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Synthesis of Sphingofungin D and Its Stereoisomer at C-14

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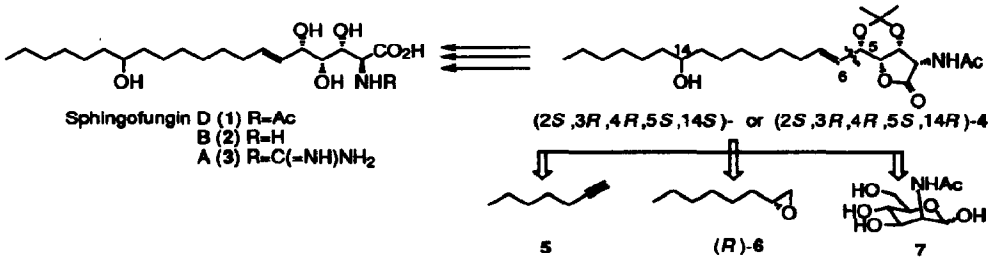
Abstract : Sphingofungin D (**1**), a new antifungal agent, and its stereoisomer at C-14 were synthesized by starting from 1-heptyne (**5**), (*R*)-1,2-epoxyoctane (**6**) and *N*-acetyl-D-mannosamine (**7**).

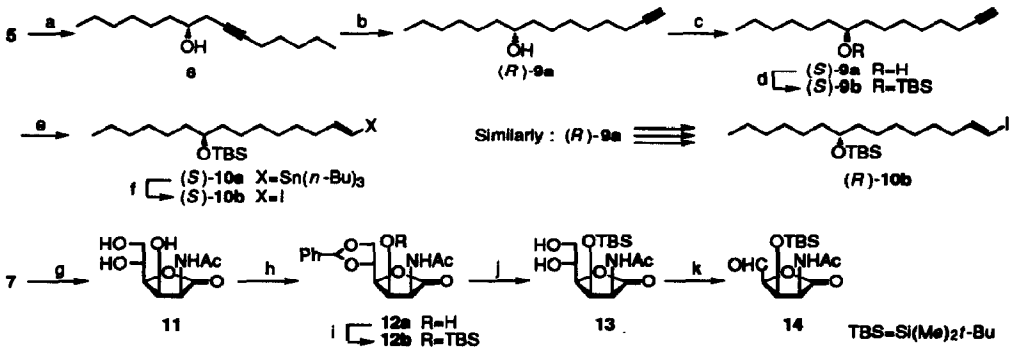
In 1992 VanMiddlesworth et al. reported the isolation[2] and structure elucidation[3] of sphingofungins, a new family of antifungal metabolites produced by *Aspergillus fumigatus* ATCC 20857. The structures **1**, **2** and **3** assigned to sphingofungins D, B and A, respectively, show their similarity to sphingolipids. Their stereochemistry at C-14, however, still remains unknown. In continuation of our synthetic studies on sphingosine relatives[4], we undertook a synthesis of both the 14*R*- and 14*S*-isomers of **4**. Because **4** derived from the natural sphingofungin C (**2**, OAc instead of OH at C-5) has been converted to sphingofungin D (**1**), B (**2**) and A (**3**)[3], the synthesis of **4** implies that of these three sphingofungins. Our retrosynthetic analysis as shown in Scheme 1 suggests that 1-heptyne (**5**), (*R*)-1,2-epoxyoctane (**6**) and *N*-acetyl-D-mannosamine (**7**) can serve as the starting materials.



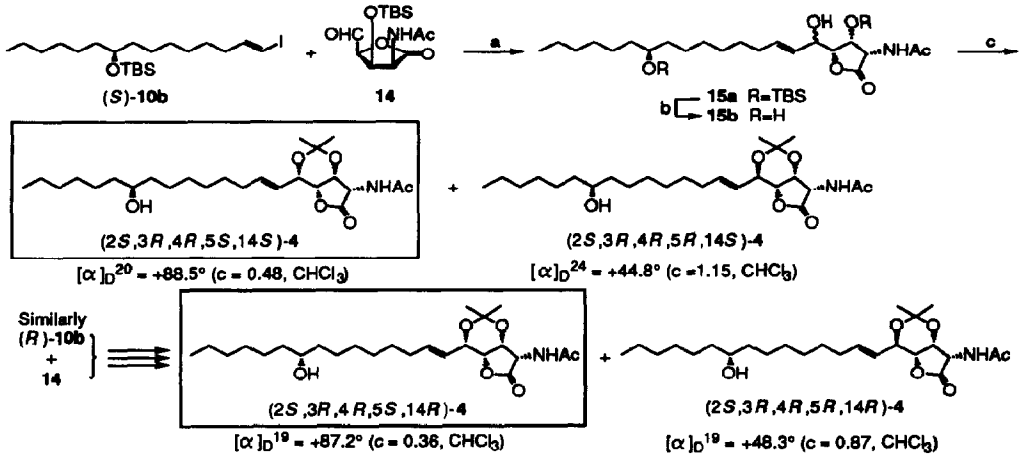
Scheme 1. Structures of sphingofungins and their retrosynthetic analysis.

Scheme 2 summarizes the preparation of the two building blocks, the non-polar **10b** and polar **14**. Cleavage of (*R*)-**6** (91% ee; purchased from Japan Energy Co.) with the acetylide derived from **5** yielded **8**, which was submitted to the acetylene-zipper reaction[5] to give(*R*)-**9a**, m.p. 42–43°C, $[\alpha]_D^{23} = -0.86°$ (c = 1.7, Et_2O). Mitsunobu inversion[6] smoothly converted (*R*)-**9a** to (*S*)-**9a**, m.p. 41–42°C, $[\alpha]_D^{22} = +0.88°$ (c = 1.7, Et_2O). The corresponding TBS ether (*S*)-**9b** was metallated with tri(n-butyl)tin hydride[7] to give the alkenylstannane (*S*)-**10a**, which furnished the alkenyl iodide (*S*)-**10b** by

treatment with iodine in diethyl ether[8]. The overall yield of (*S*)-**10b** based on **5** was 49% after 7 steps. Similarly, (*R*)-**9a** was converted to (*R*)-**10b** in 61% overall yield based on **5** (5 steps).



Scheme 2. Synthesis of the two building blocks **10b** and **14**
Reagents: (a) 1) *n*-BuLi, BF_3·OEt_2, THF ; 2) (*R*)-**6** (80%).– (b) Li, *t*-BuOK, $H_2N(CH_2)_3NH_2$ (88%).– (c) 1) $EtO_2CN{=}NCO_2Et$, Pr^i_3P, $PhCO_2H$; 2) K_2CO_3, MeOH (80%).– (d) TBSCl, imidazole, DMF (quant.).– (e) (*n*-Bu)$_3$SnH, AIBN (92%).– (f) I_2, Et_2O (95%).– (g) Br_2, H_2O (41%).– (h) $PhCH(OMe)_2$, HBF_4·OEt_2, DMF (98%).– (i) TBSOTf, 2,6-lutidine, CH_2Cl_2 (65%).– (j) $Pd(OH)_2$, cyclohexene, EtOH (85%).– (k) $NaIO_4$, H_2O, CH_2Cl_2 (crude 95%)

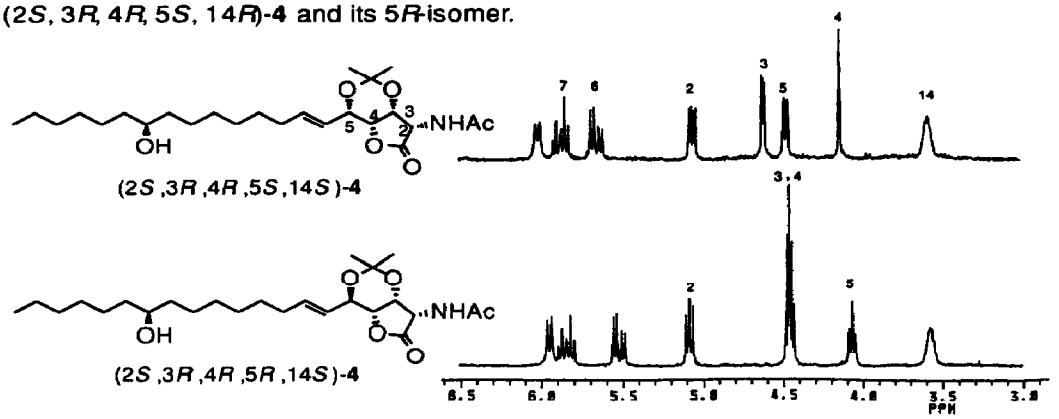


Scheme 3. Synthesis of the four stereoisomers of **4**.
Reagents : (a) $CrCl_2$ (6.0 eq), $NiCl_2$ (0.04 eq), DMSO (41%).– (b) HF aq., MeCN.– (c) $Me_2C(OMe)_2$, TsOH, DMF, chromatog. sepn. [19% of (2*S*,3*R*,4*R*,5*S*,14*S*)-**4** based on **15a**, 31% of (2*S*,3*R*,4*R*,5*R*,14*S*)-**4** based on **15a**].

In order to prepare the polar building block **14**, *N*-acetyl-D-mannosamine (**7**) was oxidized with bromine in water to give **11**[9]. Protection of the *vic*-diol system of **11** as

benzylideneacetal **12a** was followed by further protection of the remaining hydroxy group of **12a** as TBS ether to yield **12b**. Hydrogenolytic removal of the benzylidene protective group of **12b** by transfer hydrogenation with cyclohexene and the Pearlman palladium gave **13**, which was oxidized with sodium periodate to give the aldehyde **14** as a crude gum. The overall yield of **14** was 21% based on **7** (5 steps).

Coupling of **14** with (*S*)-**10b** or its equivalent was examined under several different conditions. The best result was obtained when the coupling was carried out with chromium(II) chlorlide and nickel chloride in DMSO[10] to give in 41% yield the desired product **15a** as a diastereomeric mixture. Removal of the TBS protective group of **15a** afforded **15b**. The corresponding diastereomeric mixture of the acetonide **4** could be separated by silica gel chromatography to give a more polar compound (19% yield based on **15a**) and a less polar one (31% yield based on **15a**). Careful examination of their 300 MHz ^{1}H NMR spectra (see Figure) revealed the spectrum of the more polar gum to be identical with that of (2*S*, 3*R*, 4*R*, 5*S*)-**4** derived from sphingofungin C[3]. Especially the magnitudes of the coupling constants $J_{2,3}$, $J_{3,4}$ and $J_{4,5}$ of the more polar product were in good agreement with the values reported for (2*S*, 3*R*, 4*R*, 5*S*)-**4**[3]. The more polar material was therefore (2*S*, 3*R*, 4*R*, 5*S*, 14*S*)-**4**, while the less polar one must be (2*S*, 3*R*, 4*R*, 5*R*, 14*S*)-**4**. The coupling of **14** with (*R*)-**10b** followed by the subsequent deprotection-protection and the diastereomer separation by chromatography yielded (2*S*, 3*R*, 4*R*, 5*S*, 14*R*)-**4** and its 5*R*-isomer.



compound	protons	J (lit[3]); calcd.)	J (lit[3]); found)	J (this work; found)
(2*S*, 3*R*, 4*R*, 5*S*, 14*S*)-**4**	2→3	3.7 Hz	3.9 Hz	3.9 Hz
	3→4	2.7 Hz	2.1 Hz	2.1 Hz
	4→5	1.6 Hz	1.6 Hz	1.9 Hz
(2*S*, 3*R*, 4*R*, 5*R*, 14*S*)-**4**	2→3	4.6Hz	–	5.5 Hz
	3→4	4.5 Hz	–	not determined
	4→5	7.5 Hz	–	6.8Hz

Figure. ^{1}H NMR spectra of (2*S*, 3*R*, 4*R*, 5*S*, 14*S*)- and (2*S*, 3*R*, 4*R*, 5*R*, 14*S*)-**4** (300 MHz,$CDCl_3$)

Because it was impossible to find out any notable differences between the ^1H NMR spectrum of (2*S*, 3*R*, 4*R*, 5*S*, 14*S*)-4[11] and that of 14*R*-isomer, 4 derived from the natural product was considered to be one of them. Their $[\alpha]_D$ values (see Scheme 3) were also quite similar and did not allow the distinction between the diastereomers. Thanks to the previous conversion of 4 to sphingofunin D (1)[3], and also that of 1 to 2 and 3[3], the present synthesis of (2*S*, 3*R*, 4*R*, 5*S*, 14*S*)-4 and its 14*R*-isomer can be regarded as a formal total synthesis of sphingofungins D (1), B (2) and A (3). Attempts to determine the absolute configration of sphingofungins A, B and D at C-14 will be reported in due course.

References and Notes

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11. IR (KBr): ν = 2920 (s), 1780 (s, C=O), 1645 (s, C=O), 1215(m), 1170(s, C-O) cm^{-1} – ^1H NMR (300 MHz,$CDCl_3$): δ = 0.88 (t, *J* = 6.5 Hz, 3H, H-20), 1.43 (s, 3H, acetonide Me), 1.50 (s, 3H, acetonide Me), 1.75–1.10 (m, 21H, $-CH_2-$, OH), 2.15–2.00 (m, 2H, H-8), 2.10 (s, 3H, Ac), 3.65–3.50 (m, 1H, H-14), 4.13 (dd,*J* = 1.9 Hz, 2.1 Hz, 1H, H-4), 4.47 (dd,*J* = 1.9 Hz, 7.2 Hz, 1H, H-5), 4.61 (dd,*J* = 2.1 Hz, 3.9 Hz, 1H, H-3), 5.05 (dd,*J* = 3.9 Hz, 8.2 Hz, 1H, H-2), 5.64 (dd,*J* = 7.2 Hz, 15.5 Hz, 1H, H-6), 5.86 (dt,*J* = 15.5 Hz, 6.6 Hz, 1H, H-14), 6.00 (d,*J* = 8.0 Hz, 1H, NH). – ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.1, 19.4, 22.6, 23.0, 25.5, 25.6, 28.6, 29.1, 29.2, 29.4, 29.5, 31.8, 32.2, 37.4, 37.5, 53.8, 67.8, 69.8, 72.0, 73.2, 98.8, 124.5, 136.7, 170.4, 173.5. – $C_{25}H_{43}NO_6$ (453.6): calcd. C 66.20, H 9.53, N 3.09; found. C 66.01, H.9.47, N 2.97.

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