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 1992.1 They showed significant biological activity in inhibiting serine palmitoyltransferase, and had antifungal activity against several human pathogenic fungi.1 They also bear structural resemblance to myriocin (3),2 a compound 10-100 times more potent than immunosuppressant cyclosporin A.3 Although there has been a number of works on the total synthesis and the absolute stereochemistry of 2,4 the most highly oxygenated member of the family, sphingofungin E, remained untackled, and its stereochemistry was only tentatively assigned.1 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 2.5 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 6.7 The α,β-epoxido ester structure unit of 6 was in turn
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The total synthesis of 1 is represented in Scheme 2. Aldehyde 10 was prepared from L-(+)-tartaric acid according to literature. Baylis–Hillman reaction of 10 provided a convenient access to ester 8 with moderate diastereoselectivity (70:30). Taking advantage of substrate control, the dihydroxylation of 8 gave 2,3-syn-triol as the sole product, in which the primary hydroxyl group was protected as TBS ether. Then the secondary hydroxyl group in 11 was selectively mesylated and treated with K₂CO₃ to afford the ring closure product, epoxide 6. The ester part was then reduced to hydroxymethyl group which served as a tether for subsequent Hatakeyama reaction to give oxazoline 12 with complete inversion at C-2. At this stage, all stereogenic centers had been efficiently established. 12 was then successively treated with triphosgene, K₂CO₃, and MOMCl to afford the cyclic carbamate 5. Debenzylation followed by Swern oxidation and Wittig reaction gave (Z)-13 predominantly. Isomerization of the double bond in 13 followed by desilylation and oxidation gave a carboxylic acid, which lactonized to afford bicyclic compound 14 with concomitant removal of ketal and MOM protection under acid catalysis. Finally, saponification of 14 and subsequent routine workup afforded sphingofungin E, the spectroscopic data of which are consistent with those reported in the literature.

Scheme 2

(a) methylacrylate, DABCO, rt, 70%; (b) OsO₄, NMO, acetone-H₂O (8:1), rt; (c) TBSCl, 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)₉, EtOAc-MeOH (4:1); (n) (COCl)₂, DMSO, CH₂Cl₂, Et₃N, -78 °C to rt; (o) 4, 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) NaOAc, MeOH, reflux, then neutralized with IRC-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-(-)-tartraric 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]D 20 = -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), 5.44 (dd, 1H, J = 15.4, 7.6Hz), 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) ν = 3122, 2929, 1707, 1644, 1397, 1071, 724; ESI-MS 418.5(M+H).

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