hypothesis suggested that the rates of cyclization could be modulated by changing either the substrate or the catalyst to relieve the unfavorable *syn*-pentane interactions. The goal of this method was to allow for either diastereomer to participate in the spiroketalization and obviate the need for a stereoselective substrate preparation. As such, it was postulated that a smaller catalyst might facilitate this and suggested use of the smallest Au–phosphine complex available, Me_3PAuCl, in combination with AgOTf. With these conditions, a rapid consumption of both diastereomers was observed, providing a single diastereomer of the B/C spiroketal in a reaction time of 1 min (Scheme 8). The

Scheme 8. Completion of the B/C-Ring Fragment



reaction was initially performed on small scale with high catalyst loading, which gave 99% yield. On larger scale, with 10 mol % loading, the desired spiroketal was isolated in 80% yield, efficiently completing the B/C-ring fragment. This advance will allow for a more direct synthetic route that bypasses the Weinreb amide, streamlining the synthesis. Furthermore, these conditions should be widely applicable for new synthetic endeavors, as they appear to overcome all issues with the Au-catalyzed spiroketalization reaction.

In summary, we have reported an efficient synthesis of the B/C-ring system of the spirastrellolides and have efficiently overcome the spiroketalization problem observed by us and others. This should allow for the method to be utilized in a variety of systems and, more importantly, provide a rationale for substrate design by considering the issues outlined above. The spirastrellolide program is ongoing in our laboratory, and further reports focused on the total synthesis will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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