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Spirastrellolide E: Synthesis of an advanced C(1)-C(24) southern hemisphere

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Abstract

The synthesis of a C(1)-C(24) advanced southern hemisphere fragment towards the total synthesis of spirastrellolide E has been achieved. Highlights of the route include a highly convergent Type I Anion Relay Chemistry (ARC) tactic for fragment assembly, in conjunction with a directed, regioselective gold-catalyzed alkyne functionalization to generate the central unsaturated [6,6]-spiroketal.

Keywords

Spirastrellolide; Anion Relay Chemistry; Brook Rearrangement; Gold Catalysis; Total Synthesis

In 2003 Anderson and colleagues reported the isolation, partial structural determination, and disclosure that spirastrellolide A (**1**; Figure 1) was a selective (1 nM) and extremely potent inhibitor of phosphotase 2A.[1] The complete connectivity of **1**, however, was not established until 2004,[2] with the stereochemical relationship and absolute configuration of the core remaining unknown until the 2007 isolation and X-ray characterization of the closely related spirastrellolide B (**2**; Figure 1).[3] Later that year, the complete stereostructure of **1–7**, including absolute configuration, was established *via* chemical degradation of spirastrellolide D (**4**).[4]

The combination of structural complexity, biological activity, and, at the outset, unknown relative stereochemistry led to considerable interest in the synthetic community,[5–27] culminating in the first total synthesis of spirastrellolide A (2008) by the Paterson[28–31] group, and the total syntheses of spirastrellolide F (2009, 2011)[32–34] and later A (2013),[35] both by Furstner and colleagues.

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Supplementary Material

Experimental procedures and characterization of new compounds, as well as detailed NMR analysis of compound **19** can be found in the online version of this paper.

Our interest in the spirastrellolides began in 2007, resulting early on in completed approaches to advanced fragments for a southern hemisphere relevant to spirastrellolide A and B[22,23] and a northern hemisphere relevant to B and E.[26] With these routes established, we considered a total synthesis venture; however it quickly became apparent that our first generation southern hemisphere synthesis, totaling 33 steps for the longest linear sequence, was not amenable to advancing ample material for a successful synthetic campaign. We therefore set out to design a second-generation route. Herein, we report the result of that effort, which has now led to a significantly improved approach to a related southern hemisphere congener for spirastrellolide E, featuring both a decrease in the longest linear step count and an increase in the overall yield.

Our initial 2007 spirastrellolide venture highlighted the use of Type II Anion Relay Chemistry (ARC)[36] to construct advanced spirastrellolide A southern hemisphere intermediate **11** from fragments **8**–**10** (Scheme 1). Unfortunately, this approach precluded installation of the C(14) methyl group until after spiroketalization, a tactic requiring three steps. Moreover, when attempting to install the C(23)-C(25) fragment **15**, the undesired stereoisomer predominated, which required an oxidation/reduction/reprotection sequence.

To address these shortcomings, we present here a second-generation synthetic analysis, now aimed at spirastrellolide E (Scheme 2). As a new subtarget, we selected C(1)-C(24) fragment **19** (Scheme 2A), guided by the observations of both the Patterson and Furstner groups that union with northern hemispheres might best be accomplished at C(24).[8,20,21] A key strategic consideration in our second generation analysis was to alter the bonds forged by the ARC protocol, thus permitting incorporation of the C14 methyl group as part of an appropriately designed epoxide (**24**). Thus, the revised strategy clearly showcases the flexibility inherent in the ARC tactic.

Moreover, inspired by our recent northern hemisphere synthesis,[26] we envisioned access to the southern hemisphere [6,6]-spiroketal *via* a gold-catalysed cyclization. However, given the difficulties often encountered with control of regioselectivity in gold-catalyzed spiroketalizations, we chose to exploit the method of Aponick and co-workers,[37] which employs a substrate propargylic carbinol to direct the site of ring closure, *via* an intermediate allene (Scheme 2B).

With this scenario in mind, the southern hemisphere **19** would arise from an appropriately functionalized propargylic triol **20**. Inclusion of a carbinol directing group conveniently revealed an aldehyde alkynylation retron, simplifying construction of **20** to two fragments: alkyne **21** and aldehyde **22**. Alkyne **21**, in turn, would be constructed in 8 steps using a strategy adapted from the Patterson spirastrellolide A synthesis,[30] while aldehyde **22** appeared as an ideal substrate for Type I Anion Relay Chemistry,[36] employing TES-dithiane **23** with epoxides **24**[38] and **25**.[39]

Our initial approach to aldehyde **22** is outlined in Scheme 3. Treatment of TES-dithiane **23** with *n*-butyllithium, followed by addition of epoxide (−)-**24** in a mixture of tetrahydrofuran (THF) and ether (3:1), and in turn a solvent-mediated Brook rearrangement of the intermediate lithium alkoxide, triggered by the addition of hexamethylphosphramide

(HMPA) in the presence of epoxide (−)-**25**, smoothly furnished the three component adduct (+)-**26** in 60–70% yield.

With the ARC product (+)-**26** in hand, we turned to dithiane removal, which proved to be non-trivial. A wide range of conditions (c*f*. the Stork reagent,[40] mercury salts, NCS/$AgNO_3$, [41] iodine/sodium bicarbonate,[42] methyl iodide[43]) led either to poor or inconsistent results. Eventually we discovered that a combination of NBS, silver perchlorate, and 2,6-lutidine[41,44] furnished a reliable and reproducible yield of 70–80% of the desired ketone (+)-**27**.

Having established conditions for dithiane removal, we next performed a stereocontrolled *anti*-reduction of the derived hydroxyketone to form the desired *anti* diol in 70% yield as the only observed diastereomer (Scheme 3). At this stage, all that remained was a series of functional group manipulations to arrive at the aldehyde fragment; this however also proved non-trivial. Attempted protection of the diol as a bis-TBS ether resulted in partial migration of the C(13) TES group in **27**. Unfortunately, the resulting products proved inseparable by column chromatography. Switching to bis-MOM protection (*i.e.* **29**) alleviated this problem, albeit the MOM protecting group was deemed not ideal from the point of view of a total synthesis, given the harsh conditions typically required for removal. Notwithstanding these issues, we continued with the synthesis to validate several critical late stage transformations. Removal of the benzyl group and oxidation to aldehyde **(−)-22** again proved troublesome due to TES migration and partial deprotection. Nonetheless, the stage was set to attempt the union *via* alkynylation.

Two observations proved important. First, at this stage of our spirastrellolide synthetic venture, the required configuration of the C(15) propargylic hydroxyl was unknown. Second, a number of groups had reported a strong stereochemical dependence of the propargylic stereogenic center on spiroketalizations.[37,45] We therefore decided to initially pursue a non-selective alkynylation, separate the diastereomers, and then subject each to gold catalysis (Scheme 4). To this end, treatment of alkyne (−)-**21**[46] with lithium diisopropylamide (LDA) in THF followed by addition of aldehyde (−)-**22** in THF, furnished a diastereomeric mixture of propargylic alcohols [(+)-**30a** and (+)-**30b** (1.7:1)] in a combined yield of 75%. Pleasingly, the diastereomers proved readily separable via routine flash column chromatography. Each isomer in turn was subjected to PMB removal to furnish the spiroketalization precursors (+)-**31a** and (+)-**31b**.

It quickly became evident that our originally designed spirocyclization substrates were not optimal. We had anticipated that spiroketalization conditions could be found that would permit simultaneous removal of both the C(13) TES group, a prerequisite for spiroketalization, as well as removal of the C(22) TES group, a requirement for a planned Suzuki union of the Northern and Southern hemispheres. In practice, however, the required use of methanol as either a solvent or cosolvent for the spiroketalization, along with a mild acid, lead to slow decomposition of the substrate. Only traces of spiroketals were observed under a variety of conditions.

Undaunted, we examined a differentially protected construct, in which the two alcohols required for spiroketalization could be revealed selectively without affecting the C(22) TES group. Such a scenario would greatly facilitate optimization of the key cyclization tactic. This approach would also permit replacement of the C(13) TES group, which had earlier led to significant difficulties due to its lability.

The revised strategy is illustrated in Scheme 5. Here we target differentially protected spiroketalization precursor **32**. Importantly, the requisite advanced ARC adduct (**35**, Scheme 6) could be accessed *employing the same components as the previous route*, by merely changing the order of addition of the two epoxides, again demonstrating the flexibility of Anion Relay Chemistry.

Implementation of the revised strategy is outlined is Scheme 6. Pleasingly, the ARC union proceeded smoothly with the inverted order of addition to furnish three component adduct (+)-**35** in 68% yield. Dithiane hydrolysis as before then led to (+)-**36**.

With (+)-**36** in hand, we now required a tactic to reduce the C(11) ketone with concomitant differential protection of the resulting diol. This requirement was conveniently achieved by exploiting the Evans-Tishchenko reaction[47] with benzaldehyde, followed in turn by TBS protection of the remaining hydroxyl, removal of the benzyl group, and oxidation of the resultant hydroxyl[48] to furnish aldehyde (+)-**33**. Notably, yields for the TES-free synthetic route were uniformly excellent. Alkynylation exploiting the previously established protocol then furnished a mixture of diastereomeric alcohols (+)-**32a** and (+)-32**b** (1.4:1) in 85% combined yield, which again could be readily separated and subjected to a two stage deprotection to remove the benzoyl and PMB groups to furnish spiroketalization precursors (+)-**38a** and (+)-**38b**. At this stage, we were also able to confirm the configurations of the C(15) hydroxyl group in **32a** and **32b** by conversion of **38a** to the bisacetonide, with concomitant removal of the C(22) TES ether. The relative stereochemistry of the resulting bisacetal was determined by NMR, utilizing the method of Rychnovsky.[49]

With the differentially protected adducts **38a** and **38b** in hand, we turned to the critical spiroketalization (Scheme 7). Treatment of the *cis* isomer (+)-**38a** with cationic gold catalyst **39**, first prepared by Echavarren,[50] employing methylene chloride as the solvent proceeded smoothly to furnished the desired spiroketal (**19**). The stereostructure of the spiroketal was assigned by extensive 2D NMR analysis.[51] Particularly important was observation of an nOe between the hydrogens on C(13) and C(21), which provided evidence both for the expected double carbinol addition to the alkyne, as well as the stereochemistry at the ketal center. A similar nOe was observed in a related system by Paterson.[19] We were thus confident that the spiroketalization had proceeded as predicted, thereby signaling completion of the C(1)-C(24) southern hemisphere fragment for a prospective total synthesis of spirastrellolide E (**5**).

The *anti* isomer (+)-**38b** however did not lead to the anticipated spiroketalization product under otherwise identical conditions. Structural determination of the observed product, along with the development of a rationale for the stereochemical dependence on reaction efficiency, is currently under investigation.

In summary, we have achieved a significantly improved second generation synthesis of a spirastrellolide E C(1)-C(24) southern fragment, now involving a longest linear sequence of 19 steps and an overall yield of 2%. With streamlined routes to both hemispheres now available, efforts turned to the total synthesis of spirastrellolide E, which will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This Tetrahedron Letters is presented to honor and remember Professor Harry Wasserman (Yale University), great friend, true gentleman, and scientist par excellence: Harry, thank you for everything.

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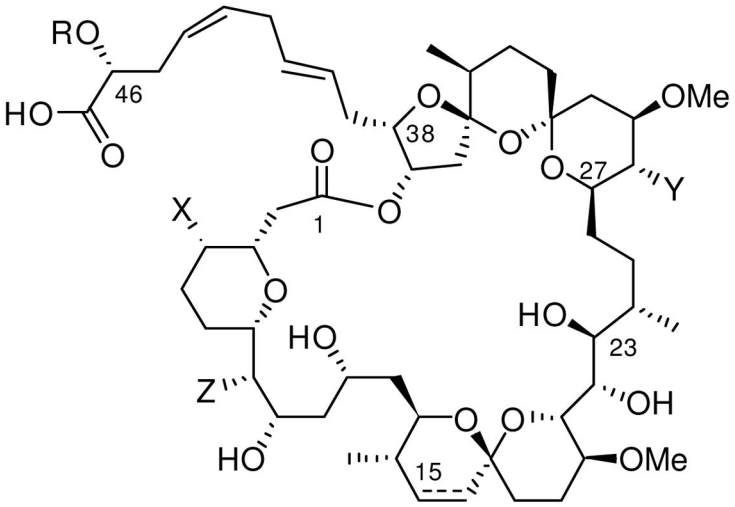
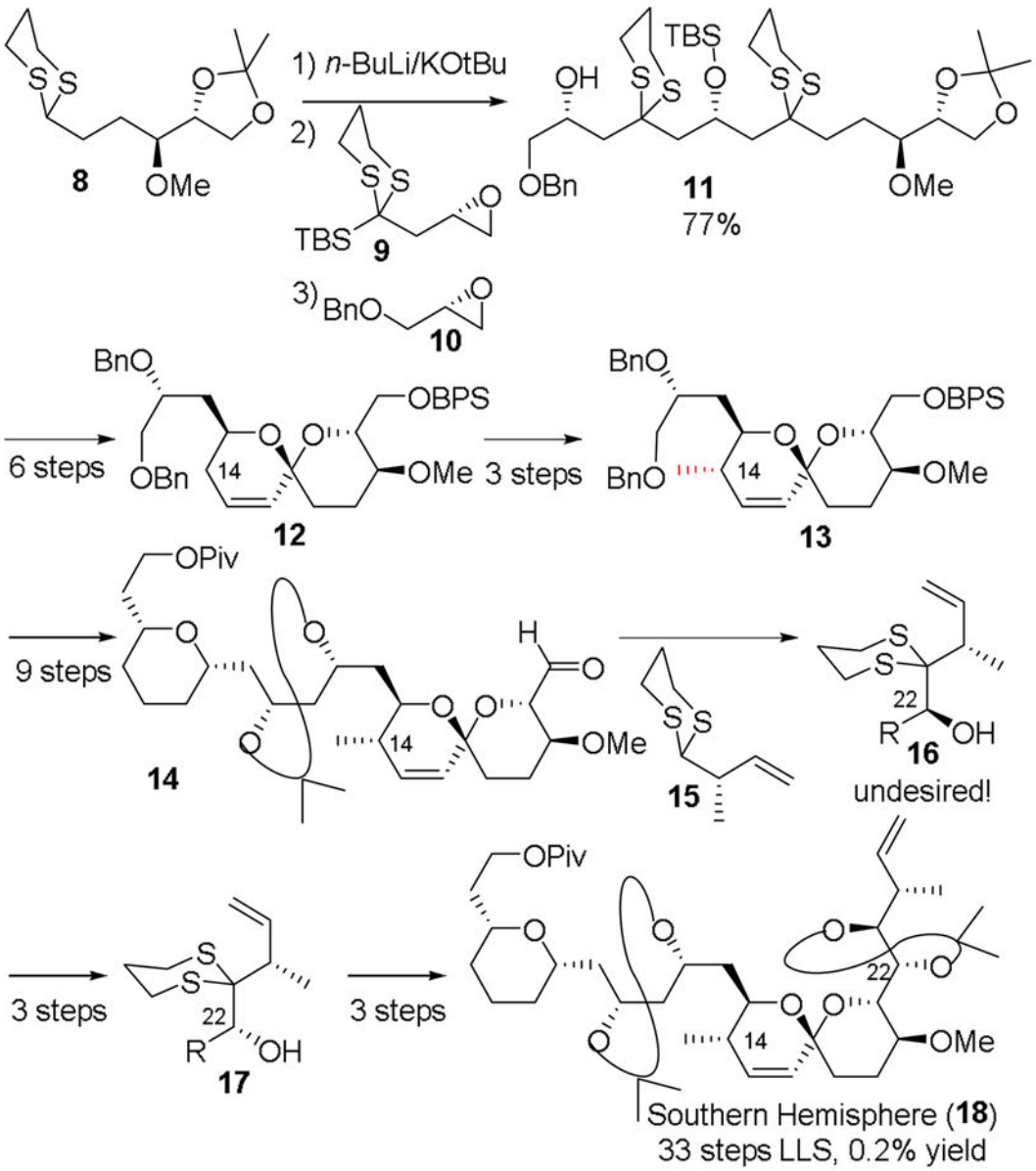


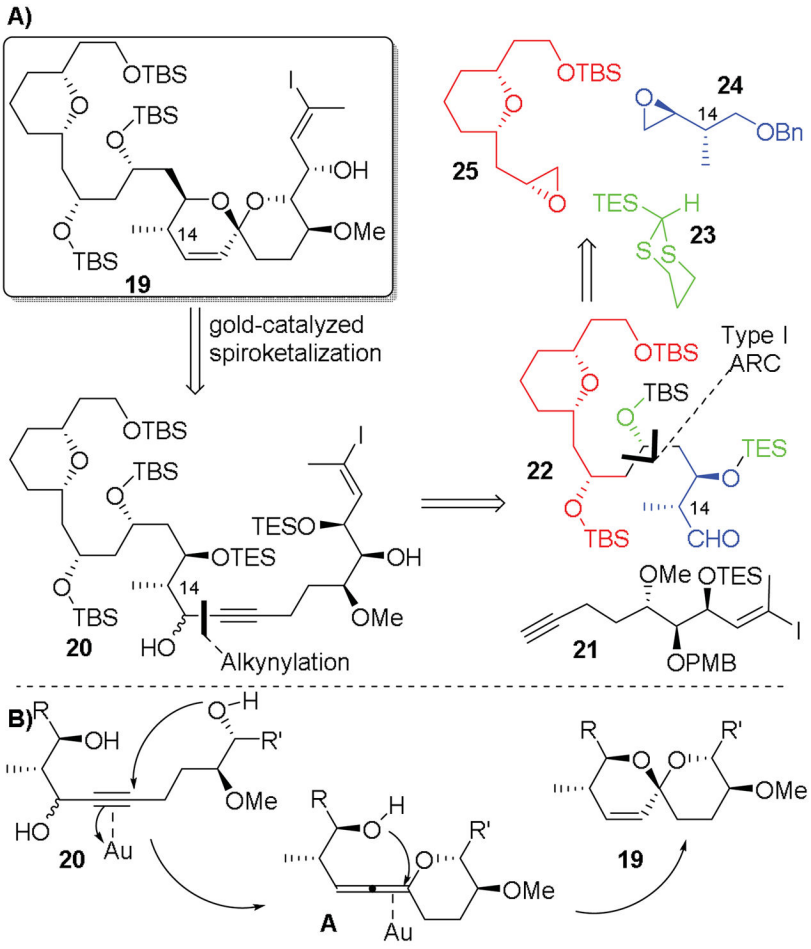
Spirastrellolide A (**1**): R=X=Z=H, Y=Cl, $\Delta^{16,16}$
Spirastrellolide B (**2**): R=X=Y=Z=H
Spirastrellolide C (**3**): R=X=Y=H, Z=OH
Spirastrellolide D (**4**): R=Z=H, X=Y=Cl, $\Delta^{15,16}$
Spirastrellolide E (**5**): R=X=Y=Z=H, $\Delta^{15,16}$
Spirastrellolide F (**6**): R=X=Z=H, Y=Cl
Spirastrellolide G (**7**): X=Z=H, R=Me, Y=Cl, $\Delta^{15,16}$

Figure 1.
The spirastrellolides A-G

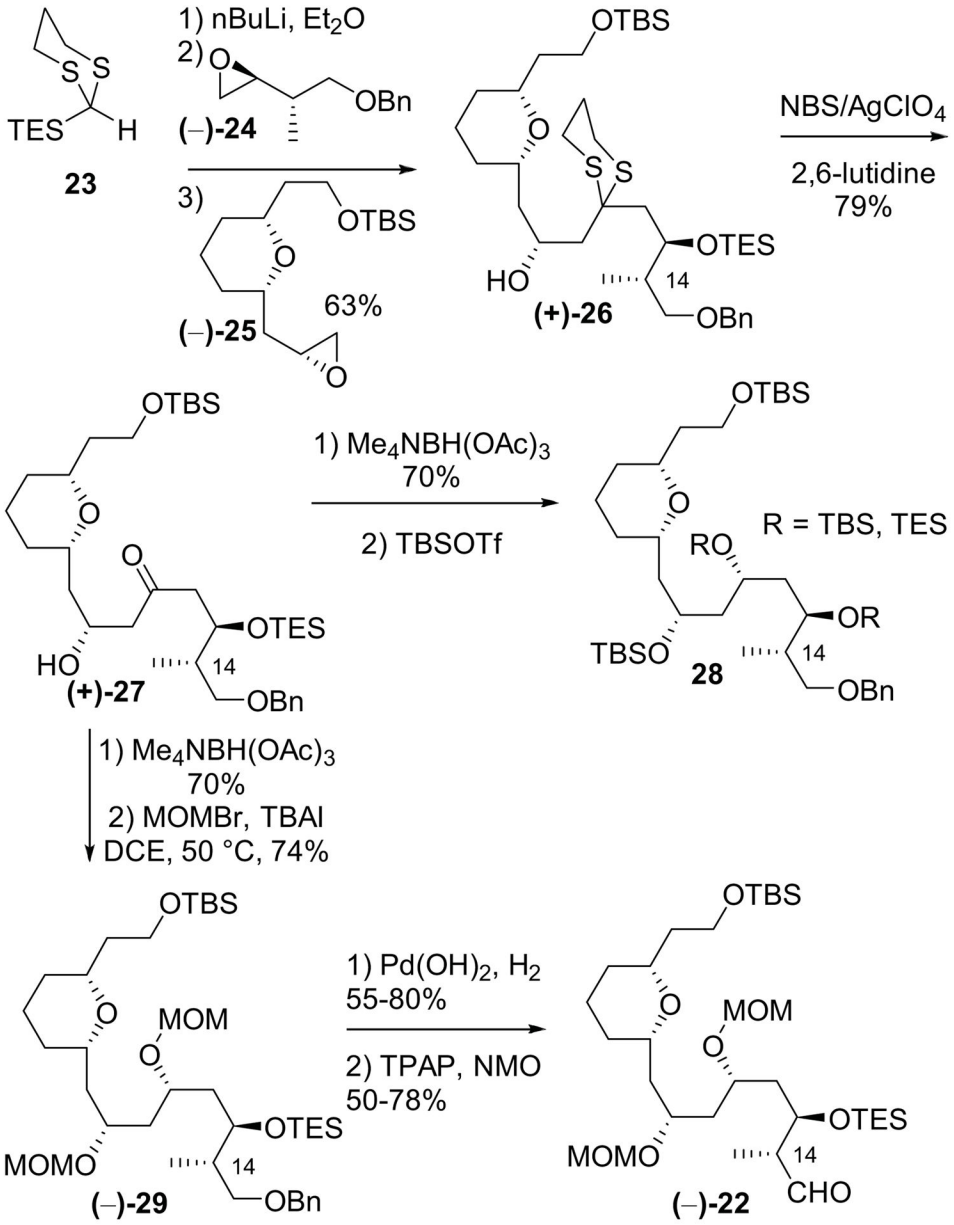


Scheme 1.

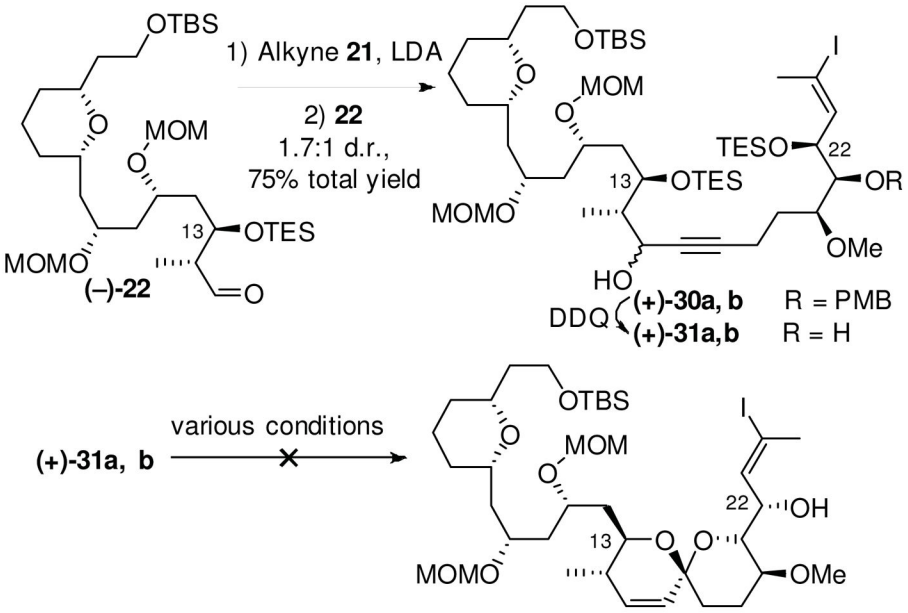
First-generation analysis of the C(1)-C(26) fragment of the spirastrellolides.



Scheme 2.
Retrosynthetic Analysis.

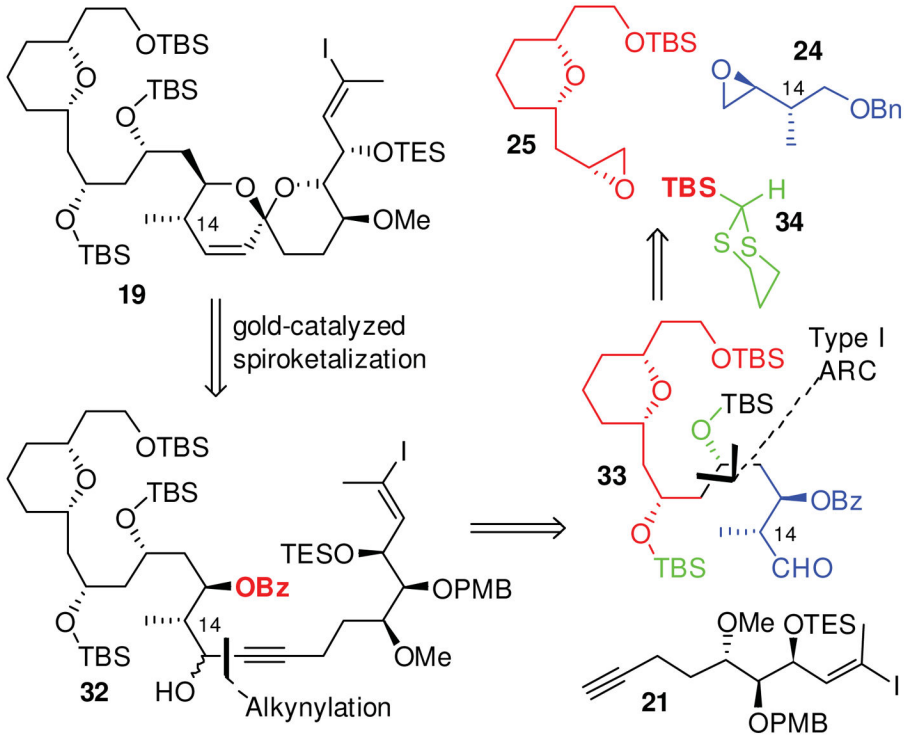


Scheme 3.
Synthesis of aldehyde **22**.

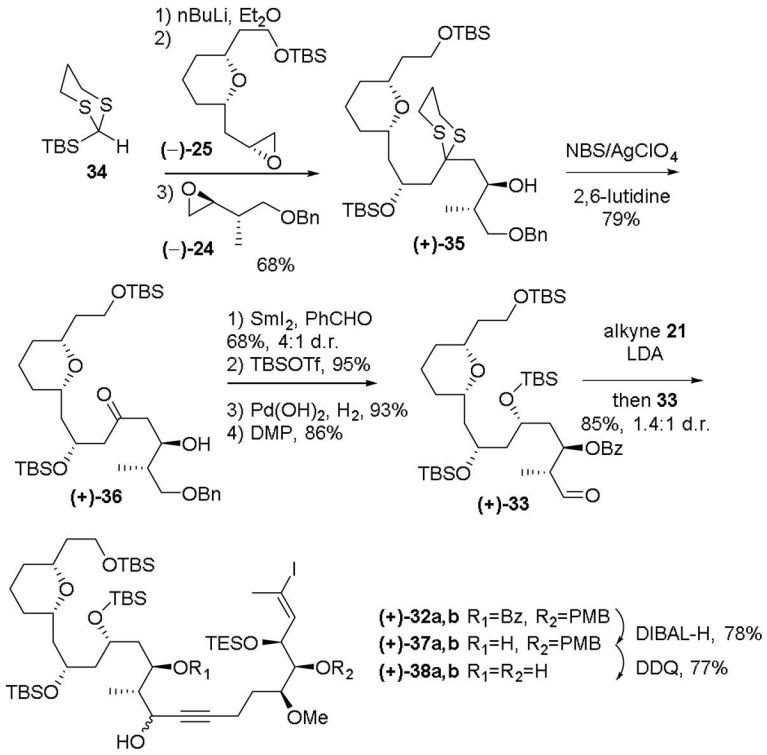


Scheme 4.

First attempts at southern hemisphere end game.

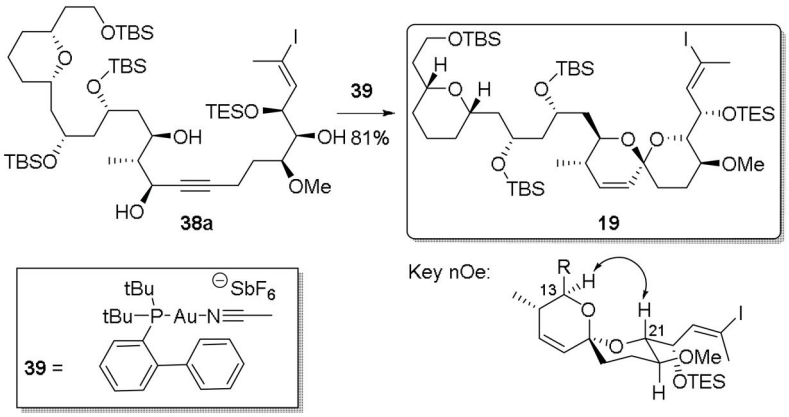


Scheme 5.
Revised retrosynthesis



Scheme 6.

Implementation of the revised retrosynthetic analysis.



Scheme 7.
Completion of the southern hemisphere.