ORGANIC LETTERS

2002
Vol. 4, No. 25
4403−4405

Total Synthesis of Sphingofungin F

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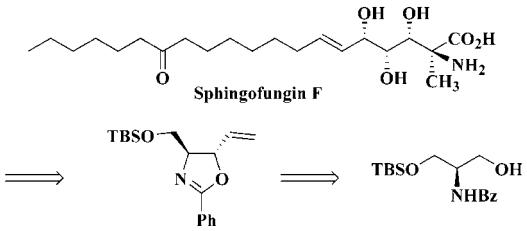
Received August 14, 2002

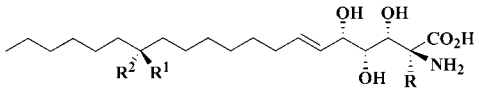
ABSTRACT



A concise, stereocontrolled synthesis of sphingofungin F was achieved. Key features involve diastereoselective oxazoline formation catalyzed by palladium(0), $MgBr_2$-promoted γ-alkoxy allylic stannane addition, and palladium(0)-catalyzed coupling of a vinyl iodide with an organozinc reagent.

Sphingofungins E and F, potent antifungal agents possessing a polar polyhydroxy amine group and long lipid chains, were isolated from the fermentation broth of *Paecilomyces variotii* by a Merck group in 1992.[1] These compounds have a quaternary center, four consecutive chiral centers, and a trans olefinic group in their polyhydroxy amine headgroups. Along with other congeners (A−D), they were found to block the biosynthesis of sphingolipid, leading to apoptosis in both yeast and mammalian cells. These cellular effects are due to their potent inhibitory activities against serine palmitoyltransferase (SPT), an essential committed enzyme involved in the first step of sphingosine biosynthesis.[2]

The combination of their potent biological activity and their novel structure has led to wide interest in the synthetic community. The first total synthesis of sphingofungin F was reported by Kobayashi and co-workers in 1998.[5a] Shortly thereafter, Trost[3b] and Lin[3c] reported the completion of sphingofungin F. On the basis of our previous research,[4] we anticipated that the palladium(0)-catalyzed oxazoline formation of homoallyl benzamide **10** formed from protected



Sphingofungin B R=H, R^1=OH, R^2=H
Sphingofungin E R=CH_2OH, R^1=R^2=O
Sphingofungin F R=CH_3, R^1=R^2=O

Figure 1.

L-serinol **9** might proceed with high stereoselectivity. As part of a program directed at expanding the synthetic utility of oxazoline as a chiral building block for the synthesis of natural products, we report herein our synthetic efforts, which led to a concise and highly stereocontrolled total synthesis of **1** using oxazoline **8**. Our retrosynthetic analysis as shown in Scheme 1 suggests that **1** may be synthesized by the

(1) Horn, W. S.; Smith, J. L.; Bills, G. F.; Raghoobar, S. L.; Helms, G. L.; Kurtz, M. B.; Marrinan, J. A.; Frommer, B. R.; Thornton, R. A.; Mandala, S. M. *J. Antibiot*. **1992**, *45*, 1693.

(2) Zweerink, M. M.; Edison, A. M.; Well, G. B.; Pinto, W.; Lester, R. L. *J. Biol. Chem*. **1992**, *267*, 25032.

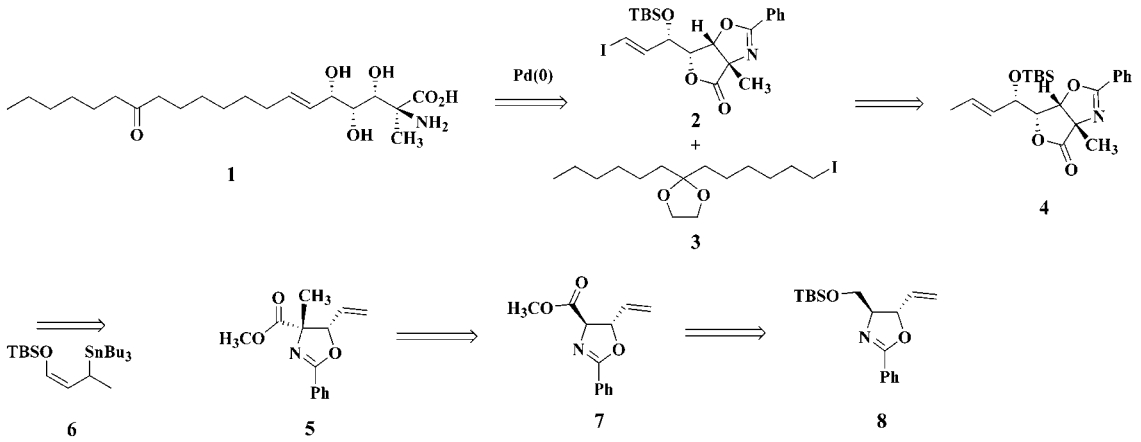
(3) (a) Kobayashi, S.; Matsumura, M.; Furuta, T.; Hayashi, T.; Iwamoto, S. *Synlett* **1997**, 301. (b) Kobayashi, S.; Furuta, T.; Hayashi, T.; Nishijima, M.; Hanada, K. *J. Am. Chem. Soc*. **1998**, *120*, 908. (c) Kobayashi, S.; Furuta, T.; Hayashi, T.; Nishijima, M.; Hanada, K. *Tetrahedron* **1998**, *54*, 10275. (d) Trost, B. M.; Lee, C. B. *J. Am. Chem. Soc*. **1998**, *120*, 6818. (e) Liu, D.-G.; Wang, B.; Lin, G.-Q. *J. Org. Chem*. **2000**, *65*, 9114. (f) Trost, B. M.; Lee, C. B. *J. Am. Chem. Soc*. **2001**, *123*, 12191.

(4) (a) Lee, K.-Y.; Kim, Y.-H.; Park, M.-S.; Ham, W.-H. *Tetrahedron Lett*. **1998**, *39*, 8129. (b) Lee, K.-Y.; Kim, Y.-H.; Park, M.-S.; Oh, C.-Y.; Ham, W.-H. *J. Org. Chem*. **1999**, *64*, 9450. (c) Lee, K.-Y.; Kim, Y.-H.; Oh, C.-Y.; Ham, W.-H. *Org. Lett*. **2000**, *2*, 4041.

(5) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem*. **1983**, *48*, 4155. (b) Meyers, A. G.; Zhong, B.; Movassaghi, M.; Kung, D. W.; Lanman, B. A.; Kwon, S. *Tetrahedron Lett*. **2000**, *41*, 1359.

10.1021/ol020164f CCC: $22.00
Published on Web 11/12/2002

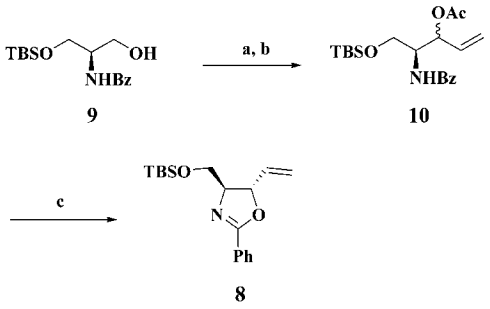
Scheme 1



palladium-catalyzed coupling reaction of **2** with **3**. A chiral quaternary carbon center could be constructed with the desired stereochemistry via methylation of ester **7** readily accessible from the protected L-*N*-benzoyl serinol **9** by our newly developed palladium (0)-catalyzed oxazoline formation reaction. The pendant vinyl group could be converted to the aldehyde, which could be employed in the diastereoselective *cis*-dihydroxylation using $MgBr_2$-promoted γ-alkoxy allylic stannane addition. It was also anticipated that **4** could be converted to **2** in two steps (ozonolysis and Takai reaction).

The synthesis of **1** began with the protected L-*N*-benzoyl serinol **9** as shown in Scheme 2. Oxidation of alcohol **9** with

Scheme 2[a]



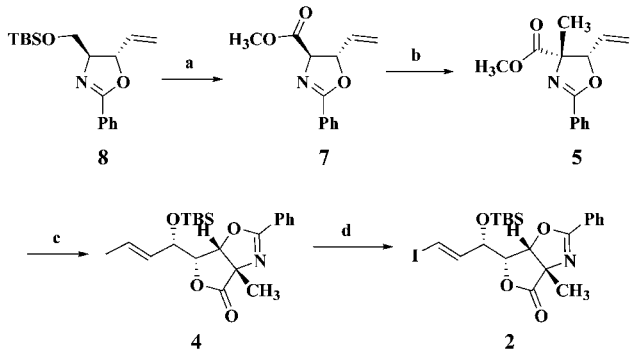
[a] Conditions: (a) (i) Dess−Martin periodinane, CH_2Cl_2; (ii) CH=CHMgBr, THF, 0 °C, 70% for two steps. (b) Ac_2O, pyr., CH_2Cl_2, 95%. (c) $Pd(PPh_3)_4$, K_2CO_3, CH_3CN, 60 °C, 87%.

Dess−Martin periodinane[4b,5] gave the corresponding aldehyde without racemization,[4b,5b] which was reacted with vinylmagnesium bromide in THF at 0 °C to afford allyl alcohol, as an ca. 1.1: 1 mixture of syn/anti isomers (^{1}H NMR) in 70% yield.[6]

Acetylation of the hydroxyl group yielded the secondary allylic acetate **10**. The palladium-catalyzed oxazoline ring formation [$Pd(PPh_3)_4$, K_2CO_3 in CH_3CN] of the allylic acetate **10** gave the desired *trans*-oxazoline **8** as a single diastereomer in good yield (87%). *No trace of the minor isomer could be detected in a number of repeated experiments.*

Deprotection of the silyl ether of oxazoline **8** gave the alcohol. Oxidation of the primary alcohol proved to be troublesome under a variety of conditions (e.g., Swern,[7] PCC,[8] Dess−Martin[4b,5]). Fortunately, oxidation with ruthenium did provide the requisite carboxylic acid.[9] The resulting carboxylic acid was converted to its methyl ester **7** with diazomethane in 68% yield (Scheme 3). The alkylation

Scheme 3[a]



[a] Conditions: (a) (i) TBAF, THF, 99%; (ii) $RuCl_3$, $K_2S_2O_8$, 1 M NaOH, CH_3CN; (iii) CH_2N_2, Et_2O, 68% for two steps. (b) CH_3I, KHMDS, HMPA, THF, −78 °C, 73%. (c) (i) O_3, MeOH, −78 °C, then DMS; (ii) **6**, $MgBr_2$−Et_2O, CH_2Cl_2, 78% for two steps. (d) (i) O_3, MeOH, −78 °C, then DMS; (ii) $CrCl_2$, CHI_3, THF, 63% for two steps.

reaction of **7** with MeI gave the anti alkylation product **5** as the major isomer with high diastereoselectivity (20:1) and in good yield (73%).[10]

(6) Denis, J.-N.; Correa, A.; Greene, A. E. *J. Org. Chem.* **1991**, *56*, 6939.

(7) (a) Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480. (b) Omura, K.; Swern, D. *Tetrahedron* **1987**, *34*, 1651.

(8) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, *16*, 2647.

(9) Green, G.; Griffith, W. P.; Hollinshead, D. M.; Ley, S. V.; Schroder, M. *J. Chem. Soc., Perkin Trans. 1* **1984**, 681.

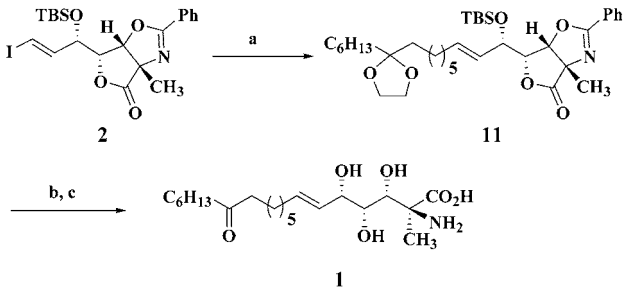
Ozonolysis of **5** gave the corresponding aldehyde. After extensive investigation of a variety of protocols, we established that when 1 equiv of aldehyde and 2.1 equiv of $MgBr_2-OEt_2$ are treated with 3 equiv of stannane, protected diol **4** was formed with >20:1 diastereoselectivity in 78% yield after silica gel chromatography.[11] This process efficiently adjusted the stereochemistry and provided simultaneous protection for the newly generated hydroxyl group.

The following steps to introduce the lipophilic side chain into compound **4** were achieved by applying Trost's method[3d,f] with some variation.

Ozonolysis and iodomethylenation of **4** with low-valent chromium generated (*E*)-alkene **2** exclusively.[3d,f,12] Although the coupling of the side chain by a Suzuki reaction[13] was well established, we tried a different coupling process using Negishi's protocol[14] and verified that it could be applied successfully as a surrogate reaction. Palladium(0)-catalyzed coupling of **2** with the alkyl zinc generated from iodide **3**[15] provided the fully protected **11** in 68% yield (Scheme 4).[14]

Acid-catalyzed hydrolysis of **11** gave lactone. Finally, a base-promoted hydrolysis cleaved the lactone and the amide groups, and subsequent neutralization with an acidic resin (Amberlite IRC-76) afforded sphingofungin F (**1**). The synthetic compound was spectroscopically in good agreement with the natural and synthetic sphingofungin F. Our $[\alpha]_D$ of +0.8 (*c* 0.25, CH_3OH) compared to the reported $[\alpha]_D$ +0.8 (*c* 0.33, CH_3OH)[3a] confirms the identity of the absolute configuration.

Scheme 4[a]



[a] Conditions: (a) **3**, *t*-BuLi, -78 °C; then, $ZnCl_2$, from −78 °C to rt, $Pd(PPh_3)_4$, THF, 68%. (b) 2 N HCl, THF, 80%. (c) 1 N NaOH, reflux, 79%.

In summary, we report a new asymmetric synthetic method for sphingofungin F utilizing oxazoline **8**. The key features in this strategy are the diastereoselective oxazoline formation reaction catalyzed by palladium(0), $MgBr_2$-promoted γ-alkoxy allylic stannane addition, and palladium(0)-catalyzed coupling of vinyl iodide with organozinc reagent. With the same protocol, our synthesis of sphingofungin E is in progress.

Acknowledgment. This study was supported by a grant of the Korea Health 21 R&D Project, Ministry of Health and Welfare, Republic of Korea (01-PJ1-PG1-01CH13-0002).

Supporting Information Available: Experimental procedure and characterization data for compounds **1**−**11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Berkowitz, D. B.; McFadden, J. M.; Chisowa, E.; Semerad, C. L. *J. Am. Chem. Soc.* **2000**, *122*, 11031.

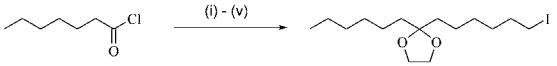
(11) For reviews, see: (a) Marshall, J. A. *Chem. Rev.* **1996**, *96*, 31. (b) Marshall, J. A. *Chem. Rev.* **2000**, *100*, 3163.

(12) (a) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408. (b) Kende, A. S.; DeVita, R. J. *Tetrahedron Lett.* **1990**, *31*, 307. (c) Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 4497. Due to the presence of α-branching in the precursor aldehydes, high proportions of the (*E*)-alkenes were obtained without the use of dioxane.

(13) (a) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314. (b) Johnson, C. R.; Braun, M. P. *J. Am. Chem. Soc.* **1993**, *115*, 11014. (c) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (d) Ohba, M.; Kawase, N.; Fujii, T. *J. Am. Chem. Soc.* **1996**, *118*, 8250.

(14) (a) Erdik, E. *Tetrahedron* **1992**, *48*, 9577. (b) Negishi, E.; Ay, M.; Culevich, Y. V.; Noda, Y. *Tetrahedron Lett.* **1993**, *34*, 1437. (c) Williams, D. R.; Kissel, W. S. *J. Am. Chem. Soc.* **1998**, *120*, 11198.

(15) Preparation of alkyl iodide:[a]



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[a]Conditions: (i) $NH(CH_3)OCH_3-HCl$, pyr., CH_2Cl_2, 92%; (ii) $CH_2{=}CH-(CH_2)_5CH_2MgBr$, THF, 93%; (iii) ethylene glycol, PTSA, PhH, 90%; (iv) O_3/MeOH, then $NaBH_4$, 92%; (v) I_2, PPh_3, CH_2Cl_2, 87%.