Enantioselective Total Synthesis of Spirofungins A and B

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ABSTRACT

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 syntheses4,5 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 aldol reaction developed in our laboratories.8 (8) Crimmins, M. T.; Tabet, E. A.; Shamszad, M. Org. Lett. 2007, 9, 149–152.

propionate aldol reaction (Scheme 2). Instead, aldehyde 8 was prepared via a diastereoselective acetate aldol reaction followed by a Frater–Seebach alkylation. The acetate aldol reaction between N-acetylthiazolidinethione 9 and 3-butenal 11 gave rise to aldol adduct 10 in 81% yield and >20:1 diastereomeric ratio. Direct displacement of the chiral auxiliary8 with iso-butyl alcohol 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 \( \beta \)/betatwo-ketophosphonate 7 commenced with an Evans syn propionate aldol addition 11 between N-propionylthiazolidinethione 13 and known aldehyde 14 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 \( \alpha,\beta \)-unsaturated ester. Upon 1,4-reduction with di-iso-butylaluminum hydride mediated by MeCu, ester 18 was obtained in 83% yield. Treatment of ester 18 with lithiated dimethyl methylphosphonate15 furnished \( \beta \)-ketophosphonate 7 in 87% yield and 48% overall yield for the six steps.

With both \( \beta \)-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 reduction14 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 (15S-isomer) and 20 (15R-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 methanol17 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 Wittig19 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 /betatwo-ketophosphonate 7 (Scheme 4). Beginning with an Evans syn propionate aldon reaction between N-propionylthiazolidinethione 13 and acrolein gave aldon 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. On the basis of 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

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reaction conditions and model substrates were examined 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 (Scheme 5).

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.

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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.

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