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An Efficient and General Enantioselective Synthesis of Sphingosine, Phythosphingosine, and 4-Substituted Derivatives†

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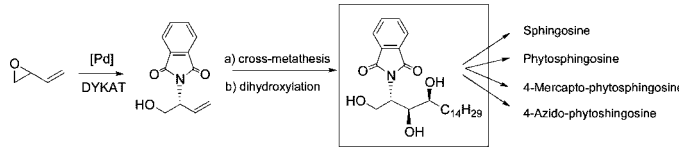
ABSTRACT



A general and efficient protocol for the enantioselective synthesis of sphingosine, phythosphingosine, and 4-substituted derivatives was established. These compounds were obtained from a common intermediate prepared from butadiene monoepoxide by a synthetic sequence involving enantioselective allylic substitution, cross-metathesis, and dihydroxylation.

Sphingolipids are important structural and functional components of the plasma membranes of essentially all eukaryotic cells. They play critical roles in many physiological processes, including immune response, cell recognition, adhesion, and apoptosis.[1] Recent studies implicate sphingolipids in many of the most common human diseases, including diabetes,[2] cancers,[3] infection by microorganisms,[4] Alzheimer's disease,[5] heart disease, and an array of neurological syndromes.[6] The most important sphingolipids are sphingosine and phytosphingosine, which when acylated with a fatty acid and glycosylated with galactose produce galactosylceramide (GalCer) and α-GalCer (KRN7000), respectively (Figure 1). Recently, structurally modified sphingosines[7] and phytosphingosines[8,9] have attracted more attention because some of their analogues have been observed to introduce morphological changes in neuronal cells[10] and behave as enzyme inhibitors.[11]

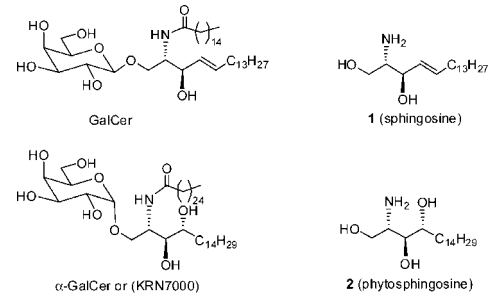


Figure 1. Glycolipids GalCer and α-GalCer and sphingolipids.

† Dedicated to Professor Josep Font on occasion of his 70th birthday.

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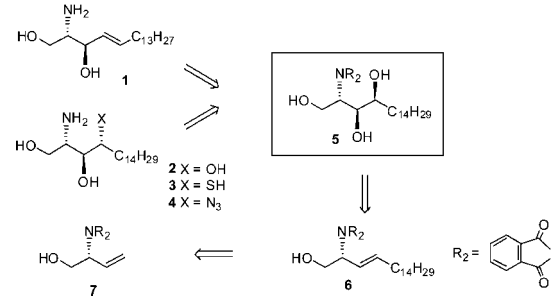
Since sphingosine and its derivatives are available only in limited amounts from natural sources and because of purity requirements for biological testing, there is a growing interest in developing efficient methods for their synthesis.[12] These compounds have been synthesized by various routes, but primarily from compounds of the chiral pool, particularly amino acids (L-serine)[13] and carbohydrates.[14] Asymmetric syntheses based on the use of chiral auxiliaries, such as sulfoxides,[15] chiral aziridines,[16] or chiral sulfur[17] and nitrogen[18] ylides, or on catalytic procedures, such as Sharpless asymmetric epoxidation[19] and dihydroxylation reactions,[16,20] the aldol reaction,[21] and organocatalytic procedures, have also been described.[22]

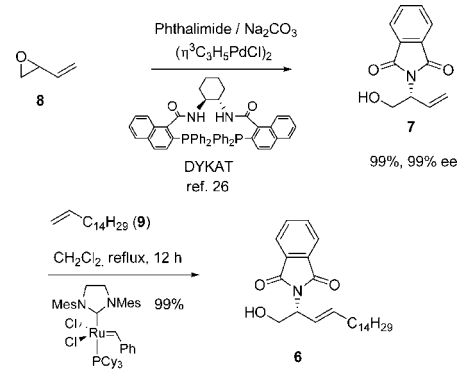
Recently, we reported efficient procedures for the glycosylation of ceramides that facilitated the synthesis of GalCer[23] and KRN 7000.[24] New analogues of these compounds containing structural modifications in the sphingolipid moiety have been reported very recently.[25] In this work, we describe a new and efficient enantioselective method for synthesizing sphingosine (**1**), phytosphingosine (**2**), and new 4-substituted derivatives (**3**, **4**) (Scheme 1) partially protected. In the proposed retrosynthesis, compounds **1**−**4** can be obtained from a common intermediate **5** (Scheme 1). Nucleophilic substitution at position 4 in **5** must allow the introduction of different substituents, affording the natural product and derivatives. Compound **5** can be obtained by the dihydroxylation of compound **6**, which in turn can be synthesized from compound **7** by a cross-metathesis reaction. The main advantage of this strategy is its high versatility, allowing the synthesis of not only sphingosine and phytosphingosine but also a range of structural analogues from a common precursor.

Scheme 1. Retrosynthesis



Chiral synthon **7** (NR_2 = phthalimido) was obtained by a palladium-catalyzed dynamic kinetic asymmetric transformation (DYKAT) from the racemic butadiene monoepoxide (**8**)[26] (Scheme 2).

Scheme 2. Synthesis of Alkene **6**



Initially we explored the cross metathesis reaction using the second generation Grubbs catalyst, which is compatible with a wide range of functionalities.[13e,14b,17,19b] In preliminary screening experiments, compound **7** was reacted with a 2-fold excess of 1-hexadecene (**9**) in refluxing dichloromethane to afford **6** at a 82% yield and an *E*/*Z* ratio of 18:1 (Scheme 2). Since the metathesis reaction proceeds under thermodynamic control, both the yield and stereose-

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lectivity can be improved by increasing the **9/7** ratio and the reaction time. In this way, using 4 equiv of **9** and maintaining the reaction for 12 h, compound **6** was obtained in an quantitative yield, and the *E* isomer was exclusively detected by NMR.

Compound **6** was then reacted with OsO_4/NMO to obtain a mixture of compounds **5** and **10** in an almost quantitative yield in a ratio of 3.3:1 (Scheme 3) (entry 1, Table 1).

Scheme 3. Dihydroxylation of Alkene **6**

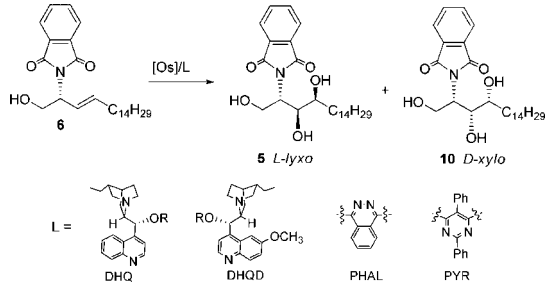


Table 1. Dihydroxylation of Alkene **6**

entry	reagent	temp (°C)	yield (%)	ratio **5**:**10**
1	OsO_4/NMO	rt	99	3.3:1
2	OsO_4/NMO	0	57	3.4:1
3[a]	OsO_4/NMO	−78	95	3.4:1
4[b]	OsO_4/NMO	−78	93	3.8:1
5	AD-MIX α[c]	rt		
6	AD-MIX β[d]	rt		
7	[Os]/$(DHQ)_2$PYR[e]	rt	99	5.1:1

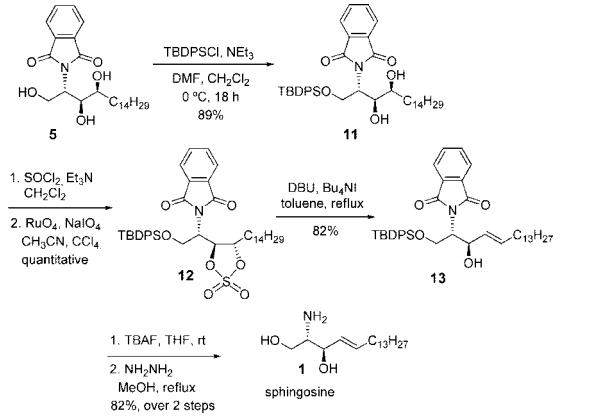
[a] OsO_4 (1 equiv) and TMDA (1.1 equiv) were used. [b] TEEDA was used as the ligand. [c] Ligand $(DHQ)_2$PHAL. [d] Ligand $(DHQD)_2$PHAL. [e] $K_2OsO_2(OH)_4$ (0.02 equiv), $(DHQ)_2$PYR (0.03 equiv), $CH_3SO_2NH_2$ (1.2 equiv), K_2CO_3 (0.03 equiv), $NaHCO_3$ (0.03 equiv), $K_3Fe(CN)_6$, (0.03 equiv).

Decreasing the temperature had a negative effect on the yield and no effect on the stereoselectivity (entry 2). An attempt was made to increase the stereoselectivity by carrying out the reaction at −78 °C and using stoichiometric amounts of OsO_4 in the presence of different diamine ligands. When tetramethylethylenediamine (TMEDA) was used, the stereoselectivity was similar to that reported in entry 1 (entry 3). The use of tetraethylethylenediamine (TEEDA) slightly increased the **5/10** ratio to 3.8:1, in an 93% yield (entry 4).

It has been reported that the asymmetric dihydroxylation reactions of related substrates afforded excellent yields and stereoselectivities of the L-*lyxo* and D-*xylo* phytosphingosines, using AD-MIX α and β, respectively;[27,28] however, when compound **6** was treated with commercial AD-MIX mixtures,[27] no reaction was observed (entries 5, 6, Table 1). The reaction was attempted using a freshly prepared mixture of $[K_2OsO_2(OH)_4]$ and $[K_3Fe(CN)_6]$ in the presence of ligands $(DHQD)_2$-PHAL or $(DHQ)_2$-PHAL, in ^{t}BuOH/H_2O (1:1), but unfortunately, the starting material was again exclusively recovered. Finally, in the presence of $K_2OsO_2(OH)_4$]/$[K_3Fe(CN)_6]$/$(DHQ)_2$PYR, compounds **5**/**10** were obtained in a quantitative yield with a ratio of 5.1:1 (Entry 7).

With compound **5** in hand, the next step involved the selective protection of the hydroxyl groups at positions 1 and 3 and the activation of the 4-OH as a leaving group. We initially attempted the simultaneous protection of 1- and 3-OH by reaction with ^{t}Bu$_2$Si(OTf)$_2$ and further activation of the 4-OH as a triflate. However, the subsequent elimination provided a very poor yield of the sphingosine derivative. Alternatively, **5** was reacted with TBDPSCl, affording compound **11** in an 89% yield, which was then treated with thionyl chloride and RuO_4/$NaIO_4$, affording sulfate **12** in a quantitative yield (Scheme 4).[8]

Scheme 4. Synthesis of Key Intermediate **12** and Sphingosine



Compound **12** was then reacted with DBU in the presence of tetrabutylammonium iodide to obtain compound **13** in an 82% yield.[8] Further deprotection of **13** by reaction with TBAF in THF at room temperature and treatment with hydrazine afforded sphingosine (**1**) in an 82% yield.

Similarly, **12** was also reacted with benzoic acid and Cs_2CO_3, to produce compound **14** in a 91% yield (Scheme 5). This excellent regioselectivity was also observed for other nucleophiles and was atributed to the steric and electronic interactions between neighboring sustituents and nucleophiles.[8] Compound **14** was also deprotected by reacting it

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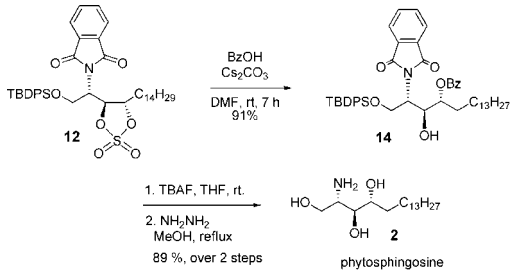
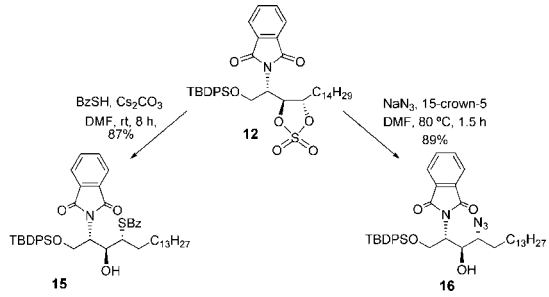
Scheme 5. Synthesis of Phytosphingosine (**2**)



with TBAF and hydrazine to furnish phytosphingosine (**2**) in an 89% yield. NMR spectra and optical rotation of compounds **1**[19b] and **2**[29] match the reported values for the natural products.

The possibility to obtain analogues of phytosphingosine modified at position 4 was illustrated by synthesizing the new 4-mercapto and the 4-azido derivatives (Scheme 6).

Scheme 6. Synthesis of Phytosphingosine Derivatives **15** and **16**



Thus, compound **12** was reacted with BzSH and Cs_2CO_3 to render compound **15** in an 87% yield. In a parallel experiment, compound **12** was reacted with sodium azide in the presence of catalytic 15-crown-5 to afford compound **16** in an 89% yield.

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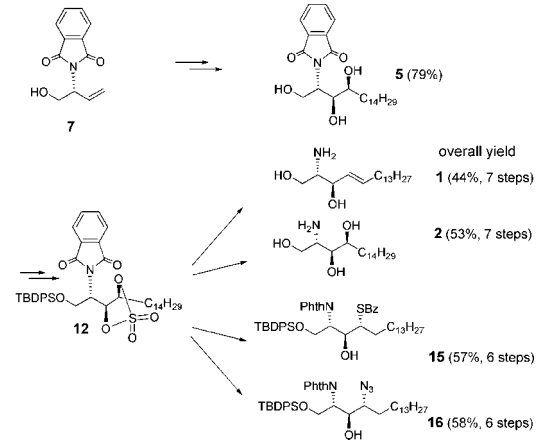
In conclusion, D-*erythro*-sphingosine (**1**), *N*-phtalimido-D-*lyxo*- (**5**), D-*ribo*-phytosphingosine (**2**), and 4-mercapto (**15**) and 4-azido (**16**) analogs were prepared by a highly efficient and enantioselective procedure (Scheme 7). This procedure

Scheme 7. Synthesis of Compounds **1**, **2**, **5**, **15** and **16** from **7**



starts from butadiene monoepoxide and uses a Pd-catalyzed DYKAT process, a cross-metathesis using a second generation Grubbs catalysis and a dihydroxylation reaction to produce the key intermediate **5**. From this intermediate, the target compounds were obtained by protection, substitution, or elimination of 4-OH and deprotection. This procedure is the most efficient for preparing **1** and **2** using asymmetric synthesis procedures and opens the way for preparing a large variety of 4-phytosphingosine derivatives.

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Supporting Information Available: General experimental methods, experimental procedures, compound characterization data, and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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