The First Total Synthesis of Sphingofungin E and the Determination of its Stereochemistry

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Dedicated to Professor R. Noyori in appreciation of his great contribution to organic synthesis

Abstract: The total synthesis of sphingofungin E has been realized for the first time and its absolute configurations were established. Starting from L-(+)-tartaric acid, our synthesis featured substrate-controlled asymmetric dihydroxylation, regiospecific epoxide formation and Hatakeyama reaction to construct the contiguous chiral centers in the target molecule.

Key words: total synthesis, amino acids, dihydroxylations, Wittig reactions, epoxides

Sphingofungin E (1) and F (2), two new members of the sphingofungin family, were first isolated from the fermentation broth of Paecilomyces variotii by Merck’s group in 1992. They showed significant biological activity in inhibiting serine palmitoyltransferase, and had antifungal activity against several human pathogenic fungi. They also bear structural resemblance to myriocin (3), a compound 10-100 times more potent than immunosuppressant cyclosporin A. Although there has been a number of works on the total synthesis and the absolute stereochemistry of 2, the most highly oxygenated member of the family, sphingofungin E, remained untackled, and its stereochemistry was only tentatively assigned. As it is our continued interest in the synthesis of polyhydroxylamines and α-substituted amino acids, we have undertaken the syntheses of both 1 and 2. Herein we report the first total synthesis of sphingofungin E and the determination of its stereochemistry.

Scheme 1 illustrates the retrosynthetic analysis. The target molecule could be disconnected into a known phosphonium salt 4 and a polar head 5 bearing four contiguous chiral centers. The C-2 configuration of 5 was expected to be established via intramolecular ring-opening of epoxide 6. The α,β-epoxido ester structure unit of 6 was in turn...
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Scheme 2
(a) methylacrylate, DABCO, rt, 70%; (b) OsO₄, NMO, acetone-H₂O (8:1), rt; (c) TBSCI, Et₃N, cat. DMAP, 89% (2 steps); (d) MsCl, Py, CH₂Cl₂, 0 °C to rt; (e) K₂CO₃, MeOH, rt, 91% (2 steps); (f) Dibal-H, CH₂Cl₂, -78 °C; (g) NaBH₄, MeOH, 0 °C, 90% (2 steps); (h) Cl₃CCN, DBU, CH₂Cl₂, 0 °C; (i) Et₂AlCl, CH₂Cl₂, 0 °C, 97% (2 steps); (j) CO(OCCl₃)₂, Py, CH₂Cl₂, -35 °C to rt; (k) K₂CO₃, MeOH, 0 °C, 81% (2 steps); (l) MOMCl, Pr₂NEt, CH₂Cl₂, reflux, 87%; (m) H₂, Pd(OH)₂, EtOAc-MeOH (4:1); (n) (COCl)₂, DMSO, CH₂Cl₂, Et₃N, -78 °C to rt; (o) BuLi, THF, -78 °C to rt, 60% (3 steps); (p) hv, PhSSPh, cyclohexane-dioxane (19:1) 95%; (q) TBAF, THF, rt; (r) PDC, DMF, rt; (s) TsOH, EtOH-H₂O (7:3), reflux, 77% (3 steps); (t) 1 N NaOH, MeOH, reflux, then neutralized with IRCl-76, 75%.

Scheme 3
As shown in Scheme 3, the absolute configurations of sphingofungin E was determined by NOESY experiment of lactone 14. Since the two chiral centers inherited from L-(-)-tartaric acid remained untouched during all synthetic steps, we reasoned that the stereochemistry of sphingofungin E is identical with that of sphingofungin F, i.e. (2S, 3R, 4R, 5S, 6E).
In summary, the first total synthesis of sphingofungin E has been achieved in 19 steps and 8.1% overall yield from commercially available alcohol 9 derived from L-(-)-tartaric acid. Moreover, its stereochemistry has been determined. It is noteworthy that by simple change of starting material, myriocin and other structurally related substances could be obtained via the same route. The minor diastereomer of the Baylis–Hillman reaction would also provide an access to 2,3-epi-sphingofungin E. Moreover, utilization of the minor Baylis–Hillman adduct would render our synthesis of sphingofungin E into a diastereconvergent one with further improvement of the overall yield. The details will be reported in due course.

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References and Notes
(10) Separated by silica gel column chromatography.
(14) [α]D20 = -13° (c = 0.19 and 0.30, MeOH); mp 147-149 °C, 1H NMR (300MHz, CD3OD) δ 0.89 (t, 3H, J = 6.6Hz), 1.25-1.60 (m, 16H), 2.05 (q-like, 2H), 2.44 (t, 4H, J = 7.3Hz), 3.65 (d, 1H, J = 7.1Hz), 3.85, 3.95 (AB, 2H, JAB = 10.9Hz), 3.96 (s, 1H), 4.10 (t, 1H, J = 7.4Hz), 5.77 (dt, 1H, J = 15.3, 6.6Hz); 13C NMR (CD3OD) δ 14.6, 23.8, 25.2, 30.3, 30.4, 30.5, 33.0, 33.3, 43.8, 65.2, 70.7, 71.4, 75.8, 76.4, 130.5, 135.9, 173.3, 214.6; IR (cm-1) = 3122, 2929, 1707, 1644, 1397, 1071, 724; ESI-MS 418.5(M+H).

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