A Stereocontrolled Synthesis of D-erythro-Sphingosine and D-ribo-Phytosphingosine†

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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 allylic2 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 roles4 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 neuritogenic14 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 alcohols3c 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.

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 Cl3CCN in the presence of NaH and n-Bu4NF 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 ([α]D20 +21.5, c 1.0, CHCl3) exclusively in 85% overall yield. The iodo hydrin 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 ([α]D20 +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; [α]D20 +24.5, c 1.0, MeOH) in 65% overall yield from 5. Swern oxidation of 617 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 ([α]D20 +16.9, c 1.5, CHCl3) was hydrolyzed to produce D-erythro-

† This paper is dedicated to the late Professor Sang Chul Shim at KAIST.
was protected to render carbamate eliminated, exhaustively hydrolyzed, and the resulting amine in 2 steps and 89% yield from diol 2,4,6-Me₃C₆H₂SO₂Cl, DMAP, Et₃N, CH₂Cl₂, 0 °C to rt; (e) NaH, o C;  +8.6, [α]D₂5  -2.7, c 1.0, CHCl₃) in 80% yield, the spectroscopic and physical data of which are in agreement with those previously reported.¹⁹

To synthesize D-ribo-phytosphingosine 2, dihydro-1,3-oxazine 10, ([α]D₂³  -34.8, c 1.0, CHCl₃) 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; [α]D₂³  -32.1, c 1.1, CHCl₃) in 75% overall yield (Scheme 2). Regioslective sulfonation of 11 followed by cyclization gave epoxy oxazolidinone 12 (mp. 77-79 °C; [α]D₂³  -13.8, c 1.4, CHCl₃) in 56% yield. The epoxy group of 12 was opened with tridecylmagnesium bromide in the presence of lithium tetrachlorocuprate²⁰ to afford oxazolidinone 13, which was secured with (mp. 85-87 o C; [α]D₂³  -8.2 c 0.7, MeOH) in 90% yield. Sequential subjection of 13 to ozonolysis, NaNBH₄ reduction and basic hydrolysis produced D-ribo-phytosphingosine 2 (mp. 95-97 °C; [α]D₂⁴  +8.6, c 0.7, pyridine) in 68% yield, the spectroscopic and physical data of which are in agreement with those reported in literatures.²⁰b,²¹

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References


