The Asymmetric Synthesis of Sphingofungin F and the Determination of Its Stereochemistry

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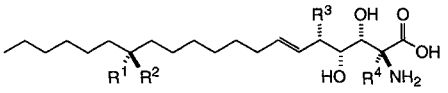
Abstract: The asymmetric synthesis of sphingofungin F has been achieved and its stereochemistry has been determined. Its structure, including the absolute configuration of the chiral centers, was found to be similar to that of sphingofungin B or myriocin. The synthesis is based on the catalytic asymmetric aldol reaction, and efficient enantioselective synthesis using a small amount of a chiral source as well as the effectiveness of our synthetic strategy for the sphingofungin family has been successfully demonstrated.

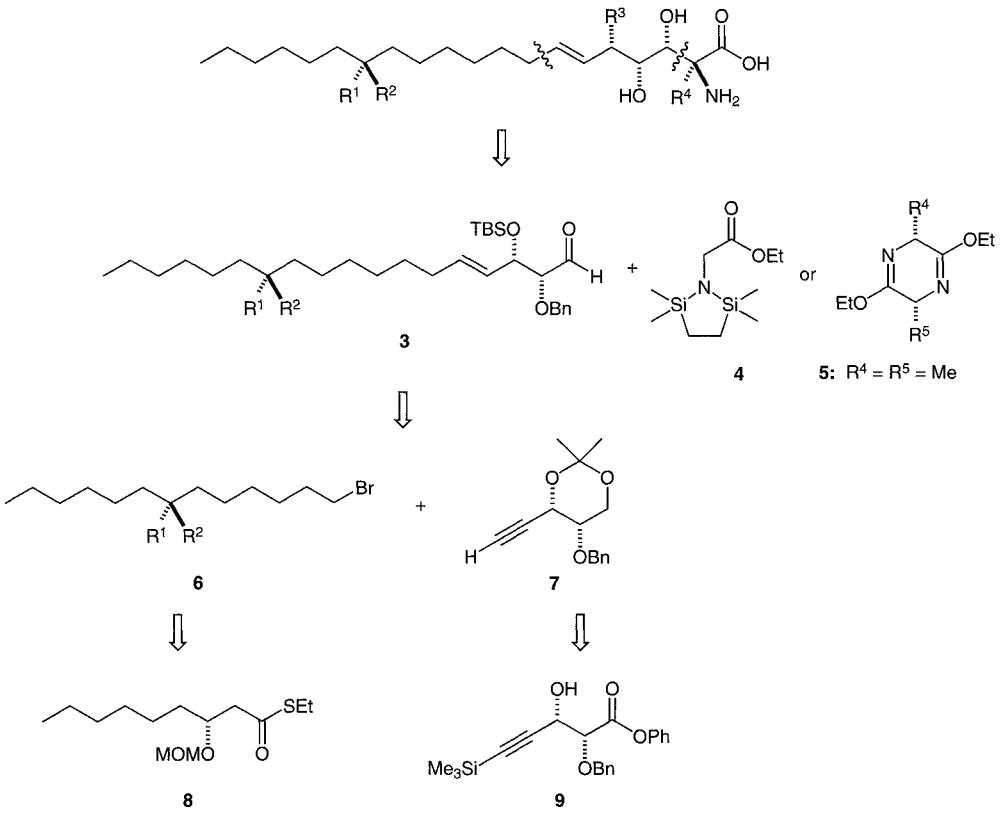
Sphingofungins E and F were first isolated from a fermentation of *Poecilomyces variotii* by Merck's group in 1992.[1] They are sphingosine-like compounds which inhibit serinepalmitoyl transferase, an enzyme essential in the biosynthesis of sphingolipids.[1,2] While these compounds bear a strong structural resemblance to myriocin,[3] their stereochemistry has not yet been determined. In this paper, we describe the first synthesis of sphingofungin F from simple achiral compounds using the catalytic asymmetric aldol reaction as a key step. The determination of its stereochemistry is also reported.



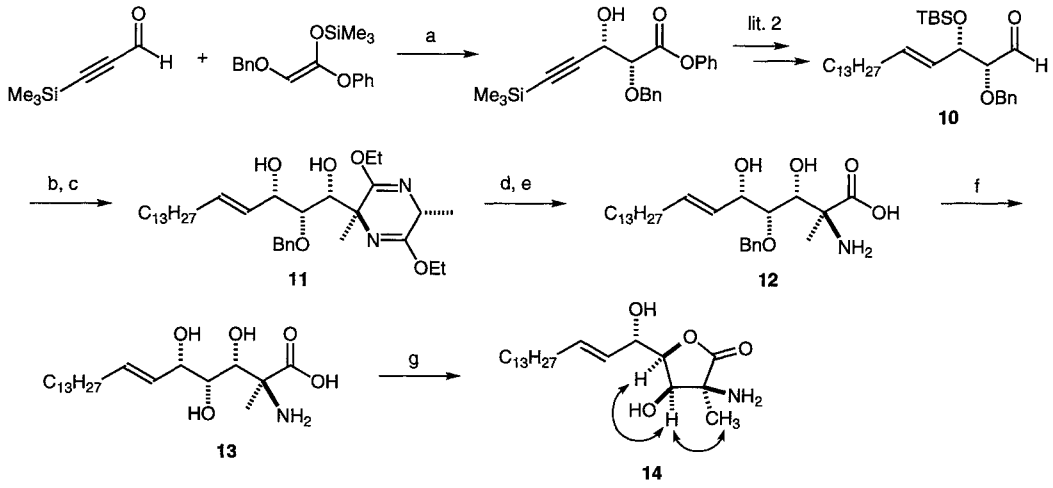
sphingofungin B	R^1 = OH, R^2 = H, R^3 = OH, R^4 = H
sphingofungin E (**1**)	$R^1 = R^2$ = O, R^3 = OH, R^4 = CH_2OH
sphingofungin F (**2**)	$R^1 = R^2$ = O, R^3 = OH, R^4 = CH_3
myriocin	$R^1 = R^2$ = O, R^3 = H, R^4 = CH_2OH

Our basic strategy for the synthesis of the sphingofungin family is shown in Scheme 1. Sphingofungins are divided into three parts: an amino acid head part, a triol part with successive asymmetric centers and *trans* olefin, and a hydrophobic side chain. We have prepared sphingofungin B very recently according to this strategy.[4] This synthetic route would be useful because sphingofungins and their derivatives can be prepared by minor modifications: simply changing the amino acid part and the hydrophobic side chain. In addition, the triol part and its stereoisomers with successive asymmetric centers, a key chiral part, can be prepared using catalytic asymmetric aldol reactions based on chiral Lewis acid-controlled synthesis (CLAC synthesis).[5]

First, synthesis of 14-deoxy sphingofungin F was undertaken (Scheme 2). Aldehyde **10** was prepared using the catalytic asymmetric aldol reaction according to our reported method,[4] and the aldol reaction of **10** with an alanine enolate was then investigated. After several trials, we found that a tin (II) azaenolate of Schöllkopf's bislactim **5**[6,7] reacted with **10** to afford the desired adduct in a 92% yield (diastereomer ratio = 45:42:13:0[8]). After a TBS group of the major stereoisomer was removed, the resulting diol was treated with *p*-toluenesulfonic acid in aqueous ethanol and then NaOH in methanol to afford amino acid **12**. Finally, deprotection of the benzyl ether part was performed under Birch conditions to give 14-deoxysphingofungin F (**13**). The ^1H and ^{13}C NMR spectra of synthetic **13** were very nearly consistent with those of sphingofungin F.[1] The stereochemistry was finally determined by NOE experiments after converting to lactone **14**. It is noted that the absolute configuration of the successive chiral centers of **13** is similar to that of sphingofungin B or myriocin.



Scheme 1

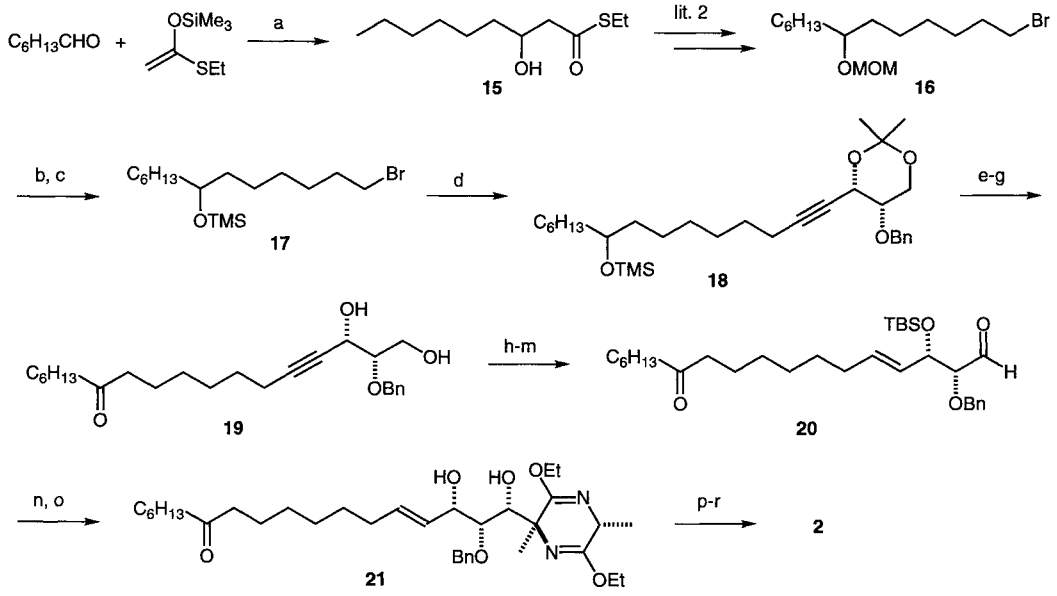


[a] (a) $Sn(OTf)_2$ (20 mol%), (*R*)-1-methyl-2-[(N-1-naphthylamino)methyl]pyrrolidine (24 mol%), SnO (20 mol%), C_2H_5CN, -78 °C, slow addition for 4 h, 87%, *syn*/*anti* = 97/3, 91% ee (*syn*); (b) **5**, BuLi, $SnCl_2$, THF, -78 °C, 92%; (c) TBAF, THF, 95%; (d) TsOH, EtOH (70% aq.), rt; (e) 0.5N NaOH, MeOH, 55% (2 steps); (f) Na, liq. NH_3-THF, -50 °C, 44%; (g) TsOH, EtOH (70% aq.), 100 °C, 64%.

Scheme 2[a]

We then carried out the synthesis of sphingofungin F. The hydrophobic side chain was prepared according to Scheme 3. The $Yb(OTf)_3$-catalyzed aldol reaction[9] was very useful for the preparation of **15**. The route from racemic **15** to alkyl bromide **16** was similar to that used in the synthesis of sphingofungin B (chiral synthesis).[4a] After deprotection of the MOM ether of **16**, the resulting alcohol was protected with a TMS group to give **17**. Bromide **17** was then coupled with **7** to afford **18**. The trimethylsilyl group of **18** was deprotected, and the resulting alcohol was oxidized and then treated with HCl to give diol **19**. After the ketone part of **19** was protected, the primary hydroxy group was protected with MMTrCl. The alkyne part was reduced to the *trans* olefin using $LiAlH_4$ and the secondary alcohol was protected with a TBS group.

The aldol-type reaction of **20** with the tin (II) azaenolate proceeded smoothly to afford the desired adduct in an 83% yield with a good dia-



[a] (a) $Yb(OTf)_3$ (5 mol%), CH_2Cl_2, 0 °C, 91%; (b) conc. HCl, MeOH, 50 °C, quant.; (c) $TMSCl$, Et_3N, CH_2Cl_2, rt, 97%; (d) **7**, BuLi, THF-HMPA, 78 °C to 0 °C, 89%; (e) TBAF, THF, rt, quant.; (f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C to -50 °C, 89%; (g) 3N HCl, THF, rt, 99%; (h) $TMSO(CH_2)_2OTMS$, cat. TMSOTf, CH_2Cl_2, 0 °C, 91%; (i) MMTrCl, Et_3N, DMAP (cat.), CH_2Cl_2, 0 °C; (j) LAH, THF, reflux; (k) TBSCl, imid., DMF, 91% (3 steps); (l) $HCOOH:Et_2O$ (1:2), 78%; (m) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -50 °C, >95%; (n) **5**, BuLi, $SnCl_2$, THF, -78 °C, 83%; (o) TBAF, THF, 94%; (p) TsOH, THF-H_2O (7:3), 0 °C; (q) 5N NaOH, MeOH, rt, 58% (2 steps); (r) BCl_3, CH_2Cl_2, -78 °C, 72%.

Scheme 3[a]

stereoselectivity (70:25:5:0[8]). Successive hydrolysis (2 steps) of the major diastereomer and final deprotection of the benzyl ether using BCl_3 worked well to afford sphingofungin F (**2**). Its spectral properties were completely identical to those reported in the literature.[1]

In summary, the first synthesis of sphingofungin F has been achieved and its stereochemistry has been determined. It is now clear that its structure, including the absolute configuration of the chiral centers, is similar to that of sphingofungin B or myriocin. The synthesis is based on the catalytic asymmetric aldol reaction, and efficient enantioselective synthesis using a small amount of a chiral source as well as the effectiveness of our synthetic strategy for the sphingofungin family (Scheme 1) have been successfully demonstrated. This method could be easily applied to the synthesis of sphingofungin E (**1**),[7] and these details will be reported in due course.

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