

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

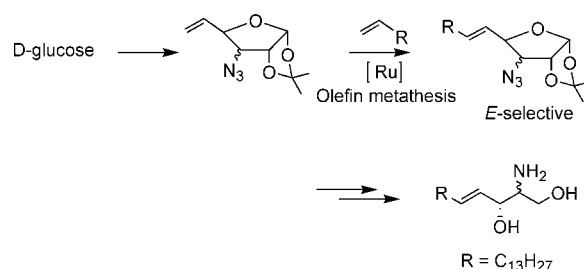
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Received September 24, 2005

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-C₁₈-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 olefination⁶ 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

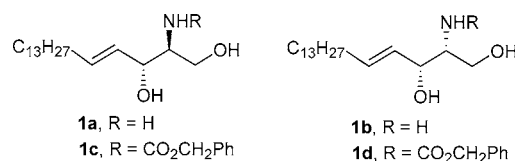


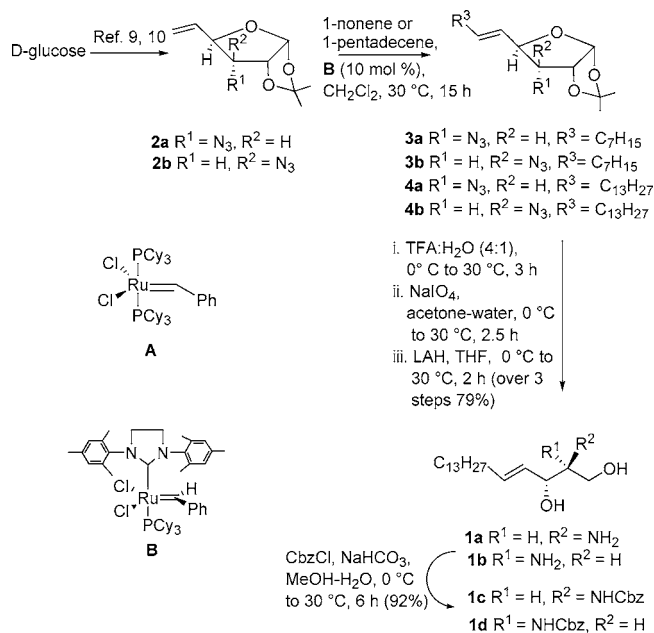
Figure 1.

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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-configured 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



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the feasibility of the CM reaction with **2a** and **2b**. Thus, use of first-generation Grubbs'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 % Grubbs'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*-stereoselectivity¹² (Scheme 1, Table 1).

Table 1. Study of Cross Metathesis Reactions

entry	sub-strate	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 CH₂Cl₂. ^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 ¹H 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 ¹H 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 benzyl-chloroformate 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.

Acknowledgment. We thank the Department of Science and Technology, New Delhi, India, for financial support (Grant No. SP/S1/G23-2000). We are grateful to Prof. M. S. Wadia for helpful discussion.

Supporting Information Available: Detailed experimental procedures and copies of ¹H and ¹³C 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>.

OL052320Z

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