

Total synthesis of spiroketal containing natural products: kinetic vs. thermodynamic approaches

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Abstract

This review details part of a lecture delivered at the 20th ICHC in Palermo Italy, July 31-August 5 2005. The published total syntheses of reveromycin A (**1**) and the assigned structure for spirofungin B (**26**) are described. The approach to **1** utilized a hetero-Diels-Alder reaction to construct the spiroketal fragment in a kinetic stereocontrolled manner. The synthesis of the proposed spirofungin B (**26**) spiroketal fragment utilized a thermodynamically controlled cyclization of a protected dihydroxyketone precursor. This allowed for the reassignment of the structure of spirofungin B as *epi*-spirofungin A (**48**).

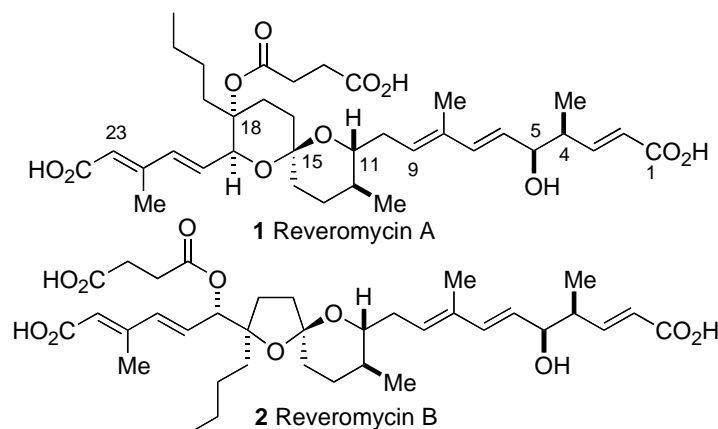
Keywords: Reveromycins, spiroketal, hetero-Diels-Alder, spirofungins

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1. Total synthesis of (-)-Reveromycin A

The reveromycins A (**1**) and B (**2**) are members of a family of compounds isolated from the soil actinomycete *Streptomyces sp.*¹ Reveromycin A (**1**) is a potent inhibitor (IC₅₀ 0.7 µg mL⁻¹) of the mitogenic activity of epidermal growth factor (EGF) in a mouse keratinocyte. In addition, compound **1** exhibits antiproliferative activity against human tumor cell lines (IC₅₀ = 1.3-2.0 µg mL⁻¹) as well as antifungal activity (MIC = 2.0 µg mL⁻¹, pH 3).^{1b} Recently, reveromycin A (**1**) has been identified as a specific inhibitor of *Saccharomyces cerevisiae* isoleucyl-tRNA synthetase (IleRS) using yeast genetics and biochemical studies.²



So far, only one total synthesis of **1** has been reported³ and several approaches to the 6,6-spiroketal core have been described⁴⁻⁶ while three total syntheses of reveromycin B (**2**), have been completed.⁷⁻⁹ The total synthesis of (-)-reveromycin A (**1**) has been achieved¹⁰ utilizing a hetero-Diels-Alder (HDA) strategy to construct the challenging spiroketal moiety of this molecule.⁶

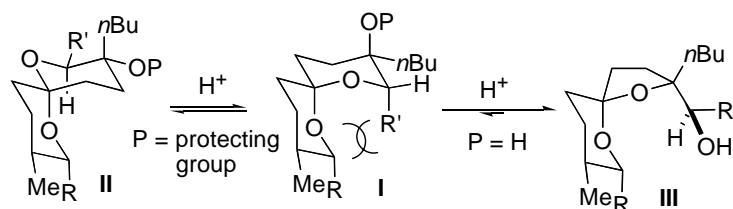
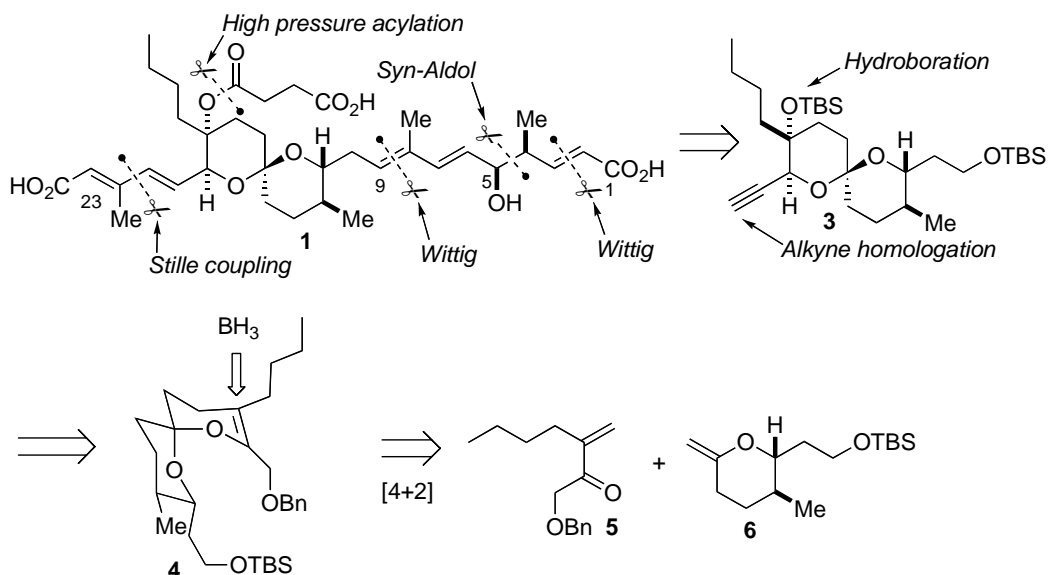


Figure 1

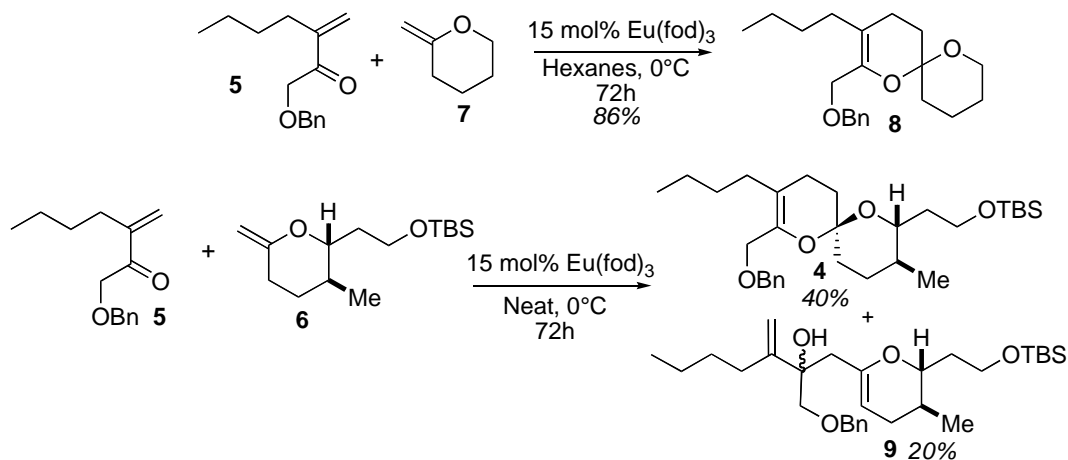
It is known that the reveromycin A (**1**) type 6,6-spiroketal core **I** can undergo acid catalyzed isomerization to afford the spiroisomer **II** due to an unfavorable steric interaction involving the axial C19 side chain in **I** which is alleviated in **II**, albeit at the cost of an anomeric effect (Figure 1).

Thus, the energy difference between the 6,6-spiroketal **I** and **II** is small. In addition, when the C18 alcohol is free, acid induced isomerization provides the more stable reveromycin B (**2**) 5,6-spiroketal core **III** exclusively. This energy profile has been observed in the reported thermodynamic approaches (i.e. cyclization of a 'dihydroxyketone' precursor) to the 6,6-spiroketal of **1** which provided mixtures of spiroisomers^{3,4,5} while degradative^{4,11} and synthetic studies^{6,7,9b,12} have demonstrated the strong preference for the reveromycin B type 5,6-spiroketal **III**.



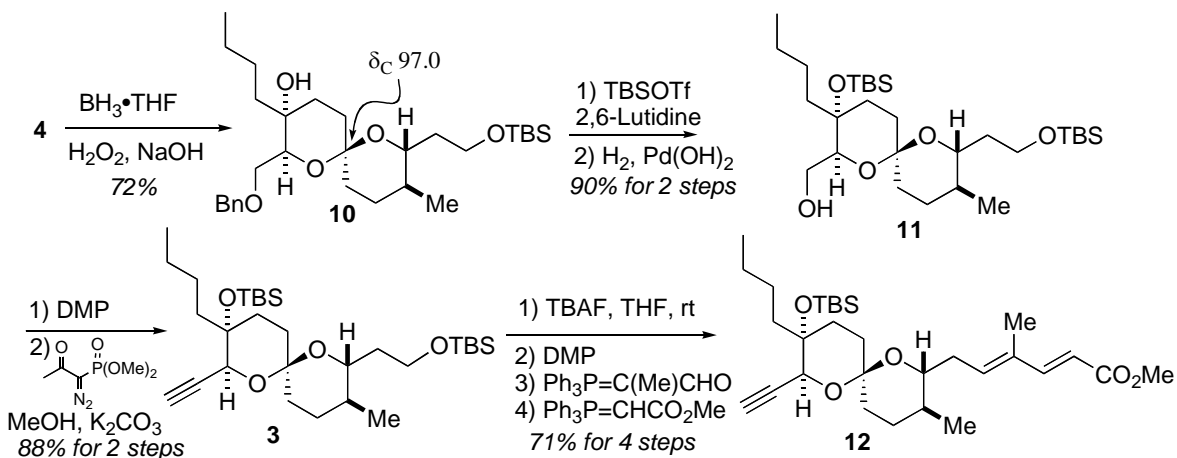
Scheme 1

In light of the above results, we envisioned that a kinetic approach to the reveromycin A spiroketal may circumvent the thermodynamic dilemma cited above. As shown in Scheme 1, the indicated retrosynthetic disconnections of **1** lead to the intermediate 6,6-spiroketal **3**. This could be obtained from unsaturated spiroketal **4** by regio- and stereoselective hydroboration from the direction shown followed by alkyne homologation. Key spiroketal **4** could be obtained by an inverse electron demand HDA reaction¹³ between the diene **5**⁶ and the chiral methylene pyran **6**.⁹ This critical reaction should set the stereochemistry at the spiro center by an axial approach of the carbonyl oxygen in the HDA transition state.⁹ The stereochemistry at C18 and C19 is then set by the hydroboration/oxidation sequence which circumvents the thermodynamic lability of the reveromycin A type spiroketal **I**. In addition to being stereoselective and convergent, this route would also avoid the need for a large number of different protecting groups.



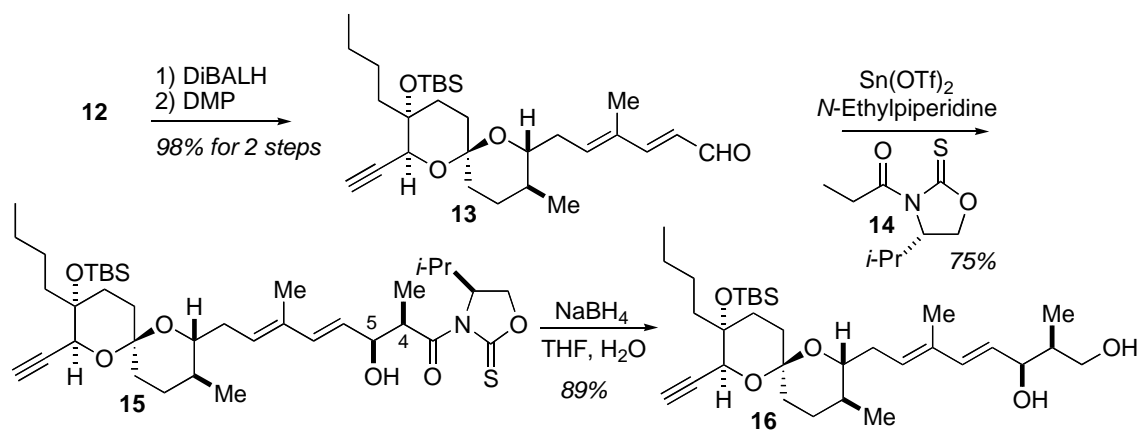
Scheme 2

Earlier, we had found that the HDA reaction of isomerizable methylene pyrans with simple hetero dienes can be achieved thermally in the presence of K_2CO_3 , which effectively reduced the amount of the thermodynamically driven *exo* to *endo* isomerization of the dienophile.^{6,9} In the case of diene **5**, using this additive gave low yields of spiroketal due to the base lability of the diene.⁶ Therefore, Lewis acid promotion of the cycloaddition was surveyed using the diene and model dienophile **7** (Scheme 2). After some experimentation, we found that the HDA between **7** and diene **5** was promoted by $Eu(fod)_3$ ¹⁴ in hexane solvent at 0°C to give the spiroketal **8** in excellent yield. Unfortunately, in the case of the substituted methylene pyran **6** required for the synthesis of **1**, no HDA reaction was observed in hexane solvent and only slow isomerization occurred to give the *endo* isomer of **6**. Eventually, we found that the cycloaddition proceeded smoothly when a neat mixture¹⁵ of the diene **5** and dienophile **6** was treated with 15 mol% $Eu(fod)_3$ at 0°C. Although the reaction gave the desired spiroketal **4** as one diastereoisomer in a higher yield than that obtained using K_2CO_3 ,⁶ the byproduct **9**, resulting from an ene reaction, was also isolated as a mixture of diastereoisomers. This was not observed during the studies using the model pyran **7**. The HDA reaction between **5** and **6** was also promoted by $ZnCl_2$ in THF at 0°C to provide the adduct **4** in a comparable yield.



Scheme 3

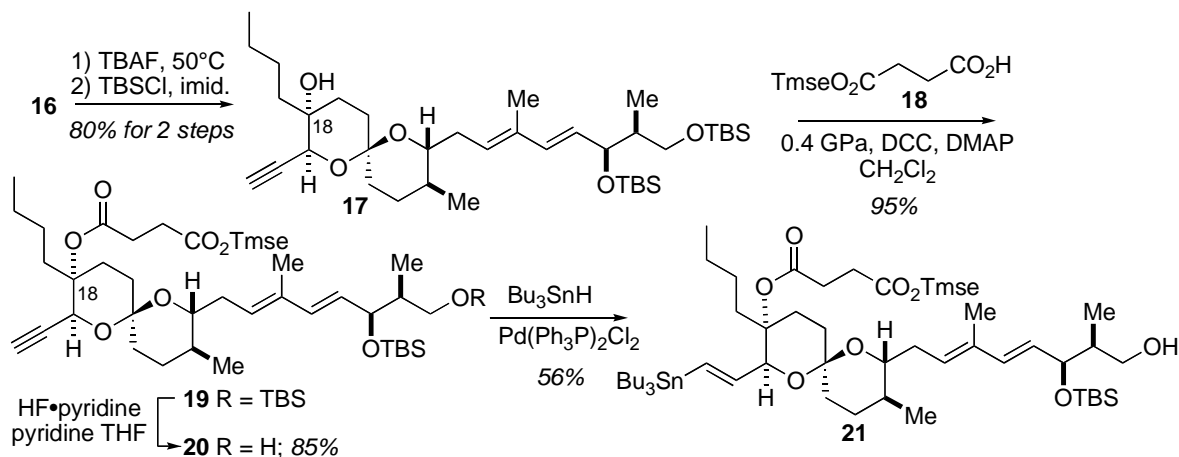
With the desired spiroketal in hand, we next tackled the introduction of the C18 and C19 stereocenters and C5-C10 chain extension as shown in Scheme 3. Hydroboration of spiroketal **4** followed by oxidation proceeded in good yield to afford the tertiary alcohol **10** as the only isomer.



Scheme 4

The integrity of the 6,6-spiroketal **10** was evidenced by the characteristic ^{13}C NMR chemical shift (97.0 ppm) observed for the spiro carbon^{9,10} while the stereochemistry was confirmed by its conversion into a known reveromycin A degradation product⁴ as described previously.⁶ Protection of the tertiary alcohol followed by debenzoylation afforded alcohol **11** ready for alkyne homologation. Oxidation¹⁶ of **11** and alkyne formation following the Bestmann protocol¹⁷ then gave compound **3**. Selective desilylation of the primary TBS group (TBAF, rt) followed by oxidation and two step Wittig extension provided the diene **12** in excellent overall yield for the four steps. Reduction of **12** and subsequent oxidation provided the substrate **13** required for the reagent controlled aldol reaction (Scheme 4). Treatment of aldehyde **13** with the tin enolate derived from oxazolidine-2-thione **14**^{9,18} afforded the desired *syn*-propionate **15** which when exposed to NaBH_4 gave the diol **16** as a result of reductive auxiliary cleavage.

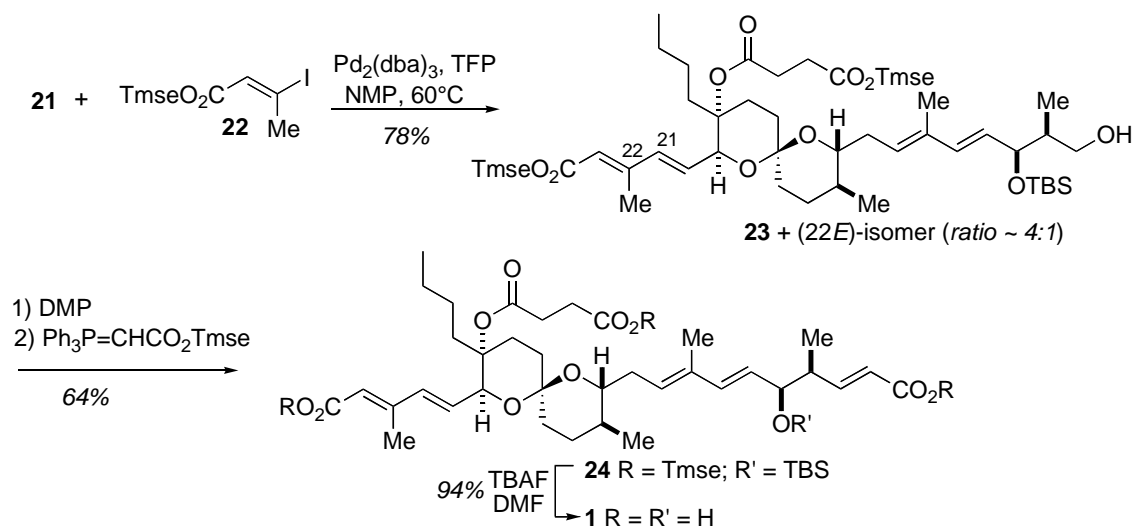
Removal of the C18 TBS ether required warming to 50°C to proceed at an appreciable rate and selective primary/secondary alcohol protection yielded *bis*-TBS ether **17** (Scheme 5). The stage was now set for the somewhat risky late stage introduction of the C18 hemisuccinate. Several methods for the acylation of hindered alcohols failed,¹⁹ affording mostly the isomerized 5,6-spiroketal as found in **2**, so we turned to the application of high pressure according to the procedure described by Shimizu and Nakata.^{3,20} Thus, treatment of a mixture of alcohol **17** and monoprotected succinic acid **18**^{9b} with DCC and DMAP at 0.4 GPa in CH_2Cl_2 solvent gave the desired ester **19** in very high yield. Interestingly, we found that the reaction proceeded efficiently at much lower pressures than reported previously (1.5 GPa)²⁰ and required the use of relatively simple high pressure equipment.



Scheme 5

Selective deprotection of the primary alcohol in **19** proceeded well using HF•pyridine complex buffered with pyridine²¹ to afford the alcohol **20**. Hydrostannylation of the alkyne in **20** proved somewhat difficult under Pd catalyzed conditions²² owing to the steric hindrance at the axial alkyne functionality and excessive amounts of protodestannylation occurred during the reaction. We found that slow addition of the catalyst (up to 30 mol% over 5 h) was required to give the vinyl stannane **21** in acceptable yields.

The final steps to the target **1** are outlined in Scheme 6. Stille coupling²³ between stannane **21** and vinyl iodide **22**^{9b} afforded the required tetraene **23** along with a small amount of what was tentatively identified as the 22*E*-isomer. This type of isomerization was observed by us during our studies on the total synthesis of reveromycin B (**2**).⁹ Oxidation of the free primary alcohol and Wittig extension²⁴ afforded the fully protected reveromycin A precursor **24** which upon exposure to TBAF in DMF gave (–)-reveromycin A (**1**) in high yield. The synthetic material was purified by reverse phase chromatography (C18 SPE cartridge, 900 mg, 40-60% MeOH/H₂O) and was identical (NMR, IR, UV, HRMS) to the natural product in all respects {[α]_D²² –122.4 (*c*, 0.16, MeOH); Lit.^{1b} [α]_D²³ –115 (*c*, 0.1, MeOH)} including retention time on RP-HPLC.

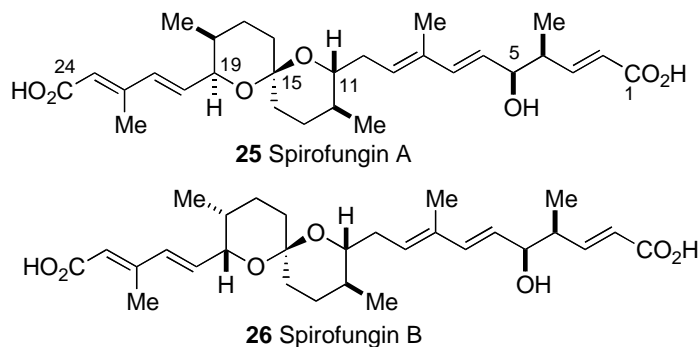


Scheme 6

In conclusion, we have completed the total synthesis of (-)-reveromycin A (1) which utilized a HDA reaction hydroboration sequence to construct the spiroketal core in a convergent and stereoselective manner.

2. Total synthesis of the proposed structure for spirofungin B: a reassignment of the stereochemistry

The spirofungins A (25) and B (26) were isolated from a *Streptomyces* strain Tü 4113 collected in the Otway National Park, Australia.²⁵ Compounds 25 and 26 possess a similar 6,6-spiroketal core to reveromycin A (1)¹ and have the same C1-C9 triene acid and C20-24 diene acid segments however there is no succinate half ester at C18 and the C18 substituent is a methyl group. The spirofungins show high inhibition activity against yeast and moderate activity against some fungi with a MIC of 15 µg mL⁻¹ against *Candida albicans*.²⁵



Compounds (**25**) and (**26**) were isolated as a ~4:1 mixture respectively. Although they possessed slightly different retention times on reverse phase HPLC, they were not separated and the structural elucidation was conducted on this mixture. The structure of the major isomer spirofungin A (**25**) was assigned using various NMR techniques with the minor component spirofungin B (**26**) identified as a diastereoisomer of **25**, epimeric at both C18 and C19. The absolute configurations of **25** and **26** are suggested by analogy to the reveromycins.

It was proposed²⁵ that the spiroketal core of **25** possessed the conformation **A** as depicted in Figure 2, with the oxygens (maximum anomeric stabilization) and the C19 diene acid sidechain in axial orientations while the C18 methyl group is equatorial. In compound **26**, the C19 sidechain is now equatorial while the C18 methyl group is oriented axial as shown in proposed conformer **B**. This was supported by the vicinal coupling constant measured between H19 and H18, the C18 change in chemical shift, and the ROE observed between H19 and H11.

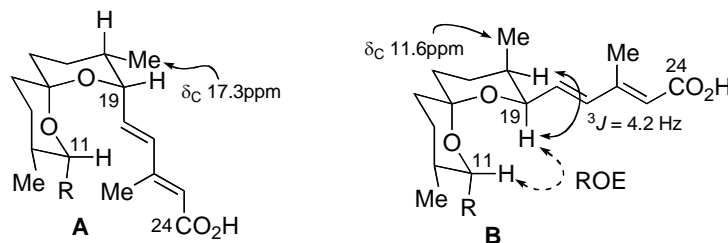
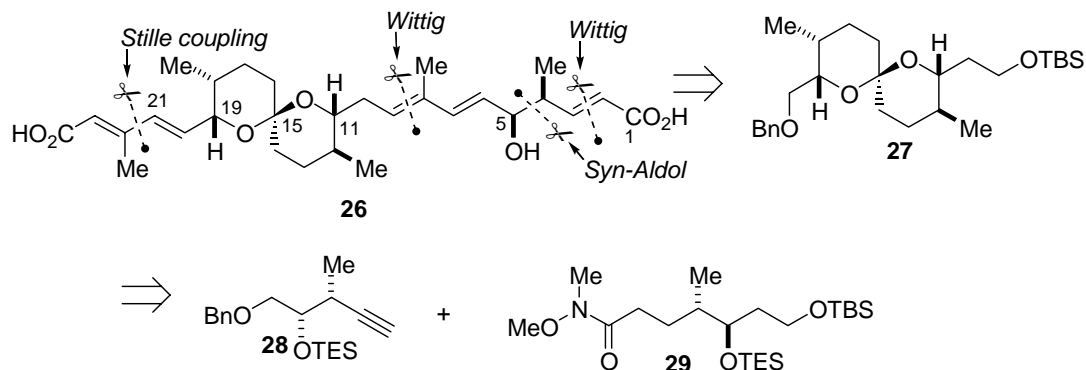


Figure 2

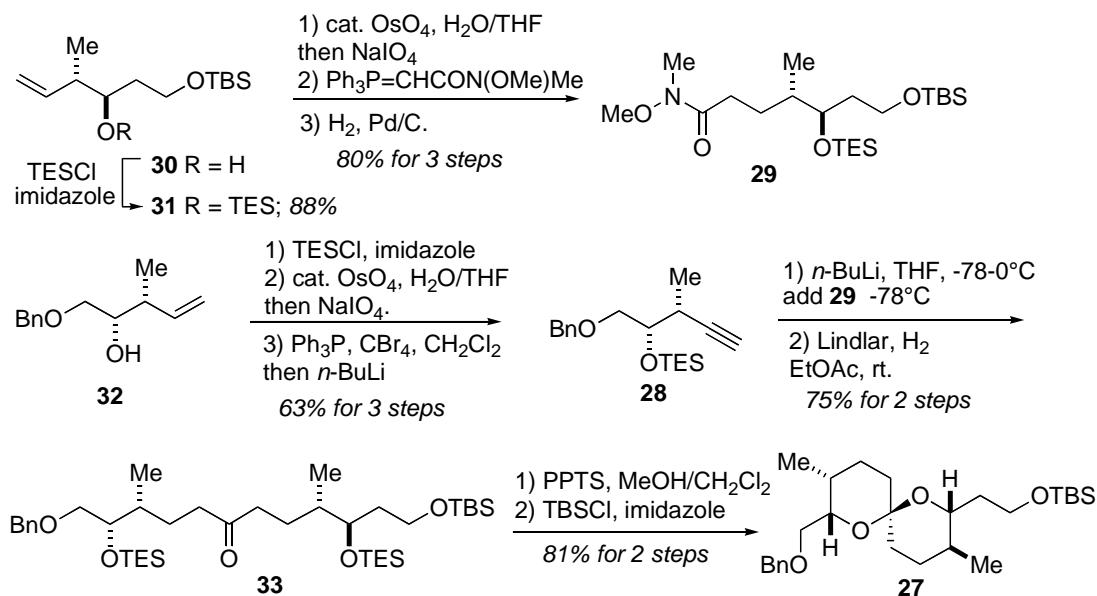
The natural occurrence of spirofungin B (**26**) is curious since it possesses a different absolute configuration at C19 to that from both spirofungin A (**25**) and the related reveromycins. Several groups have reported approaches^{26,27} to the spiroketal systems of spirofungins A (**25**). Herein, we detail our total synthesis of the structure **26** proposed for the minor component spirofungin B which lead to the reassignment of the stereochemistry of this natural product.²⁸



Scheme 7

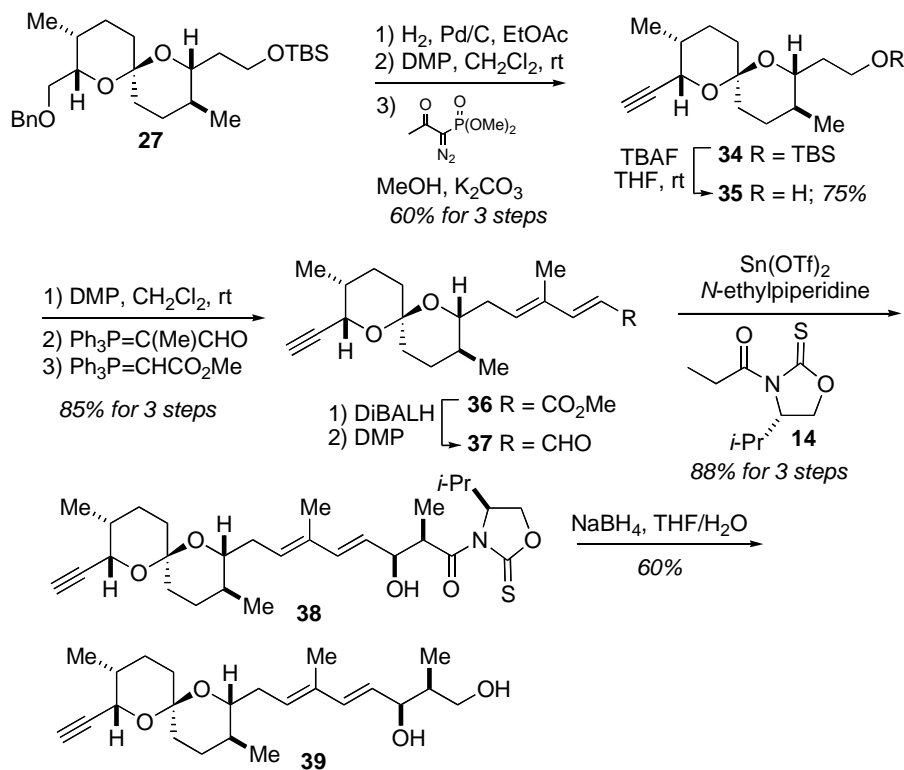
A brief retrosynthetic analysis of **26** is shown in Scheme 7. The key bond disconnections

are similar to those utilized for our total synthesis of reveromycin B (**2**).⁹ The C2-C3 and C8-C9 bonds could be formed via stabilized Wittig reactions while the the C4-C5 bond might be formed by a reagent controlled asymmetric *syn*-aldol reaction.¹⁸ Finally, the C21-C22 bond could be installed using a Stille cross coupling reaction.²³ This leads to the key spiroketal intermediate **27** which could be constructed from a coupling²⁹ between the anion derived from alkyne **28** and Weinreb amide **29** followed by alkyne saturation and acid induced deprotection and spiroketal formation.¹³



Scheme 8

The route to the proposed²⁵ structure for spirofungin B began with the known optically pure alcohol **30**⁹ (Scheme 8).



Scheme 9

Silylation of **30** gave ether **31** which was smoothly converted into Weinreb amide **29** by oxidative alkene cleavage, Wittig extension and hydrogenation. Coupling fragment **28** was synthesized from known alcohol **32**³⁰ by protection, alkene cleavage and Corey-Fuchs³¹ alkyne formation. Treatment of the alkyne **32** with *n*-BuLi followed by addition of the amide **29** and subsequent complete saturation using H₂ and Lindlar catalyst gave the corresponding ketone **33** in excellent yield without any benzyl group removal. Compound **33** was subjected to acid deprotection and spiroketalization by treatment with PPTS in MeOH to give **27** as the only spiroisomer. Some of the primary TBS group was cleaved in this sequence but this was easily reinstalled by subjection of the crude product to resilylation. With the spiroketal fragment **27** in hand we next appended the C3-C10 sidechain as outlined in Scheme 9.

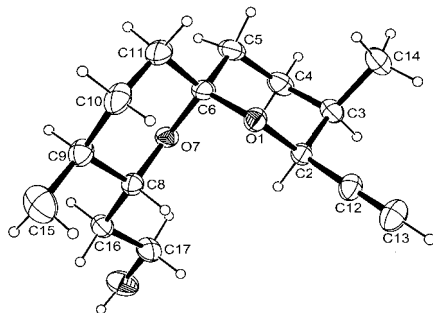
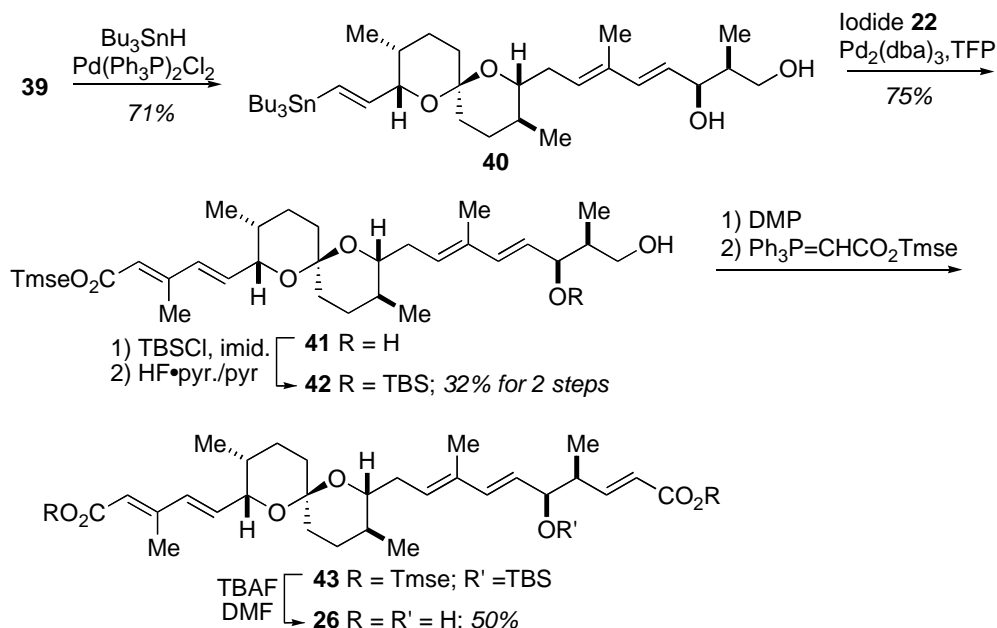


Figure 3. X-Ray structure of spiroketal **35**.

Debenzylation of **27** followed by oxidation¹⁶ and homologation using the Bestmann protocol¹⁷ gave alkyne **34**. TBAF induced desilylation then afforded the alcohol **35** which fortunately was crystalline and an X-ray crystal structure³² was obtained for this intermediate confirming the stereochemistry (Figure 3).



Scheme 10

Oxidation of alcohol **35** and sequential Wittig extensions gave the ester **36** in good yield. Adjustment of the oxidation level in **36** gave aldehyde **37** which underwent an asymmetric aldol reaction with the tin enolate derived from oxazolidine-2-thione **14**.⁹ This sequence of reactions was high yielding and easily conducted on large scale. Auxiliary removal by treatment of **38** with NaBH₄ in wet THF gave diol **39**.

The final steps to compound **26** are outlined in Scheme 10. Conversion of alkyne **39** into vinyl stannane **40** using Pd catalysis²² proceeded in good yield. The stannane was then cross coupled²³ with the known iodide **22**⁹ to cleanly provide ester **41** with the C20-C24 sidechain fully installed.

Protective group manipulation gave **42** which upon oxidation and Wittig reaction provided the protected precursor **43**. Exposure of **43** to excess TBAF in DMF caused global deprotection to give the nominal structure for spirofungin B (**26**) which was purified by reverse phase HPLC. Unfortunately, the physical data obtained for synthetic **26** did not compare with that reported for spirofungin B.²⁵ Furthermore, the ¹H NMR spectrum of an authentic spirofungin mixture measured on the same instrument did not match our synthesized material. In particular, the chemical shift for H19 in the natural product (4.76 ppm) was vastly different to that found for compound **26** (4.29 ppm). In addition to other shift differences in the ¹H NMR spectrum, the

chemical shift for C15 in the ^{13}C NMR spectrum of **26** was also measurably different to the literature value (Natural²⁵ spirofungin B: 97.7 ppm. Synthetic **26**: 96.2 ppm.) These differences lead to the obvious conclusion that the structure proposed for spirofungin B (**26**) is incorrect.

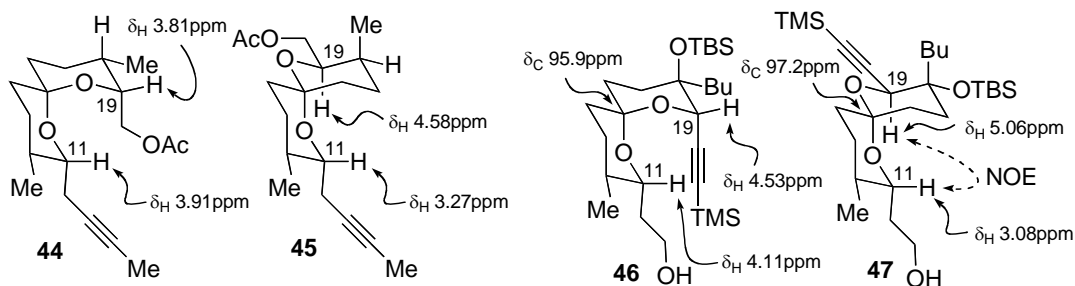
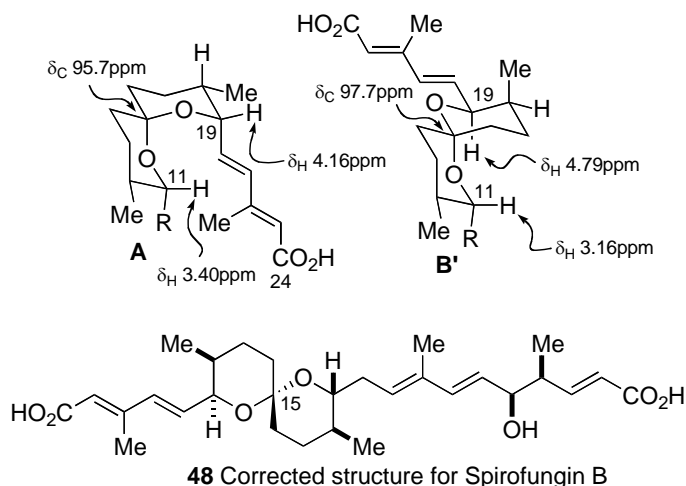


Figure 4. Related spiroketals (spirofungin numbering).

An investigation of the literature revealed a possible alternative for the structure of spirofungin B. In their synthesis of the spiroketal fragment of spirofungin A, Shimizu and co-workers²⁷ obtained a mixture of spiroketals **44** and **45** (ratio 1.53:1) isomeric at the spiro centre via a thermodynamic approach similar to that utilized above (Figure 4). This clearly demonstrates that isomerization of the spirofungin A spiroketal is possible under acidic conditions (due to the axial orientation of the C19 substituent) to afford a spiroketal with one less anomeric stabilization.³³ The chemical shift for the H19 in the preferred isomer is upfield from the corresponding shift in the minor isomer where the axial H19 is deshielded by the axial oxygen³⁴ and the opposite change in chemical shift is evident for H11 (Figure 4). Comparable chemical shift differences are also observed for H11 and H19 in spirofungins A and B themselves (Figure 5). Another example can be found in the synthesis of the spiroketal fragment of reveromycin A (**1**). Theodorakis and co-workers⁷ also obtained a mixture of spiroketal isomers **46** and **47** in a ratio of 1.5:1 respectively by acid induced spiroketalization. The chemical shift differences (Figure 4) for the H11 and H19 protons for each isomer are similar to those cited above. In addition, the C15 chemical shifts for each isomer differ in a similar manner to that for spirofungin A (95.7 ppm) versus B (97.7 ppm). This is consistent with the trend of a slight downfield shift of the spiro carbon in going from ax-ax to ax-eq oxygen orientations.³⁵ An NOE was also observed between H19 and H11 which was also seen in spirofungin B (Figure 2).

**Figure 5**

The results cited above strongly suggest that the structure for spirofungin B is in fact 15-*epi*-spirofungin A (**48**) (Figure 5). The absolute configurations at C18 (*S*) and C19 (*R*) in spirofungin B are identical to that for spirofungin A (**26**) while the spiro carbon is epimeric (15*R*). Spirofungin A (**25**) has the conformation **A** while spirofungin B has the conformation **B'** as shown in Figure 5 which is consistent with the NMR data presented. It is not unreasonable to suggest that biosynthetically, spirofungin A (**26**) could give rise to **48** by simple spiroketal isomerization in analogy to the spiroisomers of the pectenotoxins.³⁶

Acknowledgements

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