Total Synthesis of Sphingofungin F

Min Li,*[a] Anmei Wu[b]

[a] Department of Neurosciences, Georgetown University Medical Center, 4000 Reservoir Road NW, Washington, DC 20057, USA

[b] Orgchem Technologies Inc., 2201 W. Campbell Park Dr, Chicago, IL 60612, USA
Fax +1(202)6870617; E-mail: ml258@georgetown.edu

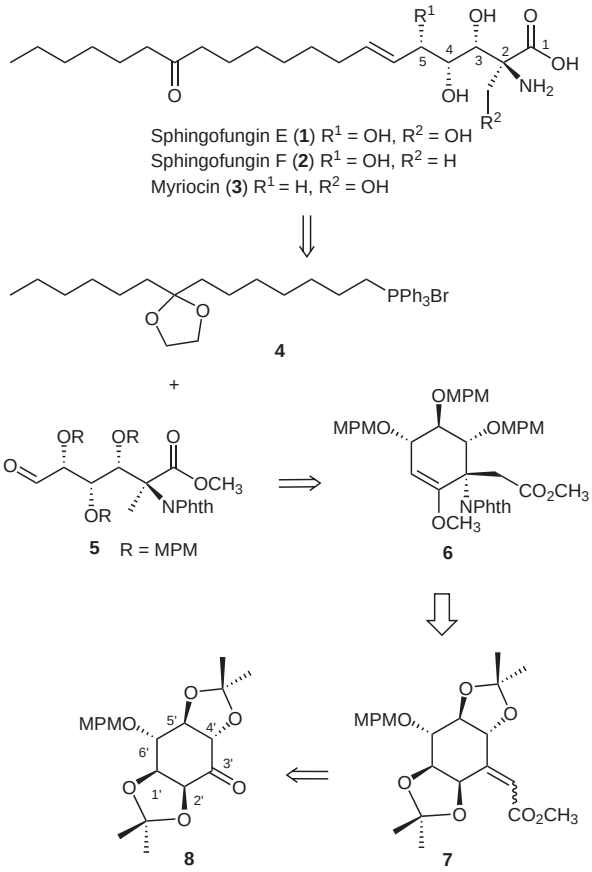
Received 23 March 2006

Abstract: A stereoselective approach toward sphingofungin F has been realized from L-quebrachitol. This synthesis featured a substrate-controlled asymmetric Michael addition, a regiospecific methylsulfonate elimination to construct the contiguous chiral centers in the target molecule.

Key words: sphingofungin F, total synthesis, Michael addition, L-quebrachitol, Wittig-type reaction

Sphingosines are member constituents involved in a number of cellular events.[1] It is believed that sphingosines, like a variety of biosynthetic intermediates, are important second messengers and regulatory molecules in the cell-signaling transduction pathway.[2] The discovery of the ability of sphingosines to inhibit Protein Kinase C (PKC) has stimulated the extensive study of the physiological activity of sphingosines and their derivatives.[3] This led to the isolation and identification of antifungal agents sphingofungin E and F along with other cogeners (A–D) by a Merck research group in 1992.[4] Just like other members of sphingosines family, sphingofungins typically possess a lipid tail and a polyhydroxylamine head moiety with four contiguous chiral centers and a *trans*-olefinic function. In particular, sphingofungin E and F bear striking structural similarity to myriocin,[5] featuring a quaternary center at the C2-position. They were also found to act as serine palmitoyl transferase (SPT) inhibitors which induce apoptosis in both yeast and mammalian cells by blocking the sphingosine biosynthesis pathway.[6] Due to their biological activity and structural novelty, the sphingofungins E and F have inspired a number of synthetic efforts. Up to now, Trost[7] and Lin[8] have reported their syntheses of both sphingofungins E and F. In addition to Trost's and Lin's work, the total synthesis of sphingofungin E has also been accomplished by Shiozaki[9] and Chida[10] from a known D-glucose derivative, while the sphingofungin F has been successfully achieved by Kobayashi[11] and Ham.[12] Herein, we wish to report an alternative synthetic route towards sphingofungin F which utilizes a readily available L-*chiro*-inositol derivative as a chiral building block.

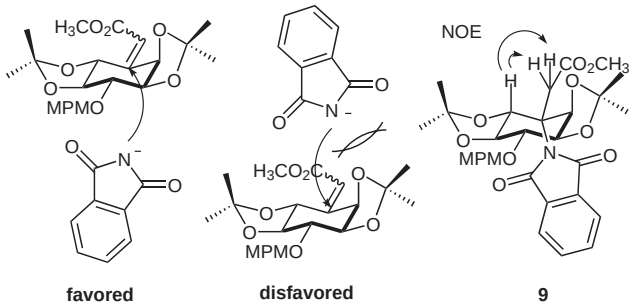
As outlined in Scheme 1, our retrosynthetic analysis suggests that the major disconnection split the target molecules into a known phosphonium salt **4**[13] and an aldehyde **5** bearing four contiguous stereocenters. As an important precursor, compound **5** was expected to be derived from **6**, which in turn, was to be prepared from a readily available inositol derivative **8**, whose synthetic protocol was identical to that of its regioisomer.[14]



Scheme 1

Ketone **8** was subjected to a Wittig-type addition to afford unsaturated ester **7** in 94% yield.[15] A Lewis acid catalyzed Michael-type[16] addition of phthalimide to **7** installed a phthalimido function to C3′ with the desired configuration. As is quite in line with our expectation, compound **9**[17] was achieved exclusively in 73% yield without detection of its diastereomer, probably due to the steric hindrance rendered by the axial acetonide.[18] The absolute configuration of **9** was determined by NOESY experiment (Scheme 2).

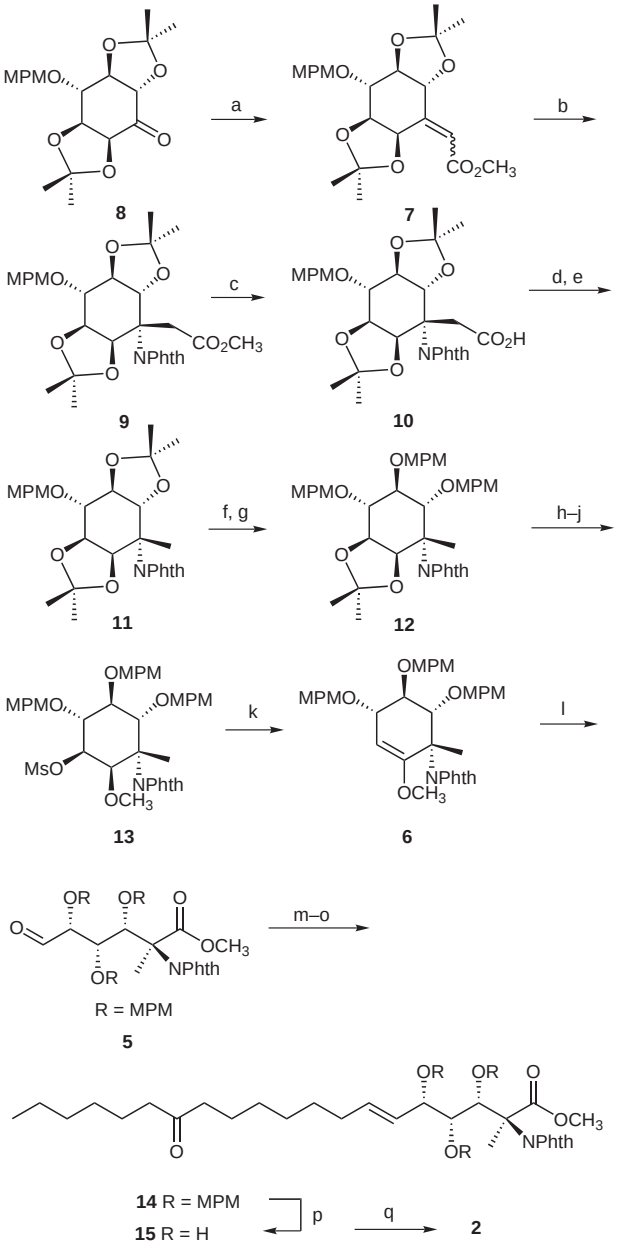
SYNLETT 2006, No. 18, pp 2985–2988
Advanced online publication: 04.08.2006
DOI: 10.1055/s-2006-947333; Art ID: S03406ST



Scheme 2

With compound **9** in hand, we then began the investigation of its transformation to the corresponding carboxylic acid and ensuing decarboxylation (Scheme 3). The methyl ester **9** was converted to carboxylic acid **10** by employing the protocol reported by Bartlett and co-workers.[19] The transformation from **10** to **11** was successfully effected via a Barton decarboxylation.[20] Upon catalytic acid hydrolysis at 0 °C, the less stable *trans*-acetonide in **11** was selectively removed[21] and protected by MPM ether to give **12**[22] as an amorphous solid. Further acidic deprotection of **12** afforded a *cis*-diol, which underwent a cyclic dibutylstannylene-mediated selective monofunctionalization,[23] followed by a methylation to deliver the C1′ methylsulfonate **13**. On treatment of DBU, compound **13** was converted to methyl enolate **6**[24] in moderate yield.[25] It should be mentioned that the methylsulfonate elimination has to be effected at high temperature (120 °C) and polar aprotic solvent (HMPA), partially due to the steric hindrance rendered by the phthalimido at C3′. Ozonolysis of **6** proceeded uneventfully, giving the desired compound **5** as the precursor for coupling. At this stage, all stereogenic centers had been successfully established. Following the protocol reported by Lin and co-workers, the skeleton of sphingofungin F was installed via a Wittig reaction followed by a photoinduced double-bond isomerization.[8a] Removal of ketal under catalytic acid hydrolysis afforded **14** that underwent an oxidative cleavage to give **15** as a sole product. Finally, saponification of the ester moiety with concomitant cleavage of the phthalimido function gave sphingofungin F, the spectral data of which are consistent with those reported in the literature.[4,26]

In summary, a total synthesis of sphingofungin F has been achieved in 17 linear steps from a readily available ketone **8** derived from L-quebrachitol. It is also worth noticing that by simple modification of the inositol derivative, myriocin and other structurally related substances could be obtained through the same route. Therefore, this strategy would provide a library of sphingofungin analogues for structure–activity relationship (SAR) study. These details will be reported in due course.



Scheme 3 *Reagents and conditions*: (a) $(CH_3O)_2P(O)CH_2CO_2CH_3$, LDA, THF, –78 °C to 0 °C, 94%; (b) phthalimide, *i*-PrMgBr, $MgBr_2{\cdot}OEt_2$, THF, 0 °C to r.t., 73%; (c) *n*-PrSLi, HMPA, r.t., 88%; (d) 2-mercaptopyridine *N*-oxide, DMAP, DCC, CH_2Cl_2, r.t.; (e) Bu_3SnH, AIBN, toluene, reflux, 67% (2 steps); (f) AcCl, MeOH–CH_2Cl_2 (2:1), 0 °C, 15 min, 74%; (g) NaH, MPMCl, NaI, DMF, 0 °C to r.t., 99%; (h) AcCl, MeOH, 0 °C to r.t., 100%; (i) (1) Bu_2SnO, toluene, reflux; (2) MsCl, $CHCl_3$, r.t., 93% (2 steps); (j) NaH, MeI, DMF, 0 °C to r.t., 95%; (k) DBU, HMPA, 120 °C, 62%; (l) O_3, MeOH, then Me_2S, 77%; (m) **4**, *t*-BuLi, THF, –78 °C to 0 °C, 93%; (n) *hν*, PhSSPh, cyclohexane–dioxane (19:1), 90%; (o) PTSA, EtOH–H_2O (7:3), 86%; (p) CAN, MeCN–H_2O (4:1), 0 °C, 20 min, 92%; (q) 2 N NaOH (aq), MeOH, reflux, then neutralized with IRC-76, reverse-phase chromatographic purification, 93%.

References and Notes

(1) For reviews, see: (a) Hakomori, S. In *Sphingolipid Biochemistry. Handbook of Lipid Research*, Vol. 3; Kafner, J. N.; Hakomori, S., Eds.; Plenum: New York, **1983**, 1. (b) Merrill, A. H. Jr.; Sweeley, C. C. In *Biochemistry of Lipids, Lipoproteins and Membranes*; Vance, D. E.; Vance, J., Eds.; Elsevier Science B. V.: Amsterdam, **1996**, 309. (c) Hannun, Y. A. *Sphingolipid-Mediated Signal Transduction*; Chapman and Hall: New York NY, **1997**. (d) Hannum, Y. A. *Science* **1996**, *274*, 1855. (e) Spiegel, S.; Milstein, S. *J. Membr. Biol.* **1995**, *146*, 225. (f) Shayman, J. A. *J. Am. Soc. Nephrol.* **1996**, *7*, 171. (g) Igarashi, Y. *J. Biochem. (Tokyo)* **1997**, *122*, 1080. (h) Ariga, T.; Jarvis, W. D.; Yu, R. K. *J. Lipid. Res.* **1998**, *39*, 1.

(2) (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.

(3) (a) Nugent, T. C.; Hudlicky, T. *J. Org. Chem.* **1998**, *63*, 510. (b) Kobayashi, S.; Furuta, T.; Hayashi, T.; Nishijima, M.; Hanada, K. *J. Am. Chem. Soc.* **1998**, *120*, 908. (c) Mandala, S. M.; Harris, G. H. *Methods Enzymol.* **2000**, *311*, 335.

(4) (a) VanMiddlesworth, F.; Dufresne, C.; Wincott, F. E.; Mosley, R. T.; Wilson, K. E. *Tetrahedron Lett.* **1992**, *33*, 297. (b) VanMiddlesworth, F.; Giacobbe, R. A.; Lopez, M.; Garrity, G.; Bland, J. A.; Bartizal, K.; Fromtling, R. A.; Polishook, J.; Zweerink, M.; Edison, A. M.; Rozdilsky, W.; Wilson, K. E.; Monaghan, R. L. *J. Antibiot.* **1992**, *45*, 861. (c) 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) (a) Fujita, T.; Inoue, K.; Yamamoto, S.; Ikumoto, T.; Sasaki, S.; Toyoma, R.; Yoneta, M.; Hoshino, Y.; Okumoto, T. *J. Antibiot.* **1994**, *47*, 208. (b) Miyake, Y.; Kozutsumi, Y.; Nakamura, S.; Fujita, T.; Kawasaki, T. *Biochem. Biophys. Res. Commun.* **1995**, *211*, 396. (c) For synthesis of myriocin, see: Oishi, T.; Ando, K.; Chida, N. *Chem. Commun.* **2001**, 1932; and references cited therein.

(6) Zweerink, M. M.; Edison, A. M.; Wells, G. B.; Pinto, W.; Lester, R. L. *J. Biol. Chem.* **1992**, *267*, 25032; and references cited therein.

(7) (a) Trost, B. M.; Lee, C. B. *J. Am. Chem. Soc.* **2001**, *123*, 12191. (b) Trost, B. M.; Lee, C. B. *J. Am. Chem. Soc.* **1998**, *120*, 6818.

(8) (a) Wang, B.; Yu, X.-M.; Lin, G.-Q. *Synlett* **2001**, 904. (b) Liu, D.-G.; Wang, B.; Lin, G.-Q. *J. Org. Chem.* **2000**, *65*, 9114.

(9) (a) Nakamura, T.; Shiozaki, M. *Tetrahedron* **2002**, *58*, 8779. (b) Nakamura, T.; Shiozaki, M. *Tetrahedron Lett.* **2001**, *42*, 2701.

(10) Oishi, T.; Ando, K.; Inomiya, K.; Sato, H.; Iida, M.; Chida, N. *Org. Lett.* **2002**, *4*, 151.

(11) (a) Kobayashi, S.; Furuta, T.; Hayashi, T.; Nishijima, M.; Hanada, K. *J. Am. Chem. Soc.* **1998**, *120*, 908. (b) Kobayashi, S.; Furuta, T. *Tetrahedron* **1998**, *54*, 10275.

(12) Lee, K.-Y.; Oh, C.-Y.; Ham, W.-H. *Org. Lett.* **2001**, *4*, 4403.

(13) (a) Sano, S.; Kobayashi, Y.; Kondo, T.; Takebayashi, M.; Maruyama, S.; Fujita, T.; Nagao, Y. *Tetrahedron Lett.* **1995**, *36*, 2097. (b) Payette, D. R.; Just, G. *Can. J. Chem.* **1981**, *59*, 269.

(14) The following reference provides detailed procedures for both the preparation of precursors of both **8** and its regioisomer, and the preparation of the regioisomer of compound **8** from the corresponding precursor. It should be mentioned that the synthesis of **8** was accomplished from its corresponding precursor following the same procedure. See: Qiao, L.; Hu, Y.; Nan, F.; Powis, G.; Kozikowski, A. P. *Org. Lett.* **2000**, *2*, 115.

(15) For recent examples of Wittig and Horner–Wadsworth–Emmons reaction, see: (a) List, B.; Doehring, A.; Fonseca, M. T. H.; Job, A.; Torres, R. R. *Tetrahedron* **2006**, *62*, 476. For reviews, see: (b) Harvey, R. G. *Curr. Org. Chem.* **2004**, *8*, 303. (c) Quan, L.-G.; Cha, J.-K. *Chem. Phys. Lipids* **2004**, 128. (d) Rein, T.; Vares, L.; Kawasaki, I.; Pedersen, T. M.; Norrby, P.-O.; Brandt, P.; Tanner, D. *Phosphorus, Sulfur Silicon Relat. Elem.* **1999**, *144-146*, 169.

(16) (a) Cardillo, G.; Simone, A. D.; Gentilucci, L.; Sabatino, P.; Tomasini, C. *Tetrahedron Lett.* **1994**, *35*, 5051. (b) Trost, B. M.; Dake, G. R. *J. Org. Chem.* **1997**, *62*, 5670. (c) Krawczyk, H. *Synth. Commun.* **2000**, *30*, 1787.

(17) **Analytical Data of Compound 9.**
Amorphous solid, $[\alpha]_D^{25}$ +15.6 (*c* 0.35, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.67–7.85 (m, 4 H), 7.29 (d, *J* = 8.2 Hz, 2 H), 6.95 (d, *J* = 8.4 Hz, 2 H), 4.65 (d, *J* = 11.0 Hz, 2 H), 4.43 (d, *J* = 4.1 Hz, 1 H), 4.40 (s, 3 H), 4.28 (m, 1 H), 4.19 (d, *J* = 10.6 Hz, 1 H), 4.07 (dd, J_1 = 10.2 Hz, J_2 = 9.0 Hz, 1 H), 3.92 (s, 3 H), 3.65 (dd, J_1 = 9.6 Hz, J_2 = 8.8 Hz, 1 H), 2.27 (d, *J* = 7.4 Hz, 2 H), 1.53 (s, 3 H), 1.49 (s, 3 H), 1.39 (s, 3 H), 1.34 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.03, 166.48, 166.50, 159.31, 158.70, 134.57, 134.45, 134.43, 133.63, 131.66, 131.38, 129.89, 129.50, 129.48, 116.45, 110.76, 110.54, 80.02, 79.89, 79.07, 76.75, 75.34, 73.36, 72.16, 71.40, 57.86, 27.33, 27.06, 26.68, 24.65. HRMS: *m/z* calcd for $C_{31}H_{35}NO_{10}$: 581.2261; found: 581.2263.

(18) (a) Paulsen, H.; Heiker, F. R. *Angew Chem., Int. Ed. Engl.* **1980**, *19*, 904. (b) Paulsen, H.; Heiker, F. R. *Liebigs Ann. Chem.* **1981**, 2180.

(19) Bartlett, P. A.; Johnson, W. S. *Tetrahedron Lett.* **1970**, 4459.

(20) For recent examples of Barton decarboxylation, see: (a) Masterson, D. S.; Porter, N. A. *Org. Lett.* **2002**, *4*, 4253. (b) Elena, M.; Taddei, M. *Tetrahedron Lett.* **2001**, *42*, 3519. (c) For a review, see: Barton, D. H. R. *Aldrichimica Acta* **1990**, *23*, 3.

(21) (a) Gigg, J.; Gigg, R.; Payne, S.; Conant, R. *J. Chem. Soc., Perkin. Trans. 1* **1987**, 423. (b) Vacca, J. P.; de Solms, S. J.; Huff, J. R. *J. Am. Chem. Soc.* **1987**, *109*, 3478. (c) Vacca, J. P.; de Solms, S. J.; Huff, J. R.; Billington, B. C.; Baker, R.; Kulagowski, J. J.; Mawer, I. M. *Tetrahedron* **1989**, *45*, 5679.

(22) **Analytical Data of Compound 12.**
Amorphous solid, $[\alpha]_D^{25}$ +20.3 (*c* 0.15, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.70–7.88 (m, 4 H), 7.27–7.33 (m, 6 H), 6.86–6.89 (m, 4 H), 6.85 (d, *J* = 8.3 Hz, 2 H), 4.63–4.68 (m, 6 H), 4.40 (d, *J* = 3.8 Hz, 1 H), 4.29 (m, 1 H), 3.90 (d, *J* = 10.6 Hz, 1 H), 3.83 (2 × s, 6 H), 3.80 (s, 3 H), 3.48 (dd, J_1 = 10.6 Hz, J_2 = 10.2 Hz, 1 H), 3.45 (dd, J_1 = 10.6 Hz, J_2 = 9.8 Hz, 1 H), 1.67 (s, 3 H), 1.36 (s, 3 H), 1.33 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.68, 166.50, 159.31, 159.16, 157.35, 138.56, 138.45, 135.46, 135.15, 134.43, 133.10, 131.58, 131.38, 130.73, 129.89, 129.50, 128.55, 128.38, 128.37, 128.00, 127.99, 113.91, 110.89, 83.22, 81.49, 81.28, 76.50, 75.60, 71.73, 69.19, 55.63, 27.35, 25.91.

(23) (a) Bredenkamp, M. W.; Holzapfel, C. W.; Swanepoel, A. D. *Tetrahedron Lett.* **1990**, *31*, 2759. (b) David, S.; Hanessian, S. *Tetrahedron* **1985**, *41*, 643. (c) Pereyre, M.; Quintard, J.-P.; Rahm, A. *Tin in Organic Synthesis*; Butterworths: London, **1987**, 261.

(24) **Analytical Data of Compound 6.**
Amorphous solid, $[\alpha]_D^{25}$ +8.9 (*c* 0.20, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.74–7.90 (m, 4 H), 7.26–7.33 (m, 6 H), 6.86–6.89 (m, 4 H), 6.85 (d, *J* = 8.0 Hz, 2 H), 5.31 (s, 1 H), 4.64–4.68 (m, 4 H), 4.64 (d, *J* = 9.6 Hz, 2 H), 3.86 (d, *J* = 9.2 Hz, 1 H), 3.85 (s, 3 H), 3.81 (s, 3 H), 3.80 (s, 3 H), 3.46 (dd, J_1 = 9.6 Hz, J_2 = 7.8 Hz, 1 H), 3.35 (br s, 1 H), 3.35 (s, 3 H),

1.66 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.78, 165.50, 159.31, 159.26, 139.77, 138.85, 138.46, 135.46, 135.02, 134.44, 133.20, 132.66, 131.75, 131.23, 129.89, 129.88, 128.05, 127.98, 127.85, 126.88, 110.91, 110.89, 83.63, 81.62, 81.28, 80.66, 75.81, 75.47, 74.27, 73.97, 55.23, 55.20. HRMS: *m/z* calcd for $C_{40}H_{41}NO_9$: 679.2781; found: 679.2785.

(25) (a) Chida, N.; Yamada, L.; Suzuki, M.; Ogawa, S. *J. Carbohydr. Chem.* **1992**, *11*, 137. (b) Paulsen, H.; Roeben, W. *Liebigs Ann. Chem.* **1985**, *5*, 974.

(26) **Analytical Data for Compound 2 (Sphingofungin F).** Amorphous solid, $[\alpha]_D^{25}$ +1.33 (*c* 0.20, MeOH). ^{1}H NMR (400 MHz, CD_3OD): δ = 5.78 (dt, J_1 = 15.6 Hz, J_2 = 6.6 Hz, 1 H), 5.46 (dd, J_1 = 15.5 Hz, J_2 = 8.0 Hz, 1 H), 4.11 (t, *J* = 7.6 Hz, 1 H), 3.86 (br s, 1 H), 3.67 (d, *J* = 7.5 Hz, 1 H), 2.45 (t, *J* = 7.5 Hz, 4 H), 2.04–2.06 (m, 2 H), 1.49–1.56 (m, 4 H), 1.48 (s, 3 H), 1.26–1.43 (m, 12 H), 0.90 (t, *J* = 6.7 Hz, 3 H). ^{13}C NMR (100 MHz, CD_3OD): δ = 214.53, 175.32, 135.75, 130.30, 76.25, 75.73, 72.44, 67.03, 43.50, 33.52, 32.79, 30.26, 30.03, 25.02, 23.67, 21.80, 14.43.