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

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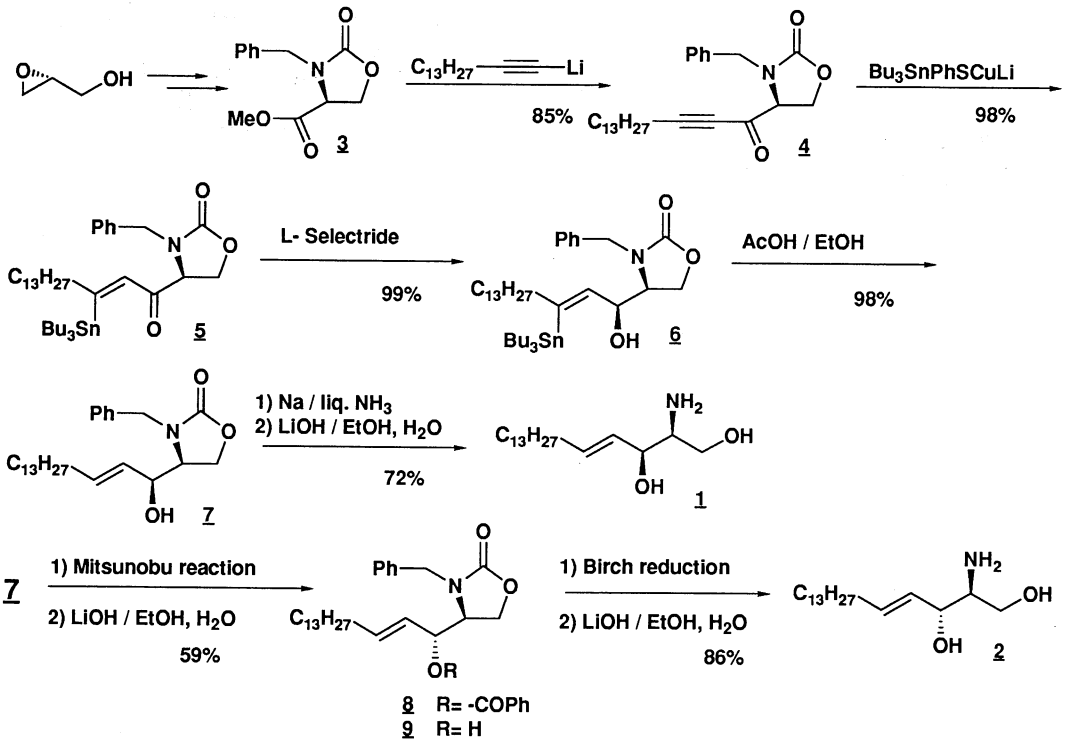
D-*Threo*- and D-*erythro*-sphingosine, (**1**) and (**2**), inhibitors of protein kinase C, have been efficiently synthesized from glycidol through (R)-4-methoxycarbonyloxazolidinone (**3**) by selective mono-alkylation followed by highly diastereoselective reduction of the tin-substituted pentadecenyl 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)cuprate[6] in THF at -40 °C to afford a 1,4-addition product **5** in 98% yield, which showed 95% geometrical purity by ^{1}HNMR.[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 **7**[9] 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, $[\alpha]_D^{23}$ -2.7° (c 0.95, $CHCl_3$) 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, $[\alpha]_D^{23}$ +10.0° (c 1.0, $CHCl_3$), [lit. mp 44.5-45.5 °C, $[\alpha]_D^{25}$ +10.4° (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 (2S, 3R)-*erythro*-sphingosine (**2**) in 86% yield for two steps. The physical data of the triacetylated derivative of **2**, mp 105-105.5 °C, $[\alpha]_D^{22}$ -12.9° (c 0.95, $CHCl_3$), [lit. mp 105-106 °C, $[\alpha]_D^{25}$ -12.9° (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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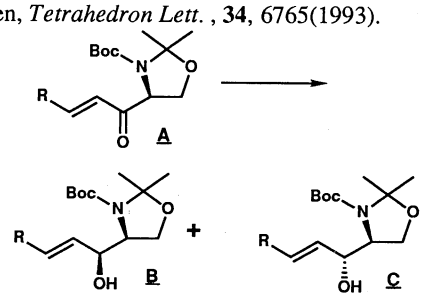

9 **7**: mp 65-66 °C, $[\alpha]_D^{24}$ -14.6° (c 0.9, $CHCl_3$); IR(KBr) 3432, 1754 cm^{-1}; ^{1}H NMR ($CHCl_3$) δ= 0.88(3H, t, J=6.8 Hz), 1.20-1.40(22H, brm), 1.8(1H, d, J=3.4 Hz), 2.03(2H, m), 3.68(1H, m), 4.13(1H, dd, J=5.6, 9.0 Hz), 4.17(1H, dd, J = 8.8, 9.0 Hz), 4.23(1H, m), 4.34(1H, d, J=15.2 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 $C_{26}H_{41}O_3N$: C, 75.14; H, 9.93; N, 3.37%.

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12 **9**: mp 56-57 °C; $[\alpha]_D^{22.2}$ -11.8° (c 1.07, $CHCl_3$); IR(KBr) 3584, 1734 cm^{-1}; ^{1}H 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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