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Asymmetric Total Synthesis of (−)-Spirofungin A and (+)-Spirofungin B

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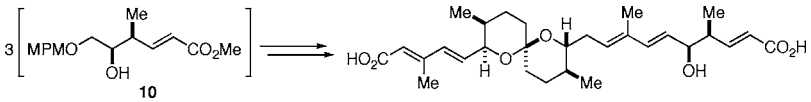
ABSTRACT



The stereocontrolled total synthesis of (−)-spirofungin A (1) and (+)-spirofungin B (2a), polyketide-type antibiotics having various antifungal activities, has been achieved employing the Weinreb amide 8, the alkyne 9, and the vinyl boronate 5 readily available from the common intermediate 10. The first synthesis proceeded with a longest linear sequence of 31 steps, affording (−)-1 and (+)-2a in 7.9% and 5.2% overall yields, respectively.

Spirofungins A (**1**) and B (**2**) are novel polyketide-type antifungal antibiotics isolated from *Streptomyces violaceus-niger* Tü 4113 as a 4:1 mixture.[1] Structurally, they are related to reveromycins, antibiotics produced by another *Streptomyces* strain (Figure 1).[2] The relative configurations of the spiroketal ring systems within **1** and **2** were determined by various NMR spectroscopic methods. Unfortunately, the absolute stereochemistry of the stereogenic centers at C(4) and C(5) was not initially determined.[3] Rizzacasa and coworkers reported the total synthesis of the initially proposed structure for spirofungin B, namely **2**, which was shown to be incorrect.[4] They then proposed a new structure for spirofungin B (**2a**), which is simply the C(15) epimer of **1**. Spirofungin B (**2a**) is a spiroketal with only one anomeric stabilization and an equatorially oriented large substituent at C(19). On the other hand, the relative configuration of the spiroketal core in **1** with its double anomeric stabilization and its C(19) diene acid side chain in an axial position is quite similar to reveromycin A (**3**), a potent inhibitor of mitogenic activity induced by the epidermal growth factor.[2] We have already reported the first asymmetric total synthesis of **3**.[5]

In connection with our studies on the chemical modifications and structure−activity relationships of **3**,[6] we planned to synthesize **1** and **2a** to provide further material for more extensive biological studies as well as to confirm the absolute configurations at C(4), C(5), C(11), C(12), C(15), C(18), and C(19).[7] In this paper, we report the first asymmetric total synthesis of natural spirofungins A and B (−)-**1** and (+)-**2a**, starting from the common intermediate **10**.[7b]

A brief retrosynthetic analysis of **1** and **2a** is shown in Figure 2. The unsaturated left and right side chains would be produced by a Horner−Emmons reaction and a Suzuki coupling.[5,8] The construction of **6** would be achieved by the intramolecular ketalization of the 11,19-dihydroxy-15-ketone derived from ketone **7** from reduction of the alkyne and

(1) Holtzel, A.; Kempter, C.; Metzger, J. W.; Jung, G.; Groth, I.; Fritz, T.; Fiedler, H.-P. *J. Antibiot.* **1998**, *51*, 699.

(2) (a) Takahashi, H.; Osada, H.; Koshino, H.; Kudo, T.; Amano, S.; Shimizu, S.; Yoshihama, M.; Isono, K. *J. Antibiot.* **1992**, *45*, 1409. (b) Takahashi, H.; Osada, H.; Koshino, H.; Sasaki, M.; Onose, R.; Nakakoshi, M.; Yoshihama, M.; Isono, K. *J. Antibiot.* **1992**, *45*, 1414. (c) Koshino, H.; Takahashi, H.; Osada, H.; Isono, K. *J. Antibiot.* **1992**, *45*, 1420. (d) Ubukata, M.; Koshino, H.; Osada, H.; Isono, K. *J. Chem. Soc., Chem. Commun.* **1994**, 1877.

(3) The absolute configurations depicted for **1** and **2** were proposed by analogy with **3** and remained unconfirmed until our total synthesis.

(4) Zanatta, S. D.; White, J. M.; Rizzacasa, M. A. *Org. Lett.* **2004**, *6*, 1041.

(5) Shimizu, T.; Masuda, T.; Hiramoto, K.; Nakata, T. *Org. Lett.* **2000**, *2*, 2153. A second total synthesis: El Sous, M.; Ganame, D.; Tregloan, P. A.; Rizzacasa, M. A. *Org. Lett.* **2004**, *6*, 3001.

(6) Shimizu, T.; Usui, T.; Machida, K.; Furuya, K.; Osada, H.; Nakata, T. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3363.

(7) Synthetic studies on the spiroketal parts of spirofungin A and B: (a) Shimizu, Y.; Kiyota, H.; Oritani, T. *Tetrahedron Lett.* **2000**, *41*, 3141. (b) Shimizu, T.; Kusaka, J.; Ishiyama, H.; Nakata, T. *Tetrahedron Lett.* **2003**, *44*, 4965. (c) Dias, L. C.; de Oliveira, L. G. *Org. Lett.* **2004**, *6*, 2587. (d) La Cruz, T. E.; Rychnovsky, S. D. *Org. Lett.* **2005**, *7*, 1873.

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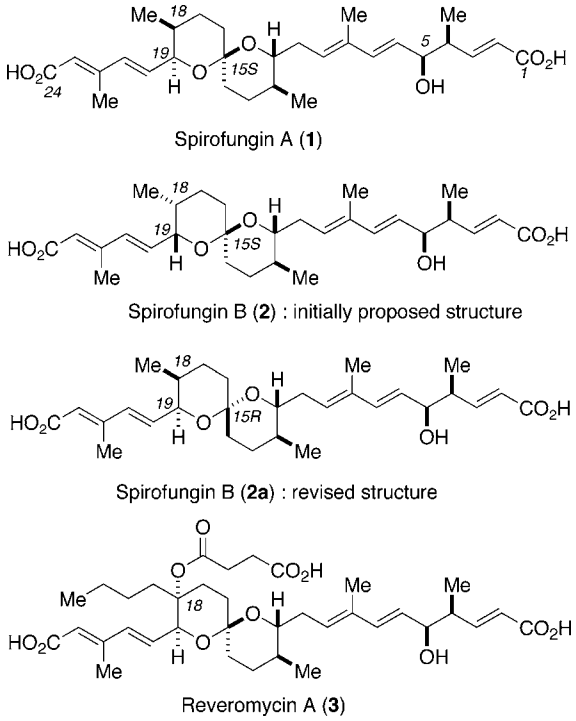


Figure 1. Spirofungins A (**1**) and B (**2a**) and reveromycin A (**3**).

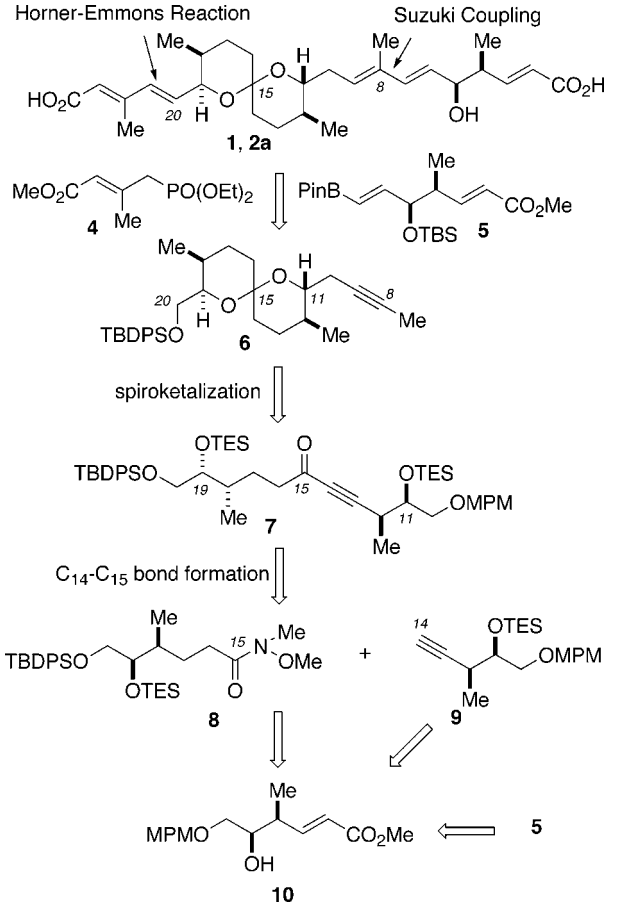


Figure 2. Retrosynthetic analysis of spirofungin A (**1**) and B (**2a**).

stereoinversion at C(11). Ketone **7** would itself be synthesized via the coupling reaction of Weinreb amide **8** and alkyne **9**, which in turn would be prepared from the common precursor **10**.[9] The 1-alkenylboronic acid pinacol ester **5**, required for the Suzuki coupling, could be also prepared from **10**.[8d] Since the epimer of **10** could also be readily prepared by the same protocol,[10] the epimers of **1** or **2a** could be synthesized.

We have already reported the synthesis of the 6,6-spiroketal parts corresponding to spirofungin A (**1**) and B (**2a**) starting from a Weinreb amide and an alkyne.[7b] However, this procedure was not suitable for the synthesis on a large scale. We therefore reexamined the protecting group strategy and many of the individual reaction conditions, and our new results are shown in Scheme 1. The coupling of amide **8**, with a TBDPS group at the C(20) position, and the lithio derivative of **9**, having a TES group at the C(11) position, furnished the coupled product **7** (which is the latent C_2-symmetric ketone) in 87% yield. The deprotection of the two TES groups in **7** with PPTS in MeOH was followed by the simultaneous intramolecular ketalization of the left half to give the methylketal−alkynol **11** in 97% yield ($\alpha/\beta = \sim$5:1), as expected. It is important to note that only the C19-hydroxyl group forms the ketal with the C15-carbonyl group being distinguished from the C11-hydroxyl group. The next task was introduction of propyne through a stereo-inversion at the C(11) position. Accordingly, the alcohol **11** was treated with MsCl in pyridine to give the *O*-mesylate, which was then treated with DDQ in CH_2Cl_2−MeOH to cleave the MPM group. The alcohol was treated with K_2CO_3 in MeOH to provide the epoxide **12** in 86% yield in three steps. The alkyne **12** was hydrogenated on Pd/C and treated with PPTS in MeOH to provide the saturated ketal as one isomer, which was then reacted with propyne and *n*-BuLi in the presence of $BF_3{\cdot}OEt_2$ to afford the alcohol **13** with the desired configuration at the C(11) position.[11] Treatment of **13** with PPTS in MeOH at room temperature gave an equilibrium mixture of the 6,6-spiroketal **14** (15*S*/15*R* = 10:7).[12]

Alkyne **14** was heated with Cp_2ZrHCl in benzene at 50 °C and treated with I_2 at 0 °C to regio- and stereoselectively provide the vinyl iodide,[13] which was then exposed to TBAF in THF to afford the separable alcohols **15** (15*S*-isomer) and

(8) (a) Miyaura, N.; Yamada, Y.; Suzuki, A. *Tetrahedron Lett.* **1979**, *20*, 3437. (b) Miyaura, N.; Suginome, H.; Suzuki, A. *Tetrahedron Lett.* **1981**, *22*, 127. (c) Suzuki, A. *Pure Appl. Chem.* **1985**, *57*, 1749. (d) Takagi, J.; Takahashi, K.; Isiyama, T.; Miyaura, N. *J. Am. Chem. Soc.* **2002**, *124*, 8001.

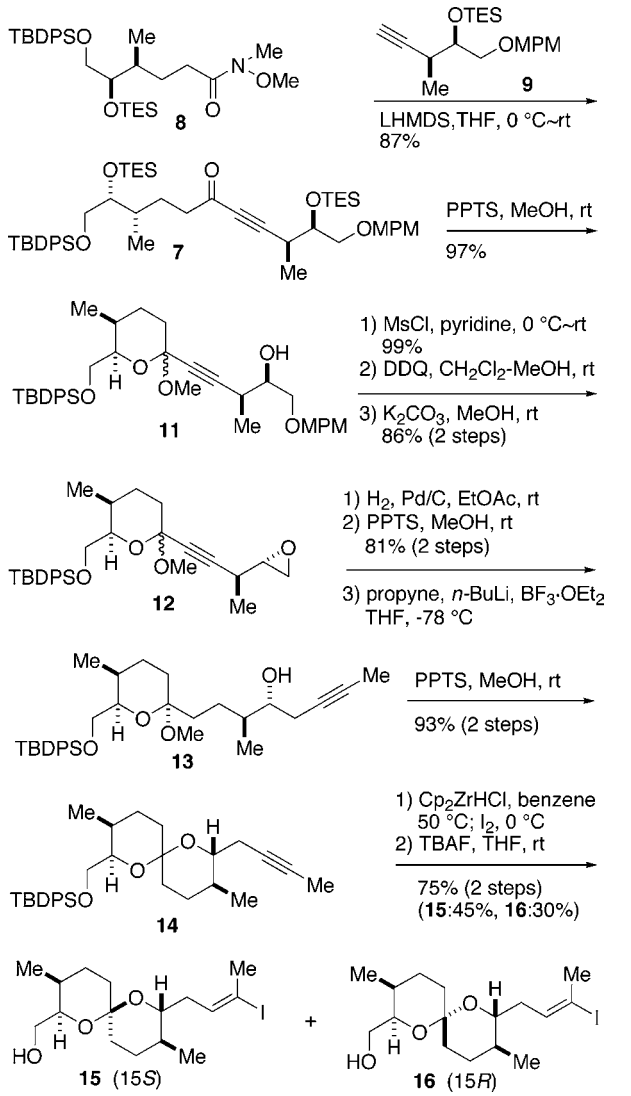
(9) For the synthesis of **8**, **9**, and **10**, see the Supporting Information.

(10) Oshima, M.; Yamazaki, H.; Shimizu, I.; Nisar, M.; Tsuji, J. *J. Am. Chem. Soc.* **1989**, *111*, 6280.

(11) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391.

(12) The MM2 calculation (MM2*/MacroModel 6.0) of the spiroketals **17a** and **18a** (Figure 3, R = CH_2OMe) corresponding to **14**, **15**, and **16** revealed an energy difference of only 0.08 kcal/mol, which means a 46:54 ratio of **17a**/**18a**.

Scheme 1. Synthesis of the 6,6-Spiroketals **15** and **16**



16 (15*R*-isomer) in 45% and 30% yields, respectively. The structures of **15** and **16** were confirmed by extensive NMR analyses (^{1}H NMR, ^{13}C NMR, NOE, and HMBC). The vicinal coupling constants between H11 and H12 (J = 10.0, 9.2 Hz, respectively) in **15** and **16** reflect the diaxial relationships between these two protons. The vicinal coupling constant between H18 and H19 (J = 4.6 Hz) as well as the chemical shift of the C18-Me (15.1 ppm) in **15** indicated that H18 was axial and H19 was equatorial; these data correlated well with that of **1**. On the other hand, the vicinal coupling constant between H18 and H19 (J = 2.7 Hz) as well as the chemical shift of the C18-Me (11.8 ppm) and C15 (97.6 ppm) in **16** indicated that H18 was equatorial and H19 was axial. Such data was in line with data previously reported for **2a**.

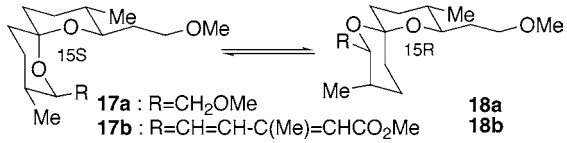
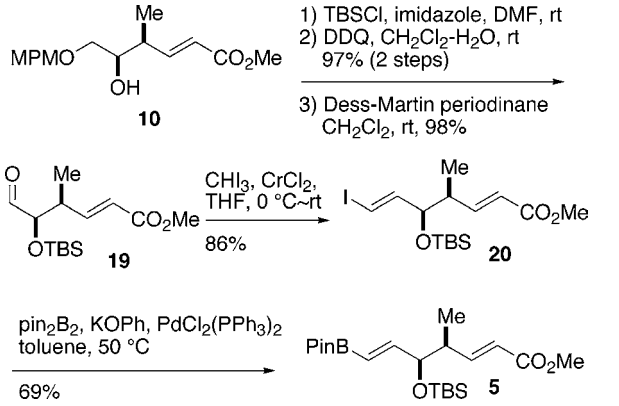


Figure 3. Conformation of 6,6-spiroketals **17** and **18**.

Next, the 1-alkenylboronic acid pinacol ester **5** was prepared for the Suzuki coupling (Scheme 2).[8] The common

Scheme 2. Synthesis of the 1-Alkenylboronic Acid Pinacol Ester **5**



precursor **10** was converted into the aldehyde **19** in the following three steps in a 87% overall yield. Silylation of **10** with TBSCl, followed by cleavage of the MPM group with DDQ, afforded the alcohol which was oxidized using Dess−Martin periodinane to provide **19**. Homologation of aldehyde **19** to the iodoalkene, with iodoform and chromium chloride, proceeded with high selectivity for the (*E*)-product.[14] The synthesis of **5** from **20** was carried out with bis(pinacolate)diboron via a palladium-catalyzed cross-coupling reaction in toluene at 50 °C in the presence of KOPh and $PdCl_2(PPh_3)_2$.[8d]

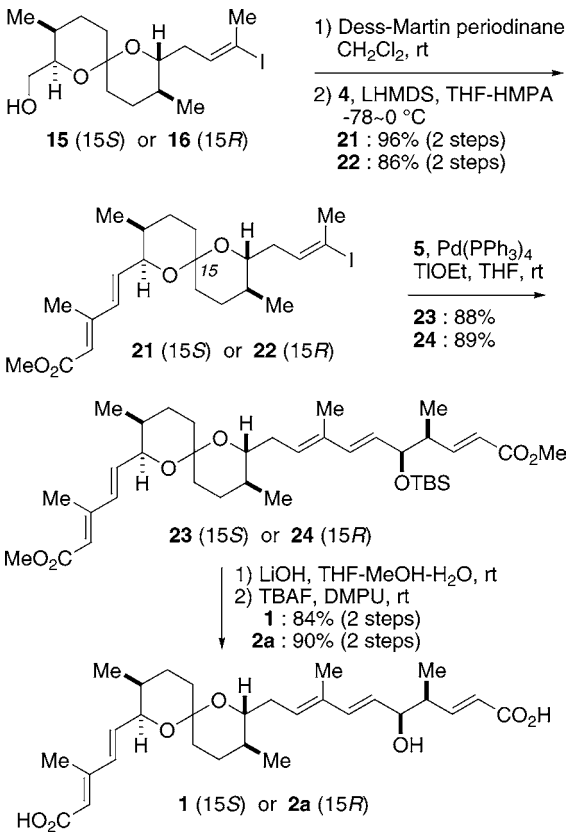
The 6,6-spiroketal **15** with the 15*S* configuration needed for **1** was first subjected to the introduction of the dienoic ester (Scheme 3). Dess−Martin oxidation of **15** gave an aldehyde, which was subjected to the Horner−Emmons reaction with $(EtO)_2P(O)CH_2C(Me)=CHCO_2Me$ and LHMDS in the presence of HMPA to give the desired (20*E*,22*E*)-dienoic esters **21** in 96% yield.[15] Final elaboration of the labile unsaturated right side chain was accomplished in one step using the Pd(0)-mediated diene synthesis developed by Suzuki and co-workers.[8] The reaction of **21** with **5** in the presence of $Pd(PPh_3)_4$ and TlOEt in THF smoothly proceeded

(13) (a) Hart, D. W.; Glackburn, T. F.; Schwarz, J. *J. Am. Chem. Soc.* **1975**, *97*, 679. (b) Panek, J. S.; Hu, T. *J. Org. Chem.* **1997**, *62*, 4912. (c) Drouet, K. E.; Theodorakis, E. A. *J. Am. Chem. Soc.* **1999**, *121*, 456. (d) Thompson, C. F.; Jamison, T. F.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 9974.

(14) (a) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408. (b) Pontikis, R.; Musci, A.; Le Merrer, Y. *Bull. Soc. Chim. Fr. Part 2* **1991**, 968.

(15) Corey, E. J.; Katzenellenbogen, J. A.; Roman, S. A.; Gilman, N. W. *Tetrahedron Lett.* **1971**, *21*, 1821.

Scheme 3. Total Synthesis of (−)-Spirofungin A (**1**) and (+)-Spirofungin B (**2a**)



to afford **23** in 88% yield, while retaining the original configuration of both **21** and **5**. Hydrolysis of the two ester groups in **23** was cleanly achieved by treatment with LiOH in THF−MeOH−H_2O. Finally, the removal of the TBS group with TBAF in DMPU gave (−)-spirofungin A (**1**) in 84% yield in two steps. The spectral data (^{1}H NMR, ^{13}C NMR, IR, HRMS) of the synthetic **1** were identical with those of the natural **1**, and the $[\alpha]^{27}_D$ value was −125.8 (*c* 0.28, $CHCl_3$).

It had been postulated that it would be difficult to synthesize the natural spirofungin B (**2a**) because of its instability[16] and there being no (15*R*)-isomer of **3**. However, **2a** could be synthesized from **16** with the 15*R* configuration using the same procedure as described for **1** in five steps. Both side chains of **24** were introduced via Horner−Emmons and Suzuki coupling reactions. After the treatment of **24** with LiOH or the desilylation with TBAF, the crude reaction mixture was washed with a mixture of 1 N HCl and aqueous NH_4Cl solution or H_2O at 0 °C. No epimerization of the spiroketal was observed under the workup conditions, and **2a** was obtained as a single stereoisomer. The spectral data (^{1}H NMR, ^{13}C NMR) of the synthetic **2a** were identical with those of the natural **2a**, and the $[\alpha]^{28}_D$ value was +102.6 (*c* 0.31, $CHCl_3$).

The $[\alpha]^{30}_D$ value of a mixture of natural spirofungins A and B (∼2:1) which was supplied from Professor Fiedler was −30.7 (*c* 0.16, $CHCl_3$), as expected. Thus, it was determined that the absolute configuration of natural spirofungin A is 4*S*,5*S*,11*R*,12*S*,15*S*,18*S*,19*R* and that of spirofungin B is 4*S*,5*S*,11*R*,12*S*,15*R*,18*S*,19*R* as shown in the structures **1** and **2a**.

With pure **1** and **2a** in hand, **1** and **2a** were then independently treated with 0.01 N HCl in MeOH at room temperature to afford an equilibrium mixture of **1** and **2a** in a ratio of ∼2:1.

In summary, the first asymmetric total synthesis of (−)-**1** and (+)-**2** has been achieved employing the Weinreb amide **8**, the alkyne **9**, and the vinyl boronate **5** readily available from the common intermediate **10**. Both olefinic side chains were installed via Horner−Emmons and highly convergent Suzuki cross-coupling reactions. The synthesis proceeded with a longest linear sequence of 31 steps, affording (−)-**1** and (+)-**2a** in 7.9% and 5.2% overall yields, respectively. Pure spirofungins (−)-**1** and (+)-**2a** were easily epimerized to afford a mixture of (−)-**1** and (+)-**2a** in the ratio of ∼2:1 under acidic conditions.

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Note Added after ASAP Publication. The NMR spectra were not included in the Supporting Information published ASAP November 9, 2005; the corrected file was published ASAP November 15, 2005. Subsequently, an error was found in the structure of **15** or **16** in Scheme 3. The corrected file was published ASAP November 21, 2005.

Supporting Information Available: Synthetic scheme for **8**−**10** and spectroscopic data and NMR spectra as well as experimental procedures for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) MM2 calculation of the spiroketals **17b** and **18b** having the C19 dienoic ester (R = CH=CHC(Me)=$CHCO_2$Me) suggested a large energy difference (4.19 kcal/mol) in favor of **17b**.