

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*^{*,†}

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

$$\begin{array}{c|c} & & & \\ & & & \\ & & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & \\ & & \\ &$$

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. 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. In this letter, we succeeded in the integrating ester compatibility with the original Overman rearrangement 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 $(2 \rightarrow 4)$. 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 $(5 \rightarrow 6 \rightarrow 7)$, 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 $\mathbf{2}'$ and $\mathbf{2}''$ (Scheme 2). The aza-Michael addition would be stereoelectronically preferred from the major conformer $\mathbf{2}'$ 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 $\mathbf{2}''$ 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 \mathbf{R}^2 were installed at the α -

Received: February 14, 2015

[†]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

Organic Letters Letter

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

A^{1,2}-strain

$$R^2$$
 R^2
 R^2

position of unsaturated ester 2, the resulting trisubstituted olefin 8 would have a large $A^{1,2}$ -allylic strain as shown in conformation 8′. 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 $140\,^{\circ}$ C, resulting in the formation of the rearranged product 3a in only 46% yield, along with aza-Michael byproducts $4a\alpha$ (31%) and

Table 1. Overman Rearrangement of Unsaturated Esters^a

^a2 or 8, t-BuPh (0.015 M), 140 °C in a sealed tube. ^bYield of isolated product after purification by column chromatography. ^cThe diastereomeric ratio was 1.5:1.

 $4a\beta$ (3%) (entry 1). 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.

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

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

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 CCl₃CN 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 CCl₃CN (1.3 equiv), DBU (30 mol %), and ZnCl₂ (10 mol %). The orthoamide-type Overman rearrangement of 14 underwent the single rearrangement at 220 $^{\circ}\text{C}$ 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.

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

Organic Letters Letter

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 NaBH₄, followed by oxidative cleavage of the resulting diol, provided lactol 18.17 The Wittig reaction and one-pot BOM protection provided the E-unsaturated methylester, 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 $\alpha_i \alpha_j$ 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. 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 ₂ O, pyridine, CH_2Cl_2 , $-20~^{\circ}C$	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

"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. After the Dess-Martin oxidation of 25, the hydrophobic side chain 27 was successfully installed on aldehyde 26 by the CrCl₂-mediated Takai coupling reaction, which was originally developed by the Kan group for the total synthesis of a sphingofungin derivative. 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.

Organic Letters Letter

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

S Supporting Information

Experimental procedures; copies of ¹H NMR and ¹³C 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 ¹³C 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 $4a\alpha$, $4a\beta$, and $10c\alpha$ 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, 93–220

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