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Sphingolipid Synthesis via Olefin Cross Metathesis: Preparation of a Differentially Protected Building Block and Application to the Synthesis of D-*erythro*-Ceramide

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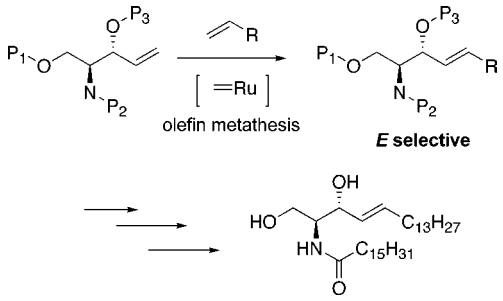
ABSTRACT



The sphingolipid backbone is readily assembled by *E*-selective olefin cross metathesis of a suitable building block.

Sphingolipids are an important class of natural products found in abundance in eukaryotic cell membranes.[1] Variations in sphingolipid structure occur both at the *N*-acyl moiety and at the group attached to the primary alcohol, which is usually a phosphate, a phosphatidyl choline, or a carbohydrate. Additional skeletal diversity in the main carbon chain has also been identified.[2] Sphingolipids are involved in molecular recognition processes at the cell membrane and are important components of lipid rafts and influence cell signaling events at the membrane. As a result of our interest in glycosphingolipid recognition processes, we sought a general synthetic route to sphingolipids that would allow systematic variation of both the O- and N-linked functionalities, as well as the identity of the main carbon chain.[3] In practice, this requires the preparation of a building block such as **I**, which contains all of the conserved and requisite functionality differentiated with orthogonal protecting groups.[4] In this paper we report an approach to sphingolipid synthesis in which the main carbon chain is installed via a highly stereoselective olefin cross metathesis reaction.[5]

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(2) (a) Alam, N.; Wang, W. H.; Hong, J. K.; Lee, C. O.; Im, K. S.; Jung, J. H. *J. Nat Prod.* **2002**, *65*, 944−945. (b) Inagaki, M.; Nakamura, K.; Kawatake, S.; Higuchi, R. *Eur. J. Org. Chem.* **2003**, 325−331; Ojika, M.; Yoshino, G.; Sakagami, Y. *Tetrahedron Lett.* **1997**, *38*, 4235−4238.

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(4) Gargano and Lees have reported the preparation of an orthogonally protected sphingosine with the main carbon chain already installed; See ref 3c.

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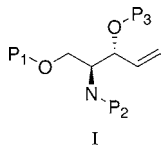
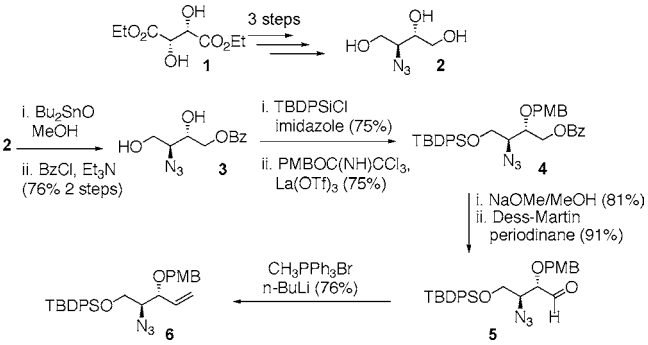


I

We chose diethyl tartrate as the starting material for the five-carbon building block **I**, as both enantiomers are readily available, allowing entry into both natural and *ent*-sphingolipids.[6] The (−)-D-tartrate diester was converted to the known azidotriol **2** in three steps using reported procedures.[7−9] Selective benzoylation of **2** was accomplished via the stannylene ketal intermediate.[10] Silylation of the remaining primary alcohol followed by installation of the *p*-methoxybenxyl ether afforded the differentially protected intermediate **4**.[11] Deacylation followed by oxidation with the Dess−Martin periodinane proceeded smoothly to provide the aldehyde **5**. The requisite fifth carbon of the core building block **6** was installed via Wittig methylenation.[12]

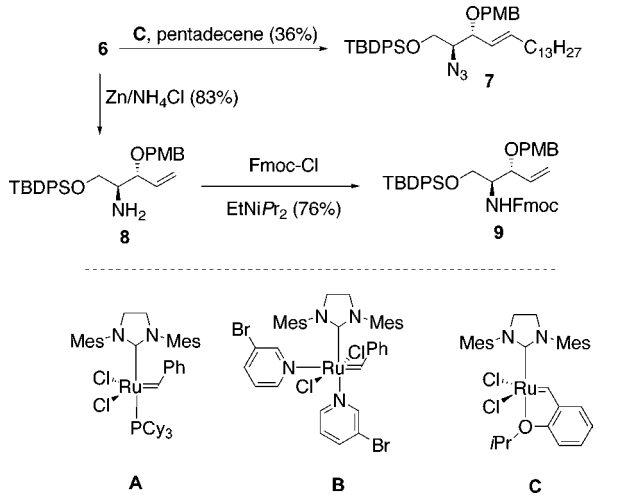
Scheme 1



With building block **6** in hand, its cross-metathesis reactivity with 1-pentadecene was examined. Exposure of **6** to 5 equiv of pentadecene in the presence of 20 mol % of the Grubbs generation II catalyst (**A**) did not provide any of cross-coupled product **7**, and an intractable mixture of compounds was obtained. Use of the phosphine-free catalyst **B**[13] did not provide any improvement, and a 36% yield of **7** was obtained with the catalyst **C**.[14,15] However, the mass balance of the reaction was also very low, and extensive efforts to increase the yield by variations in concentration, olefin ratios, solvent, temperature, and catalyst loading were unsuccessful. The failure of cross-metathesis reactions in the presence of azide-containing molecules is precedented.[16−18] Reaction of the phosphine ligands with the azide and/or metal-mediated nitrene processes are possible complications that can arise under these conditions.

In an effort to increase the yield of this critical olefin metathesis step, the azide was reduced to the amine and protected as the Fmoc carbamate **9**. The carbamate **9** undergoes cross metathesis reactions in the presence of **A** with a variety of alkenes to provide the products shown in Figure 1 in high yields. Reaction of **9** with pentadecene provides **10** with the natural ceramide backbone. The use of nonene as the coupling partner produced **11**, a precursor to a known short chain ceramide analogue.[19] The product **12** is an alkene thiol derivative that can undergo facile conjugation to a variety of protein or polymeric carriers and gold surfaces or nanoparticles.[20]

Scheme 2



We have prepared the natural product ceramide in four steps from the coupling product **10**. The Fmoc group was

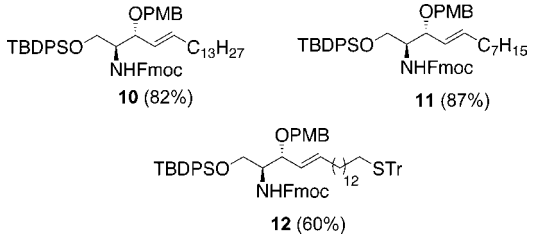


Figure 1.

(5) During the preparation of this manuscript, we became aware of a report by Torssell and Somfai describing a cross metathesis approach to sphingosines using a different five-carbon building block. See: Torssell, S.; Somfai, P. *Org. Biomol. Chem.* **2004**, *2*, 1643−1646. A patent (WO 03/101937) by Rich and Bundle refers to olefin cross metathesis reactions of similar structures, but reduction to practice is not disclosed in the patent.

(6) An alternative and very efficient route to the natural enantiomer of building block **I** that starts with 1,2-*O*-isopropylidene-α-D-glucofuranose has been reported by Rich and Bundle (WO 03/101937) and has also been used in their synthesis of thio-linked GM_3: Rich, J. R.; Bundle, D. R. *Org Lett.* **2004**, *6*, 897−900.

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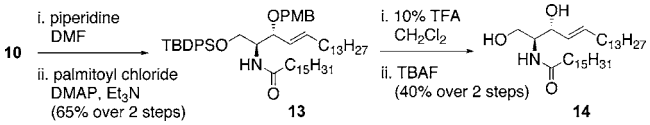
(12) During their synthesis of sphingolipids, Nugent and Hudlicky noted that reaction of azido aldehydes with Wittig reagents also resulted in reaction of the ylide at the azide functionality. See: Nugent, T.; Hudlicky, T. *J. Org. Chem.* **1998**, *63*, 510−520. We have found that careful addition of the ylide to the aldehyde at −78 °C results in clean olefination, while higher temperatures give rise to products derived from both olefination and reaction at the azide.

removed using piperidine in DMF, followed immediately by acylation with palmitoyl chloride to provide the fully protected ceramide **13**. Removal of the PMB ether followed by silyl deprotection provided natural D-*erythro*-ceramide. The spectroscopic data for **14** are in agreement with that reported in the literature.[21]

Scheme 3



In each of the cross metathesis reactions, the *E* olefin is the only isomer detected in the NMR spectrum of the crude reaction mixture prior to chromatographic purification. *E/Z* selectivity in cross metathesis reactions of terminal alkenes is notoriously fickle and is sensitive to the substitution adjacent to the reacting alkenes.[22,23] We have found that cross metathesis reactions using analogues of **9** with an acetyl, pivaloyl, palmitoyl, or benzoyl amide in place of the Fmoc group all provide the *E* alkene as the sole detectable and isolable isomer.[24] This work illustrates the utility of the olefin cross metathesis reaction for the synthesis of sphingolipids and should permit facile access to a large number of derivatives of this increasingly important class of lipids.

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Supporting Information Available: Full experimental details for the preparation of all compounds and ^{1}H and ^{13}C 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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