

Highly Diastereoselective Synthesis of *D-threo*- and *D-erythro*-Sphingosine from Glycidol

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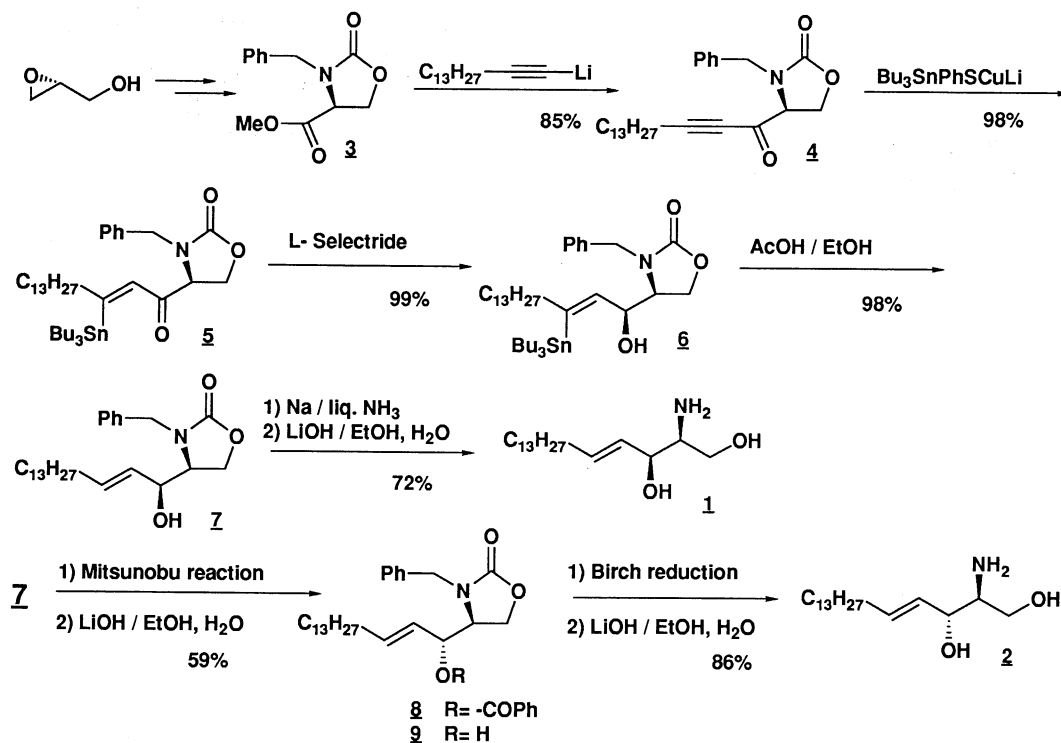
D-Threo- and *D-erythro*-sphingosine, (1) and (2), inhibitors of protein kinase C, have been efficiently synthesized from glycidol through (R)-4-methoxycarbonyloxazolidinone (3) by selective mono-alkylation followed by highly diastereoselective reduction of the tin-substituted pentadecenyl ketone 5.

Sphingosine is the backbone component of various sphingolipids which are constituents of cell membranes,¹ and is usually present as its *D-erythro* isomer (2S, 3R). Recently, it was reported that four stereoisomers of sphingosine, due to two asymmetric carbon atoms, showed approximately the same potency as inhibitors of protein kinase C,² which participates in modulating cell growth, cell differentiation, and signal transduction. Because of the biological importance of sphingolipids, a great deal of efforts have been devoted to the synthesis of optically active sphingosines employing various strategies and starting materials.³

Previously, we had developed a 4-hydroxymethyl-oxazolidinone derivative as a chiral building block from enantiomerically pure glycidol,⁴ and reported the diastereoselective synthesis of saturated γ -hydroxy- β -amino alcohols from it.⁵ As a further demonstration of our own method toward the stereo-controlled synthesis for various types of γ -hydroxy- β -amino alcohols, herein, we describe the synthesis of *D-threo*- and *D-erythro*-sphingosine, (1) and (2), starting from (R)-glycidol through (R)-4-methoxycarbonyloxazolidinone derivative 3. In this synthesis, completely diastereoselective generation of the

secondary hydroxyl group of sphingosine was achieved.

The carbon chain of sphingosine was successfully arranged by a mono-alkynylation of the ester 3 with lithium acetylide.⁵ Thus, to a frozen mixture of the methyl ester 3 in THF was added an ice-cold solution of pentadecynyllithium in THF and HMPA at -130 °C. The reaction mixture was gradually warmed up to -78 °C and stirred for 2 hours to give ketone 4, mp 44.5-45.5 °C, in 85% yield. An introduction of tributyltin group to a β -position in 4 made the complete stereocontrolled reduction of the carbonyl in 5 with L-Selectride possible, whereas reduction of 4 with the same reagent gave a 2 to 1 mixture of stereoisomers of the corresponding alcohol. In addition, the introduction of tributyltin group accompanied the highly selective generation of the E-olefin in sphingosine. Thus, the alkynyl ketone 4 reacted with lithium (phenylthio)-(tributylstannyl)cuprate⁶ in THF at -40 °C to afford a 1,4-addition product 5 in 98% yield, which showed 95% geometrical purity by ¹HNMR.⁷ Reduction of 5 with L-Selectride followed by treatment with acetic acid in ethanol under reflux afforded quantitatively *syn* alcohol possessing the same geometrical purity as the starting ketone. The reduction of the ketone 5 proceeded under the complete control of stereochemistry.⁸ After purification by chromatography, the E-isomer 7⁹ was treated with sodium in liquid ammonia followed by treatment with aqueous lithium hydroxide in ethanol to afford (2S, 3S)-*threo*-sphingosine (1), mp 84-85 °C, [α]_D²³ -2.7° (c 0.95, CHCl₃) in 72% yield for two steps. The physical data (IR,



^1H and ^{13}C NMR) of the triacetylated derivative of this compound, mp 44-45 °C, $[\alpha]_{\text{D}}^{23} +10.0^\circ$ (c 1.0, CHCl_3), [lit. mp 44.5-45.5 °C, $[\alpha]_{\text{D}}^{25} +10.4^\circ$ (c 0.1, CHCl_3)], were identical with those reported.^{3d}

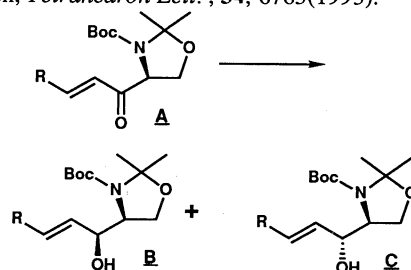
Synthesis of *erythro*-sphingosine was achieved by Mitsunobu inversion of the hydroxyl group in the compound **7**.¹⁰ Thus, slow addition of diethyl azodicarboxylate to a mixture of the allyl alcohol **7**, benzoic acid, and triphenylphosphine in THF at room temperature followed by stirring gave the benzoate **8** in 65% yield beside the rearranged compound.¹¹ Hydrolysis of **8** gave **9** in 90% yield,¹² which was submitted to the same reactions as above to give (2*S*, 3*R*)-*erythro*-sphingosine (**2**) in 86% yield for two steps. The physical data of the triacetylated derivative of **2**, mp 105-105.5 °C, $[\alpha]_{\text{D}}^{22} -12.9^\circ$ (c 0.95, CHCl_3), [lit. mp 105-106 °C, $[\alpha]_{\text{D}}^{25} -12.9^\circ$ (c 1.0, CHCl_3)], were identical with those reported.^{3d}

In conclusion, all four stereoisomers of sphingosine can be synthesized by the method mentioned here, since enantiomerically pure *S*-(-)-glycidol as well as *R*-(+)-isomer are available based on a biological resolution.¹³

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- 9 **7**: mp 65-66 °C, $[\alpha]_{\text{D}}^{24} -14.6^\circ$ (c 0.9, CHCl_3); IR(KBr) 3432, 1754 cm^{-1} ; ^1H NMR (CHCl_3) δ = 0.88(3H, t, *J*=6.8 Hz), 1.20-1.40(22H, brm), 1.8(1H, d, *J*=3.4 Hz), 2.03(2H, m), 3.68(1H, m), 4.13(1H, dd, *J*=5.6, 9.0 Hz), 4.17(1H, dd, *J* = 8.8, 9.0 Hz), 4.23(1H, m), 4.34(1H, d, *J*=15.2 Hz), 4.79(1H, d, *J*=15.2 Hz), 5.37(1H, m), 5.77(1H, m), 7.26-7.40(5H, m); ^{13}C NMR(CHCl_3) δ = 14.1, 22.7, 28.9, 29.1, 29.3, 29.4, 29.6, 29.7, 31.9, 32.3, 47.4, 57.6, 63.8, 73.9, 126.5, 127.8, 128.3, 128.7, 136.3, 137.0, 158.87; Anal. Found: C, 75.04; H, 9.92; N, 3.36%. Calcd for $\text{C}_{26}\text{H}_{41}\text{O}_3\text{N}$: C, 75.14; H, 9.93; N, 3.37%.
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- 12 **9**: mp 56-57 °C; $[\alpha]_{\text{D}}^{22.2} -11.8^\circ$ (c 1.07, CHCl_3); IR(KBr) 3584, 1734 cm^{-1} ; ^1H NMR(CDCl_3) δ = 0.88(3H, t, *J*=6.8 Hz), 1.20-1.40(22H, brm), 2.01(2H, td, *J*= 6.7, 7.6 Hz), 2.08(1H, d, *J*= 3.4 Hz), 3.66(1H, ddd, *J*=2.9, 6.4, 9.0 Hz), 4.17(1H, dd, *J*=8.8, 9.0 Hz), 4.25(1H, dd, *J*=6.4, 8.8 Hz), 4.25-4.30(1H, br), 4.33(1H, d, *J*=15.4 Hz), 4.74(1H, d, *J*=15.4 Hz), 5.27(1H,m), 5.79(1H, m), 7.30-7.40(5H, m); ^{13}C NMR (CDCl_3) δ = 14.1, 22.7, 28.9, 29.1, 29.3, 29.4, 29.6, 31.9, 32.3, 46.7, 58.5, 62.7, 69.6, 126.1, 128.0, 128.1, 128.9, 135.5, 136.2, 159.2.
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