Carbohydrate Research 407 (2015) 148–153

Contents lists available at ScienceDirect

Carbohydrate Research

journal homepage: www.elsevier.com/locate/carres

C-glycosphingolipid precursors via iodocyclization of homoallylic trichloroacetimidates

Ahmad S. Altiti [a, b], David R. Mootoo [a, b, *]

[a] Department of Chemistry, Hunter College, 695 Park Avenue, New York, NY 10065, USA
[b] The Graduate Center, CUNY, 365 5th Avenue, New York, NY 10016, USA

ARTICLE INFO

Article history:
Received 18 December 2014
Received in revised form
10 February 2015
Accepted 12 February 2015
Available online 21 February 2015

Keywords:
Glycomimetic
C-Glycoside
Glycolipid
KRN7000
Imidate
Oxazine
Iodocyclization

ABSTRACT

The iodocyclization of homoallylic trichloroacetimidates derived from α-*C*-allyl galactoside were investigated. In line with the stereochemical trend observed for less substituted non-glycosylated frameworks, *E* and Z substrates delivered stereoselectively the 1,3-*anti* and 1,3-*syn* amino alcohol motifs, respectively. These products are advanced precursors to *C*-glycosides of the potent immunostimulatory glycolipid KRN7000.

1. Introduction

The involvement of glycosphingolipids in a variety of biological pathways has created a demand for unnatural analogs for use as mechanistic probes.[1–8] A popular subset thereof are *C*-glycosides, which are of interest because of their greater hydrolytic stability and conformational mobility compared to their parent O-glycosides.[9–13] However, the synthesis of these materials are not trivial, with a major challenge being the stereoselective fabrication of the pseudoanomeric bond, which is exacerbated for structures with highly substituted aglycone segments, as in the case of *C*-glycosphingolipids. One solution to this problem is to elaborate simple *C*-glycosides in which the pseudoanomeric configuration is 'preset'.[14–24] In this vein *C*-allyl glycosides of a variety of different monosaccharides are available in either pseudoanomeric configuration,[25–29] and new approaches for their transformation to more functionalized *C*-glycosides are of interest.

Towards this end, we have recently reported a strategy in which *C*-allylglycosides **1** are converted to homoallylic alcohol derivatives **2**, which serve as templates to *C*-glycosphingolipids **5** via an intramolecular nitrogen delivery strategy (Scheme 1). Our initial execution of this plan utilized the iodocyclization of a homoallylic carboimidothioate **3**.[30] Herein, we describe our results on the cyclization of related trichloroacetimidates **4**. These studies were directed at *C*-glycosides of the potent immunostimulatory glycolipid KRN7000 **9** (Scheme 2).[31]

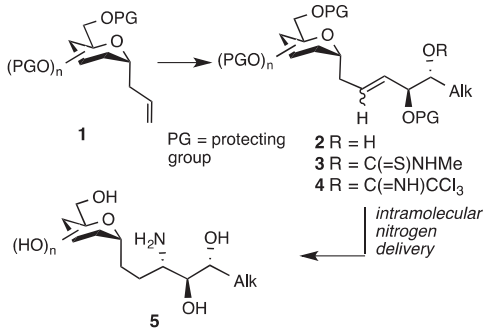
2. Results and discussion

2.1. Synthetic design

The specific templates **6** and **7**, chosen for this study were of interest because of their easily availability from known precursors, and their potential as versatile relay compounds to *C*-glycosides of KRN7000 and related sphingolipids (Scheme 2). Studies on the iodocyclization of simple homoallylic tricloroacetimidates suggest that the stereochemistry of this cyclization depends primarily on alkene geometry and the configuration at the allylic position.[32–34] Thus, the reaction of *E*-alkene **6** is expected to favor the 1,3-*anti* amino alcohol motif (cf. **22** vide infra), which would lead to the 'unnatural' stereochemistry in C-KRN7000 (i.e., **8a**), because of stereoelectronic factors due to the allylic oxygen. In contrast, the reaction of the *Z*-isomer **7** is predicted to give the 1,3-*syn* amino

* Corresponding author. Tel.: +212 772 4356; fax: +212 772 5332.
E-mail address: dmootoo@hunter.cuny.edu (D.R. Mootoo).

http://dx.doi.org/10.1016/j.carres.2015.02.005
0008-6215/



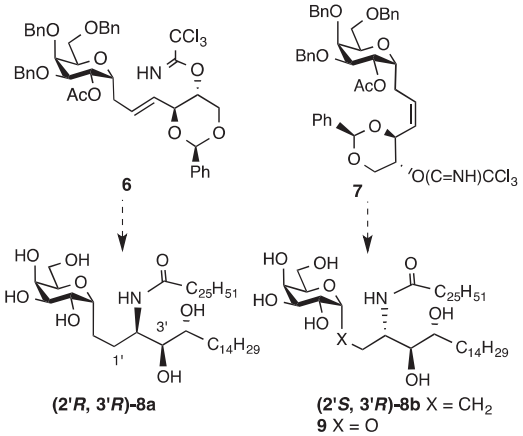
Scheme 1. *C*-glycosphingolipids via intramolecular nitrogen delivery.

alcohol derivative (cf. **23**, vide infra), because $A^{(1,3)}$ strain overrides the directing effect of the allylic substituent. However, because of the highly substituted nature of **6** and **7**, and the conformational rigidity imposed by the cyclic acetal framework, neither the expected stereoselectivity nor chemoselectivity in these reactions was assured. With regards to the latter, to reduce the likelihood of deleterious THF formation involving the C2-oxygen on the sugar ring, the 2-OH on the sugar segment was protected as an acetate[15,23,35] Schemes 3–5.

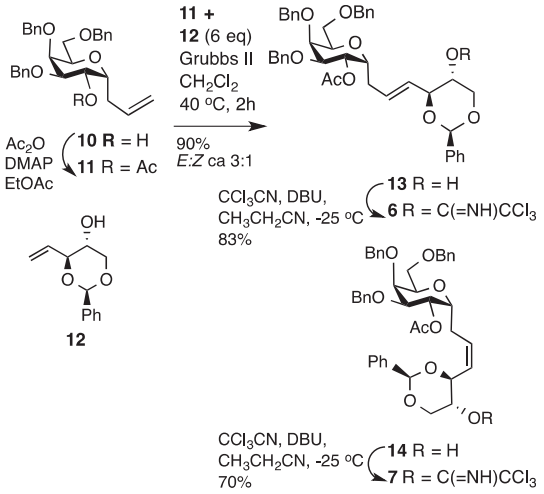
2.2. Synthesis

We envisaged that a cross metathesis (CM) strategy would provide the desired *E* and *Z* frameworks in a single step, with the former as the major isomer.[17,30,36] Accordingly, CM on known alkenes, *C*-allyl galactoside **11**[35] and the glucose derived alkene **12**[37] (6 equiv), using Grubbs II catalyst, produced an *E*:*Z* mixture of homoallylic alcohols **13** and **14** in 90% yield from **12**, as an approximately 3:1 *E*:*Z* mixture, as determined by ^{1}H NMR analysis. J_{vic} values of 15.7 and 11.0 Hz for **13** and **14**, respectively, supported the assigned alkene geometry. Treatment of **13** and **14** with DBU and trichloroacetonitrile provided the respective trichloroacetimidates **6** and **7**.

A more stereoselective synthesis of the *Z*-homoallylic alcohol **14** was performed using a Wittig olefination strategy. Thus, *C*-allyl glycoside **10** was converted to alcohol **16** through standard procedures for alcohol silylation and alkene processing. Transformation of **16** to the iodide **17** and reaction of the latter with triphenylphosphine provided phosphonium salt **18**. The use of the *tert*-butyldimethylsilyl protecting group was important for this

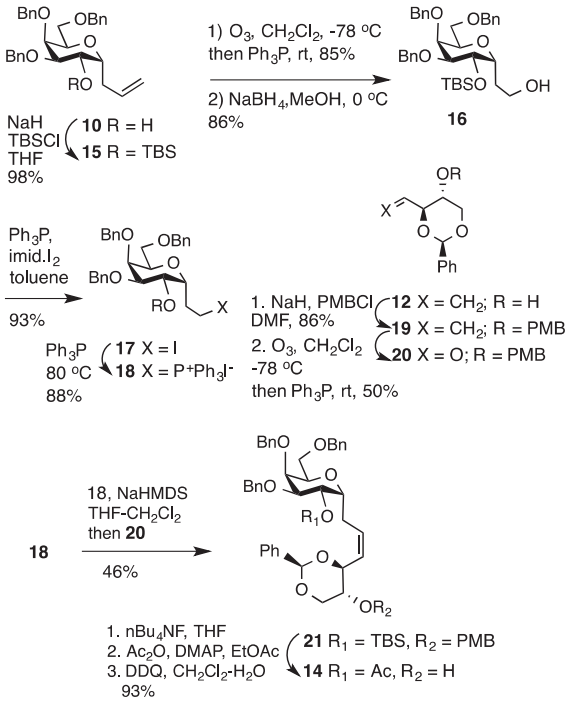


Scheme 2. Homoallylic trichloroacetimidate precursors for *C*-glycosides of KRN7000.



Scheme 3. Cross metathesis strategy for homoallylic trichloroacetimidates.

synthesis as benzyl and *p*-methoxybenzyl ethers were found to give appreciable amounts of the tetrahydrofuran product resulting from nucleophilic attack by the C2-oxygen, during the iodination step.[15,23] Aldehyde **20** was obtained from **12** after alcohol benzylation and ozonolysis of the alkene. Treatment of **18** in a mixture of THF and dichloromethane at −78 °C with NaHMDS, followed by addition of **20** to the resulting ylide, provided alkene **21** in 46% yield from **18**, as exclusively the *Z* isomer within the limits of ^{1}H NMR detection. The solvent mixture for this reaction was critical as pure THF gave lower *Z*:*E* ratios. This result may be due to a higher effective concentration of the metal cation in the reaction with pure THF, which facilitates oxaphosphetane reversion, and consequently stereochemical drift.[38,39] That the relative configuration at the α-carbon in **20** was unaffected by epimerization under the conditions of the Wittig reaction, was confirmed by correlation of the Wittig



Scheme 4. Wittig strategy for *Z*-homoallylic trichloroacetimidate.