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Synthesis of the Spirastrellolide A Trioxadispiroketal

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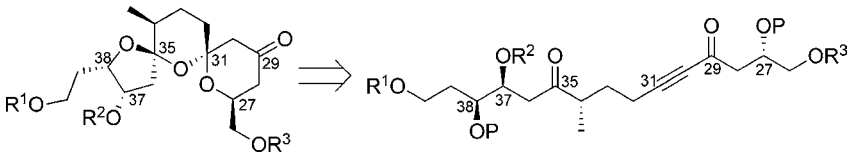
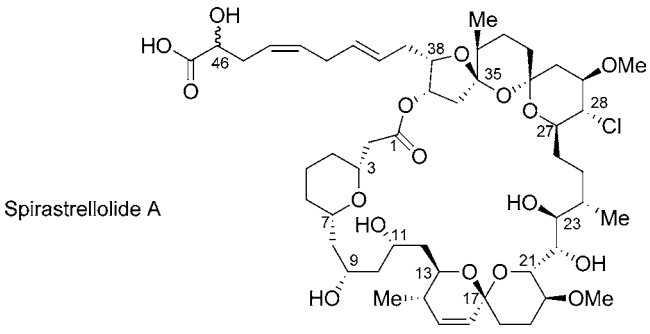
ABSTRACT



The core trioxadispiroketal system representing C26–C40 of spirastrellolide A was assembled using a sequenced double-intramolecular hetero-Michael addition process.

Spirastrellolide A (Figure 1) is a polyketide isolated from extracts of the Caribbean sponge *Spirastrella coccinea*.[1] This



Spirastrellolide A

Figure 1. Two possible diastereomers of spirastrellolide A.

natural product inhibits protein phosphatases 1 and 2A with IC_{50} values of 50 and 1 nM, respectively. The activities of spirastrellolide A[1b] are similar to those of known protein phosphatase inhibitors, including okadaic acid[2] and fostriecin,[3] which induce premature entry into mitosis and mitotic arrest. The methyl ester of spirastrellolide A also exhibited potent tubulin-independent activity in a cell-based antimitotic assay.[1a] As a structurally novel entrant to the okadaic acid class of phosphatase inhibitors,[4] spirastrellolide A and its derivatives may have therapeutic potential.

The complete stereochemistry of spirastrellolide A is undefined, but the relative configurations of three separate portions were reported.[1b] Several individual fragments have also been synthesized.[5] We were initially interested in exploring the double-intramolecular hetero-Michael addition (DIHMA) process[6] for the synthesis of spirastrellolide A's trioxadispiroketal domain **1** (Scheme 1).[7] This would represent an extension of this synthetic methodology following its success in generating the azaspiracid trioxadispiroketal domain.[8]

Trioxadispiroketal **1** (Scheme 1) was targeted in an arbitrary absolute configuration. Establishment of both C31

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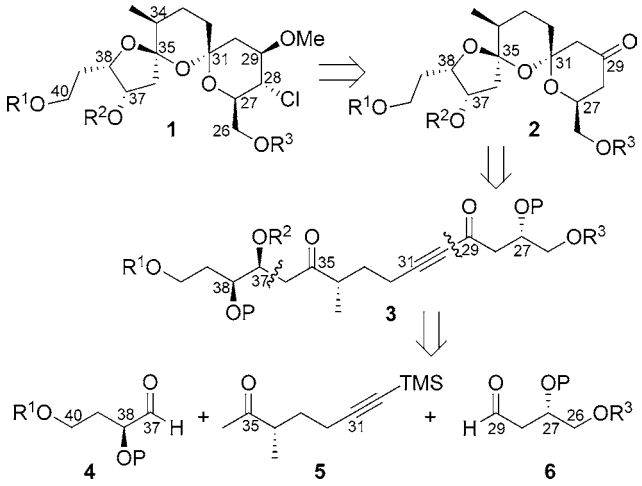
Scheme 1

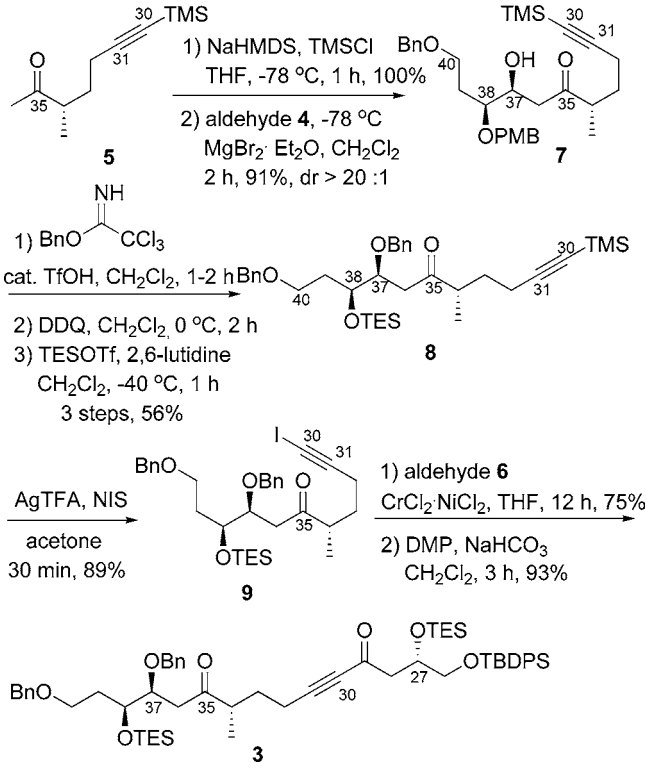


and C35 spiroketals in **1** under thermodynamic control was expected to deliver the natural product's configurational and conformational array due to double-anomeric stablization[9] and the predominant equatorial orientation of its appendages. Further, the C28 chlorine would be installed at a late stage onto the assembled trioxadispiroketal **2** by selective α-keto chlorination. Bis-spiroketal **2** would arise from linear ynone **3** via a DIHMA process.[6] Ynone **3**, in turn, would be derived from the C37−C40 aldehyde **4**, C30−C36 methyl ketone **5**, and the C26−C29 aldehyde **6**. These units could be combined sequentially to construct the linear ynone **3** by Mukaiyama aldol[10] and NHK[11] coupling reactions.

The synthesis began with ketone **5** (Scheme 2).[12] Kinetic enolization followed by trapping with TMSCl provided the corresponding silyl enol ether. This was coupled with the L-malic acid-derived aldehyde **4** by a chelation-controlled Mukaiyama aldol reaction[10] to yield **7**. This was originally protected as a TBS ether; however, the silyloxy group underwent β-elimination at later stages. Therefore, benzyl ether formation led to **8** with subsequent manipulations. Silver trifluoroacetate and *N*-iodosuccinimide were applied to convert alkyne **8** into iodide **9**.[13] NHK coupling[11] of **9** with L-malic acid-derived aldehyde **6** gave a propargylic alcohol that was oxidized to ynone **3**.

Our initial intent was to liberate the C27 and C38 hydroxyls from **3** under acidic conditions, whereupon bis-conjugate addition might ensue to form the trioxadispiroketal. This would involve successive 6-*exo* and 6-*endo* ring closures of the C35 hemiketal and C27 hydroxyls, respectively, upon the C29−C31 Michael acceptor.[6] However, all attempts to

Scheme 2[a]

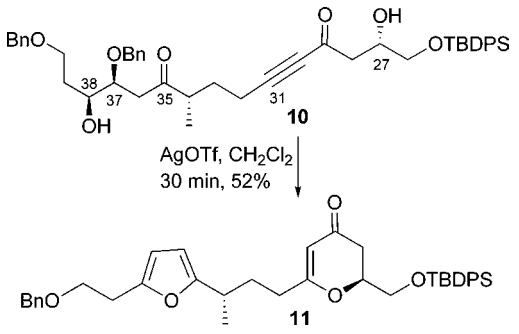


[a] DMP = Dess−Martin periodinane.

cyclize derivatives of **3** under acidic reaction conditions resulted in β-elimination of the C37 oxygen functionalities. Various Brönsted and Lewis acids were examined with different hydroxyl protecting groups at the C27 and C37 alcohols. A benzyl ether at C37 seemed to be the least labile toward elimination.

It was apparent that the rates of elimination needed to be suppressed, while the rates of conjugate addition needed to be enhanced, to accomplish the desired trioxadispiroketal formation with this type of labile substrate. Accordingly, the C27 and C38 hydroxyls were liberated from **3** at low temperature, and the resultant acid labile diol **10** was subjected to alkyne activation using various metal salts. Several silver, copper, mercury, and palladium salts were

Scheme 3



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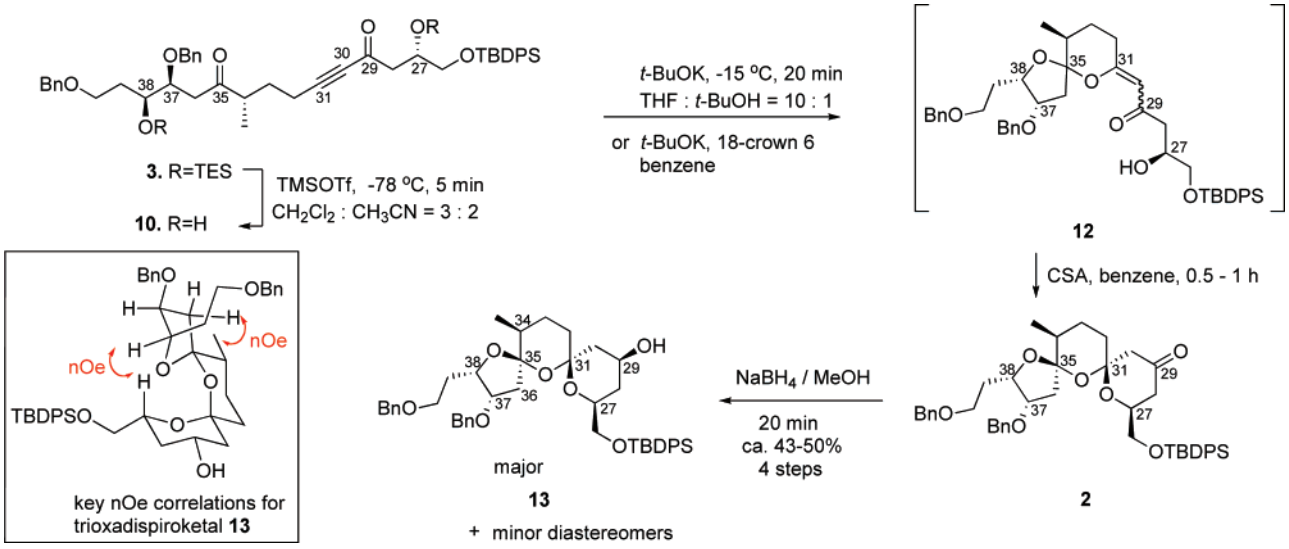
Scheme 4



surveyed, and the results were mixed. Either a single hetero-Michael addition was accompanied by β-elimination (Scheme 3) and furan formation (**11**), or no reaction occurred at all.

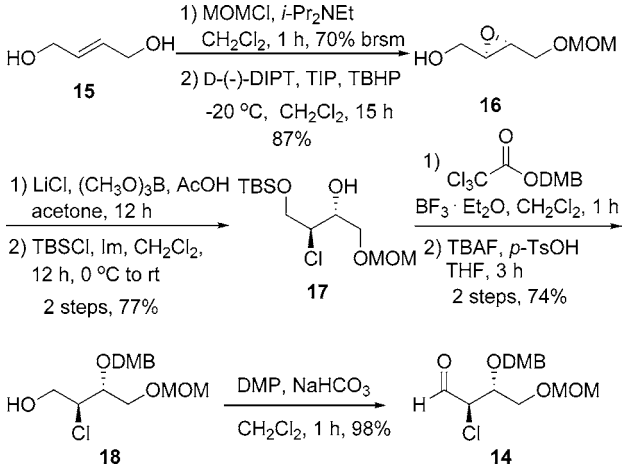
Next, basic reaction conditions were examined to cyclize diol **10** (Scheme 4). Upon treatment of **10** with potassium *tert*-butoxide, the C38−35 hemiketal conjugatively added to the C29−C31 ynone to form spiroketal **12**. This occurred without elimination of either C27 or C37 oxygen substituents. Efficient formation of the second spiroketal required acidic reaction conditions. Hence, treatment of enone **12** with CSA in benzene afforded bis-spiroketal **2**. It was presumed that the thermodynamically favored spiroketal configurations at C31 and C35 emerged from the sequenced base- and acid-induced assembly of the trioxadispiroketal **2**. Purification of ketone **2** was challenging due to its instability on silica gel. A retro-hetero-Michael reaction occurred during chromatography. As a remedy, crude ketone **2** was simply reduced to alcohol **13**, which could be isolated in moderate overall yield. As anticipated, NOE studies confirmed the configurations and conformation of trioxadispiroketal **13** which reflected the thermodynamically favored array, including double anomeric stabilization at C31 and C35.

Because tricyclic ketone **2** proved to be unstable, the original plan to install the C28 chlorine α to the ketone after trioxadispiroketal formation was revised. Instead, an early installation of the chlorine was investigated.

This revision was simple to initiate, as it required only a C26−C29 α-chloro aldehyde **14** instead of the original **6**.

The synthesis of aldehyde **14** commenced with *trans*-2-butene-1,4-diol (**15**). Monoprotection followed by Sharpless asymmetric epoxidation[14] afforded epoxide **16** (Scheme 5). Chloride opening of trimethyl borate-chelated epoxy alcohol **16** yielded the anticipated chlorohydrin in >20:1 regioselectivity.[15] Simple protecting group manipulations followed by mild Dess−Martin periodinane oxidation then gave the desired α-chloro aldehyde **14**. A dimethoxybenzyl group was strategically installed at the C27 hydroxyl to facilitate subsequent selective removal.[16]

Scheme 5[a]



[a] DMB = 3,4-dimethoxybenzyl.

The previously successful NHK coupling between aldehyde **6** and iodoalkyne **9** (Scheme 2) became problematic with α-chloro aldehyde **14**. Only trace amounts of the desired coupling product were observed, whereas dechlorinated **14** was returned as the major product. This reaction[17] could not be avoided after several attempts at optimization. Thus, the corresponding lithium acetylide derivative was employed. Alkyne **7** was desilylated and then converted into alcohol

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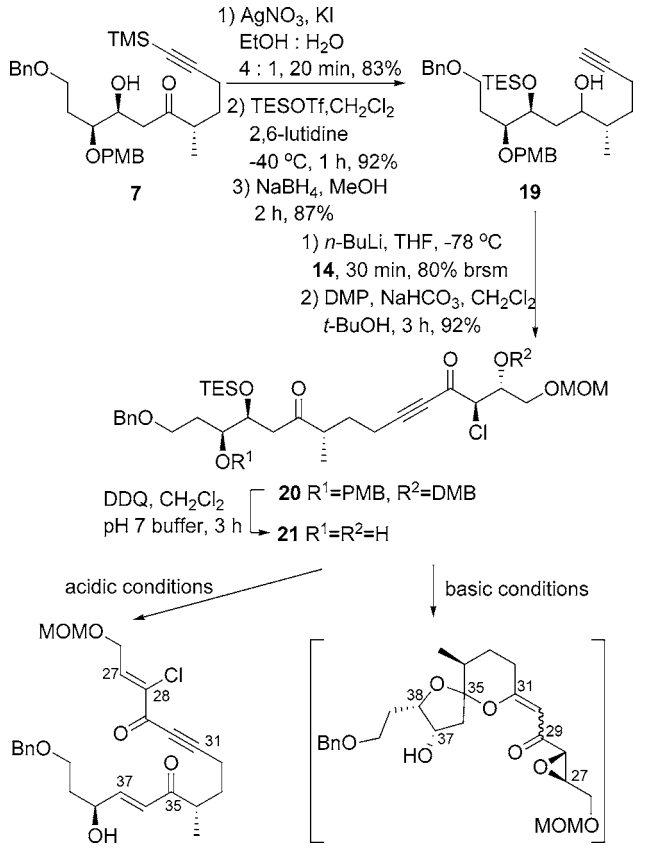
Scheme 6



19 in a stepwise process (Scheme 6). Treatment of **19** with *n*-BuLi generated the alkoxide/acetylide dianion. This was added to aldehyde **14** to give a diol that was then oxidized to ketone **20**.

Removal of the C27 and C37 hydroxyl protecting groups from **20** gave chlorohydrin diol **21** (Scheme 6). Submission of **21** to acidic or basic reaction conditions in attempts to induce spirocyclizations did not lead to the desired trioxadispiroketal. Under basic reaction conditions, **21** gave a C31−C38 spiroketal, analogous to that formed from **10** under similar conditions (Scheme 4), but with concomitant conversion of vicinal C27,28 chlorohydrin into the corresponding epoxide. In contrast, the use of acidic conditions or metal salts to induce trioxadispiroketal formation led to elimination products while retaining the chlorine atom. Thus, we have yet to define conditions that allow efficient incorporation of the vicinal C28,29 chloromethoxy functionalization into the intact trioxadispiroketal system of spirastrellolide A via the sequenced DIHMA process. To date, these approaches seem best suited for the generation of des-chloro analogues of spirastrellolide A.

In summary, a sequential conjugate addition cascade assembly of the spirastrellolide A trioxadispiroketal moiety has been developed, but incorporation of the C28 chloride was problematic. This approach is readily amenable to the synthesis of either enantiomer of the spirastrellolide A C26−C40 domain, which may accommodate either absolute configurational assignment. Extension of this synthetic entry to the generation of spirastrellolide analogues and evaluation of their biological activities are ongoing.

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

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