gem-Diacetates as Carbonyl Surrogates for Asymmetric Synthesis. Total Syntheses of Sphingofungins E and F

Barry M. Trost* and Chulbom Lee†

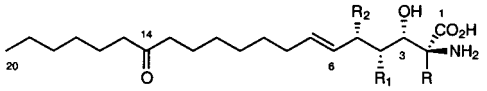
Contribution from the Department of Chemistry, Stanford University, Stanford, California 94305

Received July 27, 2001

Abstract: The equivalent of an asymmetric addition to a carbonyl group with a stabilized anion is accomplished by discriminating between the enantiotopic C−O single bonds of a *gem*-diacetate. In this way, enantioselective total syntheses of two antifugal agents, sphingofungins E and F, have been accomplished. The synthetic strategy is based on a series of catalytic processes whereby all of the chiral centers are created with high stereoselectivities. The first two stereocenters are introduced by an asymmetric allylic alkylation reaction of *gem*-diacetate **9** with azlactone **10**. The complex of Pd(0) and ligand **14** efficiently catalyzes this key reaction, which differentiates both the enantiotopic leaving groups of a *gem*-diacetate and enantiotopic faces of the enolate of an azlactone in high enantiomeric excess and diastereomeric excess. From these two stereocenters, the configurations of the remaining two centers are set by a diastereoselective Os(VIII)-catalyzed dihydroxylation reaction with excellent stereocontrol. The *trans*-alkene is established by Cr(II)-mediated olefination, and a subsequent *B*-alkyl Suzuki coupling reaction conjoins the polar head unit and the nonpolar, 13-carbon lipid tail. The efficiency of our strategy is illustrated by the completion of syntheses of sphingofungins F and E in 15 and 17 steps, and in 17% and 5% overall yields, respectively.

Sphingosines constitute the backbone of sphingolipids, ubiquitous membrane components that are involved in a number of cellular events. The discovery of the ability of sphingosine to inhibit protein kinase C (PKC) prompted a wider examination of the possible roles of sphingosines and their derived products in signal transduction.[1] These investigations have led to a recognition that sphingosines and various biosynthetic intermediates, albeit in low cellular concentrations, are important second messengers and regulatory molecules.[2] While the structure of sphingosines varies among organisms, a variety of novel analogues have been isolated mainly from the cultivation of fungi (Figure 1).[3] These sphingosine-like compounds typically possess more functionalized head and lipid tail units as compared to common *erythro*-sphingosine.

Sphingofungins E (**1**) and F (**2**) were isolated as antifungal agents from fermentation of *Paecilomyces variotii* (ATCC 74079) by Merck in 1992.[4] Along with other congeners (A−D), they were found to block the biosynthesis of sphingolipids, 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.[5] Particularly noteworthy in these compounds is their striking similarity to myriocin[6] (**4**, also known as thermozymocidin and ISP-1) and mycestericin[7] (cf. **5**), which are known to be remarkable immunosuppressive agents with potencies equivalent to and 10- to 100-fold higher than those of clinically used FK506[8] and cyclosporin A[9] (CsA), respectively. This series apparently inhibits T cell proliferation by a completely new mode of action, suggesting the prospect of developing a novel therapeutic agent on the basis of modulation of sphingolipid



1 Sphingofungin E; R = CH_2OH, R_1 = OH, R_2 = OH
2 Sphingofungin F; R = CH_3, R_1 = OH, R_2 = OH
3 Malonofungin; R = CO_2H, R_1 = OH, R_2 = OAc
4 Myriocin; R = CH_2OH, R_1 = OH, R_2 = H
5 Mycestericin D; R = CH_2OH, R_1 = H, R_2 = H

Figure 1. Sphingosine analogues of fungal origin.

† Present address: Department of Chemistry, Princeton University, Princeton, NJ 08544.

(1) (a) Hannun, Y. A.; Loomis, C. R.; Merrill, A. H.; Bell, R. M. *J. Biol. Chem.* **1986**, *261*, 2604. (b) Hannun, Y. A. *Science* **1989**, *243*, 500.

(2) (a) Hannun, Y. A. *Sphingolipid-Mediated Signal Transduction*; R. G. Landes: Austin, TX, 1997. (b) Merrill, A. H., Jr.; Sweeley, C. C. *Sphingolipids: Metabolism and Cell Signaling*; Elsevier Science: Amsterdam, 1996. (c) Merrill, A. H., Jr.; Sweeley, C. C. In *Biochemistry of Lipids, Lipoproteins and Membranes*; Vance, D. E., Vance, J., Eds.; Elsevier Science: Amsterdam, 1996; pp 309−339. (d) Hakomori, S. In *Handbook of Lipid Research*; Kafner, J. N., Hakomori, S., Eds.; Plenum: New York, 1983; Vol. 3, pp 1−164. (e) Ariga, T.; Jarvis, W. D.; Yu, R. K. *J. Lipid Res.* **1998**, *39*, 1. (f) Igarashi, Y. *J. Biochem.* **1997**, *122*, 1080. (g) Hannun, Y. A. *Science* **1996**, *274*, 1855. (h) Shayman, J. A. *J. Am. Soc. Nephrol.* **1996**, *7*, 171. (i) Spiegel, S.; Milstein, S. *J. Membr. Biol.* **1995**, *146*, 225.

(3) (a) Merrill, A. H., Jr.; Liotta, D. C.; Riley, R. E. In *Handbook of Lipid Research*; Bell, R. M., Ed.; Plenum: New York, 1996; Vol. 8, pp 205−237. (b) Mandala, S. M.; Harris, G. H. *Methods Enzymol.* **2000**, *311*, 335.

(4) 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.

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

(6) Fujita, T.; Inoue, K.; Yamamoto, S.; Ikumoto, T.; Sasaki, S.; Toyama, R.; Chiba, K.; Hoshino, Y.; Okumoto, T. *J. Antibiot.* **1994**, *47*, 208.

(7) Sasaki, S.; Hashimoto, R.; Kiuchi, M.; Inoue, K.; Ikumoto, T.; Hirose, R.; Chiba, K.; Hoshino, Y.; Okumoto, T.; Fujita, T. *J. Antibiot.* **1994**, *47*, 420.

(8) (a) Kino, T.; Hatanaka, H.; Hashimoto, M.; Nishiyama, M.; Goto, T.; Okuhara, M.; Kohsaka, M.; Aoki, H.; Imanaka, H. *J. Antibiot.* **1987**, *40*, 1249. (b) Kino, T.; Hatanaka, H.; Miyata, S.; Inamura, N.; Nishiyama, M.; Yajima, T.; Goto, T.; Okuhara, M.; Kohsaka, M.; Aoki, H.; Ochiai, T. *J. Antibiot.* **1987**, *40*, 1256.

(9) Borel, J. F. In *Cyclosporin A*; Borel, J. F., Ed.; Elsevier Biochemical Press: Amsterdam, 1982; pp 5−17.

10.1021/ja0118338 CCC: $20.00
Published on Web 11/14/2001

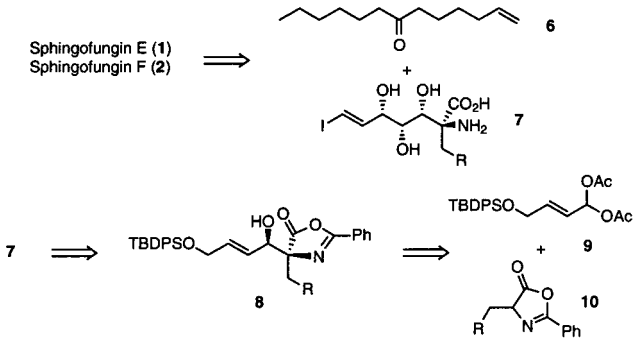
biosynthesis.[10] Recently, two murine myriocin-binding proteins have been isolated and found to be genetically linked to sphinogolipid biosynthesis.[11] However, as manifested by the seemingly independent nature of the SAR,[12] a direct connection between immunosuppression and SPT inhibition remains to be established.

Due to their biological importance and novel structures, the sphingosine analogues have stimulated a number of synthetic efforts.[13] While these studies largely made use of the "chiral pool", the structural homology imparted in these compounds led us to explore a more general synthetic strategy. Using a new asymmetric catalytic methodology, we hoped to achieve unambiguous enantiocontrol in the creation of the C2 quaternary center, which had been a major difficulty in the synthesis of this series.[14] In contrast to the chiral pool approaches, our flexible strategy was anticipated to provide ready access to not only this important class of molecules but also their analogues by simple modifications in the synthetic scheme. Herein, we report a full account on the successful realization of concise syntheses of sphingofungins E and F.[15]

Synthetic Plan

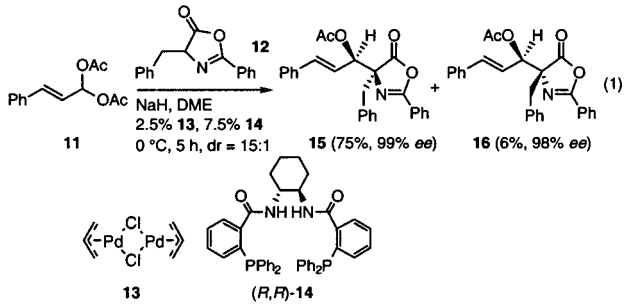
The conspicuous structural feature of the sphingofungins led us to a retrosynthetic analysis dividing these compounds into the two major parts, nonpolar lipid tail **6** and polar headgroup **7** (Scheme 1). We envisaged that these two fragments could be conjoined by a cross-coupling reaction at a late stage of the synthesis. While the preparation of **6** appeared straightforward, the presence of polyhydroxyl groups and a quaternary center in **7** made the stereocontrolled synthesis of this part more challenging. In further analysis, the polyhydroxyl groups of **7** were envisioned to derive from a stereoselective oxygenation of **8** wherein the allylic directing effect would require the inverted configuration at the allylic center based upon the known diastereoselectivity of osmium-catalyzed dihydroxylation. If the key intermediate **8** were to emanate from our newly developed asymmetric alkylation, then *gem*-diacetate **9** and serine, or alanine, derived azlactone **10** (R = OH or H) could serve as precursors for the E and F systems, respectively. Because of

Scheme 1. Retrosynthetic Analysis



anticipated elimination problems in using the enolate of **10** (R = OH), an OH surrogate will be required.

This synthetic plan required an asymmetric addition of a rather stabilized anion to a carbonyl group—a feature that suffers from an unfavorable equilibrium as well as no precedent for such asymmetric addition. Both of these issues are tackled by the key aldol-like reaction whose motif came from our continued studies on the asymmetric allylic alkylation (AAA) reaction. It has been demonstrated that *gem*-diesters can serve as "chiral carbonyl surrogates" in the Pd-catalyzed AAA reactions, giving rise to an aldol-type product with high enantiomeric excess (ee).[16] In a separate set of investigations, azlactones have proved to be potent nucleophiles to provide various α-alkylated amino acid derivatives in excellent ee.[17] These reactions, when combined together, achieved differentiation not only between enantiotopic leaving groups of a *gem*-diacetate but also between enantiotopic faces of an azlactone enolate. For example, the reaction of *gem*-diacetate **11** and azlactone **12** catalyzed by the complex of $(\eta^3\text{-}C_3H_5PdCl)_2$ (**13**) and ligand (*R*,*R*)-**14** gave readily separable diastereomers **15** and **16** with high stereoselectivities (eq 1). The relative stereochemistry of the major



product **15** corresponded well to the C2 and C3 stereocenters of the key intermediate **8**. Thus, simple structural variations of the two reaction partners would afford proper intermediates of type **8** for the synthesis of sphinogfungins E and F.

A notable advantage of this approach is the installation of two stereogenic centers, including the C2 quaternary carbon, by using a single, unambiguous asymmetric reaction. Once the configurations of C2 and C3 are established, the remaining stereocenters are set with reference to this stereochemistry by a diastereoselective oxygenation. Another point of practical consequence is that the requisite *gem*-diacetate **9** and azlactone **10** are readily available from the corresponding α,β-unsaturated aldehyde and α-amino acids, respectively.

(10) Miyake, Y.; Kozutsumi, Y.; Nakamura, S.; Fujita, T.; Kawasaki, T. *Biochem. Biophys. Res. Commun.* **1995**, *211*, 396.

(11) Chen, J. K.; Lane, W. S.; Schreiber, S. L. *Chem. Biol.* **1999**, *6*, 221.

(12) Fujita, T.; Hirose, R.; Yoneta, M.; Sasaki, S.; Inoue, K.; Kiuchi, M.; Hirase, S.; Chiba, K.; Sakamoto, H.; Arita, J. *J. Med. Chem.* **1996**, *39*, 4451.

(13) For syntheses of myriocin, see: (a) Banfi, L.; Bretta, M. G.; Colombo, L.; Gennari, C.; Scolastico, C. *J. Chem. Soc., Chem. Commun.* **1982**, 488. Banfi, L.; Bretta, M. G.; Colombo, L.; Gennari, C.; Scolastico, C. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1613. (b) Yoshikawa, M.; Yokokawa, Y.; Okuno, Y.; Murakami, N. *Chem. Pharm. Bull.* **1994**, *42*, 994. Yoshikawa, M.; Yokokawa, Y.; Okuno, Y.; Murakami, N. *Tetrahedron* **1995**, *51*, 6209. (c) Sano, S.; Kobayashi, Y.; Kondo, T.; Takebayashi, M.; Maruyama, S.; Fujita, T.; Nagao, Y. *Tetrahedron Lett.* **1995**, *36*, 2097. (d) Hatakeyama, S.; Yoshida, M.; Esumi, T.; Iwabuchi, Y.; Irie, H.; Kawamoto, T.; Yamada, H.; Nishizawa, M. *Tetrahedron Lett.* **1997**, *45*, 7887. (e) Rao, A. V. R.; Gurjar, M. K.; Devi, T. R.; Kumar, K. R. *Tetrahedron Lett.* **1993**, *34*, 1653. (f) Deloisy, S.; Thang, T. T.; Olesker, A.; Lukas, G. *Tetrahedron Lett.* **1994**, *35*, 4783. For synthesis of sphingofungin E, see: (g) Nakamura, T.; Shiozaki, M. *Tetrahedron Lett.* **2001**, *42*, 2701. For syntheses of sphingofungin F, see: (h) Kobayashi, S.; Matsumura, M.; Furuta, T.; Hayashi, T.; Iwamoto, S. *Synlett* **1997**, 301. Kobayashi, S.; Furuta, T.; Hayashi, T.; Nishijima, M.; Hanada, K. *J. Am. Chem. Soc.* **1998**, *120*, 908. Kobayashi, S.; Furuta, T.; Hayashi, T.; Nishijima, M.; Hanada, K. *Tetrahedron* **1998**, *54*, 10275. (i) Liu, D.-G.; Wang, B.; Lin, G.-Q. *J. Org. Chem.* **2000**, *65*, 9114.

(14) For reviews, see: (a) Martin, S. F. *Tetrahedron* **1980**, *36*, 419. (b) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037. (c) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388.

(15) Trost, B. M.; Lee, C. B. *J. Am. Chem. Soc.* **1998**, *120*, 6818.

(16) (a) Trost, B. M.; Lee, C. B.; Weiss, J. M. *J. Am. Chem. Soc.* **1995**, *117*, 7247. (b) Trost, B. M.; Lee, C. B. *J. Am. Chem. Soc.* **2001**, *123*, 3687. (c) Trost, B. M.; Lee, C. B. *J. Am. Chem. Soc.* **2001**, *123*, 3671.

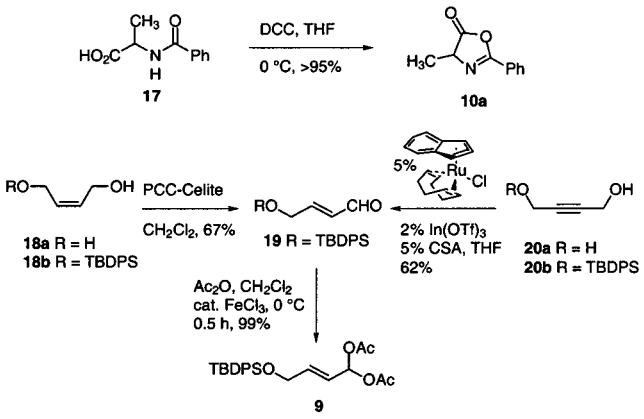
(17) (a) Trost, B. M.; Ariza, X. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2635. (b) Trost, B. M.; Ariza, X. *J. Am. Chem. Soc.* **1999**, *121*, 10727.

Table 1. Alkylation of Azlactone **10a** with *gem*-Diacetate **9** (Eq 2)

entry	catalyst	solvent	temp, time	% yield[a] (% ee)[b] **21**	% yield[a] (% ee)[b] **22**	ratio **21**:**22**[c]
1	2% $Pd(PPh_3)_4$	DME	25 °C, 5 h	28 (−)	32 (−)	1:1.6
2	2.0% **13**, 6.0% **14**	DME	0 °C, 3 h	73 (82)	17 (55)	5.3:1
3	1.0% **13**, 3.0% **14**	CH_3CN[d]	0 °C, 2 h	71 (10)[e]	10 (60)	3.5:1
4	2.0% **13**, 6.0% **14**	THF	0 °C, 3 h	68 (89)	5 (86)	9.6:1
5	0.5% **13**, 1.5% **14**	THF	−5 °C, 4 h[f]	70 (89)	5 (89)	10.5:1
6	0.2% **13**, 0.6% **14**	THF	−5 °C, 6 h[f]	70 (87)	6 (89)	11.2:1

[a] Isolated yields. [b] HPLC analysis of the corresponding methyl esters **23** and **24** (eqs 3 and 4). [c] Diastereomeric ratio determined by ^{1}H NMR integration on the crude mixture. [d] Triethylamine was used as base. [e] The ee of the opposite enantiomer, (*ent*)-**21**. [f] Slow addition (see text).

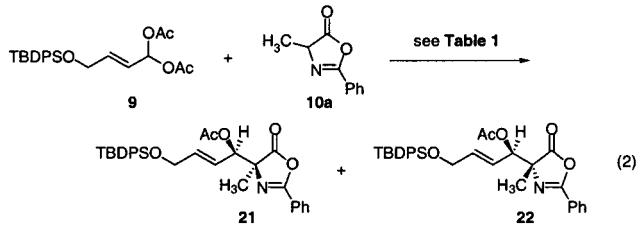
Scheme 2. Preparation of Azlactone **10a** and *gem*-Diacetate **9**



Total Synthesis of Sphingofungin F

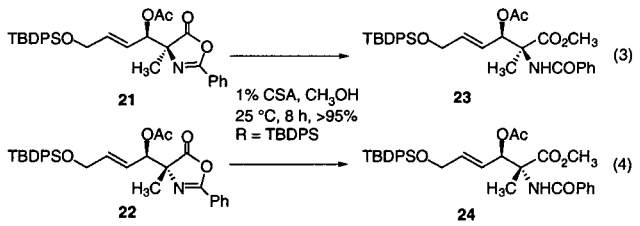
The first stage of the synthesis involved the preparation of *gem*-diacetate **9** and methyl-substituted azlactone **10a** (Scheme 2). While **10a** was synthesized from *N*-benzoyl-D,L-alanine (**17**),[18] **9** was prepared by $FeCl_3$-catalyzed addition[19] of acetic anhydride to aldehyde **19**,[20] which was readily available from *cis*-2-butene-1,4-diol (**18a**) by monosilylation (TBDPSCl, imidazole, 98%) and PCC oxidation. Alternatively, aldehyde **19** could be directly prepared from monosilylated 2-butyne-1,4-diol (**20b**) in comparable yield by an internal atom economical redox reaction under ruthenium catalysis without having recourse to stoichiometric reductants and oxidants.[21] Since the *cis*-2-butene-1,4-diol derives from 2-butyne-1,4-diol, this latter route also reduces the actual number of steps.

With the two substrates readily prepared, our initial attention focused on the Pd-catalyzed alkylation (eq 2, Table 1). The



viability of this alkylation was first tested by using achiral $(PPh_3)_4Pd$ as the catalyst. The nucleophile was generated from 2.0 equiv of sodium hydride and 2.5 equiv of azlactone **10a** in dimethyl ether (DME) at ambient temperature (entry 1). The reaction proceeded smoothly to give a mixture of diastereomers as the product in a 1.6:1 ratio as measured by ^{1}H NMR integration of the signal of the α-acetoxy methine protons, which resonated at δ 5.61 (d, $J = 6.5$ Hz) for the major isomer and 5.57 (d, $J = 6.9$ Hz) for the minor isomer. The IR absorptions, at 1824 and 1827 cm^{-1}, indicated the presence of an intact azlactone moiety in both products. The major and minor products could be easily separated by silica gel chromatography and were isolated in 32% and 28% yields, respectively.

We then set out to examine the asymmetric reaction. Accordingly, the reaction was carried out with 2 mol % **13** and 6 mol % **14** in DME at 0 °C to provide a mixture of diastereomers in a 5.3:1 ratio (entry 2). Interestingly, the major product from this asymmetric reaction turned out to be the minor product of the racemic reaction. The absolute and relative configurations of products were tentatively assigned by analogy to previous results (cf. eq 1). To determine the ee of the alkylation products, **21** and **22** were separated and each converted to the corresponding methyl esters, **23** and **24**, in quantitative yields by treatment with methanol under acid catalysis (*vide infra*, eq's 3 and 4). Chiral HPLC analysis successfully determined the ee's

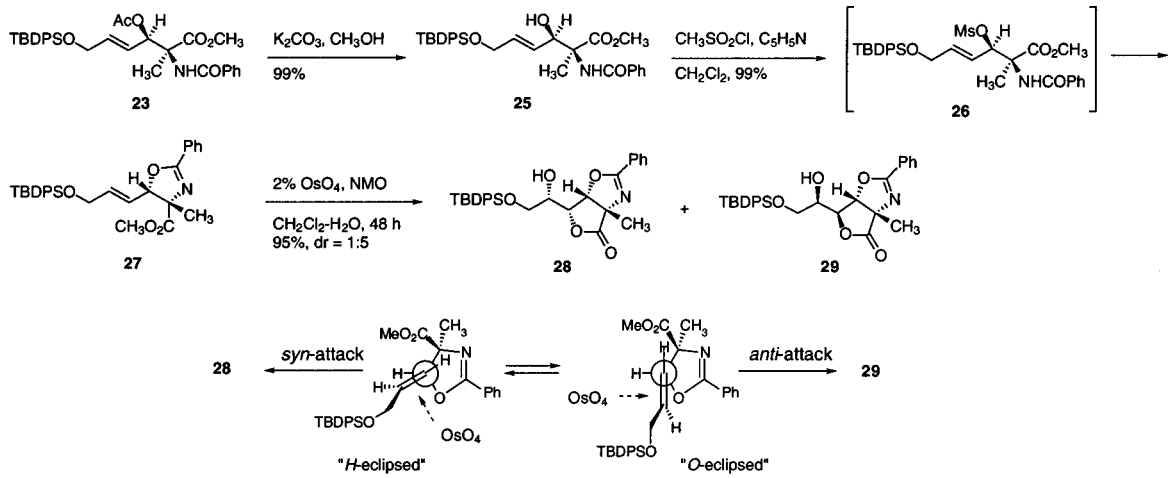


of **23** and **24**, and thus, those of **21** and **22**, to be 82% and 55%, respectively. When the azlactone enolate was generated in acetonitrile using triethylamine as base, the reaction generated a 3.5:1 mixture of diastereomers whose major product turned out to be (*ent*)-**21** with an ee of only 10% (entry 3). This result presents a sharp contrast to the previous results wherein the combination of triethylamine base and acetonitrile solvent proved most effective, leading to high ee's and diastereomeric excesses (de's) in a number of cases.[16] Significant improvement was realized by switching the solvent to tetrahydrofuran (THF) and the counterion back to sodium (entry 4). The de jumped to 9.6:1, and ee's of 89% and 86% were obtained for **21** and **22**, respectively. When a solution of **9** was slowly added at −5 °C over 4 h by a syringe pump to a solution containing 0.5 mol % **13**, 1.5 mol % **14**, and the sodium enolate of **10a**, the two diastereomers were formed in a 10.5:1 ratio with an ee of 89% for both isomers (entry 5). Using this slow addition protocol, the load of **13** and **14** could be further reduced to 0.2 mol % and 0.6 mol %, respectively, with little effect on the stereochemical outcome (entry 6).

As the asymmetric reaction could consistently be conducted with satisfactory ee and yield, we turned to dihydroxylation as a means for introducing the *syn*-hydroxyl groups at C4 and C5.

(18) Chen, F. M. F.; Kuroda, K.; Beneiton, N. L. *Synthesis* **1979**, 230.
(19) Kochhar, K. S.; Bal, B. S.; Deshpande, R. P.; Rajadhyaksha, S. N.; Pinnick, H. W. *J. Org. Chem.* **1983**, *48*, 1765.
(20) Quimpere, M.; Ruest, L.; Deslongchamps, P. *Synthesis* **1992**, 132.
(21) Trost, B. M.; Livingston, R. C. *J. Am. Chem. Soc.* **1995**, *117*, 9586.

Scheme 3. Dihydroxylation after Inversion at C3



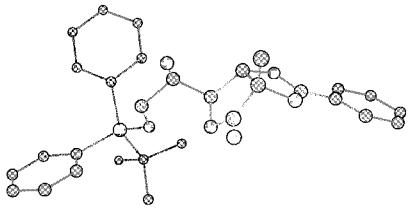
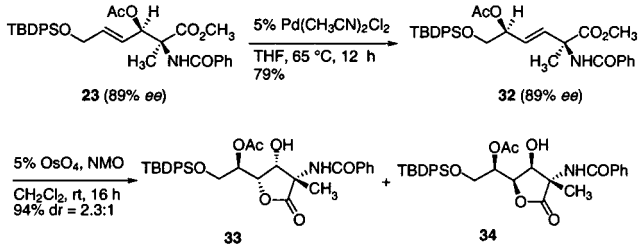


Figure 2. X-ray crystal structure of **29**.

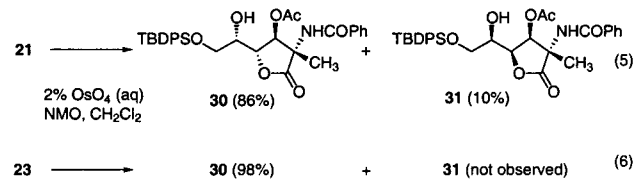
We first explored a sequence that involved inversion of C3 configuration prior to the introduction of the two hydroxyl groups (Scheme 3). The inversion at C3 was achieved by hydrolysis of **23** and subsequent activation via mesylate **26**, which led to the formation of oxazoline **27**. Exercising the dihydroxylation reaction, we noted that the *anti* directing effect[22] of allylic heteroatoms had often been reversed in rigid cyclic systems.[23] In particular, a *syn*-dihydroxylation seemed viable if OsO_4 would approach the alkene from the face opposite the sterically encumbering C2 center in the "*H*-eclipsed conformation".[24] However, the dihydroxylation of **27** gave an inseparable mixture of lactones **28** and **29** in a 1:5 ratio, favoring the undesired *anti*,*syn*-isomer over the desired *syn*,*syn*-isomer. The attempt to override this stereochemical bias by using an asymmetric method (AD-mix-α)[25] provided little improvement, generating a diastereomeric mixture in a 1:2 ratio. The results seemed to indicate that the steric hindrance to OsO_4 attack can be avoided if the olefin adopts an alternate "*O*-eclipsed conformation" that led to the *anti*-attack. Although chromatographic separation of the two isomers was not feasible, gratifyingly, the major product **29** spontaneously crystallized from the mixture. An X-ray crystallographic analysis was performed on a single crystal of this isomer to establish the stereostructure of **29** (Figure 2). Thus, the relative stereochemistry of the two hydroxyl groups (C4, C5) and the tentative structural assignment (C2, C3) for the asymmetric alkylation products were verified at this point.

The stereochemical outcome of the dihydroxylation reaction of **27** reverted our strategy back to the original plan based on

Scheme 4. Dihydroxylation of Transposed Allylic Acetate **32**



Kishi's empirical rule[22] for predicting the stereoselectivity of dihydroxylation reactions (eqs 5 and 6). Hence, azlactone **21**



was treated with catalytic OsO_4 and NMO at 25 °C in methylene chloride. The reaction furnished an 8:1 mixture of diastereomeric lactones **30** and **31** from which the major isomer **30** could be isolated in 86%. This rather encouraging selectivity led us to examine other substrates in the hope of further improvement. *When methyl ester **23** was subjected to the same dihydroxylation conditions, the desired lactone **30** was generated in 98% yield as a single diastereomer!* No trace of the minor isomer **31** could be detected in a number of repeated experiments.

Intrigued by these results, we took a brief excursion to further explore the cooperative effect of the two chiral centers on the stereoselectivity of the dihydroxylation reaction. One interesting substrate for this study was the isomeric allylic acetate **32** derived from a Pd(II)-catalyzed allylic transposition of **21** in 79% yield with complete transfer of chirality (Scheme 4).[26] By contrast, the transposed allylic acetate **32**, bearing an alkene flanked by two stereogenic centers, exhibited only a mediocre selectivity (dr = 2.3:1), despite proceeding with an excellent 94% yield.

The remarkable diastereoselectivity of the dihydroxylation of **23** seems to be a consequence of a strong cooperative effect of the two vicinal stereogenic centers on the conformation. To

(22) (a) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3943; Christ, W. J.; Cha, J. K.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3947. (b) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247.

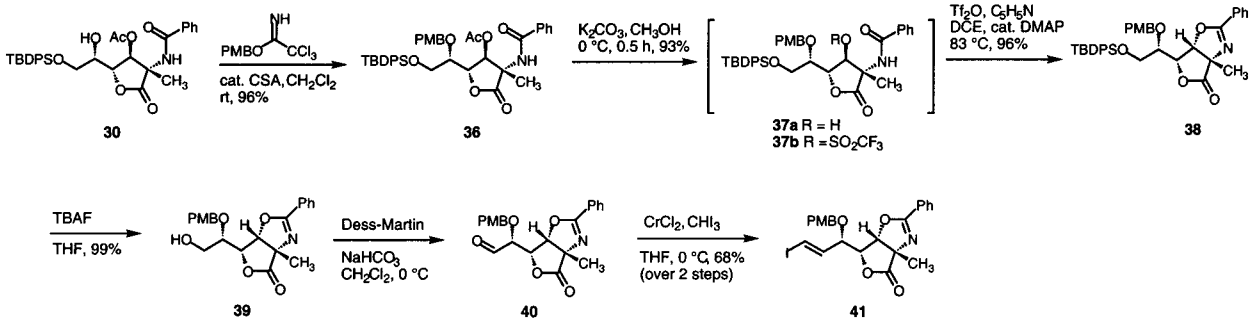
(23) (a) Brimacombe, J. S.; Kabir, A. K. M. S. *Carbohydr. Res.* **1986**, *150*, 35. (b) DeNinno, M. P.; Danishefsky, S. J.; Schulte, G. *J. Am. Chem. Soc.* **1988**, *110*, 3925.

(24) Cha, J. K.; Kim, N.-S. *Chem. Rev.* **1995**, *95*, 1761.

(25) Kolb, H. C.; Van Nieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

(26) (a) Overman, L. E.; Knoll, F. M. *Tetrahedron Lett.* **1979**, 321. (b) Also see ref 16c.

Scheme 5. Completion of the Synthesis of Polar Headgroup **41** for Sphingofungin F



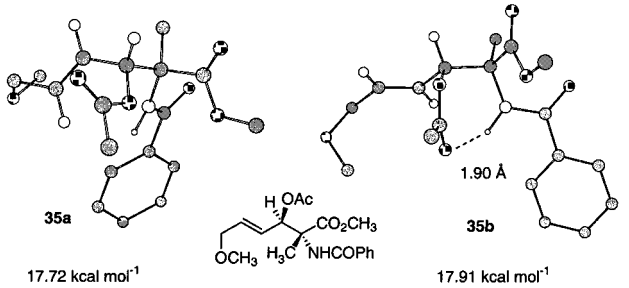
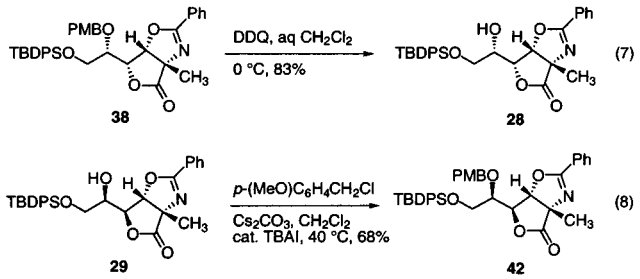


Figure 3. MM2 calculation and stable conformations of **35**.

the extent that the dihydroxylation process occurs through an early transition state, the relative energy of the ground-state conformation will be reflected in the facial selectivity. To examine the conformation of **23**, an MM2* calculation was performed wherein the TBDPSO group was simplified to a methyl ether (Figure 3).[27] A computer simulation revealed two low-energy conformers for **35**, while other conformations were found to be at least 2 kcal/mol higher in energy. In the model of the lowest energy conformer **35a**, one olefinic face is much more exposed to external reagents, whereas the acetoxy group effectively shields the other face. The osmylation onto the more open face of the double bond, however, leads to the unobserved diastereomer **31**. On the other hand, the second lowest energy conformation **35b** presents one face of its alkene readily accessible to osmylation and corresponds to the formation of **30**. Interestingly, **35b** places the NH proton within a hydrogen-bonding distance (r_{O-H} = 1.90 Å) of the carbonyl oxygen of the acetate, thus efficiently blocking the other face of the alkene from the approach of OsO_4. Although the effect of hydrogen bonding may be small due to the distortion of the N−H−O dihedral angle and the presence of water in the reaction medium, it appears to be a contributing factor to such an unusually high degree of acyclic stereocontrol.[28] An alternative rationale arises from the possible directing ability of a remote NH group rather than the effect of the allylic substitutent.[29] Considering the evidences that suggest the possible interaction between OsO_4 and a nitrogen group,[30] the observed selectivity may be due to the NH templating effect or, at the minimum, a combination of such an effect and conformational preference thereof.[31]

With the two C−O bonds at C4 and C5 installed, we set out to complete the synthesis of the polar headgroup (Scheme 5). For setting the proper configuration at C3, lactone **30** was protected as a PMB ether, and the C3 acetate was hydrolyzed. Activation of the C3−O bond of **36** via the formation of triflate **37b** induced cyclization to afford bicyclic oxazoline **38** in high yield. This oxazoline-forming process efficiently adjusted the C3 stereochemistry and provided simultaneous protection for both the hydroxyl and benzamide groups as well. At this juncture, we established all of the required stereogenic centers. To append a one-carbon unit for C7, the primary alcohol was liberated by fluoride-induced removal of the silyl protecting group, and the resulting alcohol **39** was oxidized[32] to afford the unstable aldehyde **40**. Upon subjection of **40** to a $CrCl_2$-mediated iodomethylenation reaction,[33] the desired polar headgroup, vinyl iodide **41**, was generated as a single isomer. The formation of an (*E*)-alkene was verified later by ^{1}H NMR analysis on a more advanced intermediate. The exclusive (*E*)-selectivity in this case mirrors a previously reported literature example in which a similar Takai−Utimoto olefination of an α-alkoxy-aldehyde exhibited complete (*E*)-selectivity.[34]

To establish the stereochemistry of the C−O bonds, correlation studies were conducted. First, the PMB ether **38**, obtained as in Scheme 5, was treated with DDQ to give the corresponding alcohol (eq 7).[35] The product of this reaction was found to be identical in all aspects to the minor diastereomer **28** from the previous route (cf. Scheme 3). On the other hand, the *O*-



(27) The force field calculation was carried out by using Macromodel 6.0 on a Silicon Graphics System. Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

(28) For example, see: Ikemoto, N.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 9657.

(29) (a) Haiza, M.; Lee, J.; Snyder, J. K. *J. Org. Chem.* **1990**, *55*, 5008. (b) Trost, B. M.; Guo, G.-H.; Benneche, T. *J. Am. Chem. Soc.* **1988**, *110*, 621. (c) Houser, F. M.; Ellennberger, S. R. *J. Am. Chem. Soc.* **1984**, *106*, 2458. (d) Johnson, C. R.; Barbarchyn, M. R. *J. Am. Chem. Soc.* **1984**, *106*, 2459. (e) Hacksell, U.; Daves, G. D. *J. Org. Chem.* **1983**, *48*, 4144.

(30) (a) Walsh, P.; Bennani, Y. L.; Sharpless, K. B. *Tetrahedron Lett.* **1993**, *34*, 5545. (b) Xu, D.; Park, C. Y.; Sharpless, K. B. *Tetrahedron Lett.* **1994**, *35*, 2495.

(31) However, the NH *syn*-directing model may require a more rigorous assessment of such effects: (a) Davis, F. A.; Chen, B.-C. In *Stereoselective Synthesis*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Houben-Weyl: Stuttgart, 1996; Vol. 8, pp 4592−4593. Also see: (b) Poli, G. *Tetrahedron Lett.* **1989**, *30*, 7385. (c) Donohoe, T. J.; Blades, K.; Helliwell, M.; Moore, P. R.; Winter, J. J. G. *J. Org. Chem.* **1999**, *64*, 2980.

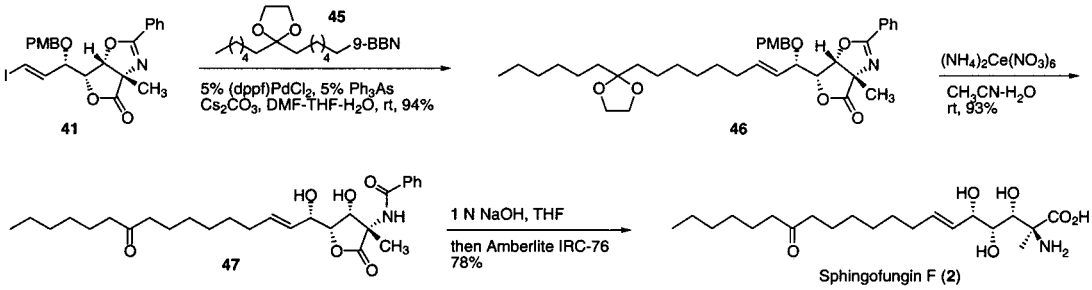
(32) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4156. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

(33) Takai, T.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408.

(34) Kende, A. S.; DeVita, R. J. *Tetrahedron Lett.* **1990**, *31*, 307. For a related study of the solvent effect on the (*E*)-selectivity, see: Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 4497.

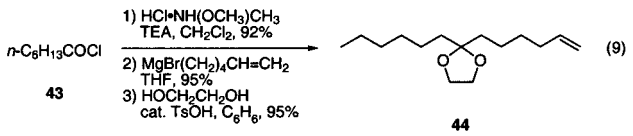
(35) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *33*, 671.

Scheme 6. *B*-Alkyl Suzuki Merger and Completion of the Total Synthesis of Sphingofungin F



alkylation[36] of lactone **29** afforded PMB ether **42** whose spectroscopic properties were different from those of **38**. Since alcohol **29** had been analyzed by an X-ray crystal structure (cf. Figure 3), these chemical correlations globally confirmed our stereochemical assignment on the alkylation, dihydroxylation, and inversion reactions.

Upon preparation of the polar headgroup **41**, we set out to synthesize the lipid tail unit **44** via a three-step sequence starting from heptanoyl chloride (**43**) (eq 9). After formation of a



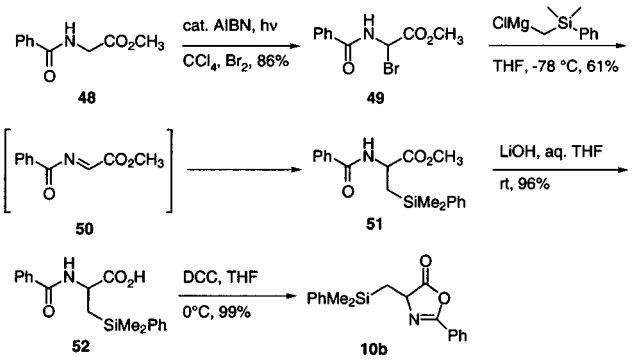
(9)

Weinreb amide,[37] the Grignard addition reaction with 5-hexenylmagnesium bromide gave ketoalkene **6**. Subsequent treatment of **6** with ethylene glycol and catalytic *p*-TsOH under azeotropic dehydration conditions provided ketal **44**.

The final stage of the synthesis involved a cross-coupling of the polar headgroup **41** with the nonpolar lipid tail **44** and deprotection (Scheme 6). The Pd-catalyzed *B*-alkyl Suzuki reaction of **41** with organoborane **45**, prepared in situ from **44** by hydroboration with 9-BBN-H, provided the fully protected **46** in excellent yield.[38] In the ^{1}H NMR spectrum of alkene **46**, a characteristic *trans*-coupling constant (J = 15.6 Hz) between the two olefinic protons (δ 6.02 and δ 5.54) was observed, thus providing support for an (*E*)-geometry. Removal of the PMB group by CAN effected simultaneous hydrolysis of the ethylene ketal and oxazoline to give ketolactone **47**. 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 (**2**).

The synthetic compound was spectroscopically (^{1}H and ^{13}C NMR, IR, and MS) in good agreement with the natural[4] and synthetic[13h,i] sphingofungin F.[39] Our melting point, 143−145 °C, also agreed with that reported, mp 142−144 °C[13h] and 145−147 °C.[13i] In the ^{13}C NMR data, the chemical shifts of C2 and C10 showed some difference among the reported values. For C2, the ^{13}C shifts were δ 66.2 (Merck), 67.7 (Kobayashi et al.[13h]), 67.1 (Liu et al.[13i]), and 66.7 (the present work). It is possible that the variability in the chemical shift of C2 could be a consequence of the difference in the pH of the medium from which sphingofungin F was isolated, in that the pH affects the degree of protonation of the amino acid.[13i,40] The chemical shift of C10 (δ 25.6) reported by Merck's group is different compared to the values from Kobayashi et al. (δ 23.6), Liu et al. (δ 23.9), and the present work (δ 23.6). While a plausible explanation for this disparity should await direct comparisons, unfortunately, a sample or the data therefrom of the natural product was not available.[41]

Scheme 7. Synthesis of Silyl Analogue of Serine Azlactone



Total Synthesis of Sphingofungin E

Having accomplished the synthesis of sphingofungin F (**2**), we then sought to extend this strategy to the total synthesis of sphingofungin E (**1**). For this synthesis, however, an additional issue had to be addressed due to the presence of a C21 hydroxyl group. Namely, the alkylation required an "enolate of serine".[42] Mindful of the potential problem in the direct use of azlactone **10** (R = OH in Scheme 1) as nucleophile, we sought to prepare a silyl analogue of azlactone (R = SiR′$_3$) that would serve as a serine enolate equivalent, avoiding the β-elimination. It was envisioned that the requisite C−O bond would emerge from the C−Si bond by Tamao−Fleming-type oxidation after the alkylation.[43] Accordingly, methyl hippurate (**48**, methyl *N*-benzoylglycine), prepared from hippuric acid or methyl glycinate, was converted to a silyl analogue of serine and advanced to the corresponding azlactone **10b** (Scheme 7). The sequence started with photoinitiated bromination of **48**, which gave the unstable bromide **49**. Treatment of bromide **49** with 2.5 equiv

(36) Dueno, E. E.; Chu, F. X.; Kim, S.-I.; Jung, K. W. *Tetrahedron Lett.* **1999**, *40*, 1843.

(37) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.

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

(39) Although the melting point and optical rotation are in good agreement among synthetic samples, those for the natural compound had not been reported.

(40) A similar observation has been made: Ohfune, Y.; Shimamoto, K.; Ishida, M.; Shinozaki, H. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 15.

(41) Although the differences between the values reported for the natural and synthetic samples might result from a pH effect as well, it could be simply a typographical error.

(42) For related examples, see: (a) Meyers, A. I.; Mihelich, E. D. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 270. (b) Seebach, D.; Aebi, J. D. *Tetrahedron Lett.* **1984**, *25*, 2545. (c) Yu, L.-C.; Helquist, P. *J. Org. Chem.* **1981**, *46*, 4536. (d) Adam, W.; Ehrig, V. *Synthesis* **1976**, 817.

(43) (a) Tamao, K.; Ishida, N.; Tanaka, T.; Kumada, M. *Organometallics* **1983**, *2*, 1694. (b) Fleming, I.; Henning, R.; Plaut, H. *J. Chem. Soc., Chem. Commun.* **1984**, 29. For a review, see: (c) Jones, G. R.; Landais, Y. *Tetrahedron* **1996**, *52*, 7599.

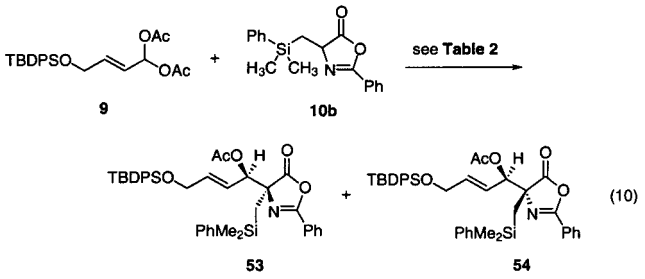
Table 2. Alkylation of Azlactone **10b** with *gem*-Diacetate **9** (Eq 10)

				% yield[a] (% ee)[b]		
entry	catalyst	solvent	temp, time	>**53**	>**54**	ratio **53**:**54**[c]
1	1.0% **13**, 3.0% **14**	THF	0 °C, 3 h	68 (96)	23 (96)	2.4:1
2	1.0% **13**, 3.0% **14**	DME	0 °C, 2 h	40 (94)	22 (94)	1.7:1
3[d]	0.5% **13**, 1.5% **14**	THF	0 °C, 5 h	60 (96)	27 (96)	1.6:1
4[f]	1.0% **13**, 3.0% **14**	THF	0 °C, 2 h	49 (93)	26 (96)	1.5:1

[a] Isolated yields. [b] HPLC analysis of the corresponding methyl esters **55** and **56** (eqs 11 and 12). [c] Diastereomeric ratio determined by ^{1}H NMR integration on the crude mixture. [d] Slow addition via syringe pump. [e] Not determined. [f] *n*-BuLi was used as base (see text).

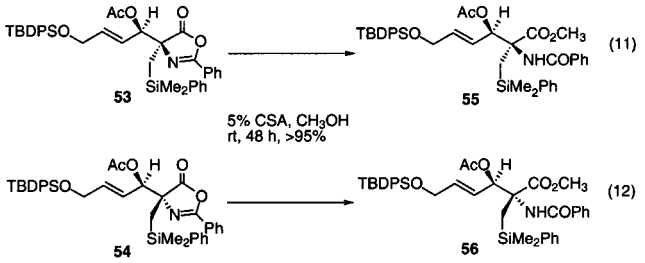
of the Grignard reagent afforded the silyl analogue of serine **51** in moderate yield through the intermediacy of glycine imine **50**.[44] After hydrolysis of the methyl ester, the resulting acid **52** was converted to azlactone **10b** by a DCC-promoted cyclodehydration.[18]

With the silylazlactone **10b** in hand, we then examined its Pd-catalyzed asymmetric alkylation with *gem*-diacetate **9** (eq 10, Table 2). Following the previous procedure, **9** was reacted



with the sodium enolate of **10b** in the presence of 1 mol % **13** and 3 mol % **14** at 0 °C in THF (entry 1). The reaction was completed in 3 h, giving rise to a 2.4:1 mixture of diastereomers **53** and **54** as determined by ^{1}H NMR integration. The signals for α-acetoxy methine protons of the major and minor products had chemical shifts of δ 5.47 (d, $J = 7.3$ Hz) and 5.53 (d, $J = 8.3$ Hz), respectively, providing signals for the measurement of the diastereomeric ratio.

The alkylation products were separated by chromatography and converted to the corresponding methyl esters **55** and **56** by acid-catalyzed methanolysis (eqs 11 and 12). In contrast to



methyl-substituted azlactones **21** and **22**, the methanolysis of these silylazlactones was very sluggish and required additional amounts of acid catalyst (1% vs. 5%) and a longer reaction time (8 h vs. 48 h) for completion. Nevertheless, the reactions furnished the methyl esters in nearly quantitative yields, and chiral HPLC analyses successfully measured the ee of both products to be 96%. Changing the solvent from THF to DME had a slightly adverse effect, as lower de and ee were obtained

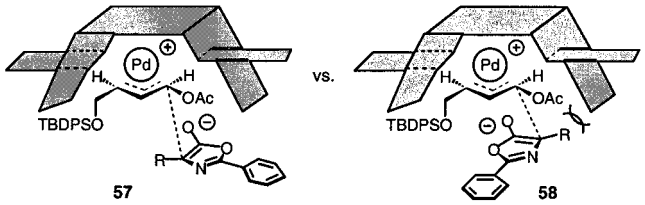
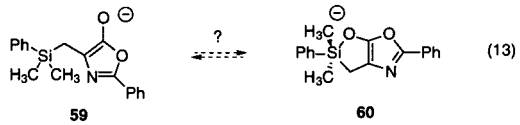


Figure 4. Model for the double asymmetric induction.

(entry 2). Reducing the amount of the catalyst and implementing a slow addition procedure gave a similar stereochemical outcome (entry 3).

In the Pd-catalyzed alkylation of azlactone nucleophiles, increasing the size of the alkyl chains of azlactones resulted in a dramatic increase in the diastereomeric ratio.[17] The observed trend was explained by using a simplified transition-state model in which the chiral pocket of the catalyst discriminated two prochiral faces of the azlactone enolate, as illustrated in Figure 4. In this model, the interaction between the oxyanion of the azlactone enolate and the positively charged π-allylpalladium complex is considered to be important.[45] As a result, the major isomer arises from the preferred approach (**57**), in which the alkyl group is oriented away from steric congestion while the phenyl group is positioned near the "flap" of the chiral pocket.

It is difficult, however, to apply this model to explain the rather surprising results obtained from the alkylation of **10b**, because the sterically demanding silylalkyl chain gave rise only to poor diastereomeric ratios. The possibility is that the effective size of the silylmethyl group may become much smaller if the anion of silylazlactone **10b** adopts a bicyclic structure due to the ability of a silicon atom to accommodate hypervalent coordination (eq 13). The interaction between the oxyanion and



silicon atom in enolate **59** could facilitate the formation of bicyclic oxazole **60**, in which the pentavalent silicon atom adopts a trigonal bipyramidal geometry.

If the bicyclic structure **60** constituted the more reactive limiting structure or, at least, contributed to the reactivity of the enolate, the model established for the previous alkylation may no longer be applicable. Delocalization of the anionic charge by hypercoordination and the pseudo-C_2 symmetry imparted in the relatively flat bicyclic oxazole may allow the nucleophile to adopt four orientations with respect to the π-allylpalladium intermediate (Figure 5). Consequently, the differentiation of the two prochiral faces of the nucleophile by the chiral pocket would occur in a much less selective fashion. On the basis of this hypothesis, the enolate with more oxophilic

(44) (a) Kober, R.; Hammes, W.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 203. (b) Kober, R.; Steglich, W. *Liebigs Ann. Chem.* **1983**, 599. (c) Munster, P.; Steglich, W. *Synthesis* **1987**, 223. (d) Bretschneider, T.; Miltz, W.; Munster, P.; Steglich, W. *Tetrahedron* **1988**, *44*, 5403.

(45) (a) Reference 16. (b) For detailed discussions, see: Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4545.

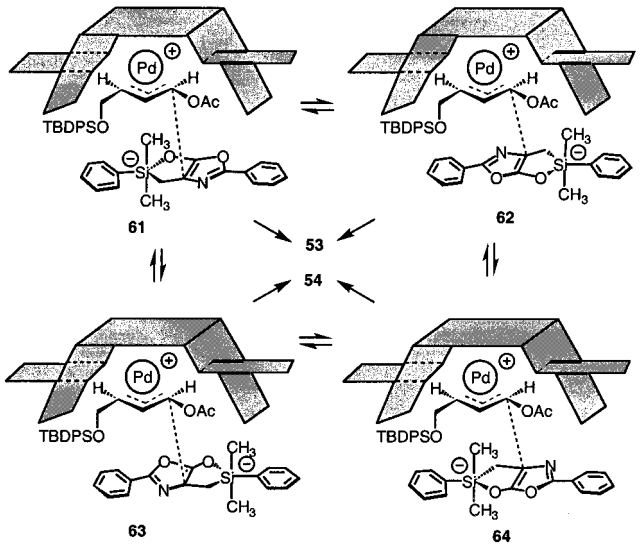
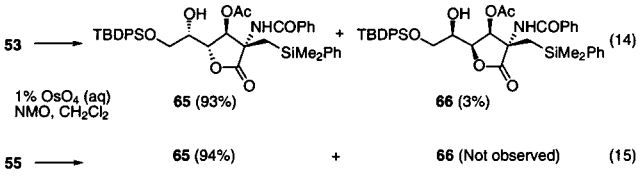


Figure 5. Model for the chiral induction at a bicyclic nucleophile.

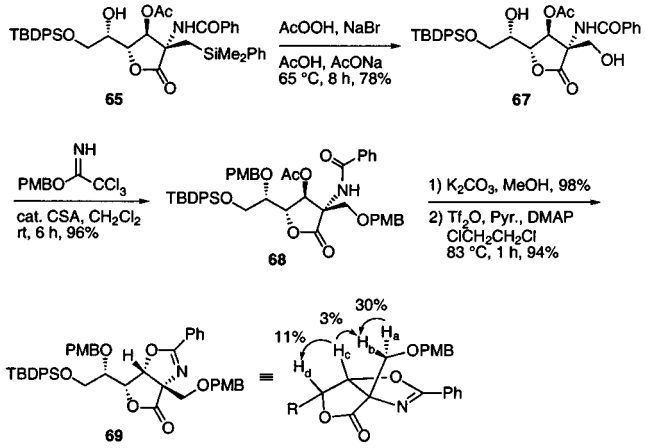
lithium as counterion was expected to disfavor formation of the hypervalent structure (entry 4, Table 2). Whereas lithium hydride failed to deprotonate azlactone **10b**, treatment with *n*-butyllithium at −78 °C in THF generated a lithium enolate without effecting the carbonyl addition. The subsequent Pd-catalyzed reaction with *gem*-diacetate **9** afforded the desired alkylation products. However, the ratio (dr = 1.5:1) turned out to be similar to that obtained when a sodium enolate was employed as nucleophile. The ee's of both products were still excellent and were determined to be 93% and 96% for the major and minor products, respectively. Although the structure of the reacting enolate remains unclear, the enolate derived from silylazlactone **10b** appeared to be a kinetically potent nucleophile in that high chiral induction was achieved at the electrophile (C3 center), regardless of the counterion.

The major product **53**, though of unproven stereochemistry, was carried on to the next step of the synthetic sequence in the hope that more advanced intermediates would provide an opportunity to determine the stereochemistry. The introduction of the C4 and C5 hydroxyl groups was first attempted using an osmium-catalyzed dihydroxylation reaction (eq 14). Treatment of azlactone **53** with 1% OsO_4 and NMO in moist CH_2Cl_2 at 25 °C generated a 14:1 mixture of diastereomeric lactones in 89% yield. Decreasing the reaction temperature to 0 °C improved the ratio to 21:1, furnishing **65** and **66** in isolated yields of 93% and 3%, respectively. These selectivities are significantly higher than those observed with the methyl-substituted azlactone **21** (dr = 8:1), attesting to rather strong facial guidance exerted by the C2 stereogenic center in the dihydroxylation reaction. Methyl ester **55** was also used as



substrate to examine the possibility of achieving complete selectivity as encountered previously (eq 15). Indeed, the dihydroxylation of **55** under identical conditions at 25 °C for 12 h produced lactone **65** as a single diastereomer in 94% yield. Thus, we secured two routes to the desired lactone **65** in which the C4 and C5 hydroxyl groups were installed with high diastereoselectivity.

Scheme 8. Installation of 21-OH Group and C3 Configuration

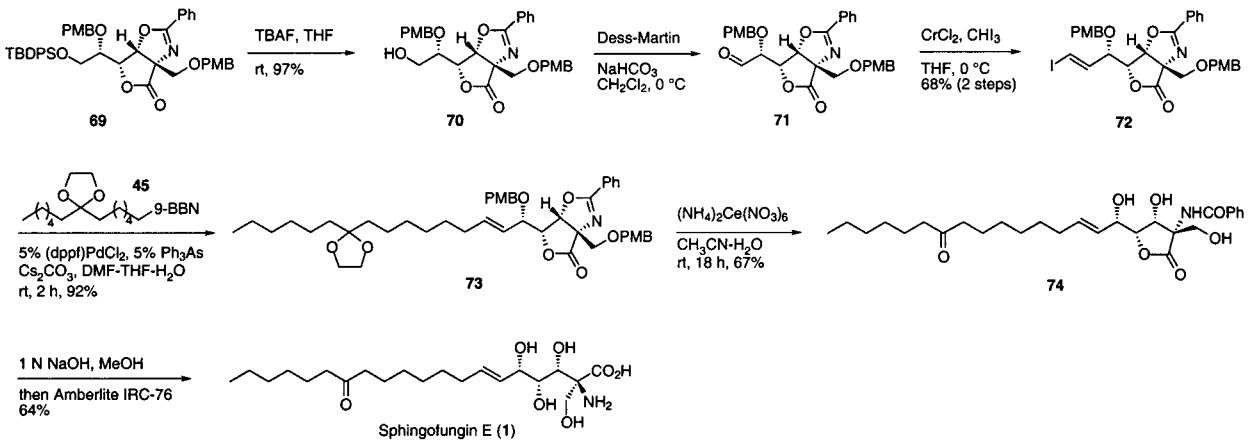


Our next concern was installation of a primary hydroxyl group at C21 and adjustment of the C3 configuration (Scheme 8). The former was readily achieved by activation of the C−Si bond of lactone **65** by using a one-pot, modified Fleming oxidation procedure.[46] Upon treatment of **65** with a mixture of peracetic acid and sodium bromide, the C−Si bond was smoothly oxidized to give diol **67** in good yield. It is worth noting that all other functional groups including the *tert*-butyldiphenylsilyl (TBDPS) moiety, a diarylsilane, remained unaffected under these conditions. As a prelude to inversion of the configuration at C3, the two hydroxyl groups at C5 and C21 were converted to PMB ethers. After the hydrolysis of the C3 acetoxy group, the resulting alcohol was subjected to a cyclodehydration reaction with triflic anhydride to provide bicyclic oxazoline **69** in high yield. To determine the relative stereochemistry, an NOE study on **69** was conducted. Irradiation of H_c at δ 5.28 (d, J = 4.9 Hz) induced an enhancement of the intensity of the H_d signal at δ 5.08 (dd, J = 7.3, 4.9 Hz) and the H_b signal at δ 3.67 (d, J = 8.8 Hz) by 11% and 3%, respectively. Interestingly, H_a at δ 4.28 (d, J = 8.8 Hz) did not exhibit any NOE upon irradiation of H_c or H_d while showing strong geminal correlation with H_b. It appears that only one of two C21 methylene protons is in proximity of H_c, presumably because of hindered rotation. Based on these observations, the *syn* relationship among carbon−oxygen bonds was reasonably established.

With all of the necessary stereocenters introduced, we set out to finish the synthesis of sphingofungin E (**1**) using a sequence similar to the synthesis of sphingofungin F (**2**) (Scheme 9). After removal of the TBDPS group, primary alcohol **70** was oxidized with Dess−Martin periodinane to aldehyde **71**, which was directly subjected to Takai−Utimoto olefination to afford iodide **72** as a single geometric isomer. To this fully elaborated polar headgroup was attached the nonpolar lipid tail by the *B*-alkyl Suzuki coupling reaction. Under palladium catalysis, the vinyl iodide **72** smoothly reacted with the *B*-alkyl borane **45** to afford alkene **73** in excellent yield. The large coupling constant (J = 15.5 Hz) between the two olefinic protons (δ 6.00 and 5.53) established the olefin geometry to be of the *E*-configuration. The final stage of the synthesis required sequential deprotection reactions. Treatment of the alkene **73** with CAN in aqueous acetonitrile effected removal of the two PMB groups with simultaneous cleavage of the ketal and oxazoline functionalities to give triol **74**. Alternatively, this transformation could be carried out in comparable yield by a stepwise sequence involving removal of the PMB groups by

(46) Fleming, I.; Sanderson, P. E. J. *Tetrahedron Lett.* **1987**, *28*, 4229.

Scheme 9. *B*-Alkyl Suzuki Merger and Completion of the Synthesis of Sphingofungin E (**1**)



DDQ and of the oxazoline and ketal groups by subsequent acidic hydrolysis.[47] Finally, hydrolysis of triol **74** in methanolic sodium hydroxide followed by neutralization and desalting with an acidic resin afforded sphingofungin E (**1**) in 64% yield. Our synthetic sample showed spectroscopic (^{1}H and ^{13}C NMR, IR) characteristics that agreed very well with those reported for the natural compound and those recently reported for a synthetic sample.[13g] As was the case with the data of sphingofungin F, small discrepancies in the chemical shifts of C1 [δ 174.2 (Merck),[4] 173.4 (Nakamura et al.),[13g] 173.2 (present work)] and C2 [δ 71.8 (Merck), 71.1 (Nakamura et al.), 71.2 (present work)] were noted in the ^{13}C NMR spectrum. These inconsistencies may again be ascribed to the pH difference which arose from the disparity in the isolation procedures.

Summary

An efficient synthetic strategy for sphingosine analogues has been developed. This strategy, based on a series of transition-metal-catalyzed reactions, achieved relevant stereocontrol of the key transformations in a highly selective manner and culminated in concise total syntheses of antifungal agents, sphingofungins E and F. The Pd-catalyzed asymmetric allylic alkylation of a *gem*-diacetate and azlactones provided the key aldol-like products bearing two stereogenic centers, including the C2 quaternary carbon, with high ee. These reactions achieved the equivalent of an asymmetric carbonyl addition of an α-amino acid enolate by differentiation of the two prochiral elements present in both the electrophile and nucleophile, enantiotopic leaving groups of a *gem*-diacetate and enantiotopic faces of an azlactone enolate. While the synthesis of sphingofungin F utilized an alanine azlactone, the azlactone derived from a novel silyl analogue of serine proved an efficient synthon for a serine enolate in the synthesis of the E congener. Once the first two stereocenters were created by an asymmetric reaction, the additional centers were set by a directed Os-catalyzed dihydroxylation reaction with high diastereoselectivity. The requisite (*E*)-alkene was established by a Cr-mediated iodomethylenation reaction, setting the final stage which involved merger of the polar head and the lipid tail units by a Pd-catalyzed cross-coupling reaction. The efficiency of our approach is readily noted in the syntheses of sphingofungins E and F which have been accomplished in only 17 steps (5.1% overall yield) and 15 steps (17% overall yield), respectively. Due to the lack of data for the natural compounds, the present syntheses could not confirm the absolute stereochemistry. However, the origin and the biological properties suggest that the absolute stereostructure of sphingofungins E and F is likely to follow those of other fungal-originated congeners.

Given the significant biochemical role of sphingolipids, various sphingosine analogues, which are themselves potent inhibitors of sphingolipid biosynthesis, may serve as novel tools for many areas of sphingosine-related research that otherwise have proven recalcitrant to biochemical and molecular approaches. In particular, the difficulty involved in accessing these compounds through fermentation,[48] let alone analogues, makes an efficient synthesis valuable. The route described herein is useful for preparation of a number of analogues. For example, the C2 and C3 centers are controlled by the chiral ligand. The C3 epimer could be derived by carrying out the synthesis without inversion. Dihydroxylation after inversion at C3 also provides access to the C4 and C5 epimers. The use of different azlactones would allow variation of the C21 alkyl substituent. Finally, the lipid tail can be readily varied prior to the cross-coupling reaction.

Experimental Section

Pd-Catalyzed Asymmetric Alkylation: Preparation of 21 and 22. To a suspension of sodium hydride (95% powder, 290 mg, 11.5 mmol) in THF (3 mL) was added azlactone **10a**[18] (2.50 g, 14.3 mmol) in THF (10 mL). The resulting solution was stirred at 25 °C until hydrogen gas evolution ceased. The resulting red solution was briefly (~0.5 h) sonicated while being purged with a stream of nitrogen. To this solution was added a mixture of **13** (17.4 mg, 0.0476 mmol, 0.5 mol %) and the (*R*,*R*)-**14** (98.6 mg, 0.143 mmol, 1.5 mol %) in THF (2 mL) via a cannula. After 5 min, a solution of diacetate **9** (4.05 g, 9.52 mmol) in THF (10 mL) was added to the mixture at −5 °C via a pump-driven syringe over 4 h. After the addition was complete, the stirring was continued for an additional 1 h. The reaction mixture was then poured into 10% aqueous NaH_2PO_4 (50 mL) and extracted three times with ether (50 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Separation on a SiO_2 column (petroleum ether/ethyl acetate = 15:1) yielded 3.610 g (70%) of the less polar major diastereomer **21** and 0.258 g (5%) of the more polar minor diastereomer **22**, both as colorless sticky oils. The ee of major diastereomer **21** could be directly determined by chiral HPLC analysis (89%) and corroborated by the ee of methyl ester **23** (89%). The ee of **22** was indirectly determined to be 89% via the corresponding methyl ester **24**.

(1′*R*,4*S*,2′*E*)-4-[1′-Acetoxy-4′-(*tert*-butyldiphenylsilyloxy)but-2′-en-1′-yl]-4-methyl-2-phenyl-4,5-dihydro-5-oxazolone (21): t_r (2*S*,3*R*) = 7.56 min, t_r (2*R*,3*S*) = 9.43 min (Chiralpak AD, λ = 230 nm, Hep:*i*-PrOH = 99:1); $[\alpha]_D$ −51.3 (*c* 3.90, $CHCl_3$, 89% ee); IR (film) 1827,

(47) See experimental details in the Supporting Information.

(48) Riley, R. T.; Plattner, R. D. *Methods Enzymol.* **2000**, *311*, 348.

1750, 1656, 1224, 1113, 1007, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.07−8.04 (m, 2H), 7.72−7.67 (m, 4H), 7.63−7.36 (m, 9H), 6.13−5.98 (m, 2H), 5.57 (d, J = 6.9 Hz, 1H), 4.36−4.22 (m, 2H), 2.00 (s, 3H), 1.49 (s, 3H), 1.09 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.9, 169.3, 161.0, 137.7, 135.6, 135.5, 133.5, 133.4, 132.9, 129.8, 128.8, 128.2, 127.8, 125.9, 122.0, 76.6, 72.1, 63.1, 26.6, 20.8, 20.2, 19.1; HRMS calcd for $C_{28}H_{26}NO_5Si$ (M^+ − t-C_4H_9) 484.1581, found 484.1587.

(1′*R*,4*R*,2′*E*)-4-[1′-Acetoxy-4′-(*tert*-butyldiphenylsilyloxy)but-2′-en-1′-yl]-4-methyl-2-phenyl-4,5-dihydro-5-oxazolone (22): $[\alpha]_D$ −33.3 (*c* 2.81, $CHCl_3$, 89% ee); IR (film) 1824, 1750, 1656, 1228, 1113, 1007, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.02−7.99 (m, 2H), 7.66−7.33 (m, 13H), 6.03−6.02 (m, 2H), 5.61 (d, J = 6.5 Hz, 1H), 4.23−4.21 (m, 2H), 1.98 (s, 3H), 1.50 (s, 3H), 1.01 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.9, 169.6, 161.4, 137.4, 135.5, 133.5, 133.4, 133.0, 129.79, 129.75, 128.9, 128.1, 127.8, 125.7, 121.0, 76.4, 71.7, 63.0, 26.6, 20.8, 20.2, 19.1; HRMS calcd for $C_{28}H_{26}NO_5Si$ (M^+ − t-C_4H_9) 484.1580, found 484.1603.

Methyl (2*S*,3*R*,4*E*)-3-Acetoxy-2-benzamido-2-methyl-6-(*tert*-butyldiphenylsilyloxy)-4-hexenoate (23). A mixture of azlactone **21** (5.86 g, 10.8 mmol) and *p*-toluenesulfonic acid monohydrate (21 mg, 0.11 mmol) in methanol (15 mL) was stirred at 25 °C for 8 h. The mixture was concentrated and separated on a SiO_2 column (petroleum ether/ethyl acetate = 10:1) to yield 6.15 g (99%) of methyl ester **23** as a colorless, sticky oil: t_r (2*S*,3*R*) = 7.37 min, t_r (2*R*,3S) = 17.99 min (Chiralpak AD, λ = 230 nm, Hep:*i*-PrOH = 9:1); $[\alpha]_D$ −17.0 (*c* 1.25, $CHCl_3$, 89% ee); IR (film) 3385, 1749, 1669, 1522, 1488, 1234, 1113 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78−7.75 (m, 2H), 7.67−7.63 (m, 4H), 7.54−7.34 (m, 9H), 7.24 (s, 1H), 5.92−5.91 (m, 2H), 5.73 (d, J = 4.7 Hz, 1H), 4.22 (s, 2H), 3.70 (s, 3H), 2.16 (s, 3H), 1.72 (s, 3H), 1.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 171.1, 167.5, 136.2, 135.5, 134.1, 133.4, 133.3, 131.8, 129.9, 128.7, 127.8, 127.1, 121.7, 77.3, 63.6, 63.1, 52.7, 26.7, 21.1, 19.1, 17.6. Anal. Calcd for $C_{33}H_{39}NO_6Si$: C, 69.08; H, 6.85; N, 2.44. Found: C, 68.81; H, 6.71; N, 2.43.

Preparation of 30 and 31. Procedure A (from 21). To a mixture of azlactone **21** (0.167 g, 0.308 mmol) and NMO (54 mg, 0.461 mmol) in CH_2Cl_2 (3 mL) was added a 4% aqueous solution of OsO_4 (0.0038 mL, 0.0062 mmol). The mixture was stirred at 25 °C for 24 h. Upon complete consumption of the starting material, the reaction mixture was diluted with ethyl acetate (5 mL) and an aqueous solution of Na_2SO_3 (∼0.1 g in 3 mL of water) and stirred for 2 h. The organic phase was separated, and the aqueous phase was extracted with ethyl acetate (5 mL × 2). The combined organic layers were washed with 2 N HCl, 10% $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated. Purification by flash column chromatography (petroleum ether/ethyl acetate = 7:1) on SiO_2 gave 0.152 g (white solid, 86%) of alcohol **30** and 0.0178 g (sticky oil, 10%) of alcohol **31**.

Procedure B (from 23). Following the same procedure as above, methyl ester **23** (1.98 g, 3.45 mmol) was reacted with NMO (0.606 g, 5.17 mmol) and OsO_4 (4% in water, 0.42 mL, 0.069 mmol) in CH_2Cl_2 (10 mL) at 25 °C for 16 h. Purification by flash column chromatography (petroleum ether/ethyl acetate = 7:1) on SiO_2 gave 2.02 g of crude alcohol **30** as a sticky oil which, upon recrystallization from methylene chloride/pentane (1:10), afforded 1.97 g (98%) of white solid.

(1′*S*,3*S*,4*S*,5*R*)-3-Methyl-3-benzamido-4-acetoxy-5-(2′-*tert*-butyldiphenylsilyloxy-1′-hydroxyethyl)oxolan-2-one (30): mp 90−91 °C (CH_2Cl_2−pentane); $[\alpha]_D$ +24.6 (*c* 1.98, $CHCl_3$); IR (film) 3486, 3302, 1790, 1760, 1738, 1634, 1538, 1228, 1113 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.79−7.76 (m, 2H), 7.69−7.64 (m, 4H), 7.52−7.35 (m, 9H), 6.70 (s, 1H), 5.96 (d, J = 7.3 Hz, 1H), 4.65 (dd, J = 7.3, 2.5 Hz, 1H), 3.99−3.90 (m, 1H), 3.84 (d, J = 6.3 Hz, 2H), 3.35 (d, J = 6.9 Hz, 1H), 2.13 (s, 3H), 1.50 (s, 3H), 1.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 170.5, 167.7, 135.6(2), 133.2, 133.1, 132.5, 132.4, 129.9, 128.7, 127.9, 127.4, 78.5, 75.3, 70.9, 63.7, 59.9, 26.7, 20.5, 19.1, 17.5. Anal. Calcd for $C_{32}H_{37}NO_7Si$: C, 66.76; H, 6.48; N, 2.43. Found: C, 66.50; H, 6.61; N, 2.42.

(1′*R*,3*S*,4*S*,5*S*)-3-Methyl-3-benzamido-4-acetoxy-5-(2′-*tert*-butyldiphenylsilyloxy-1′-hydroxyethyl)oxolan-2-one (31): $[\alpha]_D$ +30.5 (*c* 1.15, $CHCl_3$); IR (film) 3358, 1772, 1750, 1645, 1530, 1233, 1113, 1051 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.79−7.76 (m, 2H), 7.68−7.64 (m, 4H), 7.55−7.38 (m, 9H), 6.42 (s, 1H), 5.89 (d, J = 8.8 Hz, 1H), 4.99 (dd, J = 8.8, 1.2 Hz, 1H), 3.93−3.86 (m, 1H), 3.8−3.73 (m, 2H), 2.38 (d, J = 4.2 Hz, 1H), 2.17 (s, 3H), 1.63 (s, 3H), 1.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6, 170.6, 167.4, 135.6, 132.9, 132.8, 132.6, 132.3, 130.0, 128.7, 128.0, 127.3, 76.8, 75.5, 68.6, 64.7, 58.8, 26.7, 20.6, 19.1, 17.9; HRMS calcd for $C_{32}H_{38}NO_7Si$ (MH^+) 576.2418, found 576.2422.

(1′*S*,6*R*,3*aS*,6*aR*)-6-[2′-*tert*-Butyldiphenylsilyloxy-1′-(4″-methoxybenzyloxy)ethyl]-3*a*-methyl-2-phenyl-6,6*a*-dihydro-3*aH*-furo[3,4-*d*]-oxazol-4-one (38). To a mixture of alcohol **37a** (0.175 g, 0.268 mmol), DMAP (1.6 mg, 0.013 mmol, 5%), and pyridine (0.11 mL, 1.36 mmol) in 1,2-dichloroethane (2.5 mL) was added dropwise trifluoromethanesulfonic anhydride (0.065 mL, 0.386 mmol). The mixture was stirred at 25 °C for 10 min and heated under reflux for 2 h. The mixture was cooled to room temperature, diluted with ethyl acetate (10 mL), and poured into 2 N HCl (10 mL). The organic phase was separated, and the aqueous phase was extracted with ethyl acetate (10 mL × 2). The combined organic phases were washed with 10% aqueous $NaHCO_3$ and brine and dried over $MgSO_4$. Purification by flash chromatography (petroleum ether/ethyl acetate = 10:1) on a SiO_2 column afforded 0.164 g (96%) of oxazoline **38** as a colorless, viscous liquid: $[\alpha]_D$ +25.0 (*c* 1.65, $CHCl_3$); IR (film) 1787, 1645, 1514, 1299, 1249, 1112, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.89−7.87 (m, 2H), 7.75−7.71 (m, 4H), 7.54−7.36 (m, 9H), 7.14 (d, J = 8.7 Hz, 2H), 6.79 (d, J = 8.7 Hz, 2H) 5.03 (dd, J = 7.0, 5.0 Hz, 1H), 4.95 (d, J = 5.0 Hz, 1H), 4.54−4.46 (m, 2H), 4.08−3.99 (m, 2H), 3.86−3.81 (m, 1H), 3.78 (s, 3H), 1.72 (s, 3H), 1.10 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.1, 164.5, 159.1, 135.7, 135.6, 133.1, 132.7, 132.3, 130.1, 130.0, 129.1, 128.7, 128.5, 127.92, 127.86, 126.0, 113.6, 84.6, 81.2, 78.3, 76.5, 72.5, 63.1, 55.1, 26.7, 20.6, 19.1. Anal. Calcd for $C_{38}H_{41}NO_6Si$: C, 71.78; H, 6.50; N, 2.20. Found: C, 71.83; H, 6.48; N, 2.04.

(2*E*,1′*S*,6*R*,3*aS*,6*aR*)-6-[10′,10′-Ethylenedioxy-1′-(4″-methoxybenzyloxy)hexadec-2′-en-1′-yl]-3*a*-methyl-2-phenyl-6,6*a*-dihydro-3*aH*-furo[3,4-*d*]oxazol-4-one (46). To a solution of **44** (10.7 mg, 0.445 mmol) in THF (0.5 mL) was added a solution of 9-BBN-H (0.5 M in THF, 0.10 mL, 0.050 mmol) at 25 °C. After being stirred for 1 h, the solution was treated with degassed water (0.025 mL, 1.4 mmol) and transferred to a mixture of vinyl iodide **41** (17.4 mg, 0.0341 mmol), [1,1′-bis(diphenylphosphino)ferrocene]palladium dichloride (1.25 mg, 0.0017 mmol, 5 mol %), triphenylarsine (0.52 mg, 0.0017 mmol, 5 mol %), and Cs_2CO_3 (14.4 mg, 0.442 mmol) in dimethylformamide (0.5 mL). After being stirred at 25 °C for 4 h, the dark brown mixture was poured into brine (5 mL). Extraction with ether (5 mL × 3), evaporation of solvent, and flash chromatography (petroleum ether/ethyl acetate = 10:1) on a SiO_2 column afforded 20.4 mg (94%) of olefin **46** as a pale yellow oil: $[\alpha]_D$ +19.2 (*c* 2.25, $CHCl_3$); IR (film) 1788, 1645, 1515, 1453, 1298, 1249, 1084, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.92 (dd, J = 7.1, 1.2 Hz, 2H), 7.52 (t, J = 7.4 Hz, 1H), 7.41 (t, J = 7.2 Hz, 2H), 7.20 (d, J = 8.7 Hz, 2H), 6.82 (d, J = 8.6 Hz, 2H), 6.02 (dt, J = 15.6, 6.6 Hz, 1H), 5.54 (dd, J = 15.6, 7.5 Hz, 1H), 4.85 (d, J = 4.6 Hz, 1H), 4.58 (dd, J = 8.1, 5.2 Hz, 1H), 4.54 (d, J = 11.2 Hz, 1H), 4.35 (d, J = 11.0 Hz, 1H), 4.15 (t, J = 7.7 Hz, 1H), 3.90 (s, 4H), 3.77 (s, 3H), 2.15 (q, J = 7.0 Hz, 2H), 1.69 (s, 3H), 1.62−1.54 (m, 4H), 1.47−1.27 (m, 16H), 0.87 (t, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.2, 164.7, 159.3, 138.3, 132.3, 130.1, 129.2, 128.8, 128.5, 126.2, 125.6, 124.5, 113.8, 111.9, 84.6, 82.6, 78.2, 76.5, 70.5, 64.8, 55.2, 37.1, 32.4, 31.7, 30.2, 29.64, 29.59, 29.5, 29.1, 28.9, 23.7, 22.5, 20.3, 13.0; HRMS calcd for $C_{38}H_{52}NO_7$ (MH^+) 634.3744, found 634.3764.

(6*E*,2*S*,3*R*,4*R*,5*S*)-2-Amino-2-methyl-3,4,5-trihydroxy-14-oxoeicos-6-enoic Acid (Sphingofungin F, 2). A mixture of benzamidolactone **47** (14.2 mg, 0.0291 mmol) and 1 N NaOH (1 mL) was heated under reflux for 8 h. The reaction mixture was cooled to room temperature, and Amberlite IRC-76 resin (pretreated and washed with 2 N HCl and deionized water) was added until the pH of the solution reached approximately 7. The resin was filtered off, and the filtrate was concentrated in vacuo to give a white solid. The white solid was dissolved in a minimal amount of methanol−water and separated on a SiO_2 column (2.5 g; $CHCl_3/CH_3OH/H_2O$ = 20:5:1) to yield 9.1 mg (78%) of pure sphingofungin F (**2**) as a white solid: mp 143−145 °C (CH_3OH−H_2O); $[\alpha]_D$ +0.99 (*c* 0.25, CH_3OH); IR (KBr) 3423, 1718,

1629, 1459, 1408, 1113, 790 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 5.77 (dt, $J = 15.4$, 6.8 Hz, 1H), 5.45 (dd, $J = 15.5$, 7.8 Hz, 1H), 4.10 (t, $J = 7.5$ Hz, 1H), 3.86 (d, $J = 0.7$ Hz, 1H), 3.67 (d, $J = 7.3$ Hz, 1H), 2.44 (t, $J = 7.3$ Hz, 2H), 2.44 (t, $J = 7.5$ Hz, 2H), 2.06 (q, $J = 6.8$ Hz, 2H), 1.57−1.50 (m, 4H), 1.48 (s, 3H), 1.42−1.38 (m, 2H), 1.36−1.23 (m, 10H), 0.90 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 214.4, 175.2, 135.7, 130.2, 76.2, 75.7, 72.4, 66.7, 43.5(2), 33.5(2), 32.8, 30.2(2), 30.0(2), 24.9(2), 23.6, 21.8, 14.4; LRMS calcd for $C_{21}H_{39}NNaO_6$ ($M + Na^+$) 423.3, found 423.3.

Pd-Catalyzed Asymmetric Alkylation: Preparation of 53 and 54. To a suspension of sodium hydride (95%, 0.110 g, 4.35 mmol) in THF (5.0 mL) was added azlactone **10b** (1.50 g, 4.85 mmol). The resulting solution was stirred at 25 °C until the hydrogen gas evolution ceased. After brief sonication (0.5 h), a mixture of **13** (8.0 mg, 0.022 mmol, 1 mol %) and (*R,R*)-**14** (45.4 mg, 0.066 mmol, 3 mol %) in THF (1 mL) was added. After the mixture was purged with a stream of nitrogen, a solution of geminal diacetate **9** (0.936 g, 2.19 mmol) in THF (6.0 mL) was added at 0 °C. After the addition was complete, the stirring was continued at 0 °C for 3 h. The reaction mixture was poured into 10% aqueous NaH_2PO_4 (20 mL) and extracted with ether (30 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The diastereomeric ratio was determined to be 2.4:1 by ^1H NMR analysis of the crude mixture. Separation on a SiO_2 column (petroleum ether/ethyl acetate = 20:1) yielded 1.01 g (68%) of the less polar major diastereomer **53** and 0.340 g (23%) of the more polar minor diastereomer **54**, both as colorless, sticky oils. The ee of both products was determined to be 96% by chiral HPLC analysis of the corresponding methyl esters **55** and **56**.

(1′*R*,4*S*,2′*E*)-4-[1′-Acetoxy-4′-(*tert*-butyldiphenylsilyloxy)but-2′-en-1′-yl]-4-(dimethylphenylsilyl)methyl-2-phenyl-4,5-dihydro-5-oxazolone (53): $[\alpha]_D$ −59.5 (*c* 5.12, $CHCl_3$, 96% ee); IR (film) 1819, 1750, 1657, 1428, 1225, 1114, 1045, 1023, 973, 839, 738, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.88−7.85 (m, 2H), 7.68−7.64 (m, 4H), 7.61−7.56 (m, 1H), 7.49−7.17 (m, 13H), 6.06 (dt, $J = 15.6$, 3.2 Hz, 1H), 5.97 (dd, $J = 15.6$, 7.3 Hz, 1H), 5.47 (d, $J = 7.3$ Hz, 1H), 4.30−4.18 (m, 2H), 1.94 (s, 3H), 1.62 (d, $J = 14.7$ Hz, 1H), 1.45 (d, $J = 14.6$ Hz, 1H), 1.06 (s, 9H), 0.29 (s, 3H), 0.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.1, 169.2, 160.5, 138.1, 136.9, 135.4, 133.7, 133.4, 133.3, 132.6, 129.6(2), 129.2, 128.6, 128.1, 127.7, 125.8, 121.9, 78.3, 74.0, 63.2, 26.7, 21.4, 20.9, 19.2, −1.9, −2.4. Anal. Calcd for $C_{40}H_{45}NO_5Si_2$: C, 71.07; H, 6.71; N, 2.07. Found: C, 71.21; H, 6.89; N, 2.03.

(1′*R*,4*R*,2′*E*)-4-[1′-Acetoxy-4′-(*tert*-butyldiphenylsilyloxy)but-2′-en-1′-yl]-4-dimethylphenylsilylmethyl-2-phenyl-4,5-dihydro-5-oxazolone (54): $[\alpha]_D$ −5.5 (*c* 1.12, $CHCl_3$, 96% ee); IR (film) 1818, 1751, 1654, 1428, 1226, 1113, 1024, 980, 824, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.88−7.85 (m, 2H), 7.67−7.64 (m, 4H), 7.60−7.51 (m, 1H), 7.48−7.19 (m, 13H), 6.06 (dt, $J = 15.4$, 7.9 Hz, 1H), 5.91 (dd, $J = 15.4$, 3.7 Hz, 1H), 5.53 (d, $J = 8.3$ Hz, 1H), 4.30−4.18 (m, 2H), 1.88 (s, 3H), 1.55 (d, $J = 14.9$ Hz, 1H), 1.41 (d, $J = 14.9$ Hz, 1H), 1.03 (s, 9H), 0.32 (s, 3H), 0.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.1, 169.3, 160.9, 137.5, 137.1, 135.4, 133.7, 133.4, 133.0, 132.7, 129.7, 129.2, 128.7, 128.0, 127.74, 127.67, 125.6, 120.8, 127.74, 127.67, 125.6, 120.8, 77.8, 73.4, 63.1, 26.7, 21.6, 20.9, 19.2, −1.8, −2.2; HRMS calcd for $C_{40}H_{46}NO_5Si_2$ (MH^+) 676.2915, found 676.2904.

(6*E*,2*R*,3*R*,4*R*,5*S*)-2-Amino-2-hydroxymethyl-3,4,5-trihydroxy-14-oxoeicos-6-enoic acid (Sphingofungin E, 1). To a solution of benzamidolactone **74** (10.2 mg, 0.0203 mmol) in methanol (0.5 mL) was added 1 N NaOH (1 mL) at 25 °C. The mixture was heated at 65 °C for 2 h and cooled to room temperature. Amberlite IRC-76 resin (∼1 g, pretreated with 2 N HCl and washed with deionized water) was added, and the mixture was stirred until the pH of the solution reached approximately 7. The resin was filtered with the aid of methanol (2 mL), and the filtrate was concentrated in vacuo to give a pale yellow solid. The solid was adsorbed onto SiO_2 that was suspended in a minimal amount of methanol. The suspension was carefully loaded on a SiO_2 column (2.5 g) and eluted with a chloroform−methanol−water (20:5:1) mixture to give 5.4 mg (64%) of pure sphingofungin E (**1**) as a white flaky powder: mp 154−155 °C (CH_3OH-H_2O); $[\alpha]_D$ −3.5 (*c* 0.31, CH_3OH); IR (KBr) 3538, 3357 (br), 3200 (br), 3113 (br), 2929, 2853, 1708, 1639, 1519, 1466, 1397, 1071, 971, 722 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 5.76 (dt, $J = 15.6$, 6.3 Hz, 1H), 5.44 (dd, $J = 15.4$, 7.6 Hz, 1H), 4.10 (t, $J = 7.3$ Hz, 1H), 3.97 (d, $J = 11.0$ Hz, 1H), 3.94 (br s, 1H), 3.84 (d, $J = 10.7$ Hz, 1H), 3.63 (d, $J = 7.1$ Hz, 1H), 2.44 (t, $J = 7.2$ Hz, 4H), 2.05 (q, $J = 6.6$ Hz, 2H), 1.54 (br s, 4H), 1.41−1.28 (m, 12H), 0.90 (t, $J = 6.6$ Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 214.4, 173.2, 135.7, 130.2, 76.3, 75.6, 71.2, 70.1, 64.9, 43.5-(2), 33.4, 32.8, 30.18, 30.15, 30.0(2), 24.89, 24.87, 23.6, 14.4; HRMS calcd for $C_{21}H_{36}O_7$ ($M^+ - NH_3$) 400.2460, found 400.2483; LRMS calcd for $C_{21}H_{36}O_7$ ($M^+ - H$) 416.3, found 416.3.

Acknowledgment. We thank the National Science Foundation and the National Institute of Health, General Medical Sciences, for their generous support of our programs. Mass spectra were provided by the Mass Spectrometry Regional Center of the University of California−San Francisco, supported by the NIH Division of Research Resources. Dr. Athar Masood is gratefully acknowledged for the X-ray analysis.

Supporting Information Available: Detailed descriptions of experimental procedures and spectral data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA0118338