Organic LETTERS

Letter

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Total Synthesis of Sphingofungin F by Orthoamide-Type Overman Rearrangement of an Unsaturated Ester

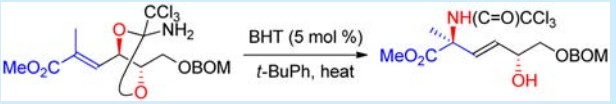
Shun Tsuzaki,[†] Shunme Usui,[†] Hiroki Oishi,[†] Daichi Yasushima,[†] Takahiro Fukuyasu,[†] Takeshi Oishi,[‡] Takaaki Sato,*[,†] and Noritaka Chida*[,†]

[†]Department of Applied Chemistry, Faculty of Science and Technology, Keio University, 3-14-1, Hiyoshi, Kohoku-ku, Yokohama 223-8522, Japan

[‡]School of Medicine, Keio University, 4-1-1, Hiyoshi, Kohoku-ku, Yokohama 223-8521, Japan

Supporting Information

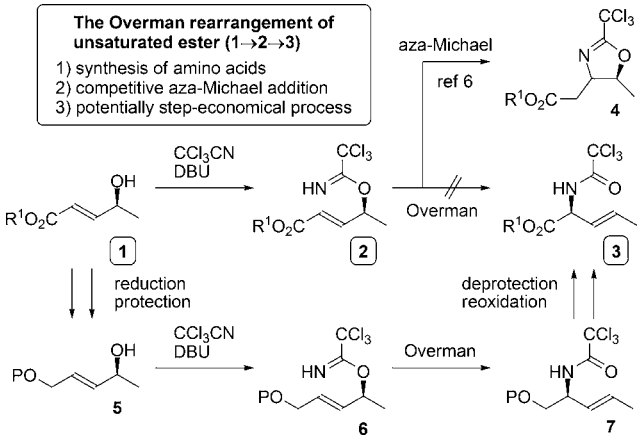
ABSTRACT: The total synthesis of sphingofungin F through the Overman rearrangement of an unsaturated ester, which is known to be an unsuitable substrate under standard conditions due to the competitive aza-Michael reaction, is described. The developed conditions enabled the ester to be compatible with the original Overman rearrangement, providing quick access to α,α-disubstituted amino acids by minimizing extra protecting group manipulations and redox reactions.



As the complexity of target molecules increases in modern organic synthesis, functional group compatibility is increasingly recognized as an important concept when developing new reactions.[1] Use of reactions with low functional group compatibility requires tedious protecting group manipulations, resulting in a decrease in total yield. Our research group is engaged in a program devoted to incorporating high functional group compatibility into transformations that are potentially useful, but suffer unsatisfactory compatibility.[2] In this letter, we succeeded in the integrating ester compatibility with the original Overman rearrangement[3] and developed the direct synthesis of α,α-disubstituted amino acid derivatives. The reaction was then applied to the concise total synthesis of a biologically active natural product.

The trichloroimidate rearrangement, the so-called Overman rearrangement, is one of the most powerful and widely used sigmatropic rearrangements in organic synthesis. The reaction proceeds even with densely functionalized and sterically hindered molecules. In addition, use of enantiomerically pure allylic alcohols enables chirality transfer to form the C−N bond stereoselectively via a tight chairlike transition state.[4] If the Overman rearrangement can be applied to unsaturated ester **1**, this reaction will be a useful synthetic tool for amino acid derivative **3** via imidate **2** (Scheme 1). However, unsaturated ester **1** has been known to be a longstanding problematic substrate in the Overman rearrangement due to inherent competitive aza-Michael addition against the Overman rearrangement (**2** → **4**).[5] Therefore, synthesis of the amino acid derivative **3** requires an indirect method using additional steps.[6] In the previous example, unsaturated ester **1** was converted to protected alcohol **5** prior to the Overman rearrangement.[5b] After the rearrangement (**5** → **6** → **7**), α-vinyl amino acid derivative **3** could then be obtained through deprotection and reoxidation of **7**. In other words, the direct Overman rearrangement of unsaturated esters will become a highly step-economical

Scheme 1. Limited Access to Amino Acid Derivatives by Conventional Overman Rearrangement



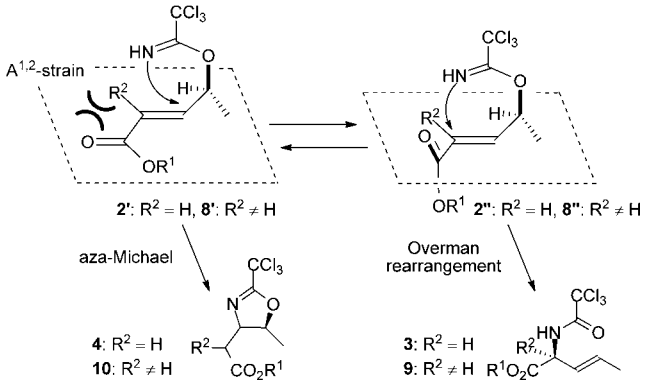
transformation[1a] by exclusion of a number of extra steps including protecting group manipulations[1c] and redox reactions.[1b]

We suspected that the origin of the competitive aza-Michael addition against the Overman rearrangement might depend on the existence of two conformations **2′** and **2″** (Scheme 2). The aza-Michael addition would be stereoelectronically preferred from the major conformer **2′** because the ester carbonyl group is located in the same plane as the olefin. On the other hand, the Overman rearrangement would proceed from minor conformation **2″** because the ester carbonyl group is not coplanar with the olefin, resulting in the suppression of the aza-Michael reaction. We considered that, if a substituent R^2 were installed at the α-

Received: February 14, 2015
Published: March 13, 2015

DOI: 10.1021/acs.orglett.5b00475
Org. Lett. 2015, 17, 1704−1707

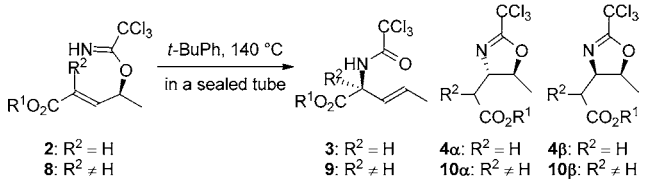
Scheme 2. Working Hypothesis: Induction of the Overman Rearrangement against the aza-Michael Reaction

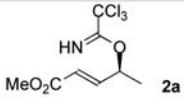
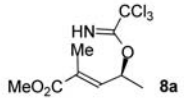
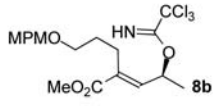
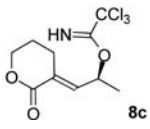


position of unsaturated ester **2**, the resulting trisubstituted olefin **8** would have a large $A^{1,2}$-allylic strain as shown in conformation **8′**.[7] This $A^{1,2}$-allylic strain would promote a conformational change from **8′** to **8″**, leading to the selective Overman rearrangement. The developed method will be a direct synthetic method of α,α-disubstituted amino acid **9**, embedded in a number of biologically active natural products.

The Overman rearrangement of unsaturated ester **2a** with a hydrogen at the α-position was investigated as a control experiment to confirm our working hypothesis (Table 1). A solution of **2a** in *t*-BuPh in a sealed tube was heated to 140 °C, resulting in the formation of the rearranged product **3a** in only 46% yield, along with aza-Michael byproducts **4a*α*** (31%) and **4a*β*** (3%) (entry 1).[8] Unsaturated ester **8a** with a methyl group at the α-position was then heated under identical reaction conditions (entry 2). Gratifyingly, the aza-Michael reaction was completely suppressed, giving the rearranged product **9a** in 83% yield. Although the aza-Michael addition was successfully inhibited, the inductive effect derived from the methyl group of **8a** might be a dominant factor instead of the $A^{1,2}$-allylic strain. Therefore, we prepared electronically similar, but conformationally different substrates **8b** and **8c** (entries 3 and 4).[9] Interestingly, while the reaction of **8b** provided **9b** in 80% yield as a single compound, use of unsaturated lactone **8c** led to the aza-Michael addition as a major pathway, probably because the lactone structure forced the carbonyl group to be situated in the same plane as the double bond (entry 4). Although the effect of the $A^{1,2}$-allylic strain was not directly proven, these results indicated that the conformational factor played an important role in the selectivity.

Table 1. Overman Rearrangement of Unsaturated Esters[a]

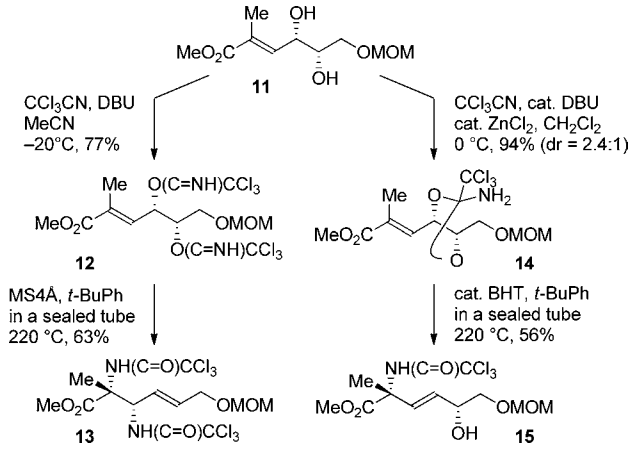


entry	2 or 8	3 or 9	yields (%)[b] 4α or 10α	4β or 10β
1	 2a	3a: 46	4aα: 31	4aβ: 3
2	 8a	9a: 83	10aα: 0	10aβ: 0
3	 8b	9b: 80	10bα: 0	10bβ: 0
4	 8c	9c: 18	10cα: 72[c]	10cβ: 0

[a]**2** or **8**, *t*-BuPh (0.015 M), 140 °C in a sealed tube. [b]Yield of isolated product after purification by column chromatography. [c]The diastereomeric ratio was 1.5:1.

With the promising rearrangement of unsaturated esters in hand, we then applied this reaction to allylic vicinal *syn*-diol **11** (Scheme 3). While sigmatropic rearrangement of a simple allylic alcohol has been widely investigated, the rearrangement of an allylic vicinal diol such as **11** had been overlooked until our reports.[10,11] Treatment of a solution of *syn*-diol **11** in MeCN with an excess amount of CCl_3CN and 2.2 equiv of DBU at −20 °C provided bis(imidate) **12** in 77% yield. Bis(imidate) **12** underwent the cascade-type Overman rearrangement at 220 °C in the presence of MS4 Å (500 wt %), providing bis(amide) **13** in 63% yield. On the other hand, the identical *syn*-diol **11** was transformed to cyclic orthoamide **14** in 94% yield upon treatment with CCl_3CN (1.3 equiv), DBU (30 mol %), and $ZnCl_2$ (10 mol %). The orthoamide-type Overman rearrangement of **14** underwent the single rearrangement at 220 °C in the presence of 5 mol % of BHT (butylated hydroxytoluene), affording **15** in 56% yield. These methods have various salient features. First, the number of the rearrangement (double or single) was precisely controlled by selective formation of either bis(imidate) or cyclic orthoamide. Both reactions took place through complete chirality transfer of hydroxy groups, giving the product as a single diastereomer. Furthermore, no aza-Michael byproduct was observed in either type of rearrangement.

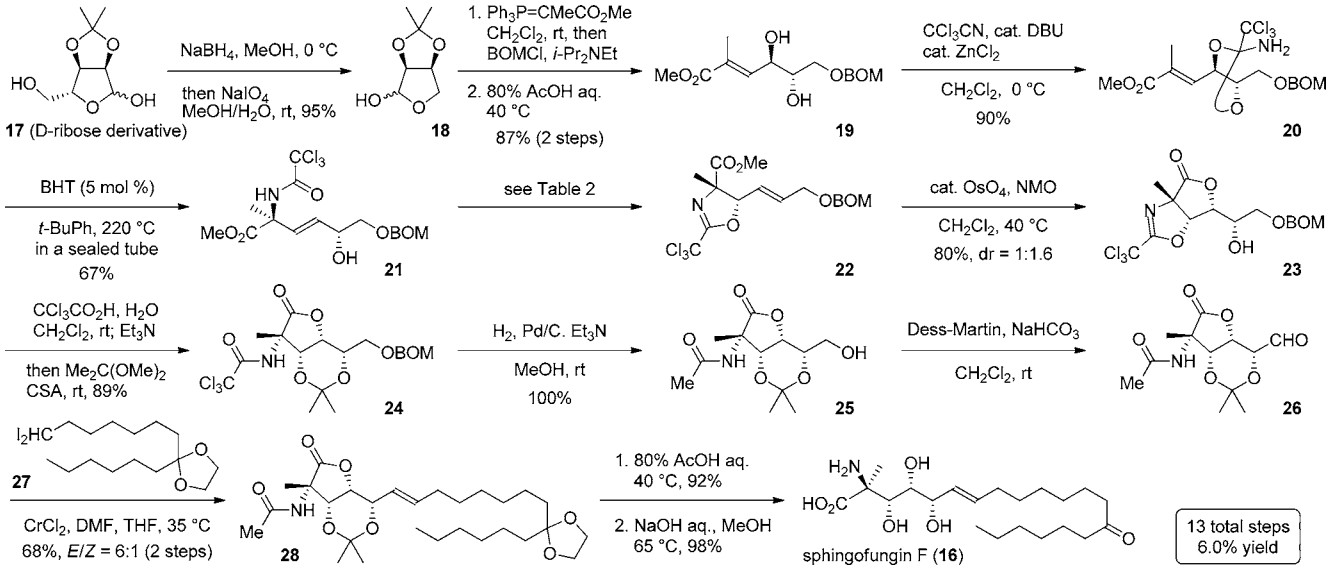
Scheme 3. Cascade-Type and Orthoamide-Type Overman Rearrangements of Allylic Vicinal Diol 11



To demonstrate the utility of our method, we took an interest in the total synthesis of sphingofungin F (**16**), which was isolated from the fermentation broth of *Paecilomyces variotii* by the Merck

DOI: 10.1021/acs.orglett.5b00475
Org. Lett. 2015, 17, 1704−1707

Scheme 4. Total Synthesis of Sphingofungin F (16)



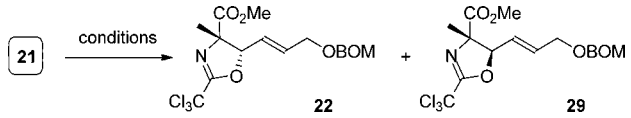
group in 1992 (Scheme 4).[12] Sphingofungin F (**16**) is a potent antifungal agent that acts by inhibition of serine palmitoyltransferase, blocking the first step of sphingosine biosynthesis.[13]

Structurally, it consists of a hydrophobic side chain and a hydrophilic moiety including an α,α-disubstituted amino acid and a triol. Its important biological activity and unique structure have inspired a number of synthetic chemists to work on the total syntheses of sphingofungin F (**16**)[14] and its congeners.[15,16]

Our central strategy toward the total synthesis of sphingofungin F (**16**) was utilization of the orthoamide-type Overman rearrangement of unsaturated ester **20** (Scheme 4). Allylic vicinal diols are readily available in enantiomerically pure form starting from naturally occurring monosaccharides. For example, synthesis of sphingofungin F (**16**) required an *anti*-diol, which was prepared from commercially available D-ribose derivative **17**. Reduction of **17** with $NaBH_4$, followed by oxidative cleavage of the resulting diol, provided lactol **18**.[17] The Wittig reaction and one-pot BOM protection provided the *E*-unsaturated methyl ester, which was exposed to 80% AcOH aq. at 40 °C, giving allylic vicinal diol **19**. Next, cyclic orthoamide **20** was selectively formed under the optimized conditions in 90% yield. The stage was now set for the crucial orthoamide-type rearrangement. In contrast to the *syn*-diol shown in Scheme 3, the reaction of cyclic orthoamide **20** derived from the *anti*-diol required a shorter reaction time (0.5 day vs 2.5 days) and provided sterically hindered α,α-disubstituted amino acid **21** in a higher yield (67% vs 56%). It is noteworthy that this key transformation achieved three selectivities simultaneously, including (i) the number of the rearrangement (single vs double), (ii) the reaction pathway (the Overman rearrangement vs the aza-Michael reaction), and (iii) the stereoselectivity through the chirality transfer.

With α,α-disubstituted amino acid **21** in hand, we turned our attention to construction of the triol (Scheme 4). Unfortunately, direct dihydroxylation of **21** afforded the unfavorable diastereoselectivity completely.[14c,f] This result caused us to attempt transposition of the double bond in **21** by a *syn*-type S_N2' reaction (Table 2). Thus, treatment of **21** with Tf_2O and pyridine at −20 °C initiated the *anti*-type S_N2' reaction to give oxazoline **29** in 86% yield (entry 1). The stereoselectivity of the S_N2' reaction using Mitsunobu conditions depended highly on the nature of the phosphines.[11c,d,18] Whereas the reaction of **21** with

Table 2. S_N2' Reaction of Trichloroacetamide 21



		yield (%)[a]	
entry	conditions	**22**	**29**
1	Tf_2O, pyridine, CH_2Cl_2, −20 °C	2	86
2	PPh_3, DEAD, toluene, 0 °C	11	37
3	$P(OEt)_3$, DEAD, toluene, 0 °C	15	28
4	PBu_3, DEAD, toluene, 0 °C	83	6

[a]Yield of isolated product after purification by column chromatography.

triphenylphosphine and DEAD showed a slight *anti*-selectivity, use of triethylphosphite resulted in no selectivity (entries 2 and 3). The highest level of *syn*-stereoselectivity was achieved when tributylphosphine was used, giving oxazoline **22** in 83% yield, along with **29** in 6% yield (entry 4). Although the factors controlling the selectivities are yet to be clarified, we found that the unique S_N2' reaction of trichloroacetamide proceeded in either *syn*- or *anti*-stereoselectivity by judicious choice of reaction conditions. As shown in Scheme 4, dihydroxylation of oxazoline **22** using a catalytic amount of OsO_4 and NMO in CH_2Cl_2 at 40 °C provided the desired triol derivative **23**, accompanied by formation of the lactone.

The remaining challenge toward the total synthesis was installation of the hydrophobic side chain (Scheme 4). Hydrolysis of oxazoline **23** and the subsequent protection of the resulting diol in a one-pot sequence gave **24** in 89% yield. Removal of the BOM group in **24** provided the primary alcohol **25** with concomitant dechlorination.[19] After the Dess-Martin oxidation of **25**, the hydrophobic side chain **27** was successfully installed on aldehyde **26** by the $CrCl_2$-mediated Takai coupling reaction,[20] which was originally developed by the Kan group for the total synthesis of a sphingofungin derivative.[15h] Finally, global deprotection of **28** completed the total synthesis of sphingofungin F (**16**) in 13 steps in 6.0% total yield from commercially available D-ribose derivative **17**.

DOI: 10.1021/acs.orglett.5b00475
Org. Lett. 2015, 17, 1704−1707

In conclusion, we have developed a direct method to give α,α-disubstituted amino acid derivatives by Overman rearrangement of unsaturated esters. The present study also highlighted the utility of sigmatropic rearrangements of allylic vicinal diols, which are readily available in enantiomerically pure form starting from a monosaccharide. Indeed, we have achieved the concise total synthesis of sphingofungin F (**16**), in which the key step was the orthoamide-type Overman rearrangement of an unsaturated ester. We successfully demonstrated that incorporation of high functional group compatibility for the original reactions is a highly useful approach in regard to the synthesis of complex molecules such as biologically active natural products and pharmaceuticals. Efforts to elucidate the mechanistic details to suppress the aza-Michael reaction in the Overman rearrangement of unsaturated esters are ongoing.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures; copies of ^{1}H NMR and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: takaakis@applc.keio.ac.jp.
*E-mail: chida@applc.keio.ac.jp.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported by a Grant-in-Aid for Scientists Research (B) from MEXT (26288018). Prof. Toshiaki Miyake and Dr. Kiyoko Iijima, Institute of Microbial Chemistry, Hiyoshi (BIKAKEN), are acknowledged for the ^{13}C NMR analysis of the synthetic sphingofungin F.

■ REFERENCES

(1) (a) Wender, P. A.; Croatt, M. P.; Witulski, B. *Tetrahedron* **2006**, *62*, 7505−7511. (b) Burns, N. Z.; Baran, P. S.; Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2009**, *48*, 2854−2867. (c) Young, I. S.; Baran, P. S. *Nat. Chem.* **2009**, *1*, 193−205. (d) Afagh, N. A.; Yudin, A. K. *Angew. Chem., Int. Ed.* **2010**, *49*, 262−310.

(2) (a) Oda, Y.; Sato, T.; Chida, N. *Org. Lett.* **2012**, *14*, 950−953. (b) Shirokane, K.; Wada, T.; Yoritate, M.; Minamikawa, R.; Takayama, N.; Sato, T.; Chida, N. *Angew. Chem., Int. Ed.* **2014**, *53*, 512−516. (c) Nakajima, M.; Oda, Y.; Wada, T.; Minamikawa, R.; Shirokane, K.; Sato, T.; Chida, N. *Chem.—Eur. J.* **2014**, *20*, 17565−17571.

(3) (a) Overman, L. E. *J. Am. Chem. Soc.* **1974**, *96*, 597−599. For reviews on the Overman rearrangement, see: (b) Overman, L. E.; Carpenter, N. E. In *Organic Reactions*; Overman, L. E., Ed.; Wiley: New York, NY, 2005; Vol. *66*, pp 1−107.

(4) For selected reviews, see: (a) Enders, D.; Knopp, M.; Schiffers, R. *Tetrahedron: Asymmetry* **1996**, *7*, 1847−1882. (b) Nubbemeyer, U. *Synthesis* **2003**, 961−1008.

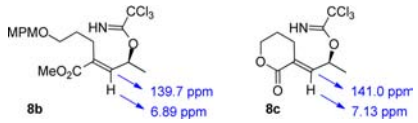
(5) (a) Bey, P.; Gerhart, F.; Jung, M. *J. Org. Chem.* **1986**, *51*, 2835−2838. (b) Mehmandoust, M.; Petit, Y.; Larchevêque, M. *Tetrahedron Lett.* **1992**, *33*, 4313−4316.

(6) For synthesis of amino acid derivatives through oxidation of an olefin after the Overman rearrangement, see: (a) Takano, S.; Akiyama, M.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1984**, 770−771. (b) Chen, Y. K.; Lurain, A. E.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 12225−12231. (c) Anderson, C. E.; Overman, L. E. *J. Am. Chem. Soc.* **2003**, *125*, 12412−12413. (d) Drummond, L. J.; Sutherland, A. *Tetrahedron* **2010**, *66*, 5349−5356.

(7) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841−1860.

(8) Retreatment of the isolated aza-Michael products **4a*α***, **4a*β***, and **10c*α*** under the developed conditions at 140 °C resulted in the recovery of the aza-Michael products, showing the irreversibility of the reaction.

(9) ^{1}H and ^{13}C NMR spectra showed that the chemical shifts of **8c** at the β-position were slightly more downfield than those of **8b**.



(10) For the Overman rearrangement of allylic vicinal diols, see: (a) Vyas, D. M.; Chiang, Y.; Doyle, T. W. *J. Org. Chem.* **1984**, *49*, 2037−2039. (b) Danishefsky, S.; Lee, J. Y. *J. Am. Chem. Soc.* **1989**, *111*, 4829−4837. (c) Momose, T.; Hama, N.; Higashino, C.; Sato, H.; Chida, N. *Tetrahedron Lett.* **2008**, *49*, 1376−1379. (d) Hama, N.; Matsuda, T.; Sato, T.; Chida, N. *Org. Lett.* **2009**, *11*, 2687−2690. (e) Hama, N.; Aoki, T.; Miwa, S.; Yamazaki, M.; Sato, T.; Chida, N. *Org. Lett.* **2011**, *13*, 616−619. (f) Nakayama, Y.; Sekiya, R.; Oishi, H.; Hama, N.; Yamazaki, M.; Sato, T.; Chida, N. *Chem.—Eur. J.* **2013**, *19*, 12052−12058.

(11) For the Claisen rearrangements of allylic vicinal diols, see: (a) Tanimoto, H.; Saito, R.; Chida, N. *Tetrahedron Lett.* **2008**, *49*, 358−362. (b) Kitamoto, K.; Sampei, M.; Nakayama, Y.; Sato, T.; Chida, N. *Org. Lett.* **2010**, *12*, 5756−5759. (c) Kitamoto, K.; Nakayama, Y.; Sampei, M.; Ichiki, M.; Furuya, N.; Sato, T.; Chida, N. *Eur. J. Org. Chem.* **2012**, 4217−4231. (d) Ichiki, M.; Tanimoto, H.; Miwa, S.; Saito, R.; Sato, T.; Chida, N. *Chem.—Eur. J.* **2013**, *19*, 264−269.

(12) 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*, 1692−1696.

(13) Zweerink, M. M.; Edison, A. M.; Wells, G. B.; Pinto, W.; Lester, R. L. *J. Biol. Chem.* **1992**, *267*, 25032−25038.

(14) (a) Kobayashi, S.; Matsumura, M.; Furuta, T.; Hayashi, T.; Iwamoto, S. *Synlett* **1997**, 301−303. (b) Kobayashi, S.; Furuta, T.; Hayashi, T.; Nishijima, M.; Hanada, K. *J. Am. Chem. Soc.* **1998**, *120*, 908−919. (c) Trost, B. M.; Lee, C. B. *J. Am. Chem. Soc.* **1998**, *120*, 6818−6819. (d) Kobayashi, S.; Furuta, T. *Tetrahedron* **1998**, *54*, 10275−10294. (e) Liu, D.-G.; Wang, B.; Lin, G.-Q. *J. Org. Chem.* **2000**, *65*, 9114−9119. (f) Trost, B. M.; Lee, C. *J. Am. Chem. Soc.* **2001**, *123*, 12191−12201. (g) Lee, K.-Y.; Oh, C.-Y.; Ham, W.-H. *Org. Lett.* **2002**, *4*, 4403−4405. (h) Li, M.; Wu, A. *Synlett* **2006**, 2985−2988. (i) Wang, B.; Lin, G.-Q. *Eur. J. Org. Chem.* **2009**, 5038−5046. (j) Gan, F.-F.; Yang, S.-B.; Luo, Y.-C.; Yang, W.-B.; Xu, P.-F. *J. Org. Chem.* **2010**, *75*, 2737−2740.

(15) For the total synthesis of sphingofungin E, see: (a) Wang, B.; Yu, X.-M.; Lin, G.-Q. *Synlett* **2001**, 904−906. (b) Nakamura, T.; Shiozaki, M. *Tetrahedron Lett.* **2001**, *42*, 2701−2704. (c) Reference 14f. (d) Oishi, T.; Ando, K.; Inomiya, K.; Sato, H.; Iida, M.; Chida, N. *Org. Lett.* **2002**, *4*, 151−154. (e) Oishi, T.; Ando, K.; Inomiya, K.; Sato, H.; Iida, M.; Chida, N. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 1927−1947. (f) Reference 14i. (g) Martinková, M.; Gonda, J.; Raschmanová, J. Š.; Slaninková, M.; Kuchár, J. *Carbohydr. Res.* **2010**, *345*, 2427−2437. (h) Ikeuchi, K.; Hayashi, M.; Yamamoto, T.; Inai, M.; Asakawa, T.; Hamashima, Y.; Kan, T. *Eur. J. Org. Chem.* **2013**, 6789−6792.

(16) For the total synthesis of sphingofungins B and D, see: (a) Mori, K.; Otaka, K. *Tetrahedron Lett.* **1994**, *35*, 9207−9210. (b) Chida, N.; Ikemoto, H.; Noguchi, A.; Amano, S.; Ogawa, S. *Nat. Prod. Lett.* **1995**, *6*, 295−302. (c) Kobayashi, S.; Hayashi, T.; Iwamoto, S.; Furuta, T.; Matsumura, M. *Synlett* **1996**, 672−674. (d) Otaka, K.; Mori, K. *Eur. J. Org. Chem.* **1999**, 1795−1802.

(17) Kotsuki, H.; Miyazaki, A.; Ochi, M. *Tetrahedron Lett.* **1991**, *32*, 4503−4504.

(18) Roush, D. M.; Patel, M. M. *Synth. Commun.* **1985**, *15*, 675−679.

(19) Mulard, L. A.; Ughetto-Monfrin, J. *J. Carbohyd. Chem.* **2000**, *19*, 193−220.

(20) Okazoe, T.; Takai, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 951−953.

DOI: 10.1021/acs.orglett.5b00475
Org. Lett. 2015, 17, 1704−1707