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Enantioselective total synthesis of (2*S*,3*R*,4*R*)-D-*xylo*-phytosphingosine from substituted azetidin-2-one

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ABSTRACT

Enantiomerically pure (2*S*,3*R*,4*R*)-D-*xylo* phytosphingosine is synthesized in 36% overall yield in seven steps from known β-lactam (**8**) derived from D-mannitol triacetonide.

Sphingolipids which play crucial roles in many physiological processes[1] comprise sphingoid bases possessing long-chain aliphatic 2-amino-1,3-diol backbones. Sphingolipids such as Ceramide (**1**), sphingomyelins (**2**), and glycosphingolipids (**3**) are important membrane components of all the eukaryotic cells, plasma membranes, and intramolecular organelles playing vital roles in a number of cellular events including cell growth, differentiation, adhesion, and neuronal repair. They have also been proved to play a prominent role in cell signaling (Fig. 1).[2]

Phytosphingosines, characterized by the 2-amino-1,3,4 triol head group, are the most important naturally occurring sphingolipids prevalent in microorganisms, plants, and many mammalian tissues such as brain, hair, intestines,[3] uterus,[4] liver,[5] skin,[6] and blood plasma.[7] They are also found in human kidney cerebrosides and some cancer cell types.[8] In addition to being base components of sphingolipids in membranes, phytosphingosines themselves are found to be bioactive lipids. For example, phytosphingosine (**5**) is a potential heat stress signal in yeast cells[9] and D-*erythro*-sphingosine (**6**) shows promising protein kinase inhibitory activity.[10] It has also been established that various diastereomers of sphingosines exhibit different activities and metabolism.[11] This subtle variation in biological activities over a range of diastereomers has led to the synthesis of all the diastereomers of sphingosines. This fact is very well reflected in the spurt of publications dealing with the synthesis of sphingosines.[8,12–14]

β-Lactams are part structures of the most widely used antibiotics and remain unsurpassed in their contribution to medicinal science as invaluable life-saving drugs. In addition to their medicinal values, β-lactams have also proved to be invaluable precursors for the syntheses of various natural products,[15–17] owing to the flexibility available for selective ring-cleavage reactions. Banik et al.[18] have utilized this property of β-lactam for the synthesis of non-natural (−)-polyoxamic acid. Furthermore, β-lactam skeletons have also been used in the synthesis of sphingosines through their ring-opening reaction using either long alkyl Grignard reagents[14a], *n*-tetradecyl *p*-toluenesulfonate/*n*-BuLi[19] or phosphonate-stabilized carbanion[20] as nucleophiles.

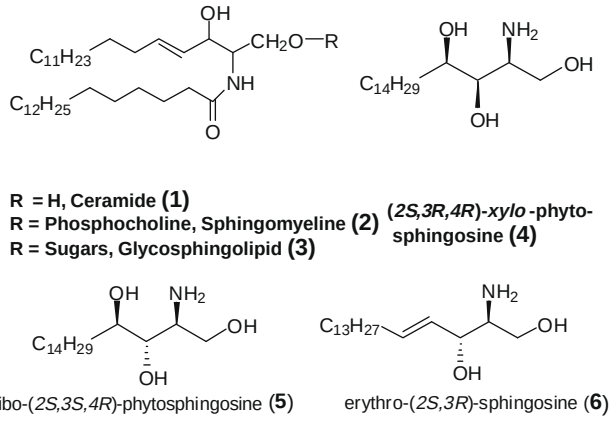

Figure 1.

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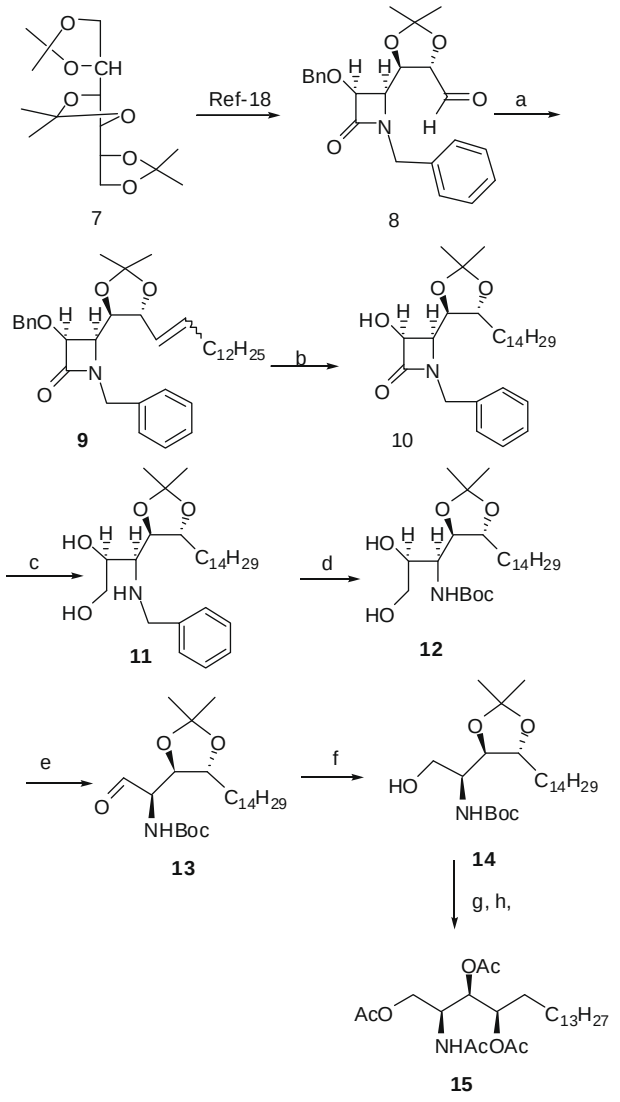

Scheme 1. Reagents and conditions: (a) $PPh_3BrC1_3H_{27}$, *n*-BuLi, dry THF, 0 °C, 1 h, 70%; (b) $HCOONH_4$, Pd/C (10%), MeOH, reflux, 4 h; 80%; (c) LAH, dry THF, reflux, 4 h, 93%; (d) H_2, Pd/C (10%), MeOH, $(Boc)_2O$, rt 10 h, 93%; (e) $NaIO_4$, EtOH:H_2O (1:1) rt, 30 min, 89%; (f) $NaBH_4$, dry. MeOH, 0 °C to rt, 10 h; 92%; (g) TFA/H_2O (20:1), DCM, 0 °C, 3 h; (h) Ac_2O, dry Py, DMAP (cat) 91%.

While all these reports present attractive approaches to sphingosines, the installation of the tetradecyl chain has not been easy and has often produced a mixture of different products.[21] Therefore, it was felt that a route which introduces the long tetradecyl chain in sphingosines before the opening of the β-lactam ring could be an attractive strategy. Toward this end, we have devised a synthetic route for D-*xylo*-phytosphingosine, starting from β-lactam **8** derived from D-mannitol triacetonide **7** and report herein our successful preliminary endeavor (Scheme 1).

The required β-lactam **8** was synthesized in 70% yield using the reported protocol from D-mannitol triacetonide **7**.[18] Subjecting **8** to Wittig olefination with a 13 carbon ylide in the presence of *n*-BuLi at 0 °C produced **9** in 70% yield as a cis, trans mixture (55:45), confirmed by ^1H NMR spectra. The geometrical isomers ratio was of no relevance to the planned synthetic sequence as the double bond was to be reduced in the immediate next step. It was also expected that during the reduction of the olefinic double bond of **9**, O-debenzylation would occur. Accordingly, **9** upon transfer hydrogenation using ammonium formate and Pd/C (10%) in methanol furnished **10** in 80% yield. Compound **10** upon reduction with lithium aluminum hydride in THF, under reflux condition produced **11** in 93% yield having a vicinal diol moiety. N-Debenzylation of **11** by catalytic hydrogenation (10%, Pd/C) at atmospheric pressure of hydrogen followed by *N*-Boc protection gave **12** in 93% over two steps. The oxidative cleavage of **12** using sodium periodate in ethanol/water (1:1) solvent at room temperature yielded **13** in 89% yield. The subsequent reduction of **13** with sodium borohydride gave compound **14** (92%). The treatment of **14** with TFA/water (20:1) in dichloromethane at 0 °C led to the concomitant *N*-Boc as well as acetonide deprotection affording **4** quantitatively. Since it was difficult to purify **4** by column chromatography, this product was acetylated using acetic anhydride/ pyridine with a catalytic amount of DMAP to obtain **15**. Compound **15** was easily purified by silica gel column chromatography in 30% ethylacetate/petroleum ether as eluent.

The spectral data and specific rotation of **15** were in excellent agreement with the reported values.[22]

In conclusion, an enantioselective synthesis of (2*S*,3*R*,4*R*)-D-*xylo*-phytosphingosine is achieved from β-lactam derived from D-mannitol triacetonide.

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