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Total Synthesis of Sphingofungin F Based on Chiral Tricyclic Iminolactone

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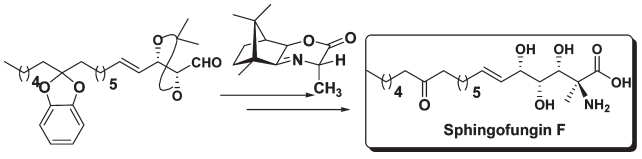

A new, efficient synthesis of sphingofungin **F** has been accomplished with 10.4% overall yield in 15 steps. The salient features of the synthesis are the utilization of methyl tricyclic iminolactone **3** for the asymmetric aldol reaction as a key step to introduce two desired stereogenic centers, one-pot reaction for the synthesis of ω-hydroxyketone from ε-caprolactone, and an effective one-step deprotection strategy to remove all protecting groups using 0.2 N HCl.

Sphingosines are important second messengers and regulatory molecules in the cell-signaling transduction pathway with inhibition to protein kinase C (PKC).[1] One of the derivatives, sphingofungin F, bearing a C_{20} straight carbon chain with *E*-olefin and four contiguous asymmetric centers, was first isolated from the fermentation broth of *Paecilomyces variotii* by a Merck group in 1992.[2] It exhibits inhibitory effects toward serine palmitoyl transferase (SPT), which induces apoptosis in both yeast and mammalian cells by blocking the sphingosine biosynthesis pathway.[3] Due to its structural novelty and biological activity, the synthesis of sphingofungin F has attracted considerable attention to synthetic chemists.[4] The first asymmetric synthesis of sphingofugin F was achieved by Kobayashi using Sn^{II}-catalyzed asymmetric aldol reaction of Schöllkopf's bislactam in 1997 with 6.5% overall yield in 24 steps.[4a] After that, Trost[4c,f] and Lin[4e] accomplished the total synthesis of sphingofungin F using palladium-catalyzed asymmetric allylic alkylation reaction and Lewis acid-catalyzed intramolecular epoxide-opening with an *N*-nucleophile as key steps with the yield of 17.0% in 15 steps and 3.7% in 22 steps, respectively. Then, Ham[4g] and Li[4h] reported the synthesis of sphingofungin F in 15 and 17 steps, with an overall yield of 6.0% and 7.7%. Recently, Wang and Lin reported a flexible common approach for the total synthesis of sphingofungin E and F with efficient use of both diastereomers of the Baylis−Hillman adduct in a stereoconvergent manner on the basis of their previous report with the yield about 4.0% in 27 steps.[4i] Among these, the strategies are all more than 15 steps, and only the route described by Trost gives overall yield higher than 10%.

Chiral tricyclic iminolactone,[5,6] a useful chiral auxiliary for the preparation of amino acids, especially β-hydroxy-α-amino acids, has been reported by our group recently.[6g] On the basis of this method, a new efficient strategy for the total synthesis of sphingofungin F is described herein. In this strategy, chiral methyl tricyclic iminolactone **3** was used as an alanine equivalent for the asymmetric aldol reaction to introduce the two desired stereogenic centers.

As shown in our retrosynthetic analysis (Scheme 1), sphingofungin F can be divided into two parts: methyl tricyclic iminolactone and polyhydroxyl long chain aldehyde **2**. The latter can be obtained by the coupling reaction of long chain lipid **4** and polyhydroxyl *trans*-olefin **5**.

The first stage of the synthesis involved the preparation of the compound **4** (Scheme 2). According to our reported method,[7] 1-hydroxydodecan-6-one (**7**) was synthesized by a convenient one-pot reaction from ε-caprolactone (**6**) and *n*-hexyl Grignard reagent in 87% yield. Then the carbonyl group was protected with catechol to afford the compound **8**

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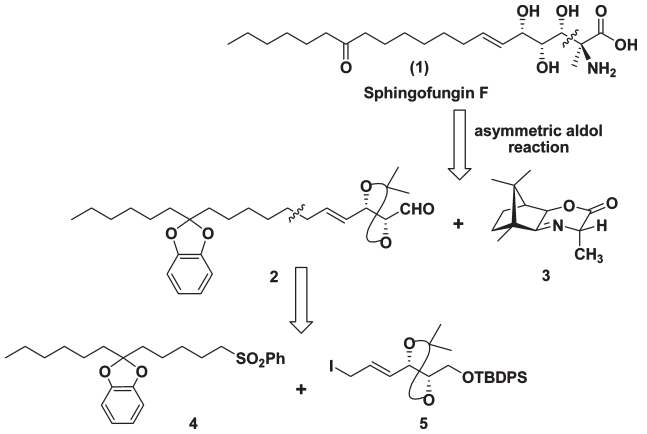
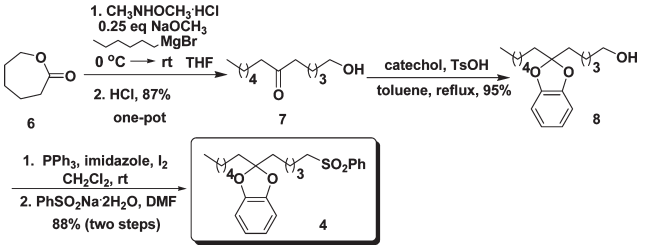
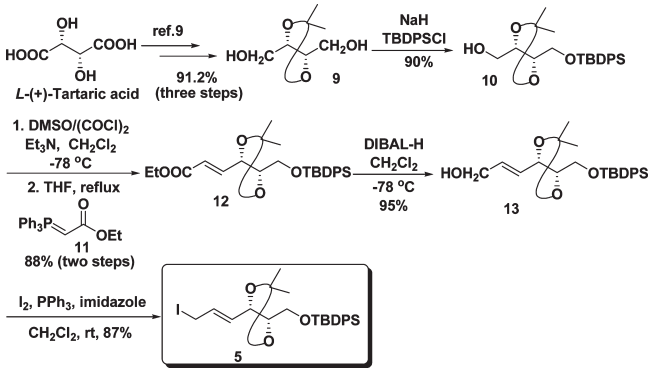
SCHEME 1. Retrosynthetic Analysis



SCHEME 2. Synthesis of Intermediate 4



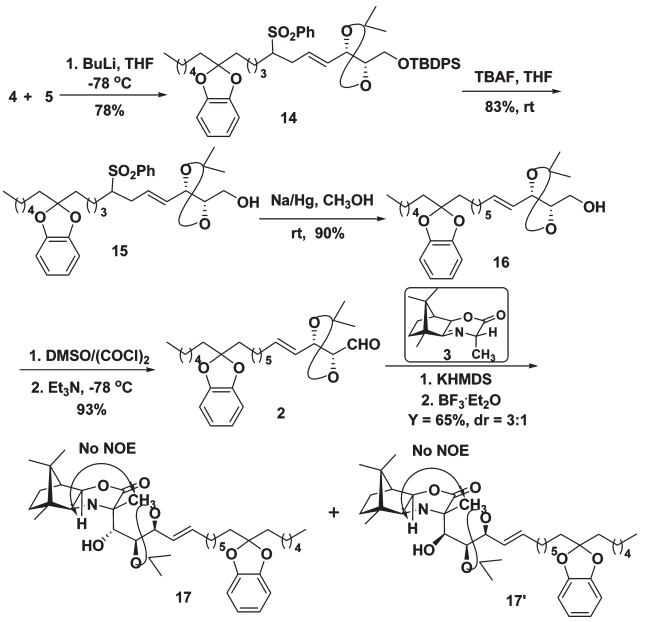
SCHEME 3. Synthesis of Intermediate 5



in 95% yield. Direct iodination of the alcohol **8** with PPh_3/I_2/imidazole followed by sulfonylation with $PhSO_2Na$ produced the sulfone **4** in satisfactory yield (88%, two steps).[8]

Next, the stage was set for the synthesis of intermediate **5** starting from known diol **9** (Scheme 3), which could be prepared from L-(+)-tartaric acid in three steps according to the reported procedure.[9] Compound **10** was obtained from compound **9** by monosilylation (TBDPSCl, NaH, 90%). Swern oxidation of **10** gave a crude aldehyde,[10] which was subjected to Wittig reaction with the ylide **11** in refluxing THF to give α,β-unsaturated ester **12** in 88% yield

SCHEME 4. Synthesis of Intermediate 2 and Its Aldol Reaction



(two steps).[11] Fortunately, an excellent (*E*)-selectivity was observed while the corresponding (*Z*)-isomer was not detected. Reduction of the ester **12** with DIBAL-H provided the alcohol **13** in 95% yield. Then the hydroxy group was replaced with iodine to afford the iodide **5** in 87% yield.

With two intermediates in hand, our attention focused on the coupling of **4** and **5** (Scheme 4). Various bases (LDA, BuLi, *t*-BuLi), additives (HMPA, DMPU), and temperatures (−78, −40 °C) were used in the attempts. As a result, the desired product **14** was prepared successfully using BuLi as base at −78 °C in 78% yield. Deprotection of the silyl ether **14** gave the alcohol **15** in 83% yield, and removal of the phenylsulfonyl group with Na/Hg alloy in anhydrous methanol afforded the compound **16** in 90% yield.[12] Then Swern oxidation of **16** furnished the crude aldehyde **2** in 93% yield. Soon afterward, asymmetric aldol reaction of compounds **2** and **3** to give the desired aldol adduct[6g] proved to be troublesome under a variety of conditions (Scheme 4). Initially, LiCl and LDA wre employed, and only a trace amount of the aldol product was obtained. To improve the yield, other Lewis acids (Et_2AlCl, $BF_3\cdot Et_2O$) and bases (KHMDS, NaHMDS, LHMDS) were tested, and finally, the desired product **17** was provided in 65% yield with dr = 3:1 (**17**:**17′**) when $BF_3\cdot Et_2O$ and KHMDS were used. Since there is no observable NOE signal between the methyl group and the hydrogen adjacent to the ester moiety, it can be assumed that the methyl group is in the equatorial position. (Scheme 4).

With compound **17** in hand, our focus then shifted to the final hydrolysis to remove the chiral auxiliary and protecting groups, which proved to be particularly challenging. A wide variety of reaction conditions (acids, temperatures, and solvents) were examined, and some of the representative results are shown in Table 1. First, according to the previous work in our laboratory,[6g] the condition of 6 N HCl at 80 °C was examined (entry 1). The reaction proved to be complicated,

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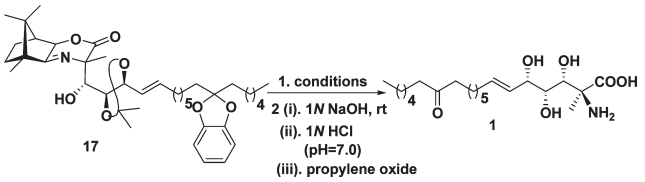
TABLE 1. Hydrolysis of Compound 17



entry[a]	acid	temp (°C)	solvent	yield[b] (%)
1	6 N HCl	80	H_2O	0
2	6 N HCl	reflux	H_2O	0
3	12 N HCl	reflux	H_2O	0
4	CF_3COOH	reflux	H_2O	trace
5	CH_3COOH	reflux	H_2O	trace
6	0.2 N HCl	reflux	H_2O/EtOH[c]	66

[a]General reaction conditions: concentration 0.2 M in solvents. [b]Isolated yield. [c]H_2O/EtOH (v/v = 1:1).

and no product was obtained. Compared with the previous molecules,[6g] aldol adduct **17** is more complex and its steric hindrance is more prominent, which may increase the difficulty of hydrolysis. When the temperature was increased to reflux and even 12 N HCl was used (entries 2 and 3), any desired hydrolyzed fragments could not be found. We had to change the strategy using weaker acids (acetic acid and trifluoroacetic acid) to remove the chiral auxiliary and protecting groups one by one (entries 4 and 5), and then some partly hydrolyzed fragments were obtained, especially 3-*exo*-hydroxycamphor. By analyzing the fragments, it was found that the catechol group was the most difficult one to remove. In this regard, when a mixture of 0.2 N HCl and ethanol (v/v = 1:1) was used, all protecting groups were removed smoothly. To our surprise, the hydrolytic molecule we obtained was not the final desired product but its corresponding lactone formed by an intramolecular cyclization. Thus, saponification of the crude lactone was carried out with 1 N NaOH solution. Then, 1 N HCl and propylene oxide were used for neutralization and removal of hydrochloride to afford the final desired product **1** in 66% yield (two steps). The ^{1}H and ^{13}C NMR spectral data of **1** were found to be in good accord with the values reported for sphingofungin F.[4g]

In summary, a new and efficient strategy for the total synthesis of sphingofungin F has been accomplished in 15 steps with 10.4% overall yield. In this strategy, methyl tricyclic iminolactone was used as a chiral template for the asymmetric aldol reaction to introduce other two desired stereogenic centers. Besides that, a convenient one-pot method for the synthesis of ω-hydroxy ketones and an effective one-step deprotection strategy simplified the synthetic route dramatically. It is also worth noticing that by simple modification of the tricyclic iminolactone or other structurally related substances, other members of sphingofungin family could be synthesized easily.

Experimental Section

1-Hydroxydodecan-6-one (7). A slurry of ε-caprolactone **6** (0.912 g, 8.0 mmol), HN(OMe)Me·HCl (0.935 g, 9.6 mmol), and NaOMe (108 mg, 2.0 mmol) in THF (100 mL) was stirred at 0 °C under argon atmosphere. *n*-HexMgBr (128 mL, 0.5 M in THF, 64.0 mmol) was added slowly. After 2 h, the reaction mixture was allowed to warm to rt and stirred for 6 h. The reaction was quenched with 1 N HCl solution (100 mL), and the mixture was stirred for another 2 h. The solvent was evaporated, and the residue was diluted with H_2O (100 mL) followed by extraction with CH_2Cl_2. The organic layer was washed with saturated $NaHCO_3$ solution and brine, respectively, and then dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 5:1) to afford **7** (1.4 g, 87%) as a white solid: mp 37−38 °C; IR (KBr) 3214, 2928, 2854, 1700, 1465, 1416, 1375, 1241, 1054, 725 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.65 (t, J = 6.6 Hz, 2H), 2.43−2.37 (m, 4H), 1.64−1.54 (m, 7H), 1.40−1.28 (m, 8H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.6, 62.4, 42.8, 42.5, 32.3, 31.5, 28.8, 25.3, 23.7, 23.4, 22.4, 13.9; ESIMS for $C_{12}H_{25}O_2$ m/z 201 $[M + H]^+$.

2-Hexyl-2-[(7*E*,9*S*,10*S*)-5-phenylsulfonyl-9,10-isopropylidenedioxy-11-*tert*-butyldiphenylsilyloxy-7-hendecene]benzo[1,3]-dioxole (14). To a stirred solution of **4** (666 mg, 1.6 mmol) in dry THF (50 mL) was added BuLi (1.26 mL, 1.52 M in THF, 1.92 mmol) at −78 °C under argon atmosphere slowly, and the mixture was stirred for 15 min. Then a solution of compound **5** (1.01 g, 1.92 mmol) in THF (10 mL) was trickled slowly down the side of the tube. After 1 h, the reaction was quenched with saturated NH_4Cl solution (1.0 mL), and the mixture was allowed to warm to rt. The resulting solution was concentrated, and the residue was purified by flash column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 8:1) to afford **14** (1.03 g, 78%) as a colorless oil: $[\alpha]^{20}_D$ −5 (*c* 1.5, $CHCl_3$); IR (KBr) 2952, 2931, 2859, 1486, 1303, 1239, 1144, 1109, 1084, 824, 737, 704, 506 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 7.6 Hz, 2H), 7.68−7.61 (m, 5H), 7.53 (t, J = 7.6 Hz, 2H), 7.42−7.34 (m, 6H), 6.73−6.68 (m, 4H), 5.64−5.54 (m, 1H), 5.44 (dd, J = 15.6, 6.8 Hz, 1H), 4.34 (dd, J = 13.8, 6.6 Hz, 1H), 3.80−3.77 (m, 1H), 3.70−3.66 (m, 1H), 2.91 (br s, 1H), 2.55−2.50 (m, 1H), 2.36−2.25 (m, 1H), 1.83−1.75 (m, 4H), 1.56 (br s, 2H) 1.41−1.25 (m, 18H), 1.04 (s, 9H), 0.86 (t, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9, 138.0, 137.9, 135.6, 133.6, 133.2, 131.3, 131.2, 129.7 (2C), 129.4, 129.1, 129.0, 128.8 (2C), 127.7 (2C), 120.8, 120.1 (2C), 109.0, 107.9, 81.2 (2C), 78.2, 78.1, 77.2, 63.8 (2C), 62.8, 62.7, 37.8, 37.2, 31.6, 31.1, 30.8, 29.2, 27.3, 27.1, 26.9, 26.8, 26.6, 26.5, 22.6, 22.5, 22.4, 19.2, 14.0; HRMS (ESI) calcd for $C_{49}H_{68}NO_7SSi$ $[M + NH_4]^+$ 842.4480, found 842.4489.

Aldol Adduct (17). To a solution of **3** (122 mg, 0.55 mmol) in dry THF (2.0 mL) was added KHMDS (0.72 mL, 1 M in THF, 0.72 mmol) at −78 °C under argon atmosphere. The mixture was stirred for 30 min, and then a solution of $BF_3 \cdot Et_2O$ (58 uL, 0.55 mmol) in THF (1.0 mL) was added. After 30 min, a solution of **2** (187 mg, 0.42 mmol) in THF (1.0 mL) was trickled slowly down the side of the tube. After 2 h, saturated NH_4Cl solution (0.5 mL) was added, and the reaction was allowed to warm to rt. The resulting solution was evaporated, and the residue was purified by flash column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 6:1) to afford **17** (181.8 mg, 65%, dr = 3:1) as a colorless oil: $[\alpha]^{20}_D$ +12.2 (*c* 4.3, $CHCl_3$); IR (KBr) 3404, 2928, 2857, 1749, 1626, 1486, 1456, 1375, 1239, 1064, 1043, 876, 736 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76−6.70 (m, 4H), 5.86−5.79 (m, 1H), 5.34 (dd, J = 15.2, 8.4 Hz, 1H), 4.64 (s, 1H), 4.23 (t, J = 8.4 Hz, 1H), 3.79 (d, J = 8.4 Hz, 1H), 3.61 (d, J = 10.4 Hz, 1H), 2.92 (d, J = 10.4 Hz, 1H), 2.20 (d, J = 4.4 Hz, 1H), 2.06−1.99 (m, 3H), 1.89−1.85 (m, 4H), 1.78−1.71 (m, 1H), 1.63 (s, 3H), 1.44−1.27 (m, 24H), 1.05 (s, 3H), 0.95 (s, 3H), 0.86 (t, J = 6.6 Hz, 3H), 0.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.3, 172.0, 148.0, 138.6, 125.3, 120.7, 120.6, 110.0, 107.9, 80.5, 80.1, 78.1, 70.5, 66.8, 52.9, 48.3, 48.0, 37.7 (2C), 32.3, 31.6, 29.4, 29.3, 29.0, 28.9, 28.8, 27.4, 26.6, 26.2, 23.9, 22.6 (2C), 22.5, 20.2, 19.4, 14.0, 10.3;

HRMS (ESI) calcd for $C_{40}H_{60}NO_7$ $[M + H]^+$ 666.4364, found 666.4376.

Sphingofungin F (1). To a solution of **17** (133 mg, 0.2 mmol) in ethanol (0.5 mL) was added 0.2 N HCl (0.5 mL). The mixture was stirred under reflux for 12 h. The solution was evaporated, and the residue was treated with 1 N NaOH solution (2 mL). The mixture was stirred at rt for 2 h and then neutralized with 1 N HCl solution. The solvent was evaporated, and the residue was treated with propylene oxide. The resulting solution was concentrated and the residue was purified by flash column chromatography on silica gel (eluent: $CHCl_3/CH_3OH/H_2O$ = 20:5:1) to afford **1** (52.9 mg, 66%) as a white solid: mp 143−145 °C (CH_3OH-H_2O); $[\alpha]^{20}_D$ +2 (*c* 0.4, CH_3OH); IR (KBr) 3405, 2927, 2855, 1713, 1628, 1462, 1409, 1373, 1055, 979, 578, 468 cm^{-1}; ^1H NMR (600 MHz, CD_3OD) δ 5.78 (dt, J = 15.0, 7.2 Hz, 1H), 5.46 (dd, J = 15.0, 7.8 Hz, 1H), 4.12 (t, J = 7.5 Hz, 1H), 3.87 (br s, 1H), 3.68 (d, J = 7.2 Hz, 1H), 2.45 (t, J = 7.2 Hz, 2H), 2.44 (t, J = 7.2 Hz, 2H), 2.06 (q, J = 7.0 Hz, 2H), 1.53−1.57 (m, 4H), 1.50 (s, 3H), 1.39−1.44 (m, 2H), 1.29−1.37 (m, 13H), 0.90 (t, J = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, CD_3OD) δ 214.3, 175.3, 135.7, 130.2, 76.2, 75,7, 72.5, 66.7, 43.5 (2C), 33.4, 32.8, 30.2 (2C), 30.0 (2C), 24.9 (2C), 23.6, 21.8, 14.4; HRMS (ESI) calcd for $C_{21}H_{39}NO_6$ $[M + H]^+$ 402.2850, found 402.2853.

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Supporting Information Available: Experimental procedures, spectral data, comparison of the NMR data of synthetic sphingofungin **F** with those reported for the natural product, and copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org