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Synthesis of the C9−C25 Subunit of Spirastrellolide B

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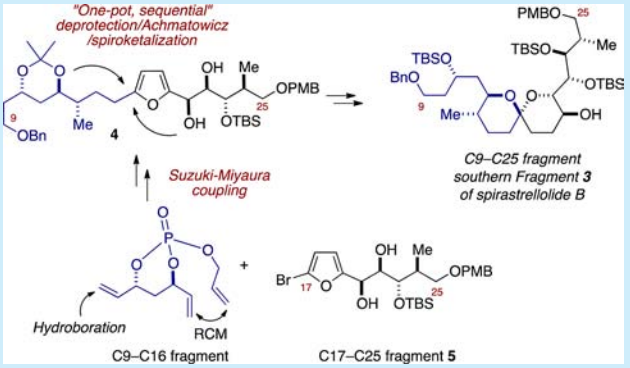
Supporting Information

ABSTRACT: The synthesis of the C9−C25 subunit of the marine natural product spirastrellolide B is reported. The key synthetic features included the union of the two key fragments **5** and **6** via a Suzuki−Miyaura coupling reaction and a late-stage, one-pot sequential deprotection/cascade Achmatowicz rearrangement−spiroketalization to install the key spirocyclic intermediate present in the C9−C25 fragment of spirastrellolide B. The synthesis of the C9−C16 fragment **6** was accomplished via a phosphate tether mediated ring-closing metathesis (RCM), a subsequent hydroboration−oxidation protocol, followed by other stereoselective transformations in a facile manner. The spirocyclic intermediate was further functionalized utilizing a Lindlar/$NaBH_4$ reduction protocol to furnish the C9−C25 subunit **3**.



Spirastrellolide A (**1**, Figure 1) was the first member of the spirastrellolide family to be isolated in 2003 by Andersen and co-workers from the extracts of the Caribbean marine sponge *Spirastrella coccinea*.[1] Subsequently, in 2007, Andersen and co-workers isolated spirastrellolide B (**2**) (Figure 1) from the same extract.[2] The key structural features of these macrolides include a 47-carbon linear polyketide backbone, a highly functionalized 38-membered lactone that contains a tetrahydropyran, and two spiro-bispyran substructures, as well as a side chain containing carboxylic acid group. Spirastrellolide A methyl ester **1** exhibited potent activity in a cell-based (human carcinoma MCF-7 cells) antimitotic assay with IC_{50} value of 100 ng/mL, and its unique cytotoxicity has been linked to the phosphatase-inhibition mechanism (a PP2A inhibitor).[3] Irregularities in protein phosphorylation are known to contribute to many human diseases such as cancer and diabetes;[4] therefore, it is imperative to identify inhibitors of phosphatases in order to understand their role in such biological problems and aid in detecting potential drug targets. The interesting biological activity and novel structural features of the spirastrellolide family have culminated in many elegant synthetic efforts toward the syntheses of spirastrellolides A, B, E, and F.[5] The total synthesis of spirastrellolide A was accomplished by both the Fürstner and the Paterson groups.[6,7] Initially, no biological activity was reported for spirastrellolide B; however, in 2012, both of the family members, spirastrellolides A and B, were reisolated as free acids from a marine sponge *Epipolasis* sp. and tested against HeLa cancer cell lines.[8] The IC_{50} values of the free acids of spirastrellolides A and B were found to be 20 and 40 nM, respectively, comparable to the corresponding methyl ester of spirastrellolides A and B, which exhibited IC_{50} values of 30 and 70 nM, respectively. However, unlike spirastrellolide A, the cytotoxicity of spirastrellolide B has not been linked to the phosphatase inhibition mechanism. Additionally, no total synthesis has been reported so far for spirostrellolide B. Given the structural similarities between spirastrellolides A and B (**1** and **2** in Figure 1), we believe that the total synthesis of spirastrellolide B will serve not merely as another synthetic campaign but also for the identification of the pharmacophore of

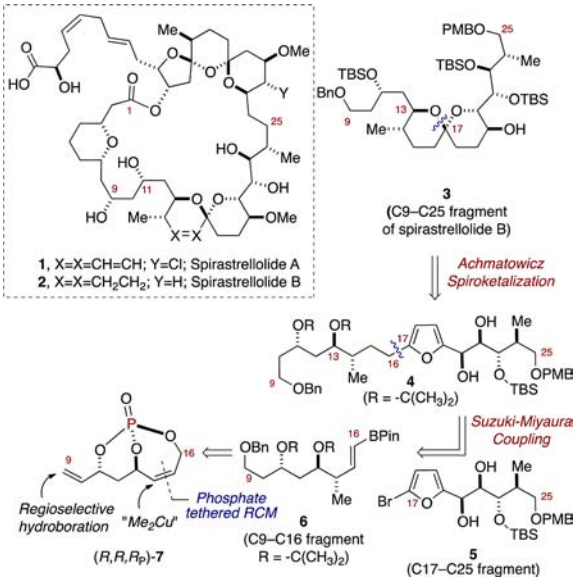


Figure 1. Structures of spirastrellolides A and B and retrosynthetic analysis of the C9−C25 fragment of spirastrellolide B.

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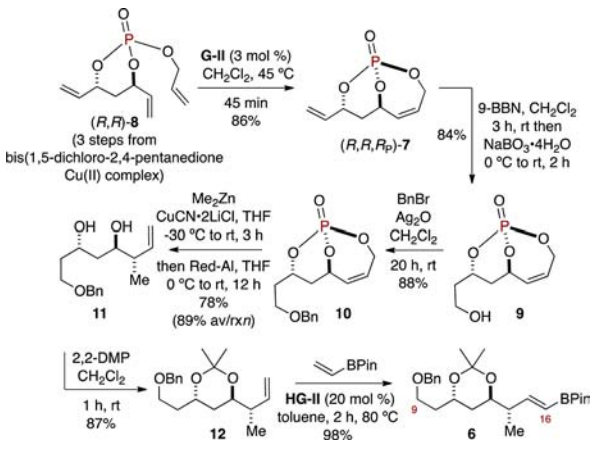
spirastrellolides A/B, which could, in turn, serve as an excellent biological tool to investigate protein phosphatase-mediated cellular regulation. Herein, we disclose a pot-efficient, phosphate tether mediated synthesis of the C9−C25 fragment of spirastrellolide B.

Our group has focused on developing efficient synthetic strategies utilizing phosphate tether mediated desymmetrization of C_2-symmetric 1,3-diene diols en route to 1,3-antidiol group containing bioactive natural products.[9] Our interest in developing modular and library-amenable strategies to access polyketide natural products has led to the completion of the total synthesis of (−)-tetrahydrolipstatin, dolabelide C, (+)-strictifolione, a formal total synthesis of (−)-salicylihalamides A and B, the macrolactone core of lyngbouilloside, and a recent total synthesis of Sch-725674, as well as simplified analogues bearing diverse α,β-unsaturated chemotypes.[10] Aligned with this goal, we attempted the synthesis of the C9−C25 fragment of spirastrellolide B, in which we envisioned to utilize the temporary phosphate tethered system, bicyclo[4.3.1]phosphate (R,R,R_P)-7, to construct the C9−C16 fragment **6** in a facile manner (Figure 1). The proposed retrosynthetic route for the C9−C25 fragment of spirastrellolide B relies on a late-stage Achmatowicz spirocyclization of the key furan-containing subunit **4**, previously utilized by Deshong and Tong[11] to generate the crucial spirocyclic intermediate. The key fragment was planned to be derived via a Suzuki−Miyaura coupling of furan substrate **5** with the 1,3-diol-containing synthon **6**. Overall, successful implementation of this route would achieve the synthesis of the C9−C25 fragment of spirastrellolide B (**3**).

Toward the aforementioned goal, we initiated our synthesis of the C9−C16 polyol-containing fragment **6** (Scheme 1). The

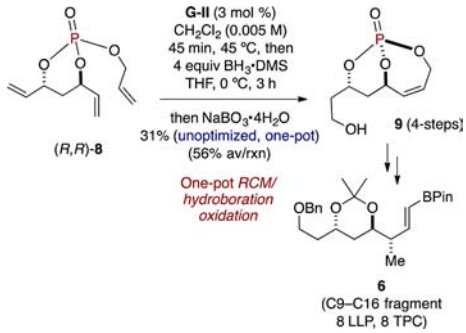
Scheme 1. Synthesis of the C9−C16 Fragment



corresponding borate ester synthesis started with the ring-closing metathesis (RCM) of triene (R,R)-**8** furnishing bicyclo[4.3.1]-phosphate (R,R,R_P)-7 in the presence of the Grubbs second-generation catalyst (**G-II**)[12] in refluxing dichloromethane. Bicyclo[4.3.1]phosphate **7** was further converted to alcohol **9** via a regioselective hydroboration−oxidation protocol. Subsequent benzylation produced benzylated bicyclo[4.3.1]phosphate **10** (Scheme 1). Regio- and diasteroselective allylic cuprate displacement followed by tether removal of **10** resulted in olefin **11**. Subsequent acetonide protection followed by cross-metathesis (CM) with vinyl pinacolatoboron provided the C9−C16 coupling partner, fragment **6**.

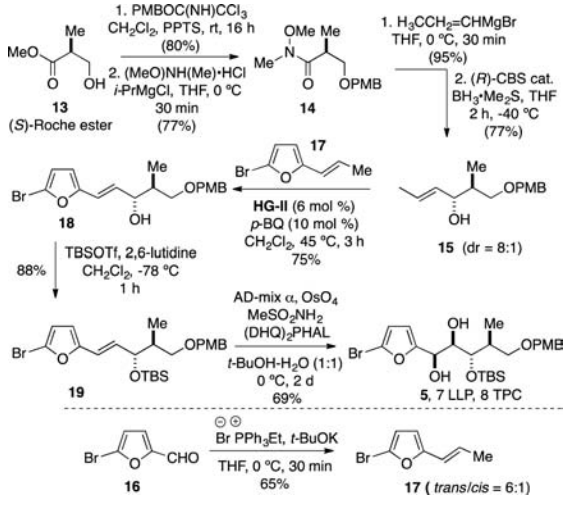
To further streamline the synthesis, we also attempted a one-pot RCM/hydroboration−oxidation protocol.[13] Accordingly, triene (R,R)-**8**[14] was treated with 3 mol % of the **G-II** catalyst in refluxing CH_2Cl_2. Upon completion of the reaction, the solvent was evaporated and treated with 4 equiv of BH_3·DMS in THF at 0 °C for 3 h. The reaction was quenched with $NaBO_3$·$4H_2O$ to generate alcohol **9** in an overall 31% yield (over two reactions in one pot, 56% average/reaction, unoptimized). It should be noted that the yield of this one-pot sequential protocol was low compared to that of the individual reactions. Therefore, further optimization studies will be necessary. However, the feasibility of combining the phosphate tether mediated RCM and hydroboration−oxidation into a single pot is promising.[15] Taken collectively, the synthesis of the C9−C16 fragment was achieved over 8 LLP (longest linear pot sequence) and 8 TPC (total pot count) (Scheme 2).

Scheme 2. One-Pot, Sequential RCM/BH_3-(ox) Protocol



The synthesis of the C17−C25 fragment commenced with the PMB protection of (*S*)-Roche ester (**13**), followed by the conversion to Weinreb amide[16] **14** in the presence of (MeO)NH(Me)·HCl and *i*-PrMgCl (Scheme 3). Subsequent

Scheme 3. Synthesis of the C17−C25 Furan Fragment



Grignard addition, followed by the CBS reduction,[17] generated the olefinic cross-partner, substituted allylic alcohol **15** in 8:1 diastereomeric ratio. Further, CM with furan substrate **17**, generated via the Wittig reaction of 5-bromo-2-furaldehyde (**16**), in the presence of Hoveyda−Grubbs second-generation (**HG-II**)[18] catalyst produced furan-substituted allylic alcohol **18** in 75% yield. Subsequent TBS-protection of the C23 hydroxyl

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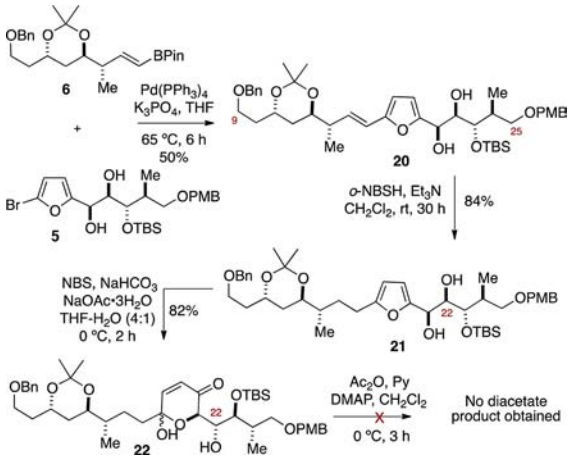
group furnished **19**, which was dihydroxylated with high diastereoslectivity (>20:1)[5r] to deliver the C17−C25 bromofuran coupling partner **5** in 7 LLP and 8 TPC.

Suzuki−Miyaura coupling of the C9−C16 boronic ester fragment **6** and furan intermediate **5** in the presence of $Pd(PPh_3)_4$ and K_3PO_4 furnished the coupling product **20** in 50% yield (Scheme 4). Subsequent hydrogenation using *o*-NBSH[19] yielded the Achmatowicz precursor **21** in 84% yield. Next, we performed the Achmatowicz cyclization by subjecting the hydrogenated product **21** to NBS, $NaHCO_3$, and $NaOAc·3H_2O$ in a THF/H_2O (4:1) mixture to produce α,β-unsaturated pyran **22**[20] in 82% yield. Our next goal was to protect the secondary hydroxyl group at C22 as an acetate prior to spiroketalization to prevent the possible formation of bridged product during spirocyclization.[21] However, when subjected to Ac_2O and pyridine/DMAP, no diacetate product was observed.

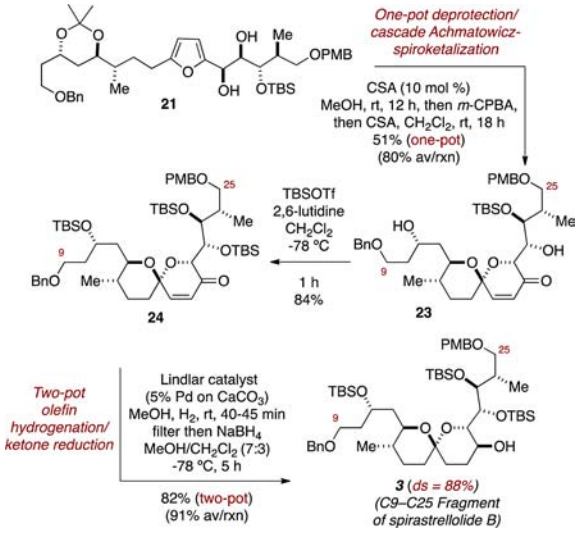
Scheme 4. Synthesis of the C9−C25 Fragment



To eliminate the possibility of other side product formation, we envisioned a one-pot, cascade Achmatowicz/spiro-ketalization reaction, whereby the spiroketalization would occur in the same pot under acidic condition after the formation of α,β-unsaturated pyran in situ. Furthermore, to ensure the formation of desired spirocyclic product in Achmatowicz/spiroketalization reaction, we also aimed to perform acetonide deprotection prior to the Achmatowicz cyclization. Since both of the reactions could be theoretically performed under acidic conditions, we also viewed this as an opportunity to implement a one-pot sequential protocol by combining the deprotection and Achmatowicz cyclization steps. Accordingly, we attempted the acetonide deprotection in the presence of CSA, MeOH, evaporated the solvent and treated the crude mixture to *m*-CPBA and CSA (sequential addition). Gratifyingly, this one-pot, sequential deprotection/cascade Achmatowicz-spiroketalization reaction sequence furnished the critical spirocyclic intermediate **23** in an excellent overall yield of 51% over three reactions in one pot (Scheme 5). The formation of the spirocycle was confirmed by NOE experiments on the C9−C25 fragment **3**. Subsequent TBS protection produced spirocycle **24** in 84% yield.

With **24** in hand, we aimed efforts at the reduction of the olefinic double bond followed by diastereoselective ketone reduction. After a couple of optimization studies on model substrates, we realized that it would be better to reduce the olefinic bond first followed by the reduction of ketone to avoid the complication of forming 1,4- and 1,2-reduction products. In addition, we believed that the order of the reactions would also

Scheme 5. Alternative Synthesis of the C9−C25 Fragment



facilitate the application of a two-pot protocol combining olefin and ketone reductions. Lindlar catalyst was chosen for the olefin hydrogenation, since simple filtration would be sufficient and the crude intermediate could be subjected to the ketone reduction step without any quenching/workup procedure. Accordingly, compound **24** was subjected to the Lindlar catalyst in MeOH; subsequent filtration followed by the treatment with $NaBH_4$ in a mixed solvent system $MeOH/CH_2Cl_2$ (7:3 ratio) furnished the desired product, the C9−C25 fragment **3**, in a two-pot, sequential manner with 88% ds.

In conclusion, the synthesis of the C9−C25 fragment **3** was achieved over 14 longest linear pots and 22 total pots. The highlights of the synthesis included phosphate tether-mediated facile synthesis of the C9−C16 fragment, a Suzuki−Miyaura coupling unifying the C9−C16 and C17−C25 subunits, and a late-stage, one-pot sequential deprotection/cascade Achmatowicz rearrangement−spiroketalization to reveal the key spirocyclic intermediate. Taken collectively, this synthesis further corroborates the utility of the temporary phosphate tether toward the synthesis of complex 1,3-diol containing natural products. Synthetic efforts toward the construction of the C26−C40 fragment are currently in progress and will be reported in due course. Additional efforts directed toward the design and synthesis of the C1−C8 subunit to complete the total synthesis campaign toward spirastrellolide B are also underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01248.

Experimental details and spectroscopic data of new compounds (PDF)

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Notes

The authors declare the following competing financial interest: P.R.H. is on the Scientific Advisory Board of Materia, Inc.

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