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

Okiko MIYATA,[a] Sayaka YAMAGUCHI,[a] Ichiya NINOMIYA,[a] Takeaki NAITO, *, [a] and Kimio OKAMURA[b]

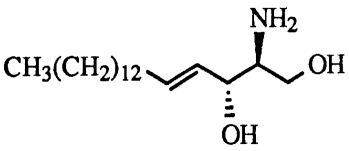
Kobe Pharmaceutical University,[a] Motoyamakita, Higashinada, Kobe 658, Japan

Analytical Research Laboratory, Tanabe Seiyaku, Co. Ltd.,[b] Kashima, Yodogawa, Osaka 532, Japan

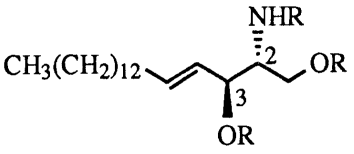
A new stereoselective synthetic route to triacetyl-L-*erythro*-C18-sphingosine has been developed by the combination of diastereoselective addition of thiophenol to chiral olefins and subsequent intramolecular substitution of the corresponding sulfonium group.

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

Sphingosine is the backbone component of various sphingolipids which are constituents of cell membranes.[1] Merrill *et al.*[2] 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.[3] We now provide a new method for the construction of two contiguous stereogenic centers at the C_2- and C_3-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[4] (**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

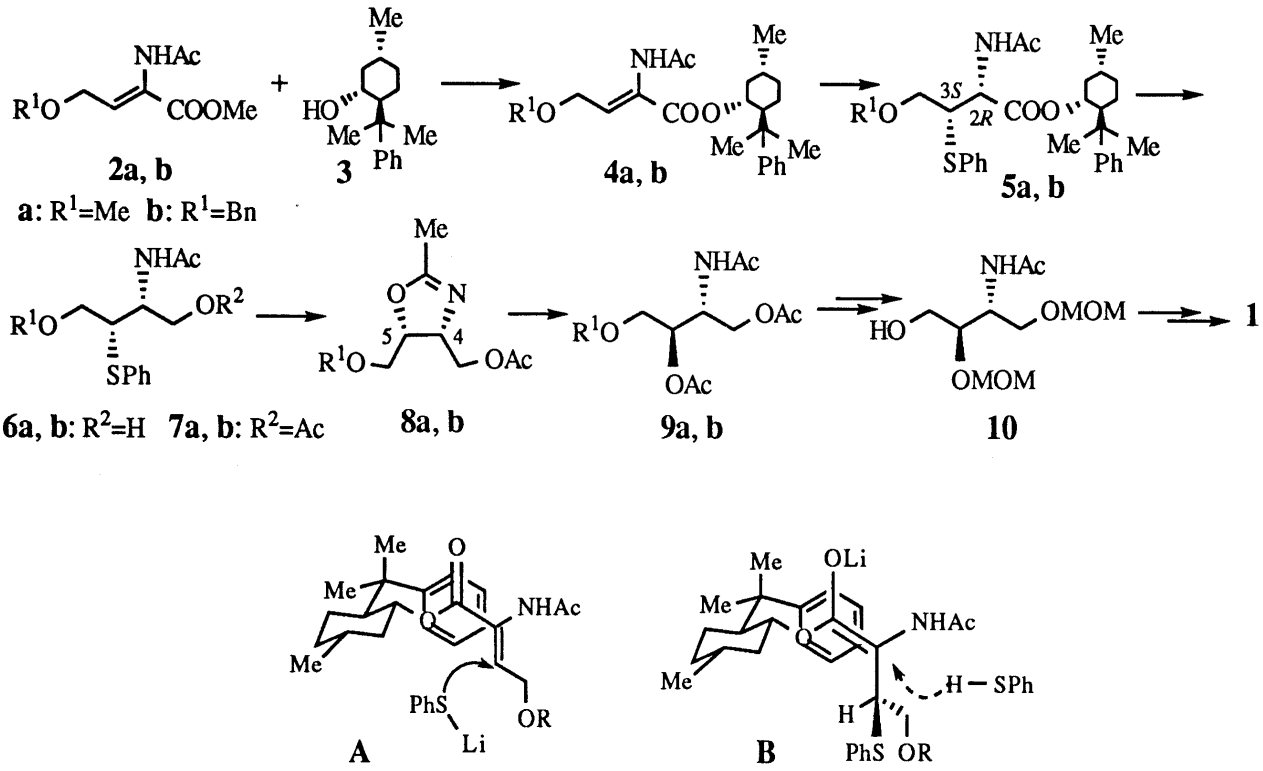


R=H: L-*erythro*-C18-sphingosine
R=Ac: **1**

Achiral dehydroamino acid esters **2a**, **b**[5,6] 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**[7] 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**[8] 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**[8] 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**.[9] Lithium thiophenoxide would attack from a

* To whom correspondence should be addressed.

convex β-face of the α,β-unsaturated ester group to form the enolate **B**, which is then protonated from α-face due to the stereoelectronic effect[4] 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**[10] 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)$_2$EtN), and debenzylation (10% Pd-C/H$_2$) in 51% overall yield from **9b**. Finally, according to Kitagawa's procedure,[3c] **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** ($[\alpha]_D^{27}$ +12.9° (*c*=0.31, $CHCl_3$) were identical with those ($[\alpha]_D^{23}$ +12.1° (*c*=1.1, $CHCl_3$) reported in the literature.[3c] Since **1** had previously been transformed into L-*erythro*-C18-sphingosine,[3c] the present method provides a new asymmetric synthesis of L-*erythro*-C18-sphingosine.

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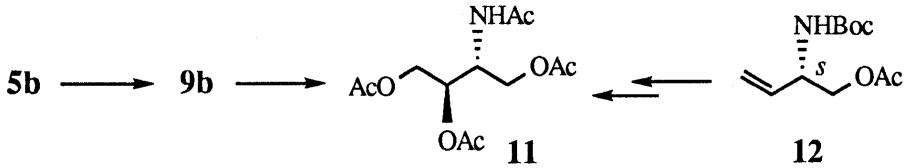
8) The absolute configurations of the adducts **5a, b** were determined as follows. The relative configuration of the newly formed two chiral centers of **5a** was firmly established by X-ray crystallography of **9a**, prepared from **5a**. ^{1}H-NMR spectral data of **5b** are very close to that of **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** ($[\alpha]_D^{22}$ -23.7° (*c*=0.76, $CHCl_3$)), which was identical with the authentic sample ($[\alpha]_D^{22}$ -23.4° (*c*=1.37, $CHCl_3$)), obtained readily from the chiral vinylglycinol **12**. The stereochemistries of minor diastereomers have not been established.



Crystal data of **9a**: $C_{11}H_{19}NO_6$, space group P1 with *a*=7.966 (1), *b*=8.957 (1), *c*= 4.964 (1) Å, V= 347.47 (1) Å^3. Final R value was 0.028 for 1029 reflections.

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10) The stereostructures of **8a, b** were confirmed by their ^{1}NMR spectral characteristics;[11] **8a**: $J_{4,5}$ =10 Hz; **8b**: $J_{4,5}$ =9.5 Hz.

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