

## DIASTEREOSELECTIVE SYNTHESIS OF TRIACETYL-L-*erythro*-C18-SPHINGOSINE

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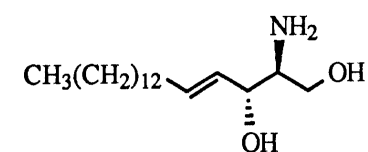
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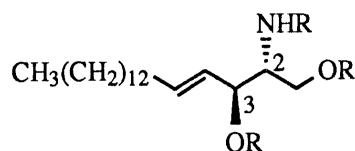
A new stereoselective synthetic route to triacetyl-L-*erythro*-C18-sphingosine has been developed by the combination of diastereoselective addition of thiophenol to chiral olefins and subsequent intramolecular substitution of the corresponding sulfonium group.

**KEY WORDS** sphingosine; thiophenol; nucleophilic addition; asymmetric synthesis; oxazoline

Sphingosine is the backbone component of various sphingolipids which are constituents of cell membranes.<sup>1)</sup> Merrill *et al.*<sup>2)</sup> reported that C18-sphingosine showed a potent inhibitory activity for protein kinase C. Because of the biological importance of sphingolipids, a great deal of effort has been devoted to the synthesis of optically active sphingosines.<sup>3)</sup> We now provide a new method for the construction of two contiguous stereogenic centers at the C2- and C3-positions of sphingosine by demonstrating asymmetric synthesis of triacetyl-L-*erythro*-C18-sphingosine (1). Our synthetic strategy consists of two crucial reactions, diastereoselective nucleophilic addition of thiophenol<sup>4)</sup> (4→5) to the dehydroamino acid esters having a (-)-8-phenylmenthyl group and stereoselective intramolecular displacement reaction of the corresponding sulfonium group (7→8).



D-*erythro*-C18-sphingosine

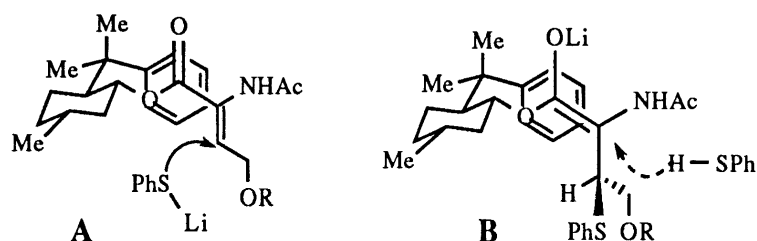
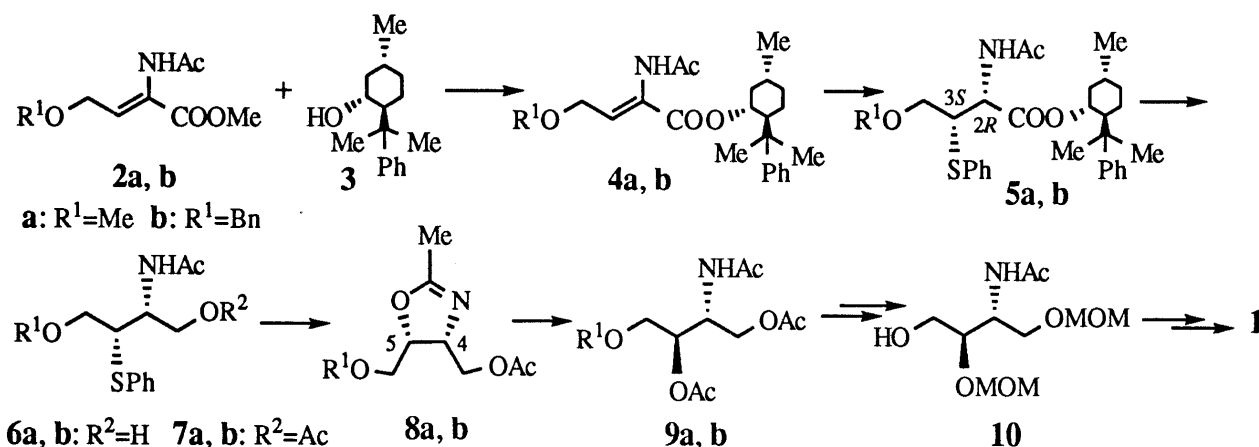


R=H: L-*erythro*-C18-sphingosine  
R=Ac: **1**

Achiral dehydroamino acid esters **2a**, **b**<sup>5,6)</sup> were treated with (-)-8-phenylmenthol (**3**) in the presence of trimethyl aluminum in THF at -60°C to give the chiral dehydroamino acid esters **4a**, **b**<sup>7)</sup> in 55–61% yield. We investigated the addition reaction of thiophenol to the dehydroamino acid esters **4a**, **b**. The chiral dehydroamino acid ester **4a** was treated with 7 eq. of thiophenol in the presence of 3 eq. of lithium thiophenoxide in toluene at -78°C to give the (2*R*, 3*S*)-adduct **5a**<sup>8)</sup> with high diastereoselectivity (**5a** : its diastereomer = 92 : 8) in 94% yield, while the addition reaction of thiophenol to **4a** in THF gave a 2 : 1 mixture of the adduct **5a** and its diastereomer in 68% yield. Similarly, **4b** underwent diastereoselective addition of thiophenol in toluene to give **5b**<sup>8)</sup> as major product (**5b** : its diastereomer = 86 : 14) in 99% yield. The mechanism for the above diastereoselective addition of thiophenol is proposed as follows. The starting chiral olefins **4a**, **b** would take *s-trans* conformation A.<sup>9)</sup> Lithium thiophenoxide would attack from a

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convex  $\beta$ -face of the  $\alpha,\beta$ -unsaturated ester group to form the enolate **B**, which is then protonated from  $\alpha$ -face due to the stereoelectronic effect<sup>4)</sup> of the newly introduced sulfur group to give the (2*R*, 3*S*)-adducts **5a, b**.



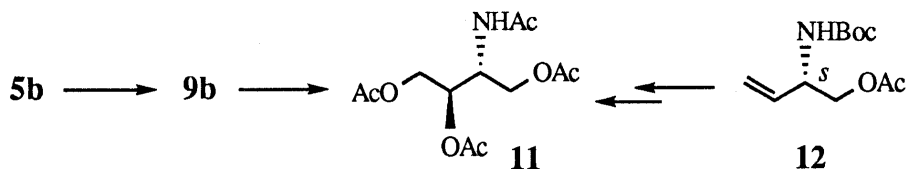
Then, **5a, b** were treated with 10 eq. of lithium aluminum hydride in THF at 0°C to give the optically active alcohols **6a, b** in 91-93% yield along with the efficient recovery of the valuable auxiliary. *S*-Alkylation of the corresponding acetates **7a, b** with methyl iodide in the presence of silver perchlorate followed by treatment of the resulting sulfonium salts with potassium carbonate gave the *cis*-oxazoline **8a, b**<sup>10)</sup> as a sole product in 62-70% yield. Hydrolysis of **8a, b** with HCl and the subsequent acetylation of the resulting amino alcohols gave the triacetyl compounds **9a, b** in 65-79% yield. **9b** was converted into **10** via hydrolysis (10% KOH), methoxymethylation (MOMCl-(*i*-Pr)<sub>2</sub>EtN), and debenzylation (10% Pd-C/H<sub>2</sub>) in 51% overall yield from **9b**. Finally, according to Kitagawa's procedure,<sup>3c)</sup> **10** was smoothly converted into triacetyl-L-*erythro*-C18-sphingosine **1** via Swern oxidation, Wittig reaction, hydrolysis, photoisomerization, and acetylation. The physical and spectral data of **1** ([ $\alpha$ ]<sub>D</sub><sup>27</sup> +12.9° (*c*=0.31, CHCl<sub>3</sub>) were identical with those ([ $\alpha$ ]<sub>D</sub><sup>23</sup> +12.1° (*c*=1.1, CHCl<sub>3</sub>) reported in the literature.<sup>3c)</sup> Since **1** had previously been transformed into L-*erythro*-C18-sphingosine,<sup>3c)</sup> the present method provides a new asymmetric synthesis of L-*erythro*-C18-sphingosine.

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- 8) The absolute configurations of the adducts **5a**, **b** were determined as follows. The relative configuration of the newly formed two chiral centers of **5a** was firmly established by X-ray crystallography of **9a**, prepared from **5a**.  $^1\text{H-NMR}$  spectral data of **5b** are very close to that of **5a** except for signals due to *O*-alkyl group. The absolute configurations of **5a**, **b** were established by the chemical conversion of **5b** into the tetraacetyl derivative **11** ( $[\alpha]_{\text{D}}^{22} -23.7^\circ$  ( $c=0.76$ ,  $\text{CHCl}_3$ )), which was identical with the authentic sample ( $[\alpha]_{\text{D}}^{22} -23.4^\circ$  ( $c=1.37$ ,  $\text{CHCl}_3$ )), obtained readily from the chiral vinylglycinol **12**. The stereochemistries of minor diastereomers have not been established.



Crystal data of **9a**:  $\text{C}_{11}\text{H}_{19}\text{NO}_6$ , space group P1 with  $a=7.966$  (1),  $b=8.957$  (1),  $c=4.964$  (1) Å,  $V=347.47$  (1) Å<sup>3</sup>. Final R value was 0.028 for 1029 reflections.

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- 10) The stereostructures of **8a**, **b** were confirmed by their  $^1\text{H-NMR}$  spectral characteristics;<sup>11)</sup> **8a**:  $J_{4,5}=10$  Hz; **8b**:  $J_{4,5}=9.5$  Hz.
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