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Spirastrellolide B: The Synthesis of Southern (C_9-C_{25}) Region

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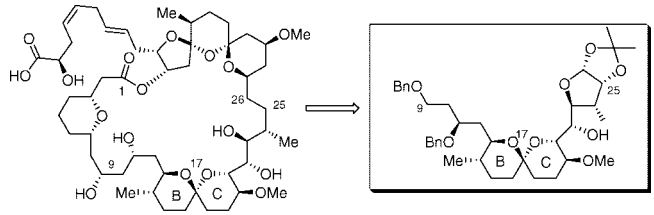
ABSTRACT



Spirastrellolide B

A combination of "chiron" and "asymmetric" approaches is utilized to construct the southern (C_9-C_{25}) region of marine natural product spirastrellolide B. The key functionalities are derived from D-glucose and Sharpless asymmetric epoxidation and dihydroxylation.

Marine invertebrates have been challenging the natural product chemist with structurally diverse and biologically very potent new chemical entities.[1] Spirastrellolides A and B (**1** and **2**) were isolated from the Caribbean sponge *Spirastrella coccinea*, and the structures were disclosed by Andersen et al.[2] The stereochemical conformation was also well-established by X-ray crystallography.[3] These complex spiro natural products have shown tremendous potential in selective inhibition of protein phosphatase PP2A, thus turning out to be promising in cancer chemotherapy.[4] Undoubtedly, these scarce natural products have attracted top schools of synthesis to embark on total synthesis.[5−11] Our group is engaged in the total synthesis of marine natural products[12] and was attracted to the fascinating biological profile of spirastrellolides. In this communication, we report our preliminary studies that resulted in the synthesis of the

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southern (C_9-C_{25}) domain of spirastrellolide B, which is also a part of the structure in another similar family of polyketides including spirastrellolide C.[13]

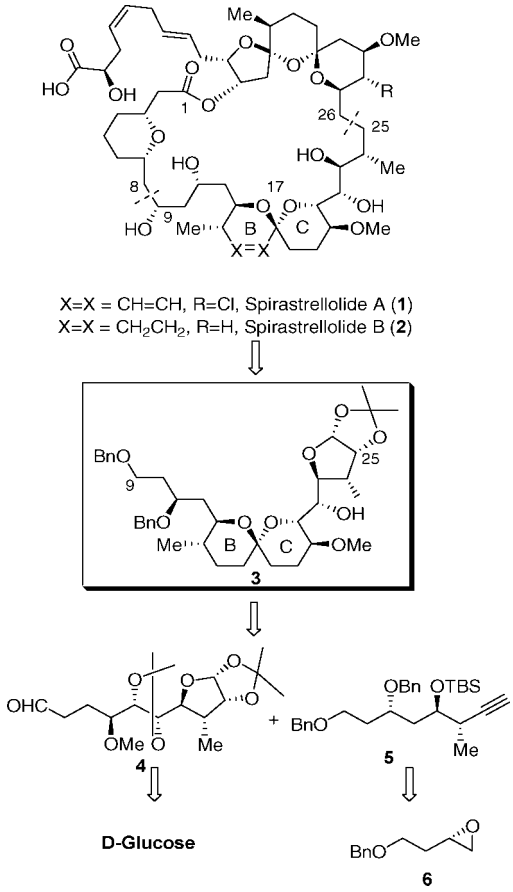
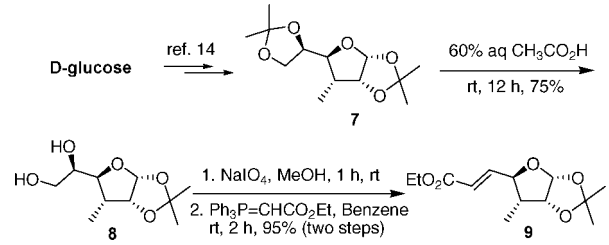


Figure 1. Structure of spirastrellolides A (**1**) and B (**2**) and retrosynthetic analysis of the spirastrellolides.

As shown in Figure 1, our overall strategy for the target fragment **3** involves disconnection at the C_8-C_9 and the $C_{25}-C_{26}$ bonds, affording two subtargets **4** and **5**, respectively. The subtarget **4** as represented was derived from D-glucose, whereas subtarget **5** was realized from known chiral epoxide **6**,[14] obtainable by Jacobsen epoxidation.

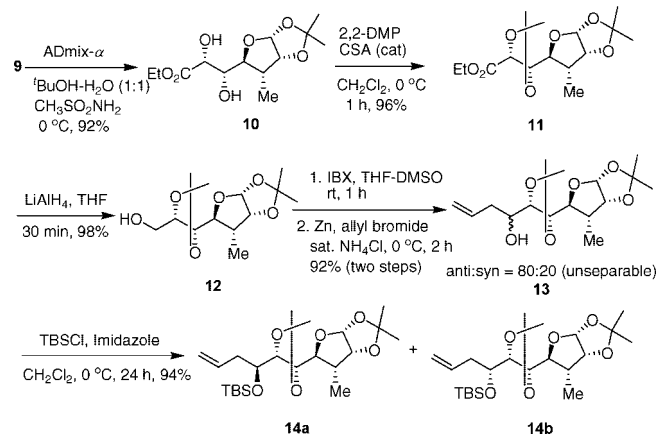
The first requirement was the preparation of the C_{17} to C_{25} fragment, which was conceived from D-glucose. The known furanose **7**[15] on selective hydrolysis yielded the diol **8** which underwent a smooth periodate cleavage and two carbon Wittig olefination to get the α,β-unsaturated ester **9** in 95% overall yield in two steps (Scheme 1). The Sharpless

Scheme 1



asymmetric dihydroxylation on **9** was highly diastereo- and enantioselective in furnishing the diol **10** in 92% yield (Scheme 2).[16] The camphorsulphonic acid catalyzed keta-

Scheme 2



lization of 1,2-diol of **10** was rather routine to furnish **11** (96% yield). A high yielding $LiAlH_4$ reduction of ester **11** to alcohol **12** (98% yield) followed by IBX oxidation and diastereoselective allylation[17] (Zn, allylbromide, sat. NH_4Cl) yielded **13** as an unseparable mixture of *syn* and *anti* isomers (20:80 by HPLC). The silylation of homoallyl alcohol **13** allowed us to separate the mixture by a simple chromatography to get **14a** and **14b** in over 94% collective yield (Scheme 2). The stereochemistry at the newly generated hydroxyl group during allylation was confirmed by NMR studies (C-20 of the target molecule).[18]

The major diastereomer **14a** was desilylated in quantitative yield to **13a** which was methylated (NaH, MeI) to **15** (Scheme 3). The hydroboration of the terminal olefin was accomplished with 9-BBN to get **16** which was further oxidized to get the subtarget **4**.

The journey toward the synthesis of subtarget **5** began from known epoxide **6** which was opened with propargyl ether **17** using *n*-BuLi as base and $BF_3{\cdot}OEt_2$ as Lewis acid

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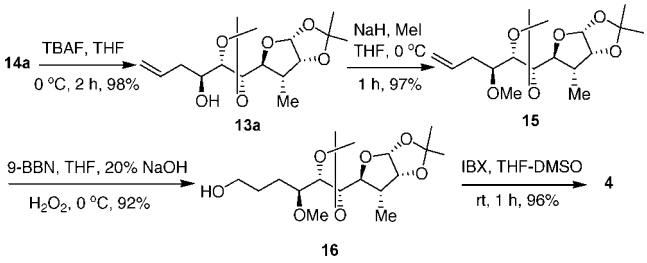
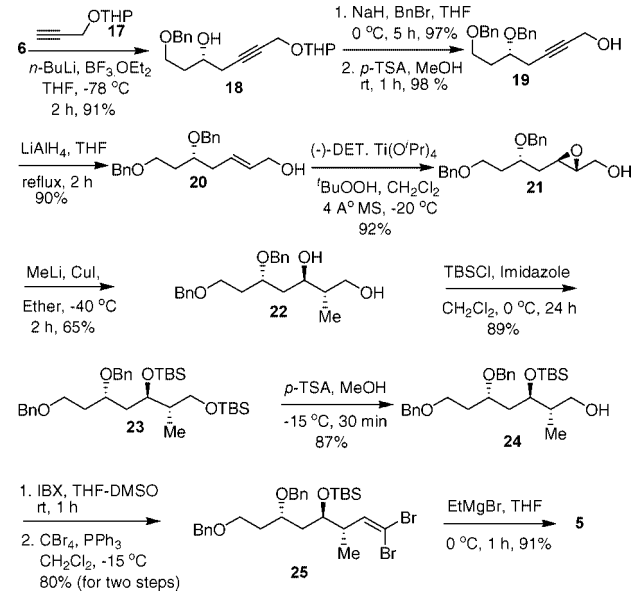
Scheme 3



catalyst to generate homopropargyl alcohol **18** (Scheme 4). The benzylation of alcohol in **18** was realized using

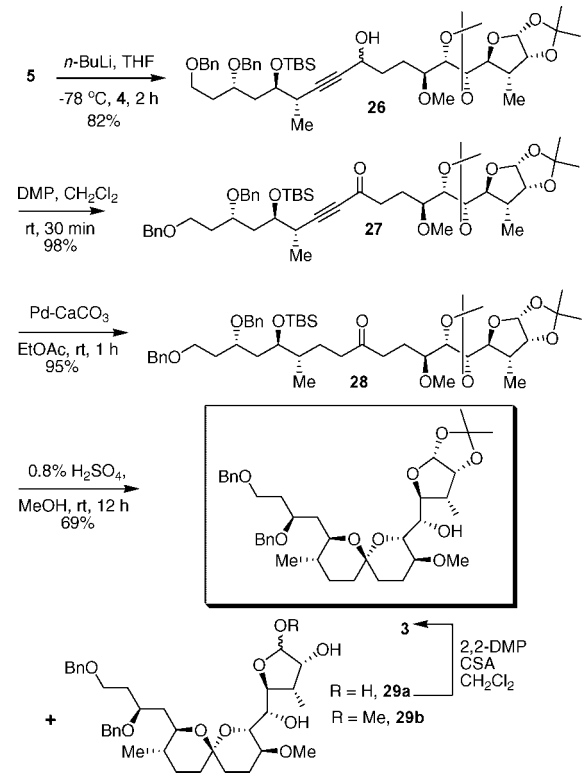
Scheme 4



NaH as base and benzyl bromide which on further hydrolysis with *p*-TSA in MeOH provided **19**. The $LiAlH_4$ reduction of propargyl alcohol to allyl alcohol **20** set the platform for introducing two more chiral centers via Sharpless asymmetric epoxidation.[19] Thus the allyl alcohol **20** on treatment with (−)-DET, $Ti(O^iPr)_4$, and TBHP yielded epoxy alcohol **21**, which was regioselectively opened with Gillman cuprate[20] generated from MeLi and CuI at −40 °C, albeit in moderate yields thus obtaining 1,3-diol **22**. Excess exposure to TBDMSCl and imidazole provided the fully protected (dibenzyl disilyl tetrol) **23**. The selective deprotection of primary silyl ether with *p*-TSA at −15 °C in MeOH furnished primary alcohol **25**. The liberated 1° alcohol functionality in **24** was oxidized (IBX) and subjected to Corey−Fuchs protocol[21] to get dibromide **25**. The reaction with EtMgBr in THF provided the subtarget **5**.

The union of the two subtargets **4** and **5** was established through the acetylenic anion of **5** and the aldehyde functionality of **4** using *n*-BuLi to generate the targeted carbon framework **26** as a diastereomeric mixture (Scheme 5). The

Scheme 5



newly created diastereomeric hydroxyl group was oxidized to **27**, which becomes the common precursor of spirastrellolides. The saturation of acetylenic functionality to **28** was followed by the in situ hydrolysis (0.8% H_2SO_4) which transformed the acyclic synthon to spiro framework **3** in reasonable yields. Slight amount of over hydrolysis was noticed as evidence in the isolation of **29a** and **29b**. The diol **29a** can be converted back to **3** in the presence of 2,2-DMP and CSA.

Thus, a stereoconvergent approach allowed us to complete the southern portion of the rather complex natural product, spirastrellolide B. Both chiron and Sharpless reactions were effectively combined to yield the target. Progress toward the total synthesis will be reported in due course.

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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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