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Spirastrellolide B: Construction of the C(26)–C(40) Northern Hemisphere and a Related [5,5,7]-Bis-Spiroketal Analogue

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Abstract

Differential synthetic access to an advanced C26–C40 northern hemisphere fragment of spirastrellolide B and to a related [5,5,7]-bis-spiroketal analogue from a common intermediate has been achieved. Central to this venture is the regiocontrolled functionalization of a C(31–32) alkyne, exploiting different transition metal catalysts (cf. Pt^{II} and Au^I).

The spirastrellolides A, B, D and F (**1–4**) comprise a novel family of architecturally complex marine macrolides isolated by Andersen and co-workers from the Caribbean marine sponge *Spirastrella coccinea*.¹ Among this family, spirastrellolide A (**1**) was found to possess potent, selective activity as an inhibitor of protein phosphatase 2A (PP2A: IC₅₀ = 1 nM; PP1: IC₅₀ = 50 nM).^{1a,b} The complete structural assignment of spirastrellolide A however remained unclear, until the isolation of spirastrellolide B (**2**), which permitted assignment of the complete relative and absolute configuration of the macrolide core by single crystal X-ray analysis.^{1c} In 2007 the remaining stereochemical issue, the C46 stereogenicity, was resolved by chemical degradation of spirastrellolide D (**3**) methyl ester.^{1d}

Given the potent biological profile, in conjunction with the complex molecular architecture, the spirastrellolides have generated considerable interest in the synthetic community.² In 2008 the Paterson group reported an elegant, first total synthesis of spirastrellolide A methyl ester;³ later in 2009 and 2011, the Furstner group disclosed their first- and second-generation syntheses of spirastrellolide F (**4**) methyl ester.⁴ During the preparation of this manuscript, the Paterson group also published a second-generation synthesis of spirastrellolide A methyl ester.^{3c} Also of note is the Forsyth approach to the northern hemisphere of spirastrellolide B.^{2k,l}

Intrigued with the spirastrellolides, we embarked in 2007 on the total synthesis of spirastrellolide B (**2**) and in 2010 reported the construction of a fully functionalized C1–C25

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

southern hemisphere (**6**).⁵ We now disclose construction of an advanced C26–C40 northern [5,6,6]-bis-spiroketal fragment (–)-**5**, in conjunction with the [5,5,7]-bis-spiroketal analogue (–)-**25** (Scheme 3).

From the retrosynthetic perspective, we envisioned construction of the requisite [5,6,6]-bis-spiroketal of spirastrellolide B (**2**) to comprise a transition metal-promoted spiroketalization reaction (i.e., AuCl),⁶ involving the C31–C32-triple bond in **7** (Figure 1). Such a tactic would require that the alkyne serve as a ketone surrogate. Critical however would be introduction of the carbonyl functionality at C31. Access to the alternative carbonyl at C32 would lead to the [5,5,7]-bis-spiroketal, not a completely unrewarding event, in that access to the latter would permit construction of novel analogues of the spirastrellolide skeleton. Exploiting an alkyne to serve as a ketone surrogate would also hold promise of an efficient synthetic sequence by eliminating otherwise required protecting group manipulations. Construction of the requisite C37 stereogenicity in **7** in turn would entail a chelation-controlled Mukaiyama aldol reaction. Further disconnection of the C30–C31 σ -bond via an alkyne-epoxide retron reveals epoxide (–)-**8**, alkyne (+)-**9** and aldehyde (–)-**10**.

We began with construction of epoxide (–)-**12**,^{2q} employing a two-step sequence from triol (–)-**11**, the latter readily prepared from commercial D-(+)-ribonic- γ -lactone⁷ (Scheme 1). Protection of the secondary alcohol as the PMB ether furnished epoxide (–)-**8**, which upon union with the anion derived from alkyne **9**, the latter prepared by the method of Baker and Brimble⁸, employing $\text{BF}_3 \cdot \text{Et}_2\text{O}$ at low temperature (–78 °C), led to (–)-**13**. Methylation of the derived alcohol and removal of the THP protecting group with PPTS in methanol completed construction of (–)-**14**. The overall yield from (–)-**11** was 28% (six steps).

For the proposed Mukaiyama aldol reaction, a la Forsyth,^{2k,l} a three-step sequence involving Ley oxidation,⁹ methyl Grignard addition, and a second Ley oxidation yielded ketone (–)-**16** (Scheme 2). Kinetic enolization employing KHMDS at –78 °C in THF, followed by capture with TMSCl then furnished silyl enol ether **18**, which in turn was reacted, in the presence of $\text{MgBr}_2 \cdot \text{Et}_2\text{O}$, with aldehyde (–)-**10**, prepared in two steps from known epoxide (–)-**17**.¹⁰ The derived aldol product (–)-**19** was obtained both in excellent yield and with high selectivity (85% over the two steps; dr > 15:1). The stereochemical outcome was assigned based on a chelation-controlled model.¹¹ The newly generated hydroxyl group was then protected as methoxy methyl (MOM) ether to furnish (–)-**20**.

To reveal the C27 and C38 hydroxyl groups in (–)-**20** for the proposed intramolecular alkyne spiroketalization, oxidative cleavage of the PMB ethers with DDQ in CH_2Cl_2 , employing a pH 7 buffer cleanly furnished **7** as a mixture of hemiketals in 70% (Scheme 3). Selective, albeit inefficient removal of the C27 PMB group could also be achieved upon slow addition of a solution of DDQ in CH_2Cl_2 at 0 °C to furnish (–)-**22** in 34% yield, with 40% recovery of (–)-**20**. The mixture of hemiacetals (**7**) was then treated with a catalytic amount of AuCl and PPTS in MeOH at room temperature. Unfortunately the only product isolated appeared to be a furan.¹² Reasoning that solvent polarity might play a critical role in this transformation, we turned to THF, a less polar/aprotic solvent. Although furan formation again dominated, we were gratified to isolate a bis-spiroketal with the correct molecular weight, albeit in low (12%) yield.

Careful analysis of the high field NMR data (500 MHz), suggested that the spiroketal appeared to be (–)-**21**, possessing the [5,5,7]- and not the [5,6,6]-bis-spiroketal skeleton. Alternatively, treatment of alcohol (–)-**22** to the same reaction conditions (AuCl, PPTS) employing MeOH as solvent led to diketone (–)-**23** in 95% yield (Scheme 3). Careful analysis of the ^1H - ^1H COSY data suggested that hydration of the alkyne had occurred at C32, instead of the desired C31 to deliver diketone (–)-**23**. Importantly, (–)-**23** could be

advanced to bis-spiroketal (–)-**21** in two steps and in 51% yield (i.e., removal of PMB ether and PPTS promoted cyclization), and subsequently to (–)-**25**, upon treatment at room temperature with TASF in DMF to remove the TBDPS group. The complete structure of (–)-**25** was assigned by 1D (¹H, ¹³C, and DEPT135) and 2D (COSY, NOESY, HSQC, HMBC, and TOCSY) NMR studies [see Supporting Information (SI)].

With this information in hand, we reasoned that in the conversion of **7** to (–)-**21** (Scheme 4), intramolecular attack of the C27 hydroxyl on the AuCl-activated alkyne, involving a six-membered transition state, was not favorable (i.e., 5-exo-dig vs 6-exo-dig). Instead the conversion of (–)-**22** to (–)-**23** more likely proceeds via an intermolecular pathway (attacked by solvent, i.e., methanol). A solution to this problem would be to eliminate both the bimolecular and the five-membered intramolecular reaction pathways by employing mono-alcohol (–)-**22** in an aprotic solvent.

To explore this scenario, we first sought to secure a more reliable, high-yielding route to alcohol (–)-**22**. The C27 PMB hydroxyl protecting group in (–)-**16** was thus interchanged for a triethylsilyl (TES) group to furnish (–)-**26** (Scheme 5), which in turn was subjected to the previously developed chelation-controlled Mukaiyama aldol reaction, followed by a two-step protecting group reorganization to furnish alcohol (–)-**22**. The overall yield for this six-step sequence was 61%.

With ample quantities of alcohol (–)-**22** in hand, we turned to the spirocyclization. Unfortunately all attempts to achieve the desired C31 alkyne hydration employing AuCl under different solvents/temperature regimes met with failure.¹³ However, treatment with a Pt(II) catalyst effectively led to the desired C31 alkyne functionalization (Scheme 5).^{6b} The optimal catalyst proved to be [Cl₂Pt(CH₂CH₂)₂]₂, employed in Et₂O in the presence of 4 Å MS. An aqueous workup furnished a mixture of hemiacetals **28**, which without isolation was subjected to a deprotection/cyclization sequence employing DDQ in a mixture of CH₂Cl₂ and H₂O (10:1). Subsequent treatment with PPTS in CH₂Cl₂ generated (+)-**5**, possessing the [5,5,6]-bis-spiroketal of spirastrellolide B; the yield was 38% for the three steps from (–)-**22**. In addition, a minor diastereomer (7:1 dr) was isolated (structure not assigned). Alcohol (+)-**29** was then obtained upon removal of the silyl protecting group (TBDPS) with TBAF in THF (83%).

Assignment of the complete structure of (+)-**29** was based on a combination of 2D NMR studies (COSY, NOESY, HMBC, and HMQC), in conjunction with comparison to the ¹H and ¹³C NMR data of the natural product and several previously reported synthetic intermediates (see SI). The strong NOE correlations between H27 and H38 confirmed the double-anomeric structure of the synthetic northern hemisphere of spirastrellolide B.

In summary, we have employed transition metal-mediated regiocontrol to achieve selective alkyne activation to arrive at an advanced spirastrellolide B northern hemisphere fragment and an intriguing [5,5,7]-bis-spiroketal analogue from common intermediate (–)-**22**. Studies toward the total synthesis of spirastrellolide B, as well as possible analogues, continue in our laboratory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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- Furan formation was also observed by the Paterson, Furstner, and Forsyth group during their synthetic ventures directed toward construction of the northern hemisphere of the spirastrellolides.
- While the reaction in THF was very slow and required excess of AuCl reagent, reaction in CH₂Cl₂ returned a complex mixture, from which the desired product was not identified.

Figure 1.
 Structure of spirastrellolide A (**1**), B (**2**), D (**3**), and F (**4**). Retrosynthesis of spirastrellolide B northern hemisphere

Scheme 1.
Fragment union of epoxide **(-)-8** and alkyne **(+)-9**.

Scheme 2.
Chelation-controlled Mukaiyama aldol reaction

Scheme 3.
Synthesis of a [5,5,7]-bis-spiroketal analogue of the spiratrellolide B northern hemisphere

5-exo-dig over 6-exo-dig **Intermolecular attack over intramolecular attack** **5-exo-dig and intermolecular attack not available
6-exo-dig vs. 7-endo-dig**

Scheme 4.
Mechanistic considerations and possible solutions

Scheme 5.
Synthesis of spirastrellolide B northern hemisphere