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Formal Total Synthesis of Spirangien A

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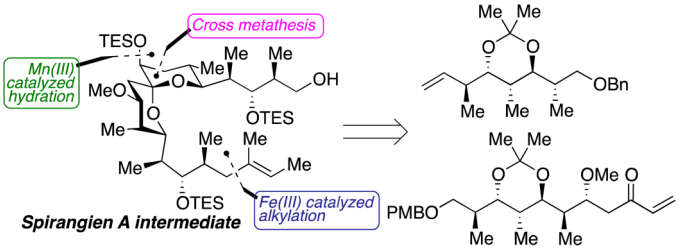
ABSTRACT



A formal total synthesis of the spiroketal containing cytotoxic myxobacteria metabolite spirangien A (1) is described. The approach utilizes a late introduction of the C20 alcohol that mirrors the biosynthesis of this compound. The key steps involved a high yielding cross metathesis reaction between enone 6 and alkene 7 to give *E*-enone 4 and a Mn-catalyzed conjugate reduction α-oxidation reaction to introduce the C20 hydroxyl group. Acid treatment of the α-hydroxyketone 4 gave spiroketal 19 which was converted into known spirangien A (1) advanced intermediate spiroketal 3.

The cytotoxic spiroketals spirangiens A (**1**) and B (**2**) were isolated from the myxobacterium *Sorangium cellulosum* (Figure 1).[1] These natural products contain a highly substituted spiroketal core and labile *Z,E,Z,E,Z*-penatene side chain and differ only at the C31 position, whereby **1** has a methyl group at this position while **2** terminates in an ethyl group. The structures of these compounds were deduced by NMR techniques and X-ray crystallographic analysis of a cross metathesis degradation product.[1] Spirangien A (**1**) showed activity against several yeasts and fungi and displayed very potent cytotoxicity against L929 mouse fibroblast cells with an $IC_{50} = 0.7$ ng mL^{-1}. To date, only one total synthesis of spirangien A (**1**) has been reported,[2] and this served to confirm the absolute configuration of this compound. Several syntheses of the cross metathesis degradation product[3] and the core spiroketal[4] have also been communicated.

It has been demonstrated that the biosynthesis of spirangien A (**1**) involves several post-polyketide synthase (PKS) P450 mediated late stage oxidations (Scheme 1).[5] This was based on analysis of extracts from several mutant strains of *S. cellulosum* whereby the genes that encode for the P450 enzymes SpiC and SpiL were inactivated. Both these monooxygenases are involved with the C20 and C21 oxidation of a PKS spiroketal precusor **A** to produce hydoxyketone **B** that cyclizes to the spiroketal core **C** of the spirangiens. Although the exact role of each was not determined, it appears that the oxidative modification and spiroketal formation mediated by these enzymes occur after release from the multienzyme complex.[5]

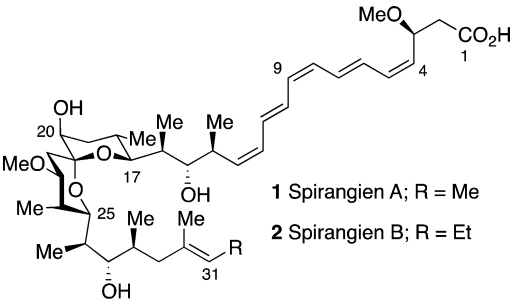


Figure 1. Structures of the spirangiens A (**1**) and B (**2**).

(1) Niggeman, J. N.; Bedorf, N.; Flörke, U.; Steinmetz, H.; Gerth, K.; Reichenbach, H.; Höfle *Eur. J. Org. Chem.* **2005**, 5013.

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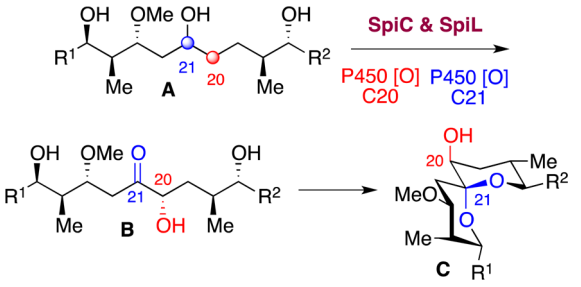
10.1021/ol3033253

We envisaged that an efficient synthesis of the spirangiens could be based on a late stage C20 oxidation as proposed in the biosynthesis. However, an effective direct conversion of a polyketide such as **A** into **B** using non-enzymatic reagents would be challenging. As shown in Scheme 2, an alternative introduction of the C20 hydroxyl group is presented. The final target was the spirangien advanced intemediate spiroketal alcohol **3**, utilized by Paterson et al. in their total synthesis of **1**.[2] This compound could be formed by spiroketalization of the protected hydroxyketone precursor **4** followed by a late-stage iron-catalyzed alkylation[4,6] to introduce the trisubstituted alkene. Hydroxyketone **4** would then arise from a one-pot Mn-catalyzed conjugate reduction/oxidation[7,8] or regioselective hydration of enone **5** mimicking the post-PKS introduction of the C20 hydroxyl group in the proposed biosynthesis.

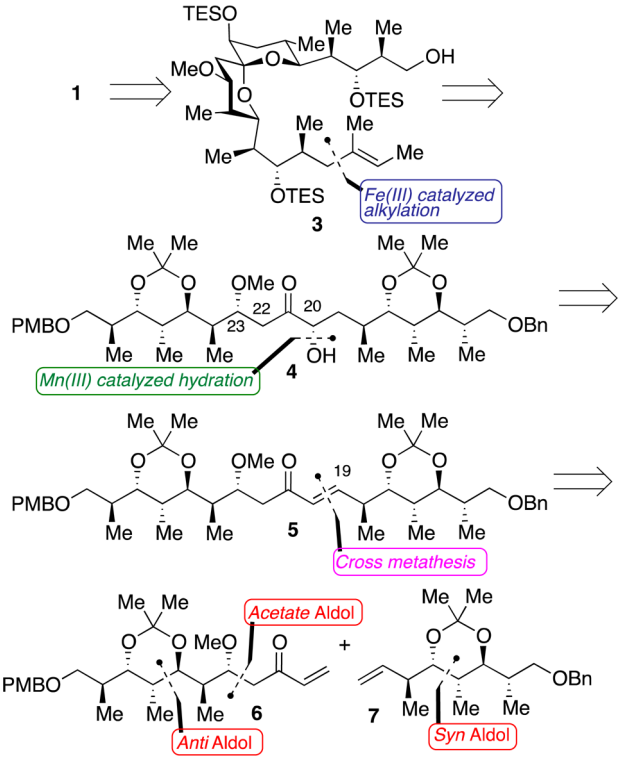
Scheme 1. Biosynthesis of the Spirangien Spiroketal



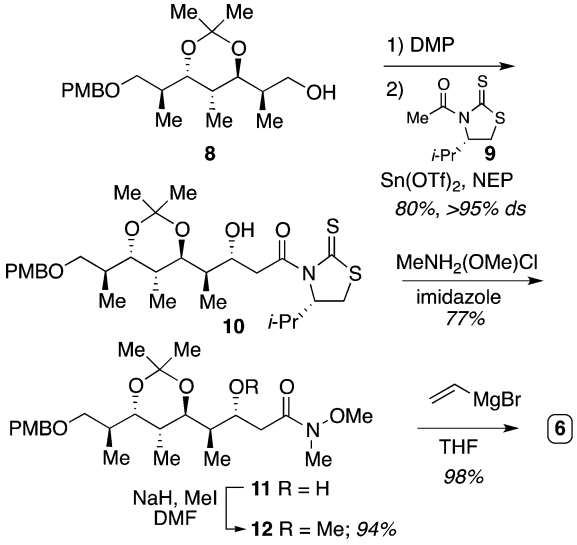
Enone **5** would be accessed by a cross metathesis (CM)[9] between enone **6** and alkene fragment **7** that would serve as an effective method for the key convergent C−C bond forming step between two large fragments. This differs from the reported approaches to related α-hydroxyketone spiroketal precursors in that all rely on a late-stage aldol condensation to form the C22−C23 bond as the convergent step.[2−4,10] The key stereoselective C−C bond forming steps for the synthesis of enone **6** include *anti*-propionate and acetate aldol reactions while **7** could be formed via a *syn*-aldol reaction as shown.

The synthesis of the enone fragment **6** is detailed in Scheme 3 and begins with the known stereopentad alcohol **8**,[11] secured by an *anti*-aldol reaction, stereoselective reduction, hydroboration, and protection.[2] Oxidation of alcohol **8** gave the corresponding aldehyde which was immediately subjected to a Nagao-type asymmetric acetate

Scheme 2. Retrosynthetic Analysis of Spirangien A (**1**)



Scheme 3. Synthesis of the Enone Fragment **6**



aldol reaction[12] with the Sn(II) enolate derived from thiazolidine-2-thione **9**[12b] to provide adduct **10** as the only detectable diastereoisomer. Auxiliary displacement[13] with

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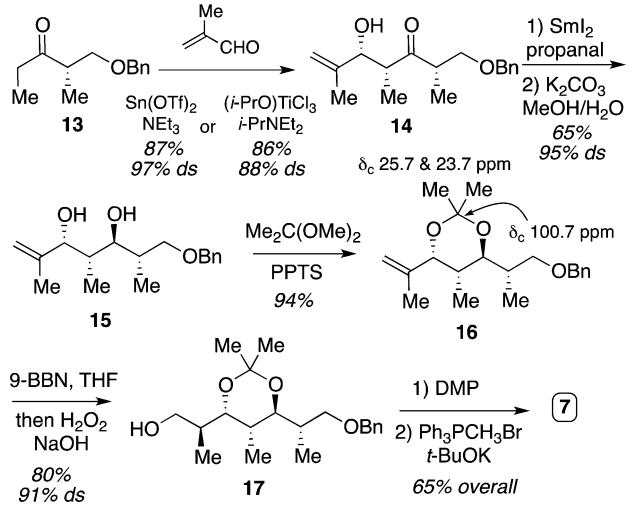
O,N-dimethylhydroxylamine and imidazole as base afforded the Weinreb amide **11**, and subsequent methylation of the free alcohol gave the ether **12** in high yield. The enone **6** was then formed in 98% yield by treatment of amide **15** with vinyl magnesium bromide.

Scheme 4. Synthesis of the Alkene **7**



The synthesis of the alkene fragment **7** began with the preparation of diol **15** by a modified route to that described for the synthesis of the enantiomer[14] (Scheme 4). A *syn*-aldol reaction[15] between the Sn enolate derived from ketone **13**[16] and methacrolein gave adduct **14**[16] in excellent yield and high diastereoselectivity. A Ti-mediated *syn*-aldol reaction[17] also provided **14** with a lower diastereoselectivity (88%), but this was a more economical process. Evans–Tishchenko reduction[18] of the ketone **14** followed by base hydrolysis gave the 1,3-*anti*-diol **15**, again with high diastereoselectivity, which was protected as the acetonide **16**. ^{13}C NMR analysis[19] confirmed that **16** possessed the desired 1,3-*anti* diol stereochemistry with significant chemical shifts for the methyl groups and acetonide carbon atom as shown in Scheme 4. Installation of the final stereocenter was achieved by stereoselective hydroboration[20] of the 1,1-disubstituted alkene in **16** using 9-BBN followed by basic oxidative workup to give the alcohol **17** in reasonable diastereoselectivity. Oxidation and Wittig extension then gave the alkene fragment **7**.

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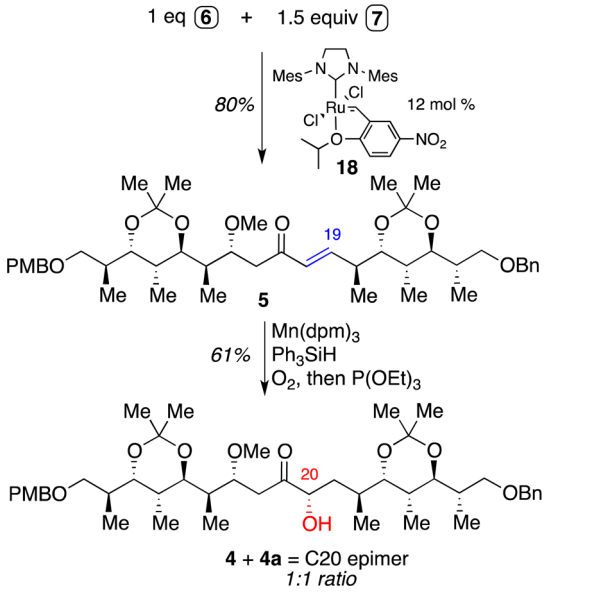
(20) (a) Still, W. C.; Barrish, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 2487. (b) Paterson, I.; Channon, J. A. *Tetrahedron Lett.* **1992**, *33*, 797.

Scheme 5. Synthesis of the α-Hydroxyketone **4**



The CM reaction[21] between enone **6** and alkene **7** was best mediated by the Grela–Grubbs–Hoveyda catalyst **18**[22] (Scheme 5). *E*-Enone **5** was formed in high yield as a single geometric isomer using 12 mol % of **18**. Hydration of enone **5** by treatment with Ph_3SiH and oxygen gas in the presence the Tris-(dipivaloylmethanato)manganese(III) {$Mn(dpm)_3$} catalyst[8a] afforded the α-hydroxyketones **4** and the C20 epimer **4a** in a 1:1 ratio after reductive workup with $P(OEt)_3$.[23] These could be separated by preparative HPLC, and their stereochemistry was assigned by conversion to the corresponding spiroketals (see below). The mechanism of this interesting transformation possibly involves formation of a Mn(II) hydride complex that reduces the enone **5** into a Mn enolate.[8a] Oxidation of the Mn(II) enolate by O_2 gives a Mn(III) peroxy complex which oxidizes the enolate to a hydroperoxide. $P(OEt)_3$ mediated reduction then gives the α-hydroxyketone.

Treatment of α-hydroxyketone **4** with CSA in methanol for 24 h resulted in deprotection and spirocyclization to give spiroketal **19** as a single isomer in good yield (Scheme 6). This reaction initially forms two products that eventually equilibrate to a single compound, and at least 0.5 equiv of CSA was required for the reaction to proceed at a reasonable rate. Similarly, exposure of **4a** to an acid resulted in the formation spiroketal **20**. Highly selective monoacetylation of each of these was achieved by treatment with acetic anhydride and pyridine to provide the C20 monoacetates **21** and **22**. ^{1}H NMR coupling constants then revealed the

(21) For related CM examples, see: (a) Marjanovic, J.; Kozmin, S. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8854. (b) Lynch, J. E.; Zanatta, S. D.; White, J. M.; Rizzacasa, M. A. *Chem.—Eur. J.* **2011**, *17*, 297.
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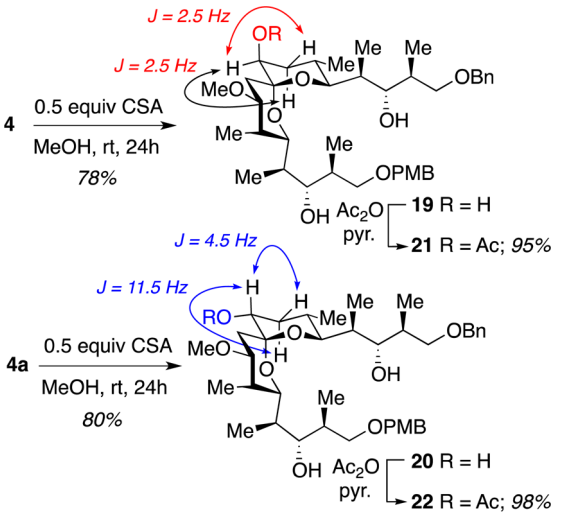
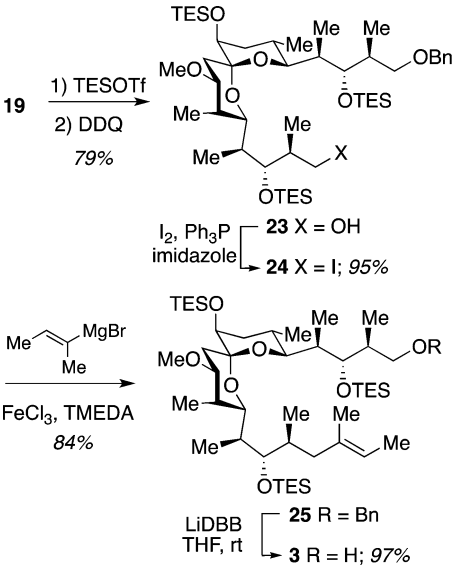
(23) For other examples of the use of this Mn(III) catalyzed hydration in complex molecules, see: (a) Bondar, D.; Liu, J.; Müller, T.; Paquette, L. A. *Org. Lett.* **2005**, *7*, 1813. (b) Cassayre, J.; Winkler, T.; Pitterna, T.; Quaranta, L. *Tetrahedron Lett.* **2010**, *51*, 1706.

Scheme 6. Spiroketal Synthesis



Scheme 7. Completion of the Formal Total Synthesis of **1**



C20 stereochemistry of each as shown, and this allowed for the assignment of the original stereochemistry of the hydroxyketone precursors. Acid treatment of the 1:1 mixture of **4** and **4a** also gave the spiroketals **19** and **20** that were easily separated by flash chromatography.

The synthesis of spirangien advanced intermediate spiroketal **3** is shown in Scheme 7. Protection of the 2° alcohols in spiroketal **19** at TES ethers followed by removal of the PMB ether afforded alcohol **23**. Conversion into the iodide **24** was achieved by exposure of **23** to iodine, PPh_3, NEt_3, and imidazole. Iodide **24** was then alkylated by a Fe(III)-mediated cross-coupling[6] with the Grignard reagent derived from *E*-2-bromobutene to give alkene **25** in good yield. Removal of the benzyl ether using LiDBB[24] at rt then yielded the final target alcohol **3**, the physical data of which were identical to those reported[2b] {$[\alpha]^{22}_D$ +19.2 (*c* 0.7, MeOH); lit.[2b] $[\alpha]^{20}_D$ +17.5 (*c* 1.5, MeOH)} thus completing a formal total synthesis of spirangien A (**1**).

(24) Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1980**, *45*, 1924.
(25) (a) Ahn, J.-W. *Bull. Korean Chem. Soc.* **2009**, *30*, 742. (b) Kwak, J. H.; Ahn, J.-W. *Arch. Pharm. Res.* **2009**, *32*, 841. (c) Ahn, J. W. *Bull. Korean Chem. Soc.* **2009**, *30*, 1218.

In conclusion, we have completed a formal total synthesis of spirangien A (**1**) by the production of the known intermediate spiroketal **3**. The key transformations in the sequence include a highly convergent CM reaction to unite the enone **6** and alkene **7**, a Mn(III)-catalyzed conjugate reduction/oxidation sequence to introduce the C20 hydroxyl group at a late stage as a mimick of the biosynthesis of spirangien A (**1**), acid induced spiroketalization, and a Fe(III)-catalyzed alkylation. The synthesis of related *S. cellulosum* metabolites[25] using this approach is underway.

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Supporting Information Available. Experimental details as well as characterization data and copies of the NMR spectra of 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.