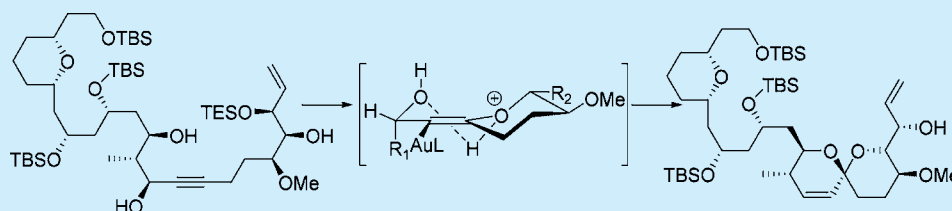


Synthesis of a C(1)–C(23) Fragment for Spirastrellolide E: Development of a Mechanistic Rationale for Spiroketalization

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S Supporting Information



ABSTRACT: Synthetic analysis of spirastrellolide E envisioned to entail a cross-metathesis union of the northern and southern hemispheres followed by a Sharpless epoxidation/methylation sequence to achieve the C(22,23) stereogenicity leads to the design of a C(1)–C(23) advanced southern hemisphere exploiting a gold-catalyzed directed spiroketalization as a key step. Stereochemical analysis of this strategic transformation provides insight on the impact of the directing group carbinol stereogenicity on the reaction efficiency and, in turn, permits the conversion of the minor isomer of the spiroketal precursor to the requisite congener for successful spiroketalization.

Spirastrellolides (A–G, 1–7; Figure 1) comprise a family of architecturally complex natural products. The first member,

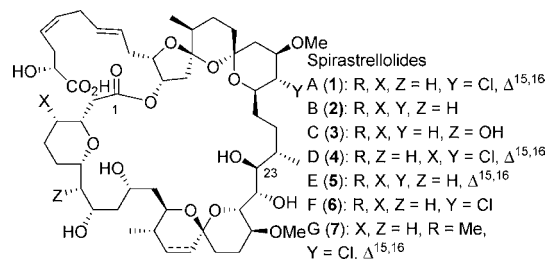


Figure 1. Spirastrellolides A–G.

spirastrellolide A (1), was isolated by Andersen in 2003,¹ followed 4 years later by spirastrellolides B–G (2–7).^{2,3} The full relative and absolute stereostructure of the C(1)–C(38) core of 1, not fully elucidated at the time of the initial report, was later assigned, employing a crystal structure of a truncated congener of spirastrellolide B (2),² with the relative configuration of the side chain established by chemical degradation of spirastrellolide D (4). Spirastrellolide A and the methyl ester display significant potency (1 nM) and selectivity against protein phosphatase 2A.¹

Given both the intriguing biological profile and architectural complexity of the spirastrellolides, a number of synthetic approaches toward this family have appeared,⁴ culminating in total syntheses of spirastrellolide A by the Paterson⁵ and Fürstner⁶ groups, as well as a total synthesis of spirastrellolide F by the Fürstner group.⁷

Our early interest in the spirastrellolides resulted in approaches toward both advanced northern^{4a} and southern⁸

hemispheres of the spirastrellolide family of macrolides. With these achievements, we turned to the evolution of our synthetic strategy with particular emphasis on scalability, in preparation for a total synthesis of spirastrellolide E. We recently described a streamlined approach to an advanced southern hemisphere fragment,⁹ which significantly increased the overall yield while reducing the longest linear sequence by 14 steps. We report here additional significant refinements of our overall synthetic strategy, including a stereochemical rationale for the strategic level gold-catalyzed spiroketalization that now permits access to a C(1)–C(23) southern hemisphere that proceeds in 7% overall yield and provides more than 500 mg of the requisite southern hemisphere.

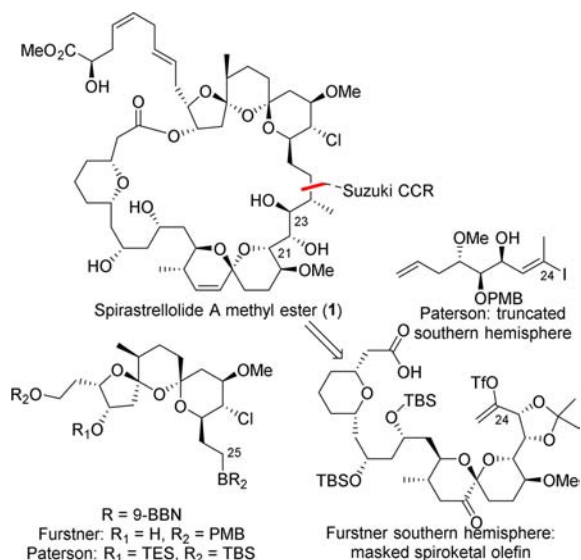
By analogy to the successful work of Paterson and Fürstner, we envisioned dividing spirastrellolide E into northern and southern hemispheres. In their approaches, Suzuki cross-coupling between a northern hemisphere sp^3 boronate and a southern hemisphere vinyl iodide⁵ or triflate^{7b} was employed to unite the hemispheres (Scheme 1). The earlier Suzuki coupling tactics suffer from subsequent chemoselectivity issues related to the unsaturated spiroketal olefin upon installation of oxygenation at C(23).

Successful syntheses of spirastrellolide congeners possessing this unsaturation have either masked the olefin⁶ or utilized a stepwise approach to construct the southern hemisphere.⁵ Given this lack of chemoselectivity, we elected to dissect spirastrellolide E at the C(23)–C(24) bond (Scheme 2), utilizing the C(22) hydroxyl as a directing group.

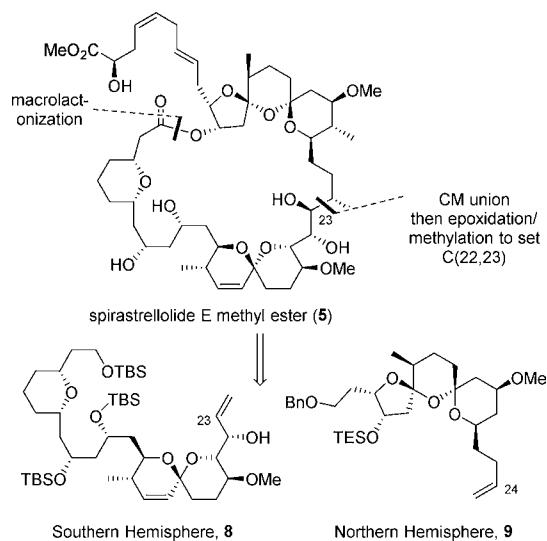
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Scheme 1. Previous Retrosyntheses of Spirastrellolide A



Scheme 2. Retrosynthesis of Spirastrellolide E



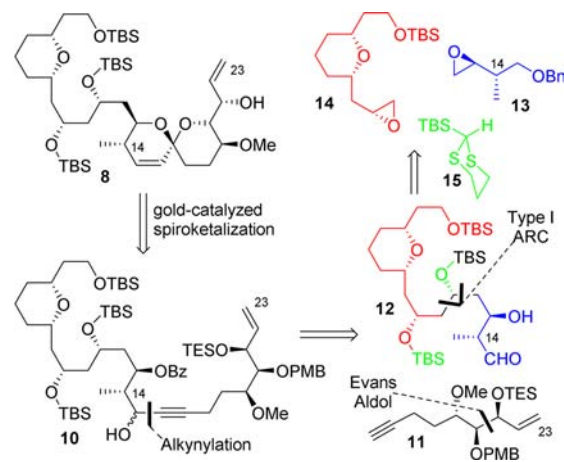
For our coupling tactic, we propose a cross-metathesis union tactic and a Sharpless epoxidation/epoxide methylation with both epoxidation and subsequent methylation controlled by the C(22) hydroxyl. With this route in mind, C(1)–C(23) southern hemisphere fragment **8** became our target.

Synthetic analysis of **8** is outlined in Scheme 3. Similar to our recently published approach to a C(1)–C(24) southern hemisphere,⁹ we chose to utilize a directed gold-catalyzed spiroketalization¹⁰ to build the unsaturated spiroketal core.

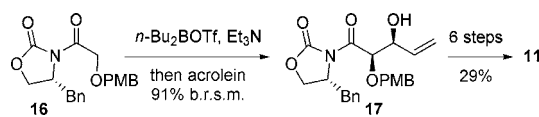
Alkynylation in the retro-sense was then envisioned to lead to a new alkyne fragment **11**, as well as aldehyde **12**, constructed previously exploiting Type I Anion Relay Chemistry.^{9,11} Requisite **11** would be prepared via an Evans glycolate aldol reaction now with acrolein to install the key *cis* stereochemistry of the diol (**17**, Scheme 4). Further manipulations of **17** were performed as previously described⁹ (see Supporting Information). Overall, the new alkyne synthesis proceeded in 22% yield, readily providing multigram amounts of **11** in one batch.

With **11** available, we turned to the alkynylation (Scheme 5), which proceeded smoothly to provide a mixture of propargylic

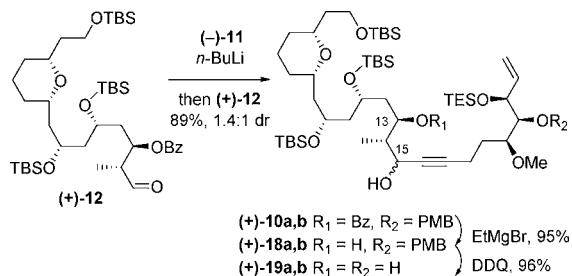
Scheme 3. Retrosynthetic Analysis of 8



Scheme 4. Synthesis of Alkyne 11



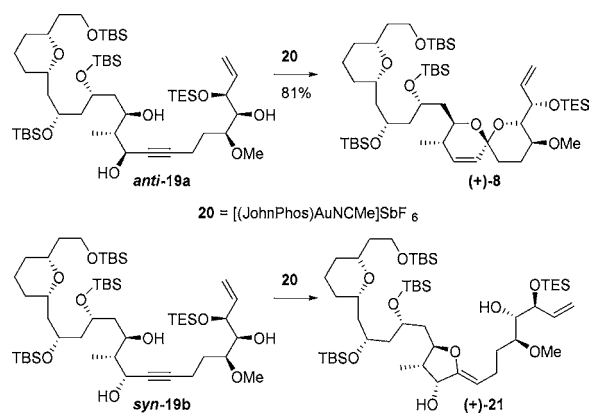
Scheme 5. Synthesis of Spiroketalization Precursors



carbinols *syn*-**10** and *anti*-**10** [note that *syn* and *anti* refer to the orientation of C(15) relative to the C(13) hydroxy]. The combined yield was 89%. Removal of the benzoyl and PMB groups then provided spiroketalization precursors *syn*-**19** and *anti*-**19**.

Treatment of *anti*-**19** with Echavarren's catalyst (**20**)¹² in dichloromethane led cleanly to the desired spiroketal (+)-**8** in 81% yield as a single isomer (Scheme 6), thus providing the desired C(1)–C(23) advanced southern hemisphere fragment.

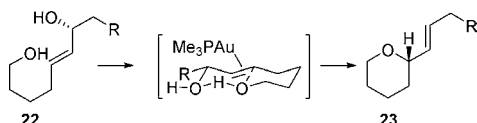
Scheme 6. Completion of the Southern Hemisphere



Treatment of *syn*-**19** under identical conditions led to a different product, which we now assign as (+)-**21**.⁹

Structural assignment of (+)-**21** required extensive 1-D and 2-D NMR studies (see Supporting Information). We envision that (+)-**21** arises from attack of the C(13) hydroxyl onto the C(16) terminus of the alkyne. Extension of a model originally developed by Aponick et al. for the cyclization of monoallylic diols¹³ permits the development of a rationale for the formation of the desired (+)-**8** and the undesired (+)-**21** and sets the stage for a full mechanistic study. In their model, **22** undergoes a gold-catalyzed cyclization to form **23** (Scheme 7). The proposed transition state

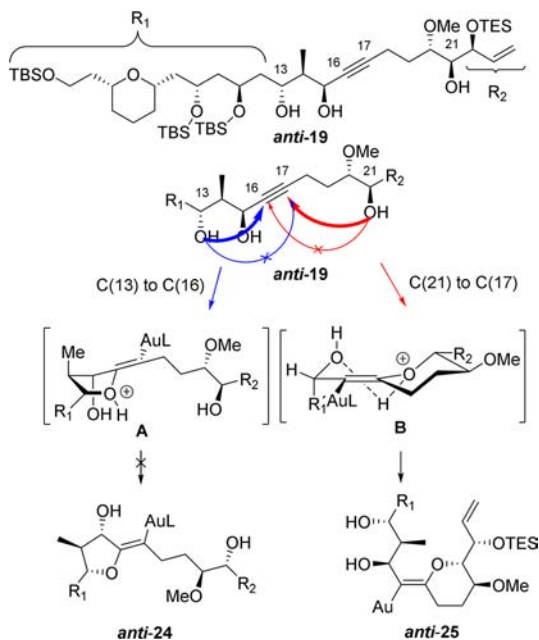
Scheme 7. Cyclization of Monoallylic Diols



entails initial attack of the pendant hydroxyl moiety onto the olefin featuring a hydrogen bond between the incoming nucleophile and the departing hydroxyl group; calculations reveal this transition state to be 5–10 kcal/mol more stable than transition states lacking a hydrogen bond.¹³

For acetylene **19**, each diastereomer could undergo attack of either the C(13) or C(21) hydroxyl. Both scenarios further present the possibility of attack at the C(16) or C(17) terminus of the alkyne. These scenarios are summarized for *anti*-**19** in Scheme 8. We postulate that a similar hydrogen bond between

Scheme 8. Possible Modes of Cyclization for *anti*-**19**



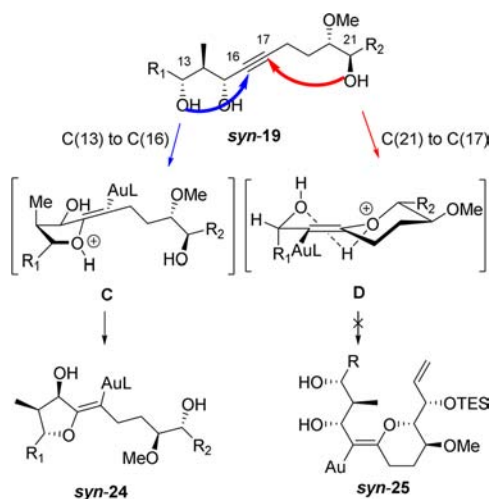
the incoming nucleophile and the propargylic hydroxyl is energetically favorable to transition states lacking such an interaction. The only transition state that possesses the key hydrogen bond in the proper orientation results from attack of C(21) onto C(17) (bold red arrow, Scheme 8). Attack of the C(13) hydroxyl onto the C(16) terminus of the alkyne (bold blue arrow, Scheme 8) is also possible.

As occurs experimentally for *syn*-**19**, attack of the C(21) alcohol onto the C(17) terminus in *anti*-**19** leads to transition

state **B**, which possesses a favorable hydrogen bond with all substituents in the equatorial position. Conversely, attack of the C(13) hydroxyl onto the C(16) terminus (transition state **A**) lacks this hydrogen bond. In addition, the C(14) methyl and C(15) hydroxyl groups in **A** are now in axial orientations, further disfavoring this mode of attack.

For *syn*-**19** (Scheme 9), C(21) hydroxyl attack at the C(17) terminus leads to transition state **D**. To maintain the favorable

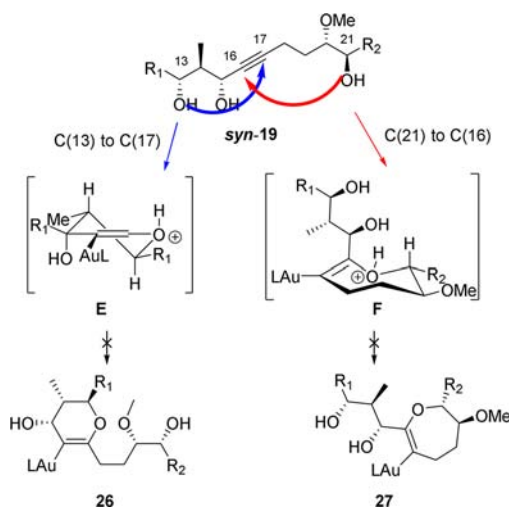
Scheme 9. Transition States for *syn*-**19**



hydrogen bond, either the R₁ or R₂ substituent would have to assume an axial orientation. Alternatively, attack of C(13) at the C(16) terminus (transition state **C**) leads to *syn*-**24**, which, after proto-deauration, provides the experimentally observed undesired product **21**.

To understand the preference of *syn*-**19** for **C** over other transition states lacking a hydrogen bond, we looked to possible alternatives (Scheme 10). Attack of C(13) at C(17) of the alkyne, a transition state corresponding to 6-*endo* attack, is disfavored relative to 5-*exo* attack for gold, as observed by De Brabander et al. in similar systems.¹⁴ Finally, the attack of C(21) onto C(16) comprising a 7-*endo* process (transition state **F**) has been shown by De Brabander to be competitive with 6-*exo* cyclization.¹⁴ While this transition state does not possess any

Scheme 10. Alternative Non-Hydrogen-Bonded Cyclization

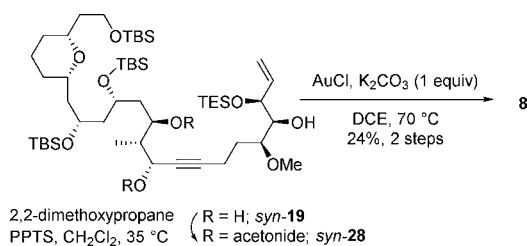


obvious steric interactions, we reason that there are two factors leading to a preference for 5-*exo* attack.

First, 7-*endo* attack is competitive with 6-*exo*; such a process is less likely to compete kinetically with five-membered ring formation. Second, formation of a seven-membered ring is clearly disfavored in this particular system, as evidenced by the fact that the [5,7]-spiroketal is not formed after initial cyclization to form *syn*-**24**, even after prolonged reaction times.¹⁵

The analysis presented above suggested that a strategy that overrides the substrate bias would be necessary to convert *syn*-**19** to (+)-**8**. To this end, we were drawn to a recent publication from the Aponick group,¹⁶ which reported the use of an acetonide to enhance the selectivity of the spiroketalization by ensuring that the C(21) hydroxyl attacks first. Conversion of *syn*-**19** to the corresponding acetonide (**28**, Scheme 11) followed by

Scheme 11. Conversion of *syn*-**19** to Southern Hemisphere **8**



cyclization indeed provided the desired (+)-**8** in 24% over two steps. With this observation, we are now able to convert both isomers of **19** to the desired spiroketal **8**.

In summary, we have achieved a second generation synthesis of the C(1)–C(23) southern fragment of spirastrellolide E, with a significantly improved overall yield of 7%. We have also identified, rationalized, and exploited the dependence of gold-catalyzed spiroketalization on the stereochemistry of directing carbinol. With streamlined routes to both hemispheres now rapidly nearing completion, efforts aimed at the total synthesis of spirastrellolide E continue in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectroscopic and analytical 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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