A Stereocontrolled Synthesis of D-*erythro*-Sphingosine and D-*ribo*-Phytosphingsine†

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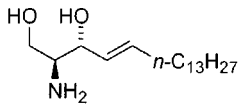
Since a variety of physiologically valuable compounds comprise β-amino hydroxy ethylene subunits,[1] we have been engaged in developing stereoselective synthetic routes to *syn*- and *anti*-β-amino alcohols. The routes have been established by the electrophile-promoted intramolecular amidations of allylic[2] and homoallylic trichloroacetimidates,[3] in which the stereochemistry is conceivably controlled by either steric or electronic effects. Sphingosine derivatives, regarded as β-amino alcohols, have attracted considerable attention due to their crucial roles[4] in a number of biological functions including inhibitory activity against protein kinase C.[5] They are essential components of sphingolipids, *e.g.*, cerebrosides, gangliosides, sphingomyelins and ceramides.[6] Sphingolipids and their metabolites are involved in signal transduction, cell regulation, and cell recognition such as growth, differentiation, adhesion and the immune response.[7] In addition, many glycosphingolipids from marine organisms display pronounced antitumor,[8] antiviral,[9] antifungal,[10] antiinflammatory,[11] immunosuppressive,[12] immunostimulatory,[13] neuritogenic[14] and cytotoxic activities.[15] The biochemical and biomedical significance of sphingosine-containing compounds as well as the synthetic utility of our developed methodology for *anti*-β-amino alcohols[3c] led us to choose (−)-D-*erythro*-sphingosine **1** and (+)-D-*ribo*-phytosphingosine **2** as the synthetic targets.[16] In this paper we describe a convenient stereoselective synthesis of the two sphingosines **1** and **2** starting from dihydro-1,3-oxazines **4** and **10**, respectively.



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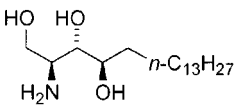
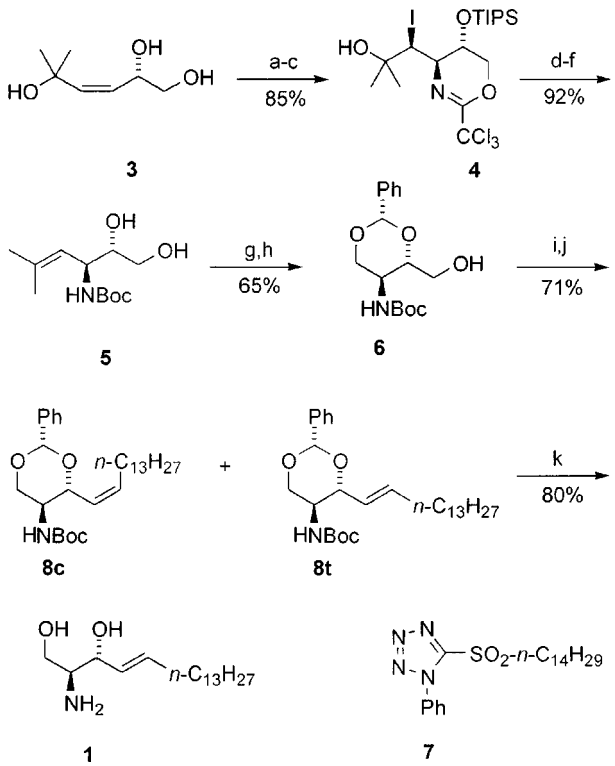


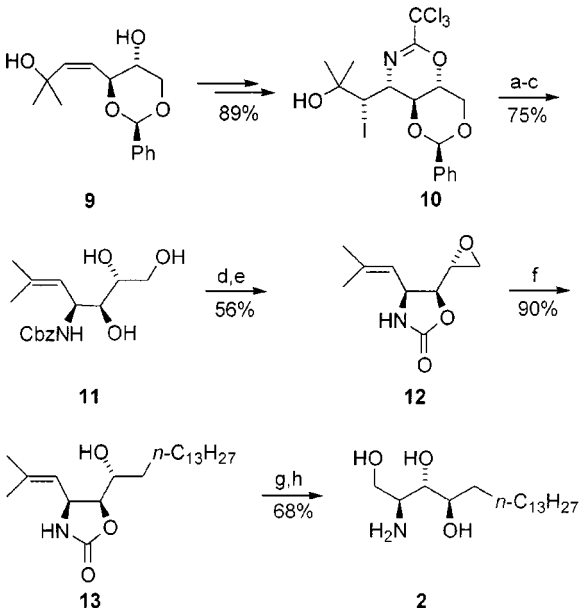
2

The synthesis of D-*erythro*-sphingosine **1** began with dihydro-1,3-oxazine **4**, which was prepared in 5 steps and 68% overall yield from triol **3**. Alternatively, **4** could be yielded more efficiently as described in the following (Scheme 1). After disilylation of **3**, the generated disilyl ether was treated with Cl_3CCN in the presence of NaH and *n*-Bu_4NF to effect chemoselective monodesilylation and monoimidate formation. The resulting silyloxy homoallylic imidate was iodoamidated using IBr to give the desired stereoisomeric dihydro-1,3-oxazine **4** ($[\alpha]_D^{26}$ -21.5, *c* 1.0, $CHCl_3$) exclusively in 85% overall yield. The iodohydrin functionality of **4** was reductively eliminated by sequential addition of trifluoroacetic anhydride and NaI to furnish alkene. The alkene was completely hydrolyzed and then protected to provide dihydroxy carbamate **5** ($[\alpha]_D^{26}$ -5.9, *c* 1.1, MeOH) in 92% overall yield from **4**. The olefinic double bond of **5** was ozonized and reduced. The resultant triol was converted into 6-membered benzylidene **6** (mp. 152-153 °C; $[\alpha]_D^{26}$ +24.5, *c* 1.0, MeOH) in 65% overall yield from **5**. Swern oxidation of **6**[17] and the subsequent modified Julia olefination[18] with **7** afforded a 2.8 : 1 mixture of *trans*- and *cis*-alkenes, **8t** and **8c**, in 71% combined yield. After chromatographic separation, **8t** ($[\alpha]_D^{20}$ +16.9, *c* 1.5, $CHCl_3$) was hydrolyzed to produce D-*erythro*-



Scheme 1. (a) TIPSOTf, Et_3N, CH_2Cl_2, -78 to -20 °C; (b) Cl_3CCN, NaH, THF, -30 °C, then *n*-Bu_4NF, -30 °C; (C) IBr, K_2CO_3, EtCN, -78 °C; (d) $(CF_3CO)_2O$, Et_3N, CH_2Cl_2, -20 °C, then NaI, DMF, 0 °C; (e) 6 N HCl, MeOH, rt; (f) Boc_2O, K_2CO_3, MeOH, 0 °C; (g) O_3, MeOH, -78 °C, then $NaBH_4$, 0 °C; (h) *p*-TsOH, PhCHO, CH_2Cl_2, rt; (i) Swern oxid.; (j) **7**, KHMDS, DME, -60 °C, then aldehyde, -60 °C; (k) CF_3COOH, H_2O, rt.

†This paper is dedicated to the late Professor Sang Chul Shim at KAIST.



Scheme 2. (a) $(CF_3CO)_2O$, Et_3N, CH_2Cl_2, -20 °C, then NaI, DMF, 0 °C; (b) 6 N HCl, MeOH, rt; (c) CbzCl, K_2CO_3, MeOH, 0 °C; (d) 2,4,6-$Me_3C_6H_2SO_2Cl$, DMAP, Et_3N, CH_2Cl_2, 0 °C to rt; (e) NaH, THF, 0 °C; (f) *n*-$C_{13}H_{27}MgBr$, Li_2CuCl_4, Et_2O, -20 °C; (g) O_3, MeOH, -78 °C, then $NaBH_4$, 0 °C; (h) 2 N KOH, MeOH, reflux.

sphingosine **1** (mp. 78-80 °C; $[\alpha]_D^{25}$ -2.7, *c* 1.0, $CHCl_3$) in 80% yield, the spectroscopic and physical data of which are identical with those previously reported.[19]

To synthesize D-*ribo*-phytosphingosine **2**, dihydro-1,3-oxazine **10**, ($[\alpha]_D^{23}$ -34.8, *c* 1.0, $CHCl_3$) which was secured in 2 steps and 89% yield from diol **9**, was reductively eliminated, exhaustively hydrolyzed, and the resulting amine was protected to render carbamate **11** (mp. 85-87 °C; $[\alpha]_D^{27}$ -32.1, *c* 1.1, $CHCl_3$) in 75% overall yield (Scheme 2). Regioselective sulfonation of **11** followed by cyclization gave epoxy oxazolidinone **12** (mp. 77-79 °C; $[\alpha]_D^{25}$ -13.8, *c* 1.4, $CHCl_3$) in 56% yield. The epoxy group of **12** was opened with tridecylmagnesium bromide in the presence of lithium tetrachlorocuprate[20] to afford oxazolidinone **13** (mp. 57-59; $[\alpha]_D^{24}$ -8.2 *c* 0.7, MeOH) in 90% yield. Sequential subjection of **13** to ozonolysis, $NaBH_4$ reduction and basic hydrolysis produced D-*ribo*-phytosphingosine **2** (mp. 95-97 °C; $[\alpha]_D^{24}$ +8.6, *c* 0.7, pyridine) in 68% yield, the spectroscopic and physical data of which are in agreement with those reported in literatures.[16b,21]

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