February 2015

Intramolecular Nitrogen Delivery for the Synthesis of C-Glycosphingolipids. Application to the C-Glycoside of the Immunostimulant KRN7000

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Intramolecular Nitrogen Delivery for the Synthesis of C-Glycosphingolipids. Application to the C-Glycoside of the Immunostimulant KRN7000

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S Supporting Information

ABSTRACT: The key reaction in this approach to C-glycosphingolipids is the stereoselective iodocyclization of a sugar-linked homoallylic carbonimidothioate. E and Z reaction substrates were assembled in a convergent fashion via an alkene metathesis strategy and exhibited the same alkene facial selectivity in the iodocyclization irrespective of alkene geometry, although the E alkene was found to be less reactive.
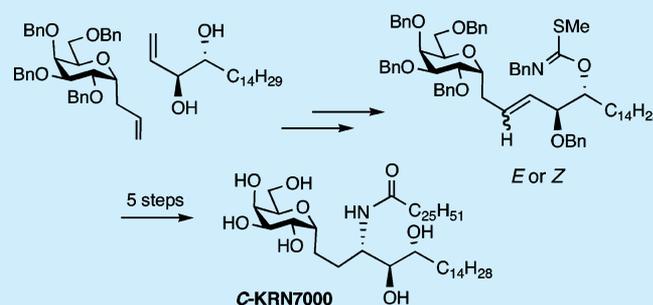
The implication of glycosphingolipids in a variety of cellular pathways has generated much interest in analogues for use as biomechanistic probes.[1−5] Structures that are modified in the polar head region of the sphingosine residue are especially important because changes in this region generally have a profound impact on their biological properties.[6−10] In this context, C-glycoside frameworks are particularly interesting because they can answer structure−activity questions relating to hydrolytic stability and conformation, while also allowing for the introduction of potentially new receptor contacts in a region that is often in intimate contact with receptor sites.[11,12] Herein, in the synthesis of **2**, the C-glycoside of the potent immunostimulatory glycolipid KRN7000 **1**, we illustrate a C-glycoside synthesis that is well-suited to C-glycosphingolipids that are structurally diverse in the polar head region (Figure 1).[13−18]
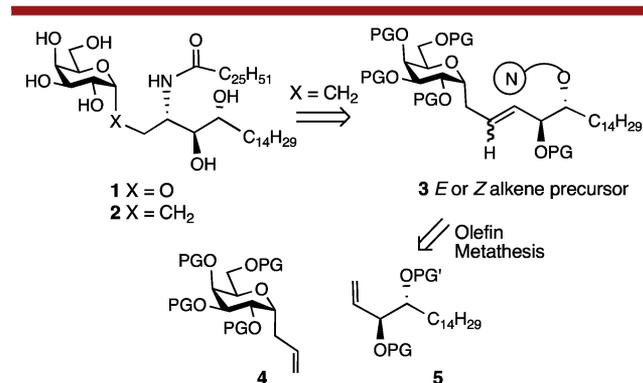
Figure 1. Intramolecular nitrogen delivery for synthesis of C-glycosphingolipids.

The general approach centers on intramolecular delivery of the C2 nitrogen on a homoallylic alcohol template **3**. This strategy is appealing for analog libraries because the latter can be assembled in a modular fashion from relatively simple sugar and lipid precursors **4** and **5**, and be relayed to diverse analogues through different alkene functionalization reactions. The specific tactic of intramolecular nitrogen delivery on an alkene precursor is to be distinguished from, and complements, less direct methods for introducing nitrogen in C-glycosphingolipids, through epoxide and allyl cyanate precursors.[16−18]

To this end, we envisaged the stereoselective Knapp halocyclization of a homoallylic carbonimidothioate to give a cyclic carbamate precursor of C-KRN7000. However, while these reactions have been reported for cyclopentenol and cyclohexenol derivatives, to the best of our knowledge conformationally unrestrained, noncyclic carbonimidothioates, as required here, have not been examined.[19,20] Related electrophilic cyclizations on acyclic unsaturated imidates suggested a homoallylic over an allylic carbonimidothioate precursor in order to obtain the stereochemical motif present in C-KRN7000.[21,22] A priori, the Z-alkene was expected to favor the desired syn selectivity for the newly created 1,3-amino alcohol residue, and the E-alkene to favor the 1,3-anti motif.[23] However, given the stereochemical uncertainty for such highly substituted frameworks, it was appropriate to examine both Z and E substrates.

An alkene metathesis strategy was selected for its long-term synthetic potential. Accordingly, compatibility with diverse functionality and delivery of both E and Z alkenes from the same sugar and lipid precursors were considered attractive attributes. In particular, while syntheses via anion-based

olefinations or alkyne precursors can be envisaged for the specific case of the C-glycoside **2**, these methods are not as general for vicinal disubstituted alkenes with electronegative substituents on both allylic carbons.[15,24] Such materials are required for C-glycosides in which there is an electronegative substituent on the pseudoanomeric carbon, an especially interesting subgroup of C-KRN7000 analogues.[25] Thus, a tethered RCM was envisaged for the *Z* and a CM for the *E* substrates. The precursors were the known materials C-allyl glycoside **6** and (3S,4R)-octadec-1-ene-3,4-diol **8** (Scheme 1).

Scheme 1. Carbohydrate and Lipid Alkene Precursors
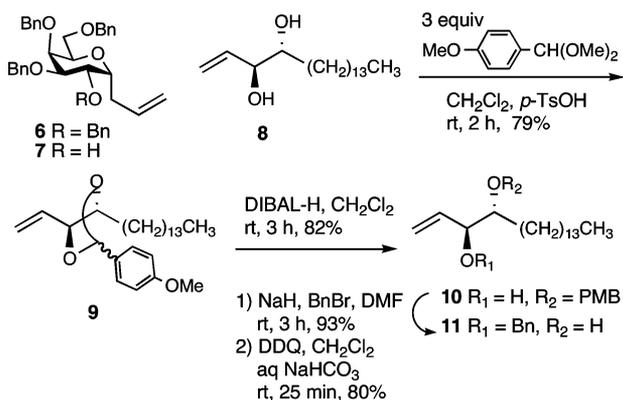
The former was obtained via an established C-allylation procedure on penta-*O*-acetyl-β-D-galactopyranose.[14,17,26] The latter can be prepared via Sharpless asymmetric epoxidation methodology on divinylcarbinol but, for this study, was obtained from D-ribose (Supporting Information).[27,28]

For the *Z* alkene synthesis, **6** was converted to hydroxyalkene **7** via a known two-step iodoetherification–reductive elimination protocol.[29] Methoxybenzylidination on **8** and reductive acetal cleavage with DIBAL-H provided the lipid partner **10**. Hydroxyalkenes **7** and **10** were then converted to the mixed phthalate **12**, in 83% yield over two steps (Scheme 2). RCM on **12** using Grubbs II catalyst led to the *Z* cycloalkene **13** in 93% yield, with no evidence for the *E* isomer. The diester **13** was then transformed into the desired *Z*-homoallylic alcohol **14** in 75% yield over three straightforward alcohol protecting group steps. For the *E* isomer, alkene partners **6** (2 equiv) and **11** (derived via routine protecting group operations on **10**) were subjected to CM using the Grubbs II catalyst. The CM product was obtained exclusively as the *E* isomer **15** within the limits of NMR detection, in approximately 48% yield based on alkene **11**. The stereochemistry of the *E* and *Z* alkenes were assigned from *J* values of the alkene protons.

The carbonimidothioate precursors **16** and **18** for the key electrophilic cyclization were next prepared by sequential treatment of **14** and **15** respectively, with sodium hydride, benzyl isothiocyanate, and iodomethane, following the Knapp protocol (Scheme 3).[19] Treatment of the *Z* substrate **16** with iodonium dicollidine perchlorate (IDCP) in dichloromethane provided the iodocarbamate **17** in 80% yield, as the only observable iodocyclization product. The stereochemistry at the newly created 1,3-amino alcohol was assigned as *syn* by conversion of **17** to the eventual target (*vide infra*). The relative stereochemistry at the iodinated carbon was deduced from the established *anti* addition in these reactions. Iodocyclization of the *E* substrate **18** also produced a single iodocarbamate **19**, albeit more slowly, and in an appreciably lower yield (ca. 54%).

Scheme 2. Synthesis of *E*- and *Z*-Homoallylic Alcohols
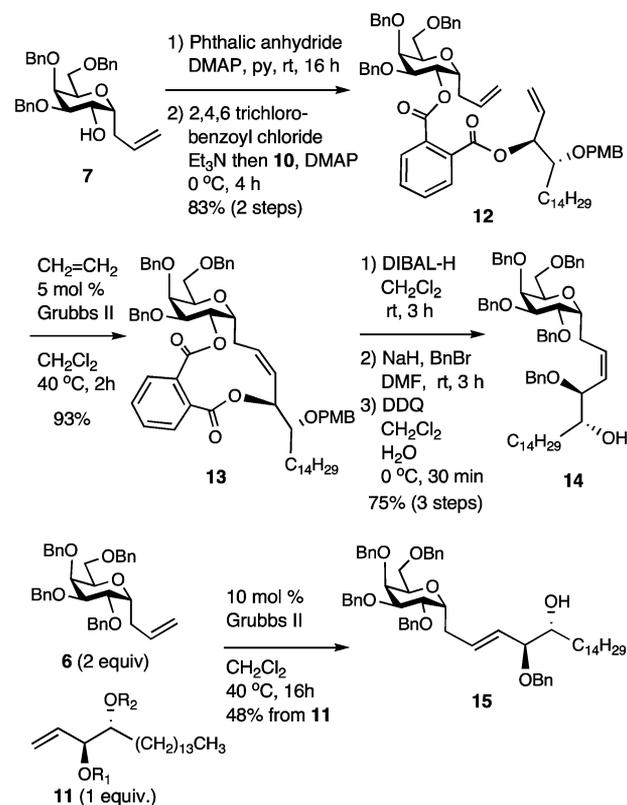
**Scheme 3**
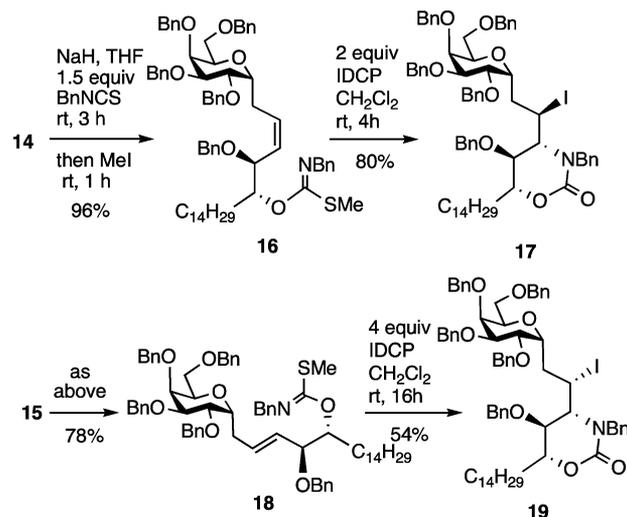
The absolute stereochemistry at the aminated carbon in **19** was shown to be the same as in **17**, by subsequent deiodination of both **17** and **19** to the identical product **20** (*vide infra*) (Scheme 4). Thus, the reactions of these homoallylic carbonimidothioates show identical facial selectivity in the iodocyclization on the alkene, regardless of alkene geometry (i.e., in both *E* and *Z* cases the *syn*-1,3-amino alcohol is formed). The result is in contrast to the iodocyclizations of *E*- and *Z*-trichloroacetimidates and related electrophilic cyclizations, in which disubstituted *Z*-alkenes give the *syn*-1,3-motif, but the *E*-substrates give the *anti*-1,3 pattern.[22,23]

The different stereochemical result seen for the *E*-alkenes in the carbonimidothioate vs trichloroacetimidate substrates may

Scheme 4. End Games for C-KRN7000
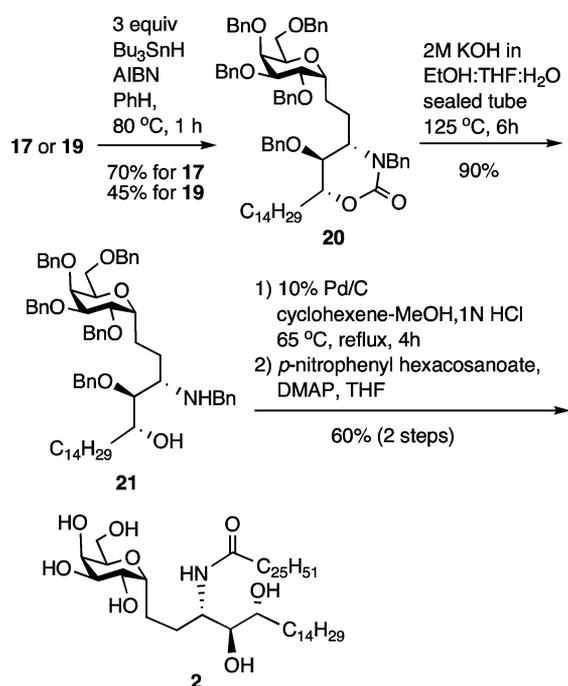
be due to steric effects brought about by the benzyl substituent that is present on the nucleophilic nitrogen in the carbonimidothioate but not on the nitrogen of the trichloroactimidate. Thus, following a reactant-like transition state (TS) generally invoked for such cyclizations competing TSs, A and A′, in which the alkene is eclipsed with the allylic C−H or C−O bond are envisaged (Figure 2).[23,30] TS A′ is disfavored in the
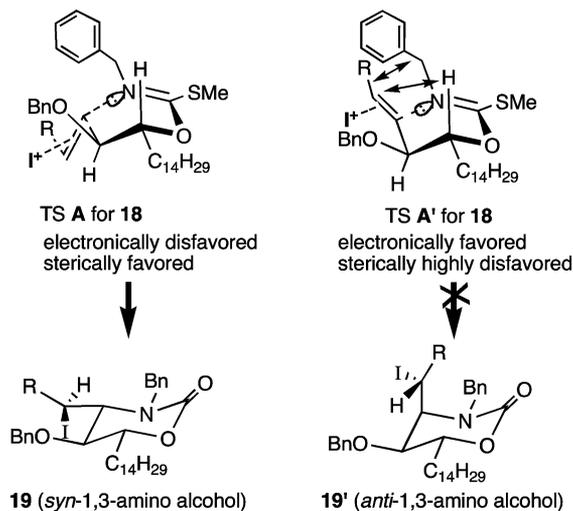

Figure 2. Transition states for iodocyclization of *E*-carbonimidothioates.

carbonimidothioate cyclization even though it is electronically stabilized (alkene eclipsing the allylic OBn), because steric interactions involving the forming pseudoaxial substituent and the pseudoaxial hydrogen and the benzyl group on the nitrogen are more crucial. Therefore TS A, which matches the *syn*-1,3 product **19**, is favored. In the case of the *E*-trichloroacetimidate, the electronically favored TS corresponding to A′ is favored over A, because the benzyl group that is responsible for

destabilizing steric interactions in the carbonimidothioate substrate is not present. The *Z*-alkenes favor the *syn*-1,3 motif for both the carbonimidothioate and trichloroacetimidate substrates, because, in both susbtrates, the *Z* TS corresponding to A′ is destabilized by A-1,3 strain (with the OBn group), relative to the A TS.

Bu$_3$SnH deiodination of **17** and **19** provided in 70 and 45% yields, respectively, the identical product **20**, as judged by HRMS as well as ^{1}H and ^{13}C NMR (Scheme 4). The synthetic ramification of these results is that either *E* and *Z* alkene precursors can be used for C-KRN7000, albeit the *Z* precursor would be more productive. Following procedures for the processing of related derivatives, **20** was transformed to **2** in 54% yield over a three-step sequence including carbamate hydrolysis, cleavage of benzyl protecting groups, and amidation with *p*-nitrophenyl hexacosanoate. The ^{1}H and ^{13}C NMR of the final product were essentially identical to the literature data for **2**. Clear differences between the NMR spectra for **2** and its amine epimer further supported the stereochemical integrity of **2** (Supporting Information).

In conclusion, a modular strategy for C-glycosphingolipids that centers on the alkene metathesis union of relatively simple carbohydrate and lipid precursors has been described. Analog diversity can be further facilitated by functionalization of the products from the metathesis step. One such strategy entailing intramolecular nitrogen delivery via electrophilic cyclization on a homoallylic carbonimidothioate has been illustrated in the synthesis of the C-glycoside of the immunostimulatory glycolipid KRN7000. More extensive investigations on these carbonimidothioate cyclizations and evaluation of other alkene functionalization strategies toward more diverse C-glycosphingolipids are underway.

■ ASSOCIATED CONTENT

ⓢ Supporting Information

Experimental procedures, characterization data for all new compounds, and copies of ^{1}H and ^{13}C NMR spectral for **2, 8−21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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