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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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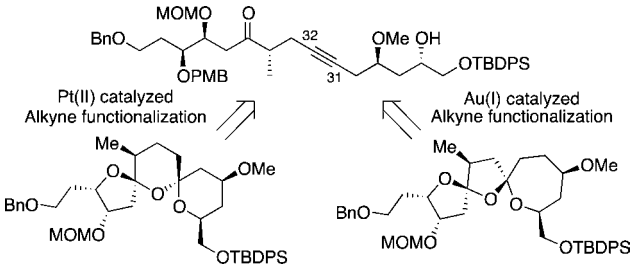
ABSTRACT



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**; Figure 1) 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: IC_{50} = 1 nm; PP1: IC_{50} = 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 Fürstner 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]

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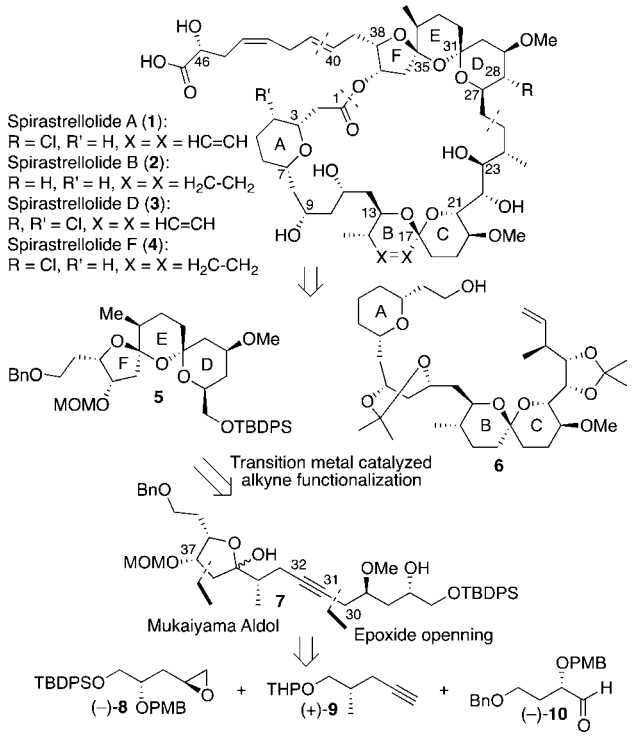


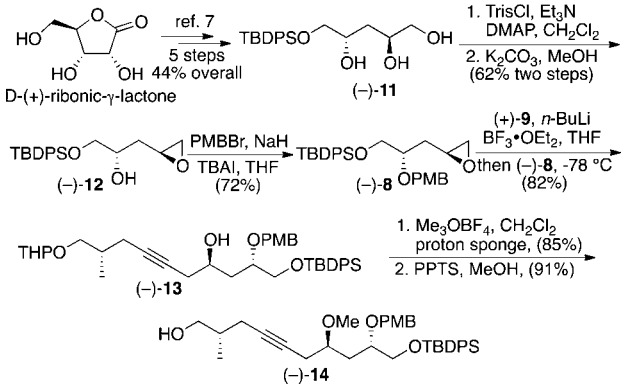
Figure 1. Structure of spirastrellolide A (**1**), B (**2**), D (**3**), and F (**4**). Retrosynthesis of spirastrellolide B northern hemisphere.

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 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-lactone[7] (Scheme 1). Protection of the secondary alcohol as the PMB ether furnished epoxide (−)-**8**, which upon union with the

Scheme 1. Fragment Union of Epoxide (−)-**8** and Alkyne (+)-**9**



anion derived from alkyne **9**, the latter prepared by the method of Baker and Brimble,[8] employing BF_3•Et_2O 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 $MgBr_2$•Et_2O, 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

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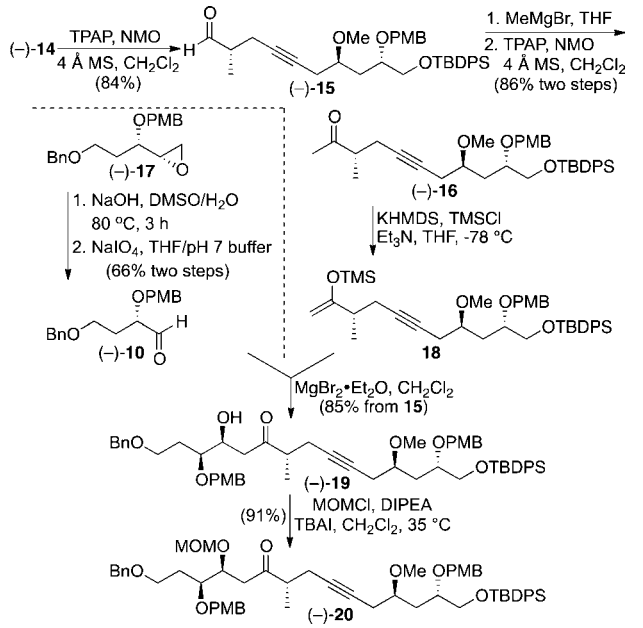
Scheme 2. Chelation-Controlled Mukaiyama Aldol Reaction



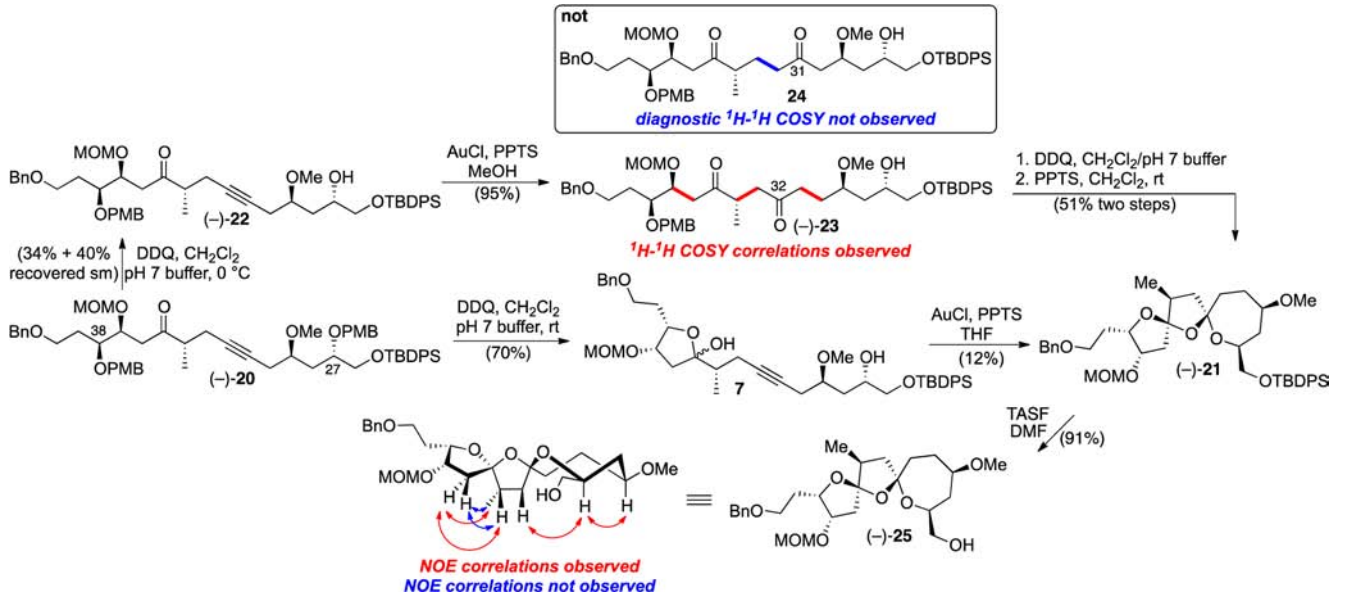
based on a chelation-controlled model.[11] The newly generated hydroxyl group was then protected as methoxy methyl (MOM) ether to furnish (−)-**20**.

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% yield (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 rt. 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.

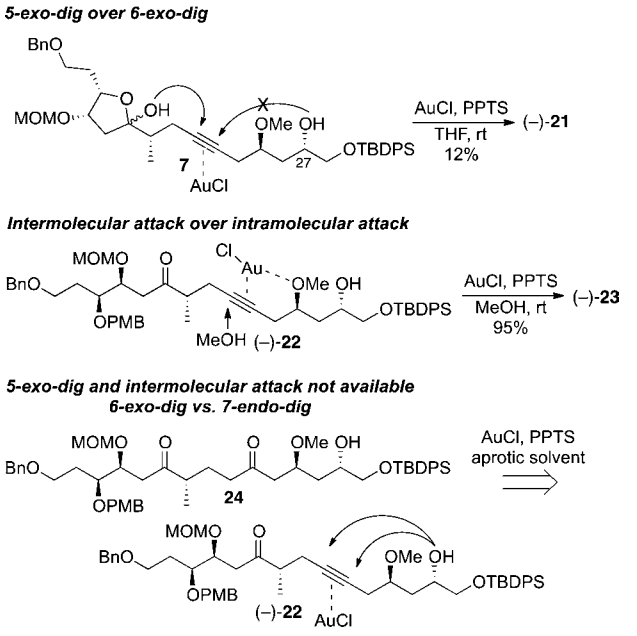
Careful analysis of the high field NMR data (500 MHz) suggested that the spiroketal appeared to be (−)-**21**, possessing the [5,5,7]- and not the [5,6,6]-bis-spiroketal skeleton. Alternatively, treatment of alcohol (−)-**22** to the same reaction conditions (AuCl, PPTS) employing MeOH as solvent led 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 subseqently to (−)-**25**, upon treatment at rt with TASF in DMF to remove the TBDPS group. The complete structure of (−)-**25** was assigned by 1D (^1H, ^{13}C, 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 monoalcohol (−)-**22** in an aprotic solvent.

Scheme 3. Synthesis of a [5,5,7]-Bis-spiroketal Analogue of the Spiratrellolide B Northern Hemisphere



Scheme 4. Mechanistic Considerations and Possible Solutions



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% .

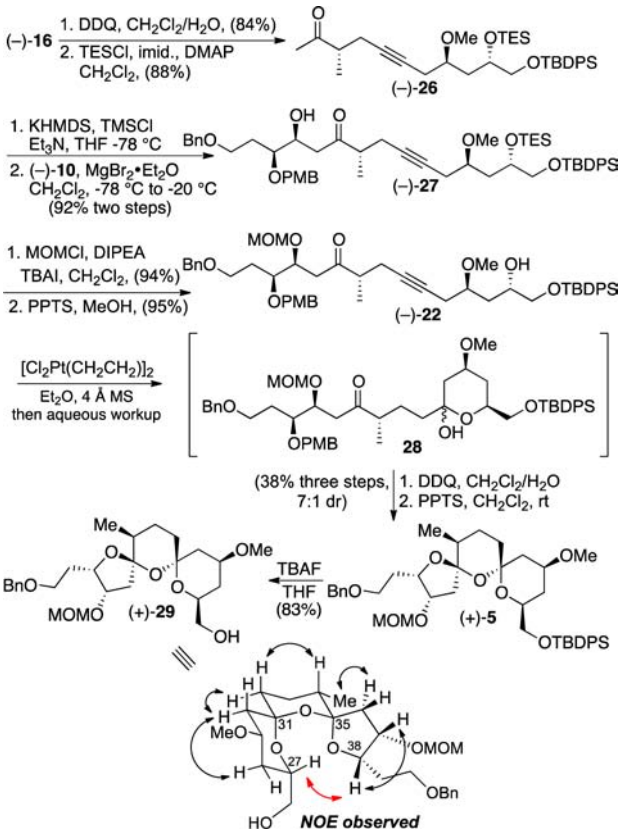
With ample quantities of alcohol (−)-**22** in hand, we turned to the spirocyclization. Unfortunately all attempts to achieve the desired C31 alkyne hydration employing AuCl under different solvents/temperature regimes met with failure.[13] However, treatment with a Pt(II) catalyst effectively led to the desired C31 alkyne functionalization (Scheme 5).[6b] The optimal catalyst proved to be $[Cl_2Pt(CH_2CH_2)]_2$, employed in Et_2O 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 CH_2Cl_2 and H_2O (10:1). Subsequent treatment with PPTS in CH_2Cl_2 generated (+)-**5**, possessing the [5,6,6]-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

(12) Furan formation was also observed by the Paterson, Fürstner, and Forsyth group during their synthetic ventures directed toward construction of the northern hemisphere of the spirastrellolides.

(13) While the reaction in THF was very slow and required an excess of AuCl reagent, reaction in CH_2Cl_2 returned a complex mixture, from which the desired product was not identified.

Scheme 5. Synthesis of Spirastrellolide B Northern Hemisphere



comparison to the ^1H and ^{13}C 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 transiton-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.

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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.

The authors declare no competing financial interest.