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A flexible approach to construct three contiguous chiral centers of sphingolipids, and asymmetric synthesis of D-*ribo*-phytosphingosine and its derivatives

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ABSTRACT

An efficient approach to build the three contiguous stereogenic centers of sphingosine unit starting from cheap glutamic acid is described. The key step of this approach is the SmI_2-mediated cross-coupling of chiral *N*-*tert*-butanesulfinyl imine **11** with sterically hindered aliphatic aldehyde **9** or **21** to construct hydroxymethyl β-amino alcohol **10** or **22** in high diastereoselectivity (>99%, de). The utility of this flexible method has been demonstrated in the synthesis of D-*ribo*-phytosphingosine **1**, its two derivatives **18** and **29**. Moreover, a practicable synthetic route for synthesis of various sphingolipids, ceramides, α-galactosylceramides and their derivatives is also described.

1. Introduction

Sphingosine and phytosphingosine are two most important long-chain constituents of cell members (Fig. 1).[1] They are widely distributed in mammalian cells, bacteria and fungi, yeasts, plants, and marine organisms.[2] Their structural function of a small positive change at neutral pH as a consequence of intermolecular hydrogen bonding enable them as an unusual class of sphingolipids, which serve as an essential components of all eukaryotic cell membranes together with glycerolipids and sterols.[3] Sphingosine and phytosphingosine **1** play critical roles in many physiological processes, which include cellular recognition, modulation of immune response, adhesion and apoptosis.[4] In addition, they can effectively inhibit the protein kinase C, and their ceramide derivatives are also potent stimulators of the mammalian immune system.[5] Phytosphingosine or its derivatives are one essential core fragment of several ceramides, which possess diverse bioactivities, such as controlling cell growth, maturity, survival and death, and inhibiting or activating certain enzymes, and lead to promising efficacies for the control of cancer and other cell proliferation.[6] As a prime instance, modification of marine natural product agelasphine-9b **4** led to an anticancer drug candidate KRN7000,[7] which can regulate immune system through interaction with CD1d protein located on the surface of antigen-presenting cells.[8] Recent studies revealed that some of sphingolipids analogues could inhibit the diabetes, cancers, infection by microorganisms, Alzheimer's disease, heart disease of human body.[9] In nature, among of eight possible

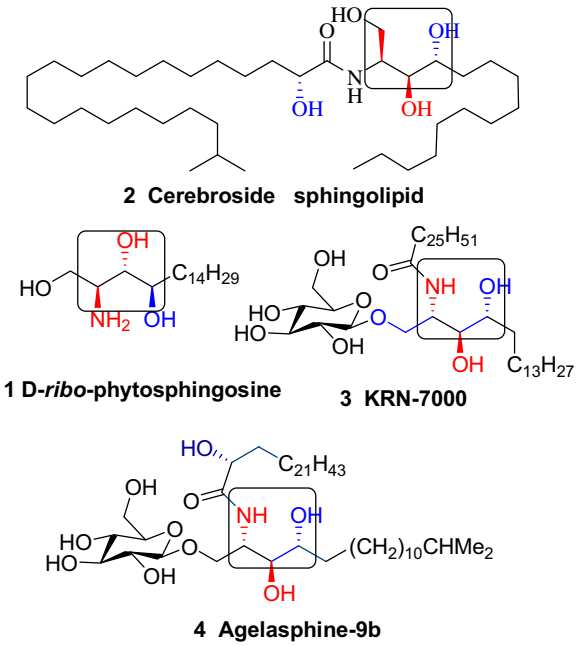

Fig. 1. The structure of several bioactive molecules.

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stereoisomers of phytosphingosines, D-*ribo*-phytosphingosine **1** is the most predominant one. Due to their biological activities and intriguing structures, the D-*ribo*-phytosphingosine **1**, agelasphine-9b **4** or their derivative KRN7000 **3** have attracted more attention of many chemists and several approaches to the asymmetric synthesis of them have been reported recently.[10] From the practical point of view, the most challenging work is the construction of three contiguous chiral centers in optically active sphingosine.

In continuation of our tremendous efforts to explore some multifunctional building blocks based on the cheap resources and utilizing them in the asymmetric synthesis of some natural products[11] including asymmetric synthesis of ceramide sphingolipid **2**, a sex pheromone of hair crab, based on the chiral lactam derived from the cheap glutamic acid.[12] As part of this program, we focus on developing efficient asymmetric methods to build the three chiral centers unit of sphingosine and using them in the asymmetric synthesis of D-*ribo*-phytosphingosine **1** and its ceramides, α-galactosylceramide derivatives. Herein we describe a flexible method for the construction two chiral centers of the D-*ribo*-phytosphingosine **1** promoted by SmI_2 and its utility in the diverse synthesis of the derivatives.

Chiral *N*-*tert*-butanesulfinamide, as pioneered by Ellman and Davis, is undoubtedly one of the most efficient auxiliaries occurring in modern organic synthesis,[13] and Lin group has achieved a powerful method for the synthesis of unsymmetrical vicinal β-amino alcohols based on it.[14] Later, our group used it to study the chemical selectivity of the imine[15b] with aldehydes in the presence of ester or ketone, and those results have been applied in the total synthesis of (−)-deoxoprosophylline **5** (Fig. 2).[15a] As shown in Fig. 2, in this work our purpose is to study the stereoselective cross-coupling reaction of imine with high sterically hindered long-chain aliphatic aldehydes derived from the glutamic acid, and to build a flexible method for synthesis of bioactive D-*ribo*-phytosphingosine **1**, agelasphine-9b **4** and their analogues.

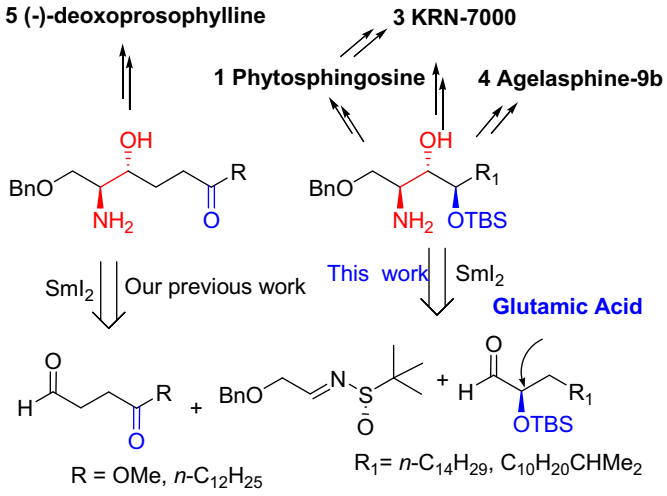
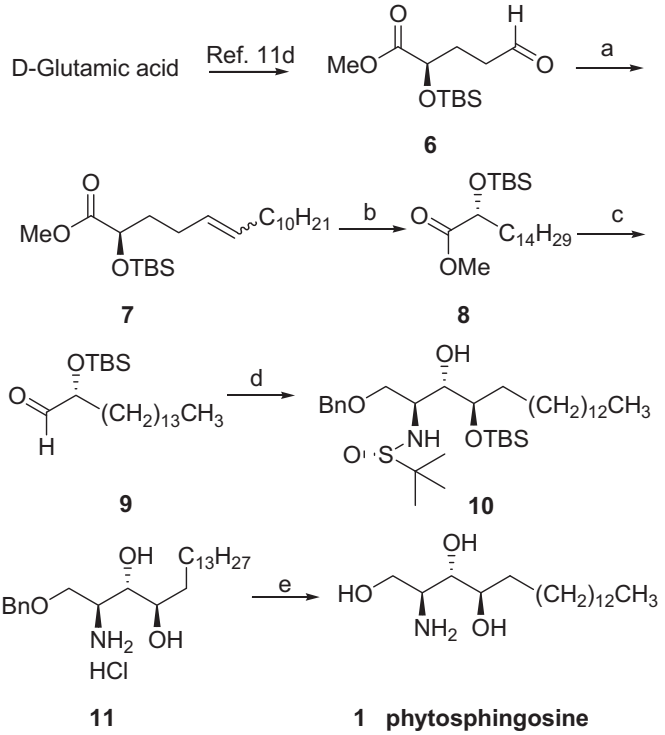


Fig. 2. The synthetic strategy of this work.

2. Results and discussion

Firstly, D-glutamic acid was selected as a starting material to prepare the aldehyde *R*-**6** for the cross-coupling reaction in our plan according to our previous method.[11d] Then the unpurified aldehyde **6** was directly subjected to the Wittig reaction with undecanetriphenylphosphonium bromide in the presence of *n*-BuLi to afford the *E* and *Z* mixture of the olefin in 89% combined yield (Scheme 1). Hydrogenation (10% Pd/C, MeOH) of the olefin afforded the ester **8** in 95% yield. Treatment of ester **8** with DIBAL-H[16] in toluene at −78 °C for 3 h gave aldehyde **9** in 85% yield. Although the cross-coupling reaction of (*S*)-*N*-*tert*-butanesulfinyl imine with aromatic aldehydes is a robust method to build the unit of β-amino alcohol, it often need 4 equiv amounts of aldehydes for the aliphatic reactants.[14a] Considering the difficulty of preparation for **9** through the multi-steps reaction, we started to screen the ratio of sterically hindered aliphatic aldehyde **9** with (*S*)-*N*-*tert*-butanesulfinyl imine[17] **11**. Fortunately, when the equivalent amount aldehydes **9** was used, the cross-coupling reaction was smoothly occurred in 5 h, and generated protective hydroxymethyl β-amino alcohol **10** with high diastereoselectivity (>99%, de) in 68% yield. Then, compound **10** was treated with dry HCl in MeOH for 4 h, the chiral auxiliary[14a] and *tert*-butyldimethylsilyl group of secondary hydroxyl was removed in one-pot. Then transfer hydrogenation[18] (HCOOH/MeOH) of the concentrated crude salt **11** in the presence of stoichiometric catalyst (10% Pd/C) at room temperature for 12 h produced crude **1**, which was purified by chromatography on silica gel (DCM/MeOH) to give D-*ribo*-phytosphingosine **1** {$[\alpha]_D^{25}$ +7.9 (*c* 0.2, C_6H_5N); lit.[19] $[\alpha]_D^{23}$ +7.0 (*c* 0.09, C_6H_5N); lit.[10g] $[\alpha]_D^{23}$ +8.0 (*c* 0.8, C_6H_5N)} in 54% overall yield. The spectroscopic and physical data of the synthetic D-*ribo*-phytosphingosine **1** were identical with the reported data.[10g]



Scheme 1. Synthesis of D-*ribo*-phytosphingosine **1**. a. *n*-$C_{11}H_{23}PPh_3Br$, *n*-BuLi, THF, −78 °C, rt, 6 h, 89%; b. H_2, 10% Pd/C, MeOH, rt, 1 h, 95%; c. DIBAL-H, toluene, −78 °C, 3 h, 88%; d. 2-benzoxyl ethyl (*S*)-*N*-*tert*-butanesulfinyl imine, SmI_2, *t*-BuOH, −78 °C, 5 h, 68%; e. (i) HCl/MeOH, 4 h; (ii) 10% Pd/C, HOOH, MeOH, 12 h, 54%.

To explore an efficient method for the synthesis of KRN7000 **3**, The crude salt **11** was treated with di-*tert*-butyl dicarbonate in the presence of 1 M NaOH to afford compound **12** in 75% yield (Scheme 2). When compound **12** was treated with TBSOTf and 2,6-Lutidine in DCM, the hydroxyl were protected, simultaneously, the deprotection of amino group was occurred in one-pot to afford amine **13** in 78% overall yield. Then compound **13** was treated with the commercial active ester **14** in the presence of DMAP to afford amide **15** in 45% yield. Hydrogenation (20% $Pd(OH)_2$−10% Pd/C, H_2) of amide **15** gave alcohol **16** {$[\alpha]_D^{25}$ −9.2 (*c* 1.0, $CHCl_3$); lit.[20] $[\alpha]_D^{16}$ −9.5 (*c* 6.2, $CHCl_3$); lit.[21]