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Total synthesis of sphingofungin E

Tsuyoshi Nakamura and Masao Shiozaki*

Exploratory Chemistry Research Laboratories, Sankyo Co. Ltd., Hiromachi 1-2-58, Shinagawa-ku, Tokyo 140-8710, Japan

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Abstract—Total synthesis of sphingofungin E (**1**) using an already known D-glucose derivative as a chiral synthon is described.

Sphingofungins have been isolated by the Merck group as new antifungal agents.[1,2] These compounds have a unique mechanism in their biological activity. They inhibit serinepalmitoyl transferase, an enzyme essential in the biosynthesis of sphingolipids.[1a,c] The sphingofungins have four consecutive chiral centers and a *trans* olefinic group in their polar head moiety. In particular, sphingofungin E (**1**) and F contain a quaternary center at the C2 position. Their structures, especially the structure of sphingofungin E, are strikingly similar to myriocin which has been reported as a potent immunosuppressive agent.[3] Many organic chemists have been interested in the structure of myriocin and its unique biological activity, and myriocin and its related compounds have already been successfully synthesized.[4] The total synthesis of sphingofungin E by Trost et al. based on the procedure of sphingofungin F synthesis has also been achieved.[5] Here we describe an alternative method for the synthesis of sphingofungin E using an already-identified D-glucose derivative.

Based on the retrosynthetic analysis depicted in Fig. 1, the molecule of **1** is divided into two fragments. We adopted the reported method[2d,5] for coupling the hydrophilic polar head **17** and the lipophilic side chain **18**.[2d] Compound **17** possesses four contiguous chiral centers and one *trans* olefin. The C1–C7 fragment of **17** should be able to be derived from the azide derivative **7**, which may be obtainable[6] from the already-identified D-glucose derivative **2**.

We attempted to synthesize the polar head of **17** starting from the benzylidene compound **2**, which was easily prepared by a modification of the procedure reported by Fukase et al.[7] (Scheme 1).

Swern oxidation of **2** afforded ketone **3** as a crystalline solid (mp 77–79°C) in 76% yield. Addition of dichloromethyllithium to the ketone moiety of **3** afforded C2-dichloromethylated tertiary alcohol **4**, exclusively, in 70% yield without detection of the C2-

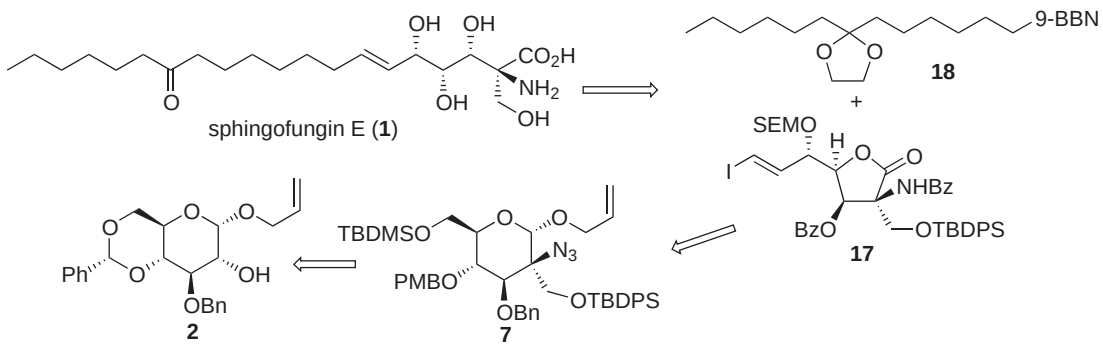

Figure 1. Structure and retrosynthetic analysis of sphingofungin E.

Keywords: antifungals; asymmetric synthesis; natural products; stereocontrol.
* Corresponding author. Fax: +81-3-5436-8570; e-mail: shioza@shina.sankyo.co.jp

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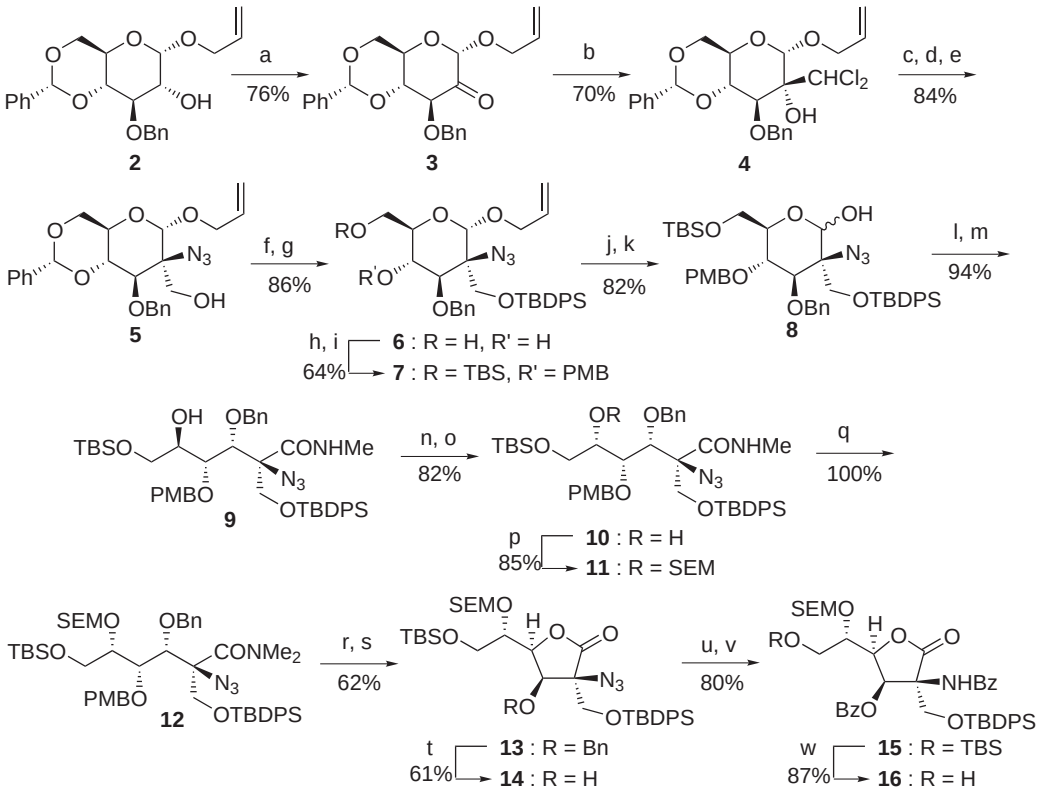
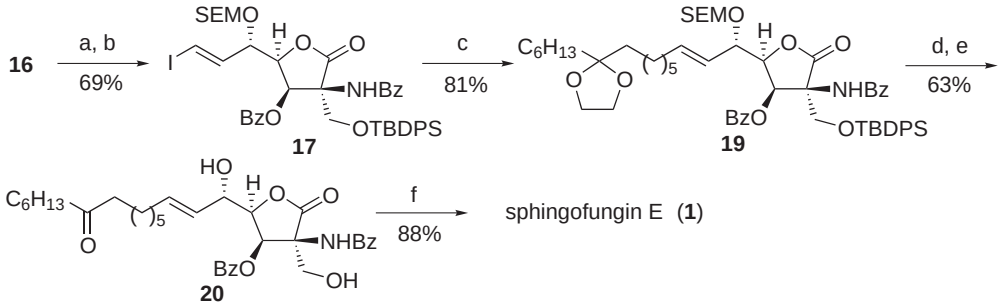


Scheme 1. Reagents and conditions: (a) Swern oxidation, −78°C, 1 h; (b) $LiCHCl_2$, THF, −78°C, 30 min; (c) DBU, DMSO, 0°C, 3 h; (d) NaN_3, cat. 15-crown-5, HMPA, 70°C, 17 h; (e) $NaBH_4$, MeOH, 0°C, 1.5 h; (f) TBDPSCl, imidazole, DMF, 60°C, 3 h; (g) cat. CSA, MeOH, rt, 26 h; (h) TBSCl, imidazole, DMF, 0°C, 2 h; (i) PMBCl, NaH, DMF, −23°C, 5 h; (j) $[Ir(COD)(PMePh_2)_2]PF_6$, THF, rt, 2.5 h; (k) NBS, H_2O, THF, 0°C, 2 h; (l) Dess–Martin periodinane, CH_2Cl_2, rt, 2 h; (m) H_2NMe, MeOH, rt, 1.5 h; (n) Swern oxidation, −78°C, 1 h; (o) L-Selectride, THF, −78°C, 30 min; (p) SEMCl, $EtN(iPr)_2$, DCE, 60°C, 4 h; (q) MeI, NaH, DMF, 0°C, 1.5 h; (r) DDQ, H_2O, CH_2Cl_2, 0°C, 3 h; (s) PPTS, toluene, 70°C, 24 h; (t) $NaBrO_3$, $NaHSO_3$, H_2O, AcOEt, rt, 1 h; (u) Pd/C, H_2, AcOEt, rt, 14 h; (v) PhCOCl, Et_3N, CH_2Cl_2, rt, 2 h; (w) 5% aq. H_2SO_4, acetone, rt, 13 h.

epimer, due to the steric hindrance by the anomeric axial allyloxy group. Treatment of a solution of **4** in DMSO with DBU gave an epoxy-chloride, which was then treated with NaN_3 in the presence of 15-crown-5 using HMPA as a solvent to give an azidoaldehyde with an accompanying inversion of configuration.[6] The attack of the azide anion was regiospecific at the C2 carbon. The aldehyde was immediately reduced with $NaBH_4$ to afford primary alcohol **5** in 84% yield in three steps. Protection of the primary hydroxyl group of **5** with *t*-butyldiphenylsilyl chloride (TBDPSCl) and imidazole using DMF as a solvent, and successive deprotection of the 4,6-*O*-benzylidene group with CSA afforded diol **6** in 86% yield. The regioselective silylation at the C6 hydroxyl group of **6** with *t*-butylmethylsilyl chloride (TBDMSCl) and imidazole, and the *p*-methoxybenzyl (PMB) ether formation at the C4 hydroxyl group with PMBCl and NaH in DMF at −23°C for 5 h afforded **7** in 64% yield. The deprotection of the C1 anomeric *O*-allyl with an Ir complex[8] and NBS–H_2O gave pyranose **8** in 82% yield. Compound **8** was oxidized to a lactone using Dess–Martin periodinane, and was successively treated with methylamine in MeOH to afford stable amide **9** in 94% yield. Since the configuration of the C5 hydroxyl group of **9** was the reverse of that of the natural sphingofungin E, we needed to inverse the configuration from *R* to *S*. Compound **9** was oxidized by Swern oxidation to give a ketone, which was then reduced to alcohol **10** by L-Selectride reduction. This hydride reduction was achieved in a >95:<5 ratio diastereoselectively. After the purification by silica gel column chromatography, an inverted alcohol **10** was obtained in 82% yield in two steps. The C5 hydroxyl group of **10** was protected by treatment with (trimethylsilylethoxy)methyl chloride (SEMCl) and diisopropylethylamine in dichloroethane to give SEM ether **11** in 85% yield.

Based on our preliminary experiment, difficulties were expected in hydrolyzing the C1 *N*-methylamide group to a carboxylic acid after introducing the lipophilic side chain. Thus, we carried out the cleavage of the amide bond via the formation of a five-membered lactone by the removal of C4 PMB ether. Treatment of **11** with MeI in the presence of NaH as a base in DMF afforded *N*-dimethylamide **12** in quantitative yield. Treatment of the resulting compound **12** with DDQ–H_2O to remove the *p*-methoxybenzyl group followed by PPTS gave lactone **13** in 62% yield. The pre-conversion to dimethylamide **12** was essential to achieve lactone formation under these moderately acidic conditions.[9]



Scheme 2. Reagents and conditions: (a) Dess–Martin periodinate, CH_2Cl_2, rt, 1.5 h; (b) CHI_3, $CrCl_2$, THF, rt, 2 h; (c) organoborane **18**, $PdCl_2$(dppf), Ph_3As, Cs_2CO_3, THF–DMF, rt, 2 h; (d) 5% aq. H_2SO_4, acetone, rt, 5 h; (e) HF–Py complex, THF, rt, 5.5 h; (f) NaOH, H_2O, dioxane, 70°C, 7.5 h, then neutralized with Amberlite IR-120.

Based on the preliminary experiment, difficulties were expected in the deprotection of the C3 *O*-benzyl group in the final stage. Therefore, we removed the benzyl group at this stage. However, applying hydrogenolytic conditions using Pd/C as a catalyst or other methods[10] to cleave the benzyl group proved fruitless. Finally, treatment of **13** with $NaBrO_3$ and $NaHSO_3$ gave **14** in 61% yield.[11] After the reduction of the azide group of **14** under hydrogen using Pd on carbon as a catalyst in ethyl acetate, the following treatment with 3 equivalents of benzoyl chloride and excess triethylamine afforded the *O*-benzoylated benzoylamide **15** in 80% yield. Selective cleavage of the C6 *O*-TBS group of **15** by treatment with 5% aqueous H_2SO_4 in acetone was accomplished to give alcohol **16** in 87% yield without cleavage of both the TBDPS and SEM groups.

The following steps to introduce the lipophilic side chain with an *E*-geometrical alkene part to compound **16** were achieved by applying the reported method[2d,5] (Scheme 2).

Thus, Dess–Martin periodinate oxidation of the C6 hydroxyl group of **16** to an aldehyde, followed by iodo olefination of the resulting aldehyde, exclusively afforded (*E*)-iodoolefin **17** in 69% yield without any detection of the (*Z*)-isomer. Suzuki coupling[12] of vinyl iodide **17** and organoborane **18** using $PdCl_2$(dppf), Ph_3As and Cs_2CO_3 in THF–DMF provided the desired (*E*)-alkene **19** in 81% yield. The deprotection reactions to convert **19** to **1** were carried out as follows. The C14 ethylene acetal of **19** was removed by hydrolysis with 5% aqueous H_2SO_4 in acetone. Treatment of the obtained ketone with a HF–pyridine complex in THF cleaved both TBDPS and SEM ethers to give keto diol **20** in 63% yield. Finally, the lactone ring, benzamide and benzoyl ester groups of **20** were saponified in the presence of NaOH in dioxane–H_2O, and neutralization with Amberlite IR-120 ion-exchange resin afforded sphingofungin E (**1**)[13] in 88% yield.

Thus, we were able to accomplish the synthesis of sphingofungin E from the already-identified D-glucose derivative **2** in a stereocontrolled manner in 29 steps in 1.1% overall yield.

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13. The melting point, optical rotatory value, and spectral data of the synthetic compound agreed closely with those of both natural and synthetic sphingofungin E reported by the Merck group[1c] and Trost,[5] respectively. Mp 145–147°C. $[\alpha]_D^{24}$ −5.43 (*c* 0.48, CH_3OH). IR (KBr) 3532, 3198, 2928, 2855, 1711, 1637 cm^{-1}. ^1H NMR (500 MHz, CD_3OD) δ 0.90 (t, 3H, $J=6.8$ Hz), 1.24–1.46 (m, 12H), 1.50–1.56 (m, 4H), 2.06 (q, 2H, $J=6.8$ Hz), 2.44 (t, 2H, $J=7.3$ Hz), 2.45 (t, 2H, $J=7.3$ Hz), 3.64 (d, 1H, $J=6.9$ Hz), 3.85 (d, 1H, $J=11.7$ Hz), 3.94–4.00 (m, 2H, involving a doublet at δ 3.98, $J=11.7$ Hz), 4.11 (t, 1H, $J=7.3$ Hz), 5.45 (dd, 1H, $J=7.8$ Hz, 15.6 Hz), 5.77 (dt, 1H, $J=15.6$ Hz, 6.8 Hz). ^{13}C NMR (125 MHz, CD_3OD) 14.37, 23.58, 24.84, 24.86, 29.99, 30.01, 30.14, 30.16, 32.81, 33.42, 43.45, 43.48, 64.95, 70.03, 71.11, 75.52, 76.27, 130.14, 135.70, 173.42, 214.34. HRMS (FAB, positive) calcd for $C_{21}H_{40}NO_7$ $(M+H)^+$: 418.2805. Found: 418.2806.