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An Efficient Synthesis of D-*erythro*- and D-*threo*-Sphingosine from D-Glucose: Olefin Cross-Metathesis Approach

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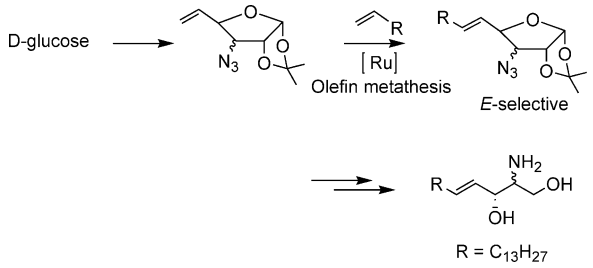
ABSTRACT



The D-*erythro*- and D-*threo*-sphingosine were synthesized via *E*-selective olefin cross-metathesis using a D-glucose-derived building block and long-chain terminal alkene.

Glycosphingolipids are commonly found in eukaryotic cell membranes, plasma membranes, and some intracellular organelles (endoplasmic reticulum, golgi complex, and mitochondria).[1] They play a crucial role in inter- and intramolecular communication as well as in the regulation of cell growth, differentiation, and programmed cell death.[2] The backbone of sphingolipids consists of a base bearing a long aliphatic chain and a polar 2-amino-1,3-diol headgroup. Although a number of structurally related sphingoid base structures are known, the most abundant sphingoid base in nature is D-*erythro*-C_{18}-sphingosine-(2*S*,3*R*,4*E*)-2-amino-octadec-4-ene-1,3-diol, **1a** (Figure 1), which is known to be a promising protein kinase C inhibitor.[3] Since the 1950s, a plethora of asymmetric as well as chiron approaches have been reported for **1a** and its analogues[4−6] wherein most of the strategies utilize more traditional C−C double bond-forming reactions such as olefination[6] or stereoselective reduction of triple bond. However, three recent reports on D-*erythro*-sphingosine made use of *E*-selective cross-metathesis (CM) olefination of two terminal alkene compounds: one with a long chain and the other with an 2-amino-1,3-diol.[5i−k] The attractive features of CM olefination are (a) high *E*-selectivity with good yield in the product formation and (b) the functional group tolerance and reasonable stability of Grubb's catalyst in the presence of amino-diol functionality.[5i−k,7] Although a number of long-chain terminal alkenes are commercially available, the preparation

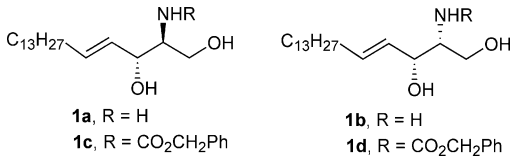


Figure 1.

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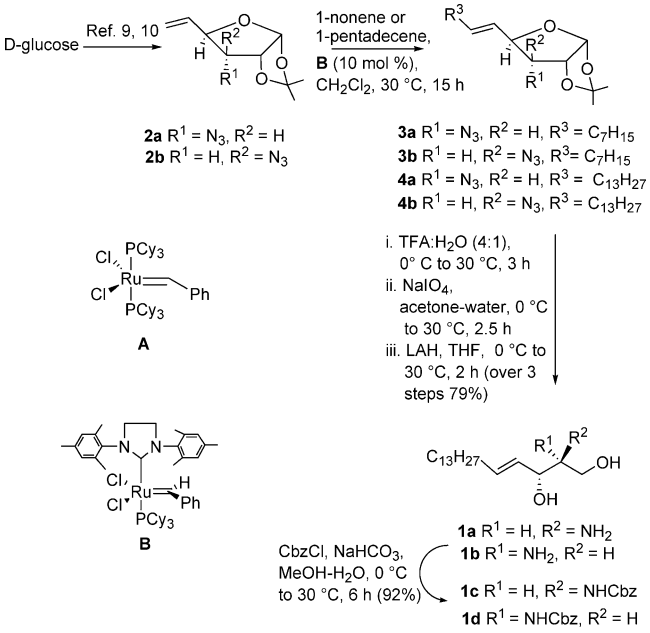
of a suitable 2-amino-1,3-diol with terminal double bond and optimization of coupling conditions are the challenges in the successful implementation of this strategy to target molecules. As a part of our interest in the synthesis of amino sugars,[8] we thought of exploiting the CM reaction with D-*ribo*- and D-*xylo*-configurated 3-azido-5,6-ene derivatives with 1-pentadecene, as a crucial step, in the synthesis of D-*erythro*- and D-*threo*-sphingosine **1a** and **1b**, respectively. Our results are reported herein.

As shown in Scheme 1, the requisite 3-azido-3,5,6-trideoxy-1,2-*O*-isopropylidene-α-D-*ribo*-hexofuran-5-ene **2a** was obtained in five steps as per known procedure from D-glucose in 79% yield,[9] while 3-azido-3,5,6-trideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuran-5-ene **2b** was derived from D-*allose* following the same reaction sequence.[10] In general, the presence of an azide functionality in a molecule *precludes CM* olefination, leading to either failure or poor yield of the product.[5j,k,7c,11] Despite these reports, we checked

Scheme 1. Synthesis of D-*erythro*- and D-*threo*-Sphingosine



the feasibility of the CM reaction with **2a** and **2b**. Thus, use of first-generation Grubb's catalyst **A** in the individual reactions of **2a** and **2b** with 1-nonene did not provide cross-coupled products, while the same reactions with 10 mol % Grubb's catalyst **B** (second generation) with 1-nonene as well as 1-pentadecene afforded the cross-coupled products **3a**/**3b** and **4a**/**4b**, respectively, in good yields with complete *E*-stereoselectivity[12] (Scheme 1, Table 1).

Table 1. Study of Cross Metathesis Reactions

entry	substrate	alkene[a]	catalyst (mol %)	reaction conditions	product (% yield)[b]
1	**2a**	1-nonene	**A** (20)	30 °C, 72 h	no reaction[c]
2	**2b**	1-nonene	**A** (20)	30 °C, 72 h	no reaction[c]
3	**2a**	1-nonene	**B** (10)	30 °C, 15 h	**3a**, 83
4	**2b**	1-nonene	**B** (10)	30 °C, 14 h	**3b**, 86
5	**2a**	1-pentadecene	**B** (10)	30 °C, 16 h	**4a**, 85
6	**2b**	1-pentadecene	**B** (10)	30 °C, 15 h	**4b**, 87

[a] 1-Nonene and 1-pentadecene (2.0 equiv) in CH_2Cl_2. [b] Isolated yield. [c] Starting compound (65−75%) was isolated.

In an attempt to synthesize the natural sphingosine **1a**, the cross-coupled product **4a** was treated with TFA−water to afford an anomeric mixture of hemiacetal that on sodium periodate cleavage and subsequent reaction with LAH

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(12) Under our experimental conditions, the ^{1}H NMR spectrum of crude products **3a** and **4a** did not show any additional signals either due to *Z*-isomer or the self-coupled products. However, in the case of **3b** and **4b**, the ^{1}H NMR spectrum of crude showed a trace amount of (<4%) self-coupled products.

(reduction of azide and aldehyde functionality in one pot) afforded D-*erythro*-sphingosine **1a** as waxy solid (Scheme 1). The reaction sequence was repeated for **4b** as above to get D-*threo*-sphingosine **1b**. Owing to the instability of **1a**,**b** toward crystallization and chromatographic purification, the sphingosines **1a**,**b** were individually treated with benzylchloroformate and sodium bicarbonate in methanol−water to give *N*-Cbz-protected D-*erythro*-sphingosine **1c** and D-*threo*-sphingosine **1d**, respectively. The spectroscopic analytical data for **1c** was found to be in consonance with that reported,[13] while **1d** was characterized independently.

In conclusion, our work illustrates the efficiency of the *E*-selective CM olefination methodology in the synthesis of D-*erythro*- and D-*threo*-sphingosine **1a** and **1b**, respectively. The four-step synthesis from **2a** and **2b** gives corresponding **1a** in 65.4% and **1b** 65.2% in overall yield. The cross-metathesis products **3a** and **3b** could also be used in the synthesis of short-chain ceramides.[14] The easy availability of starting materials and reagents, a few high-yielding steps, and compatibility of Grubb's catalyst (second generation) with sugar azides make our approach versatile for the synthesis of different types of sphingosine analogues and lipids.

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Supporting Information Available: Detailed experimental procedures and copies of ^{1}H and ^{13}C NMR spectra of compounds **3a**, **3b**, **4a**, **4b**, **1c**, and **1d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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