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The Spirastrellolides: Construction of the Southern C(1)–C(25) Fragment Exploiting Anion Relay Chemistry

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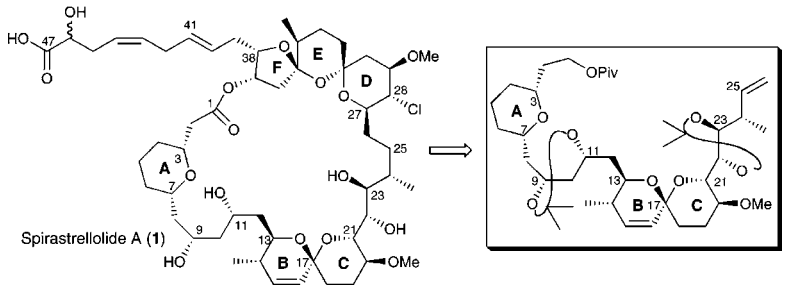
ABSTRACT



Effective construction of the southern C(1)–C(25) fragment of spirastrellolide A has been achieved. Central to this venture was the use of four dithiane unions, including the highly effective deployment of the anion relay chemistry (ARC) tactic recently introduced by our laboratory.

Spirastrellolides A and B (**1** and **2**), two unique polyketide natural products, isolated from the sponge *Spirastrella coccinea* endemic to the Caribbean, were disclosed by Andersen and co-workers in 2003 and 2007, respectively (Figure 1).[1] The relative configurations of the three major segments of **1** (C3−C7, C9−C24, and C27−C38) were elucidated via extensive NMR studies of the methyl ester.[1b] Later, the stereochemical relationships between the segments and the absolute configuration of the macrolide core were assigned via X-ray diffraction of a crystalline derivative of **2**.[1c] The absolute configuration at C(46), however, remains unknown. Spirastrellolide A acts as a potent selective inhibitor of protein phosphatase PP2A (IC_{50} = 1 nM for PP2A and 50 nM for PP1), resulting in premature cell entry into mitosis and thereby mitotic arrest.[1a,b] The challenging architecture, in conjunction with the novel biological profile of **1**, has attracted considerable attention.[2] Herein we disclose an effective construction of the C(1)−C(25) southern fragment (**3**) of spirastrellolide A.

From the retrosynthetic perspective, disconnection of **1** at the macrocyclic lactone, the C(25)−C(26) bond, and C(40)−C(41) trans double bond yields three advanced subtargets: ABC ring fragment **3**; DEF ring fragment **4**; and side chain **5** (Figure 1). Further disconnection of **3** at the C(9)−C(10) and C(22)−C(23) bonds reveals A-ring dithiane **6**, BC spiroketal **7**, and known dithiane **8**.[3] The BC spiroketal **7** in

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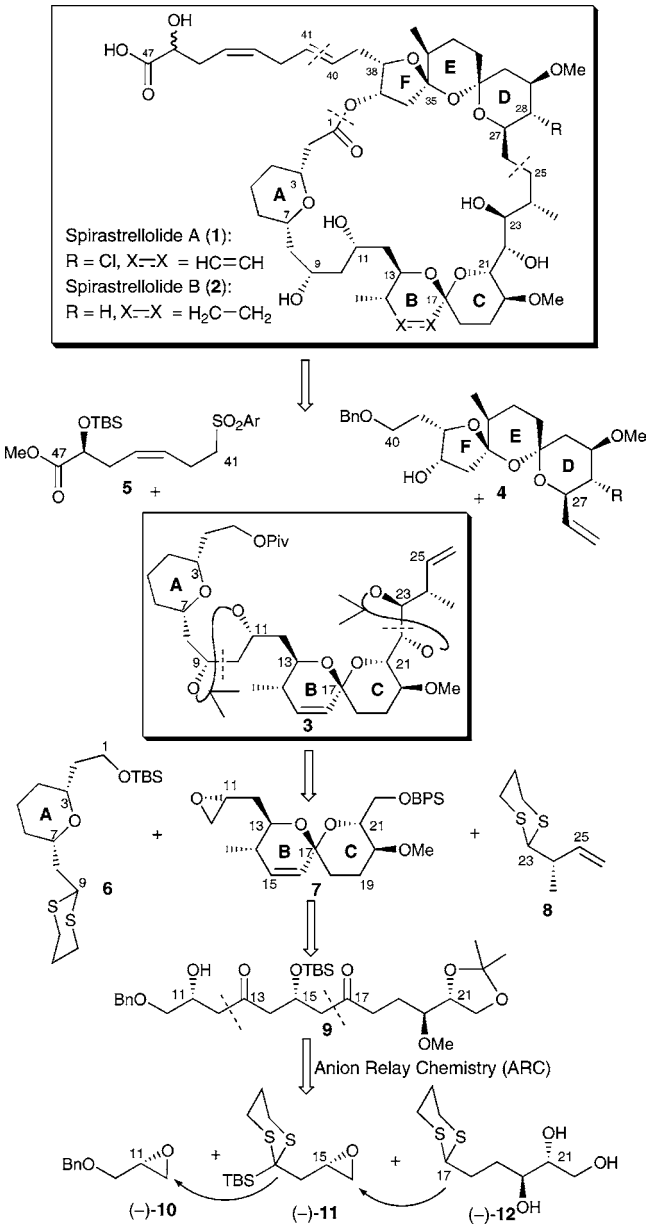
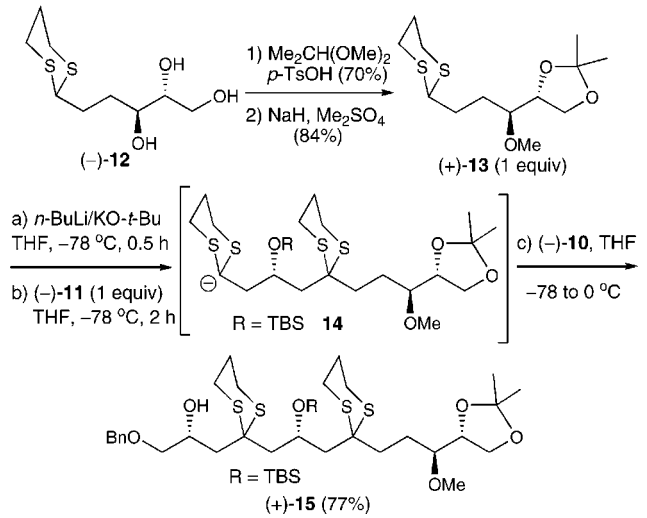


Figure 1. Structure of spirastrellolides A (**1**) and B (**2**) and retrosynthetic analysis of the spirastrellolides.

turn was envisioned to arise from bisketone **9** via 1,3-*anti* reduction of the C(13) ketone, followed by acid-catalyzed spiroketalization, and C(14) methylation. To construct **9**, the anion relay tactic (ARC),[4] recently introduced by our laboratory, appeared ideal to unite the commercially available epoxide (−)-**10**, known linchpin (−)-**11**,[4a] and a protected form of known dithiane (−)-**12**[5] in a single operation.

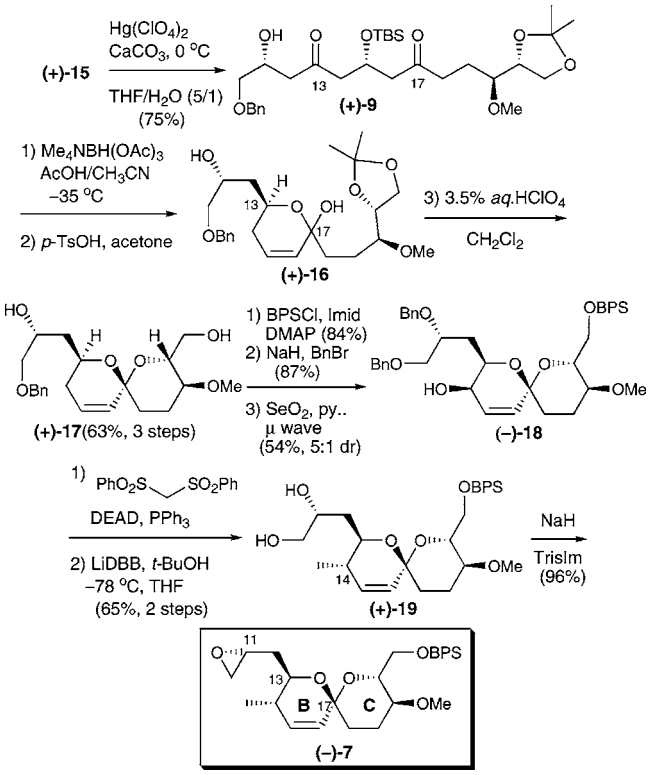
We began with a two-step construction of dithiane **13** from known triol (−)-**12**[5] (Scheme 1). Exploiting the Schlosser

Scheme 1. Anion Relay Chemistry (ARC)



base (*n*-BuLi/KO-*t*-Bu),[6] the first alkylation was achieved at −78 °C with concomitant 1,4-Brook rearrangement, leading in situ to dithiane anion **14**,[7] which upon treatment with epoxide (−)-**10** completed the three-component construction to furnish (+)-**15** in 77% isolated yield. Importantly, this ARC transformation could be carried out on a 5 g scale.

Scheme 2. Synthesis of BC spiroketal (−)-**7**



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(4) (a) Smith, A. B., III; Xian, M. *J. Am. Chem. Soc.* **2006**, *128*, 66. (b) Smith, A. B., III; Xian, M.; Kim, W.-S.; Kim, D.-S. *J. Am. Chem. Soc.* **2006**, *128*, 12368.

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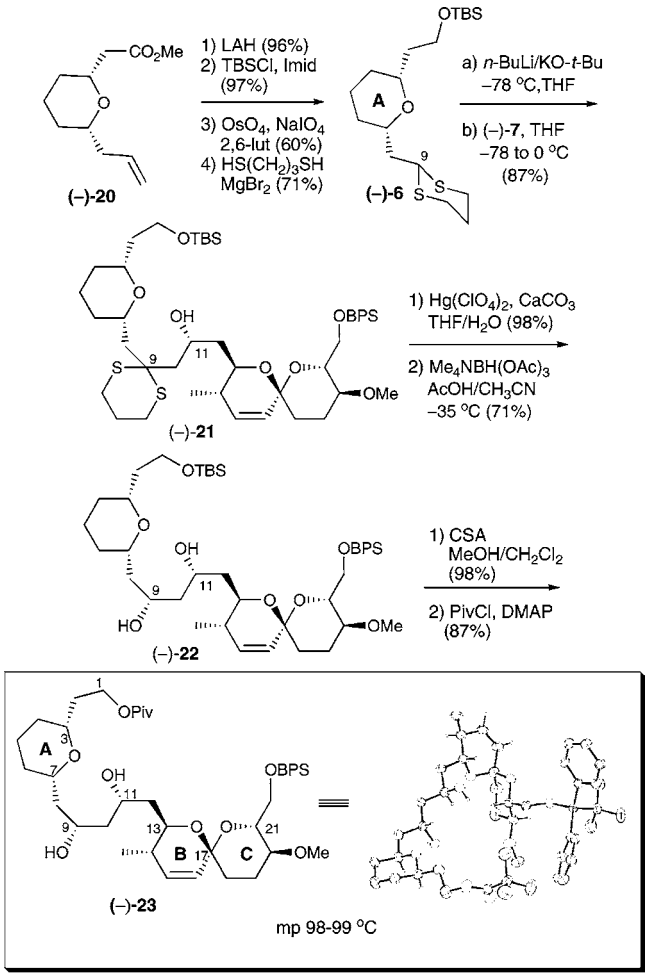
Removal of both dithianes in (+)-**15** employing $Hg(ClO_4)$[8] next furnished 1,5-bisketone (+)-**9** in 75% yield (Scheme 2). Selective 1,3-directed *anti*-reduction of the *β*-hydroxyl ketone via the Gribble−Evans protocol[9] followed by treatment with *p*-TsOH in acetone led to hemiketal (+)-**16**. Without purification, (+)-**16** was treated with 3.5% aq $HClO_4$ to afford spiroketal (+)-**17** in 62% yield (three steps). After selective protection of the primary hydroxyl as *tert*-butyldiphenylsilyl (BPS) ether and benzylation of the remaining secondary hydroxyl, allylic oxidation (SeO_2) using microwave radiation led to allylic alcohol (−)-**18** in 45% yield along with 9% yield of the α-isomer. Introduction of the requisite C(14) methyl group was next achieved via Mitsunobu alkylation with bis(phenylsulfonyl)methane,[10] followed by reduction with excess LiDBB,[11] employing *t*-BuOH as the proton source, to furnish diol (+)-**19** in 65% yield (two steps). Fraser−Reid epoxidation[12] completed construction of epoxide (−)-**7**.

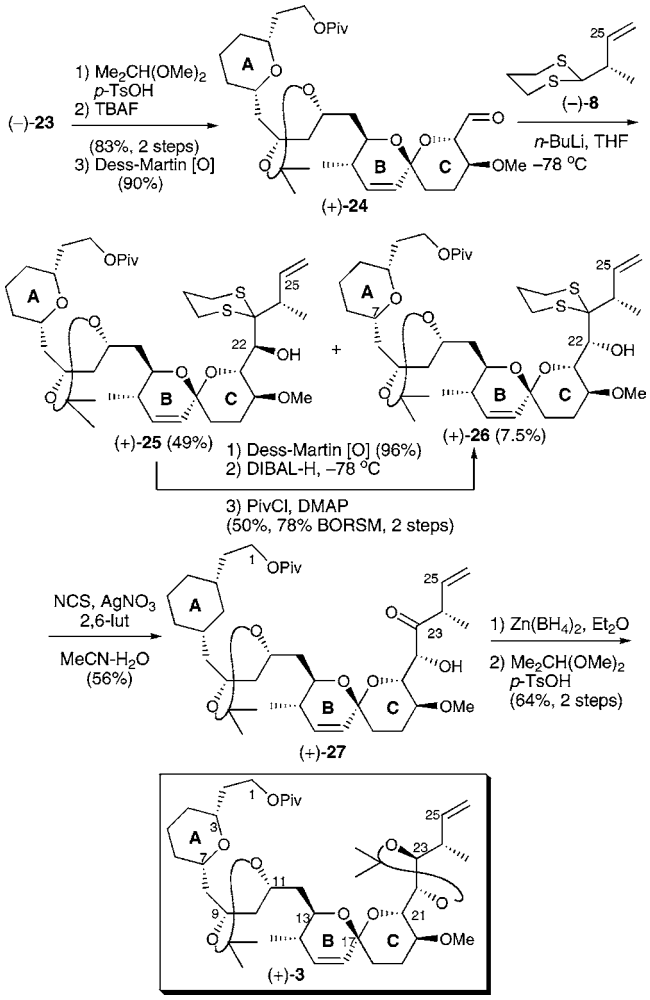
Dithiane (−)-**6** (Scheme 3) required for union with epoxide (−)-**7** was prepared from known pyran (−)-**20**,[2h] via a four-step sequence involving reduction with $LiAlH_4$, TBS protection, oxidative cleavage of the terminal double bond,[13] and dithiane formation employing $MgBr_2$ as Lewis acid;[14] the overall yield was 40%). Union with (−)-**7** employing the Schlosser base (*n*-BuLi/KO-*t*-Bu)[6] led to (−)-**21** in 87% yield. Removal of dithiane with $Hg(ClO_4)$, followed in turn by 1,3-*anti*-reduction,[9] selective removal of TBS group, and protection of the resulting alcohol as a pivalate ester then furnished diol (−)-**23** as a crystalline solid. X-ray analysis established both the structure and relative stereochemistry.

To introduce the final four-carbon side chain, we called upon the Honda protocol, fully expecting dithiane (−)-**8** (Scheme 4) to deliver the correct stereogenicity at C(22).[3]

Scheme 3. Fragment Union of A-Ring Dithiane (−)-**6** and BC Spiroketal (−)-**7**



Scheme 4. Installation of the C(23)−C(25) Fragment



Toward this end, aldehyde (+)-**24** was generated via a three-

(7) Product of **14** was obtained in 85% yield by quenching with a saturated aqueous NH_4Cl solution.

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step sequence involving diol protection, removal of the BPS group, and Dess-Martin oxidation[15]. Treatment of (+)-**24** with the lithium anion derived from (−)-**8** led to a mixture of adducts (6.5:1) in 57% yield. Surprisingly, the minor product proved to be the desired alcohol [(+)-**26**] as established by Kakisawa modified Mosher ester analyses of both isomers.[16] The desired diastereomer could, however, be obtained via a three-step sequence: Dess-Martin oxidation, DIBAL-H reduction, and selective protection of the resulting primary alcohol as a pivalate ester. Pleasingly, the reduction proceeded to furnish a single isomer (NMR). Removal of the dithiane employing the Corey conditions[17] furnished α-hydroxy ketone (+)-**27**, which was then subjected to 1,2-chelation-controlled *anti*-reduction with $Zn(BH_4)_2$.[18] Acetonide formation of the resulting 1,2-diol completed construction of the C(1)−C(25) fragment of spirastrellolide A (**1**).

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In summary, synthesis of the C(1)−C(25) southern fragment of spirastrellolide A (**1**) has been achieved via four dithiane unions. Particularly attractive, the anion relay tactic (ARC) proceeded both with high efficiency and effective union of three components. Further studies toward the total synthesis of the spirastrellolides and applications of the ARC tactic continue in our laboratory.

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Supporting Information Available: Spectroscopic and analytical data and experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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