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Enantioselective Total Synthesis of Spirofungins A and B

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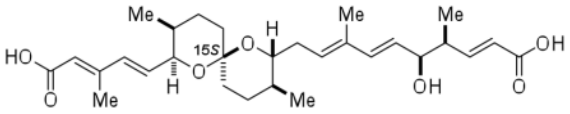
Abstract



(–)-spirofungin A (**1**) (15*S*)
(+)-spirofungin B (**2**) (15*R*)

The enantioselective total synthesis of spirofungins A (1) and B (2) is reported in 14 steps over the longest linear sequence. Key steps include the use of thiazolidinethione mediated aldol reactions to assemble the major fragments and installation of the C1–C6 side chain using a cross metathesis reaction.

Spirofungins A (**1**) and B (**2**) were isolated in 1998 as secondary metabolites of *Streptomyces violaceusniger* Tü 4113 as a 4:1 mixture.[1] These spiroketal-containing natural products differ only in the configuration about the C-15 spirocenter.[2] The spirofungins, along with the structurally related reveromycins,[3] possess high antifungal activity against yeasts, including the human pathogen *Candida albicans*. Further biological studies by the Kozmin group revealed that spirofungin A suppresses the growth of several human cancer cell lines and selectively inhibits isoleucyl-tRNA synthetase in vitro.[4] The interesting structure and biological profile of the spirofungins have resulted in two total syntheses[4,5] as well as several approaches to the spiroketal core.[6] Additionally, the Shimizu group has begun investigating derivatives of both spirofungin A and the reveromycins.[7]

Herein, we describe a highly convergent route to (−)-spirofungin A (**1**) and (+)-spirofungin B (**2**) in which a cross metathesis reaction would be employed to install the C1–C6 side chain **3** in an efficient manner (Scheme 1). The cross metathesis partner, diene **4** or **5**, was envisioned to arise from the spiroketalization of ketone **6**, available via a Horner-Wadsworth-Emmons olefination, conjugate reduction sequence. The β-ketophosphonate **7**, aldehyde **8**, and ester **3** would be prepared using chiral auxiliary mediated aldol reactions developed in our laboratories.[8, 9]

Initial efforts were focused on the synthesis of aldehyde **8**. Due to the required *anti* substitution, this fragment could not be accessed directly from a thiazolidinethione mediated propionate aldol reaction (Scheme 2). Instead, aldehyde **8** was prepared via a diastereoselective acetate aldol reaction followed by a Frater-Seebach alkylation.[10] The acetate aldol reaction between *N*-acetylthiazolidinethione **9**[9] and 3-butenal[11] gave rise to aldol adduct **10** in 81% yield and >20:1 diastereomeric ratio. Direct displacement of the chiral auxiliary[8] with *iso*-butyl alcohol

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Supporting Information Available: Experimental details and spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

provided ester **11** in 98% yield. The Frater-Seebach alkylation with methyl iodide proceeded in high diastereoselectivity, however optimization was necessary to improve the rate of conversion. After screening a variety of conditions it was determined that adding DMPU resulted in the highest and most consistent yields.[12] The alkylated ester **12** was obtained in 63% yield and a 10:1 diastereomeric ratio with the optimized conditions. Protection of **12** as the triethylsilyl ether and reduction of the ester generated aldehyde **8** in five steps and 44% overall yield.

The synthesis of β-ketophosphonate **7** commenced with an Evans *syn* propionate aldol addition[11] between *N*-propionylthiazolidinethione **13** and known aldehyde **14**[13] to deliver secondary alcohol **15** in 88% yield and >20:1 diastereomeric ratio (Scheme 3). The resultant alcohol was protected as the triethylsilyl ether and reductive removal of the thiazolidinethione auxiliary gave rise to aldehyde **16** in 81% yield over the two steps.

A Wittig reaction with stabilized ylide **17** was employed to homologate the aldehyde to the α,β-unsaturated ester. Upon 1,4-reduction with di-*iso*-butylaluminum hydride mediated by MeCu,[14] ester **18** was obtained in 83% yield. Treatment of ester **18** with lithiated dimethyl methylphosphonate[15] furnished β-ketophosphonate **7** in 87% yield and 48% overall yield for the six steps.

With both β-ketophosphonate **7** and aldehyde **8** in hand, formation of the spiroketal precursor via a modified Horner-Wadsworth-Emmons olefination[16] was next explored. Treatment of **7** with barium hydroxide followed by addition of aldehyde **8** formed the desired C13–14 bond. Conjugate reduction[14] of the resultant enone generated ketone **6** in 94% yield. Exposure of the ketone to PPTS in methanol resulted in facile cleavage of the silyl protecting groups and spontaneous spiroketalization to provide a 2:1 mixture of spiroketals **19** (15*S*-isomer) and **20** (15*R*-isomer). NOESY and COSY NMR analysis determined that the major product corresponded to the spiroketal core of spirofungin A. The spiroketals were readily separated by flash column chromatography to give **19** and **20** in 56% and 26% yields respectively, each of which was carried on separately for the remaining steps in the synthesis.

Introduction of the desired oxidation state of C24 was achieved via a manganese dioxide oxidation employing sodium cyanide and methanol[17] to deliver methyl esters **21** and **22** each in 78% yield. To arrive at the desired cross metathesis partner, installation of the C6–C8 diene was accomplished via a sequential cross metathesis/Wittig reaction.[18] Treatment of **21** or **22** with methacrolein and Grubbs second generation catalyst gave rise to enals **23** and **24** in 74% yield. A methylene Wittig[19] olefination introduced the terminal olefin, providing dienes **4** and **5** in 86% and 75% yield respectively.

Having developed an efficient route to the spiroketal core, focus was shifted to synthesis and appendage of the C1–C6 side chain. Allylic alcohol **3** could be generated in a sequence analogous to that used to prepare β-ketophosphonate **7** (Scheme 4). Beginning with an Evans *syn* propionate aldol reaction between *N*-propionylthiazolidinethione **13** and acrolein gave aldol adduct **25** in 96% yield and excellent diastereoselectivity. The alcohol was then protected as the triethylsilyl ether and the auxiliary reductively cleaved to deliver aldehyde **26** in 92% yield over the two steps. A Wittig reaction with ylide **17** and removal of the silyl protecting group furnished allylic alcohol **3** in excellent yield over the five steps.

The major bond forming event that remained was introduction of the C6–C7 bond via a cross metathesis reaction of either diene with allylic alcohol **3**. Based on the previous success of a cross metathesis between a similarly substituted diene and allylic alcohol from our group,[20] we anticipated the proposed cross metathesis between diene **4** or **5** and allylic alcohol **3** to be selective for the desired *E* alkene.[21] While the reaction was highly selective, initial attempts were plagued by low yields and conversion. Several reaction conditions and model substrates

were examined in order to optimize the key cross metathesis reaction. Ultimately, it was found that to obtain the highest yields, it was necessary to add the ruthenium catalyst as a solution over several hours. Under the optimized conditions, the cross metathesis products **27** and **28** were obtained in 83% and 71% yield respectively based on recovered diene. Finally, employing conditions used by Shimizu,[5] hydrolysis of the diester with lithium hydroxide provided (−)-spirofungin A (**1**) in 87% yield and (+)-spirofungin B (**2**) in 88% yield.

In summary, a highly convergent total synthesis of spirofungins A and B has been completed in 14 steps as the longest linear sequence from known aldehyde **14**. The key fragments were assembled using the thiazolidinethione mediated propionate and acetate aldol reactions developed in our laboratories. A cross metathesis reaction provided an efficient strategy for appending the right-hand side chain to the spiroketal core.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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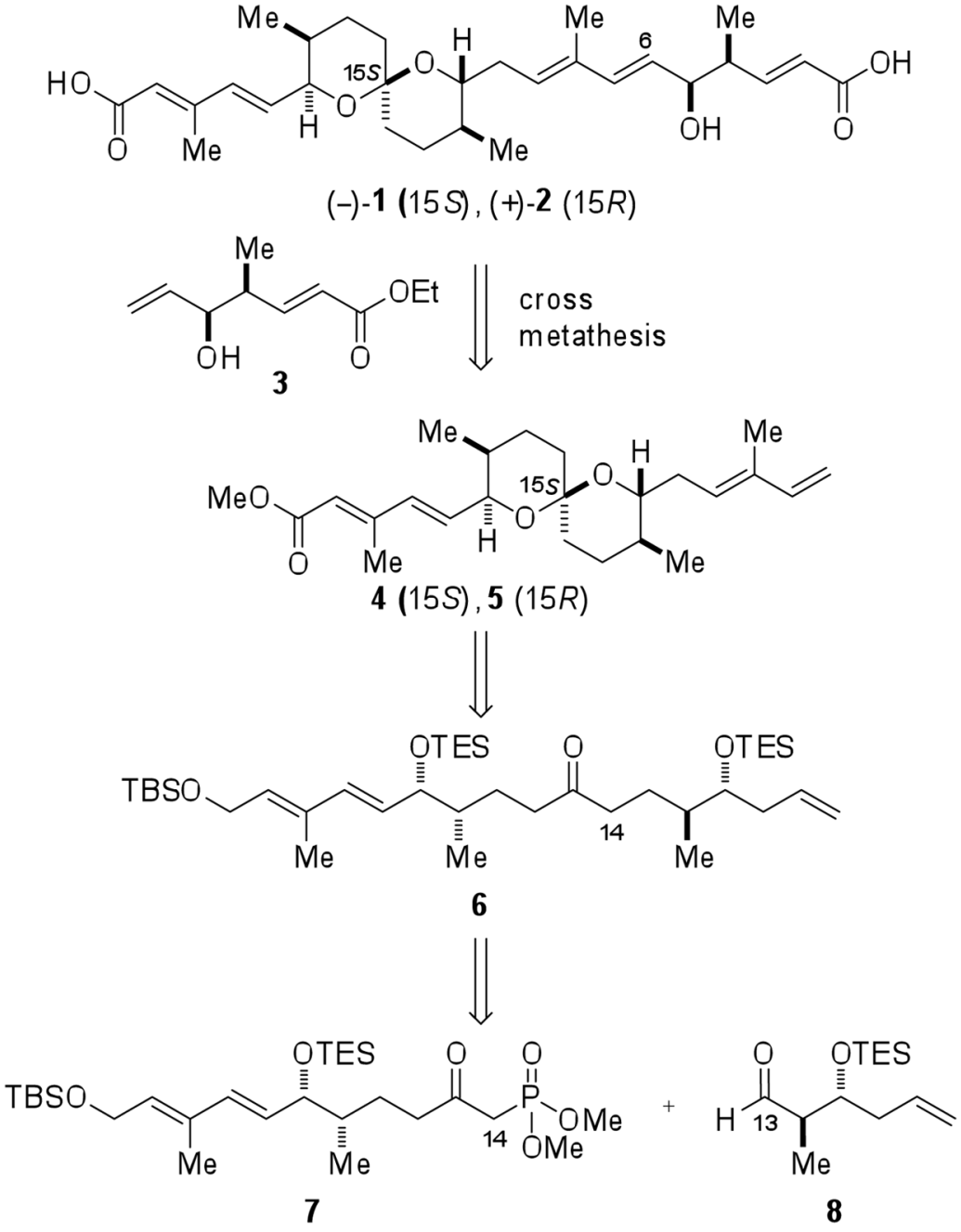
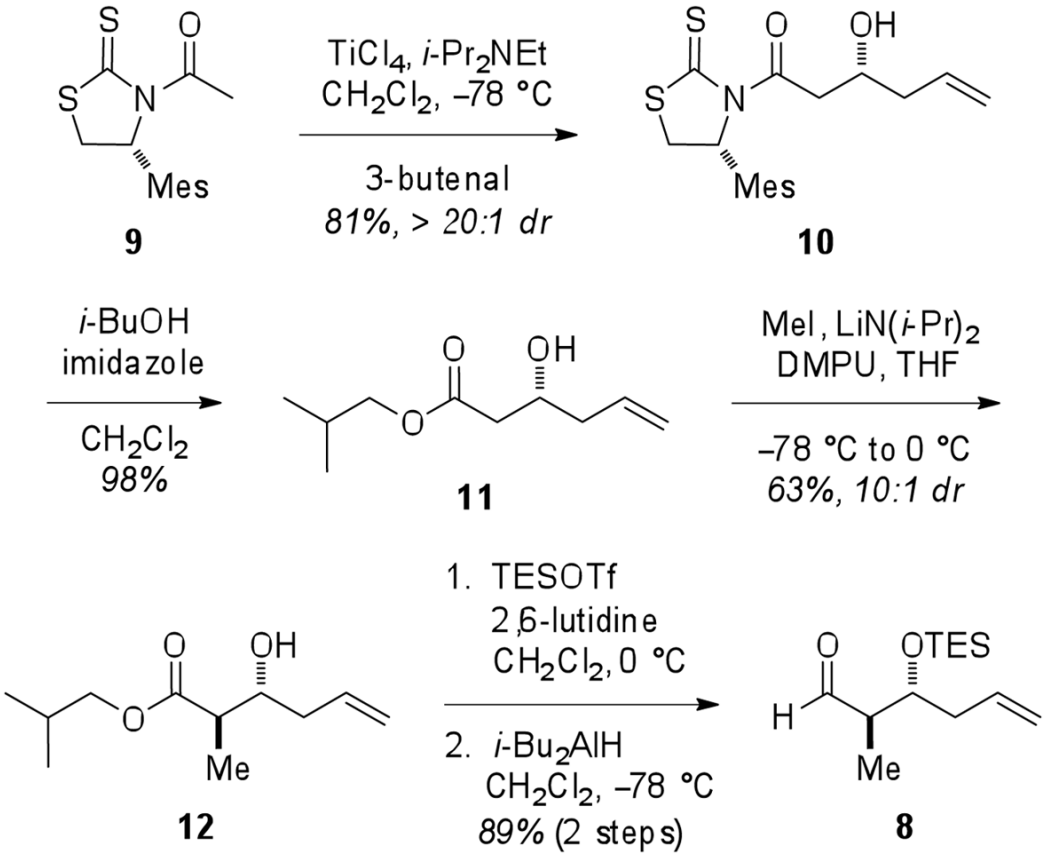
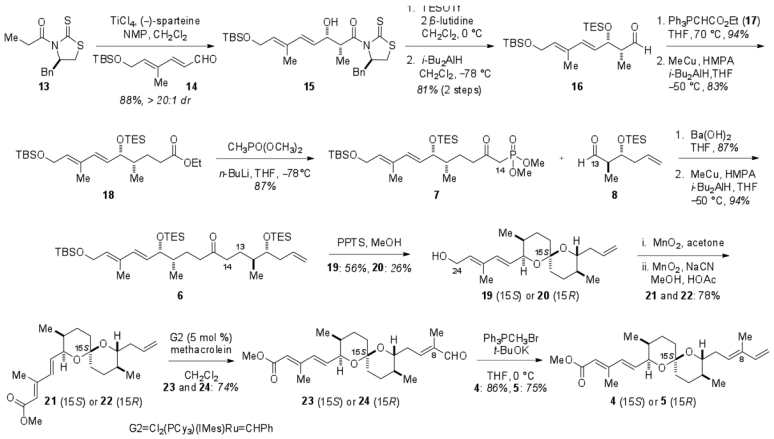


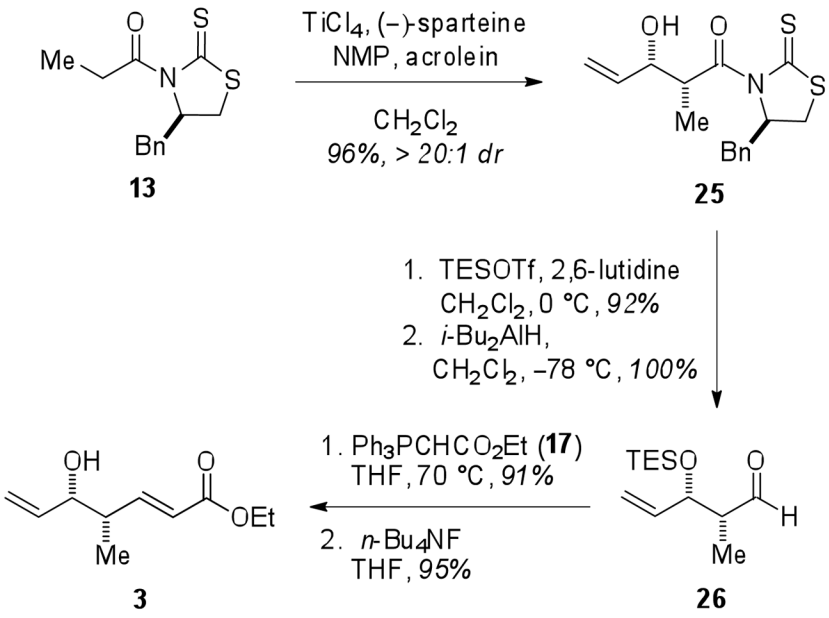
Scheme 1.
Retrosynthetic analysis of the spirofungins.



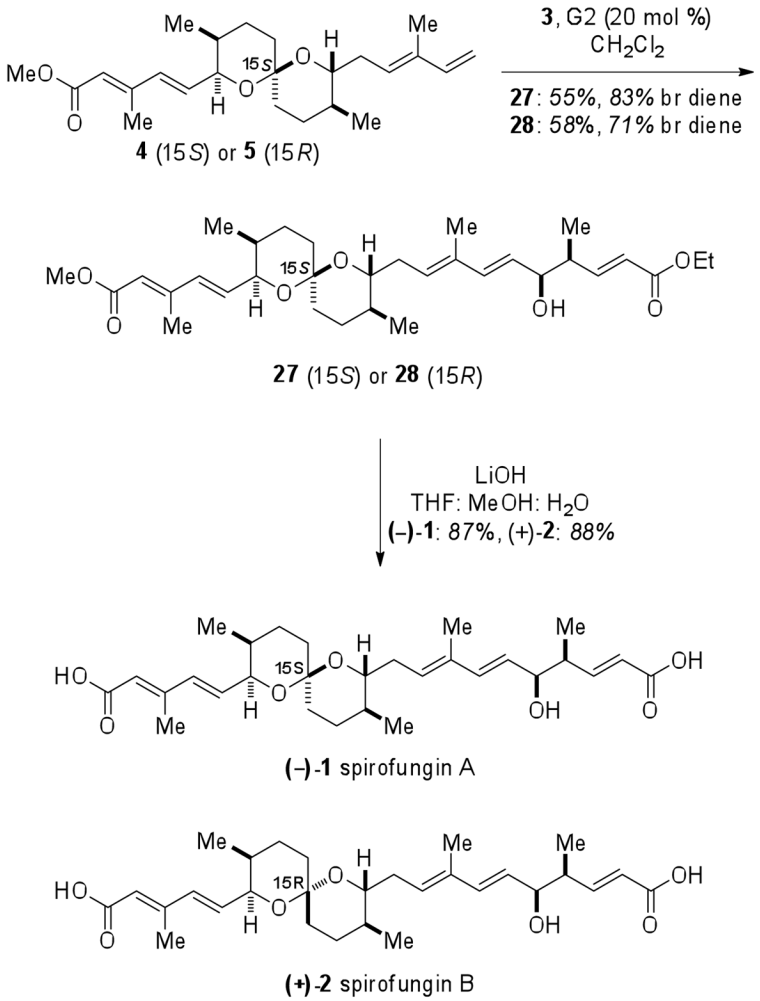
Scheme 2.
Synthesis of aldehyde **8.**



Scheme 3.
Synthesis of spiroketals **4** and **5**.



Scheme 4.
Synthesis of allylic alcohol **3**.



Scheme 5.
Total synthesis of spirofungins A and B.