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TETRAHEDRON: *ASYMMETRY*

Synthesis of cyclitols via ring-closing metathesis

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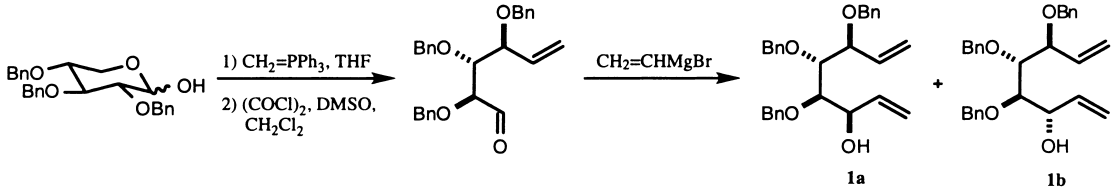
Abstract

A convenient synthesis of enantiomerically pure and differentially protected L-*chiro*- and *myo*-inositols as well as conduritols B and F from 2,3,4-tri-*O*-benzyl-D-xylopyranose via ring-closing metathesis is reported. The facile synthesis of conduritol B constitutes a short formal synthesis of (−)-cyclophellitol.

Recognition of the biological importance of cyclitols has stimulated considerable synthetic activity, generating an increasing demand for their enantiomerically pure and differentially protected derivatives.[1] Natural carbohydrates have proven to be excellent synthetic precursors for this class of compounds due to their ready availability and practicality of the published approaches.[2] The carbocyclization step in these syntheses has been achieved by several methods, the most useful being the Ferrier reaction[3] and SmI_2-mediated pinacol coupling.[4] In this paper, we report the application of ring-closing metathesis as a strategy for carbohydrate to cyclitol transformation.[5]

Installation of the terminal double bonds into the carbohydrate skeleton was readily achieved as previously reported[6] for the synthesis of diastereomeric alcohols **1a** and **1b** from 2,3,4-tri-*O*-benzyl-D-xylopyranose (Scheme 1). It should be noted that diastereoselectivity of the Grignard addition was moderately controllable by adjustment of solvent and chelating salt as indicated in Scheme 1.[6]



1a **1b**

conditions **A** (CH_2Cl_2 : THF (5:1); -78 °C) 1 : 3

conditions **B** (CH_2Cl_2; 3 eq $MgBr_2$•OEt_2; -78 °C) 8 : 1

Scheme 1.

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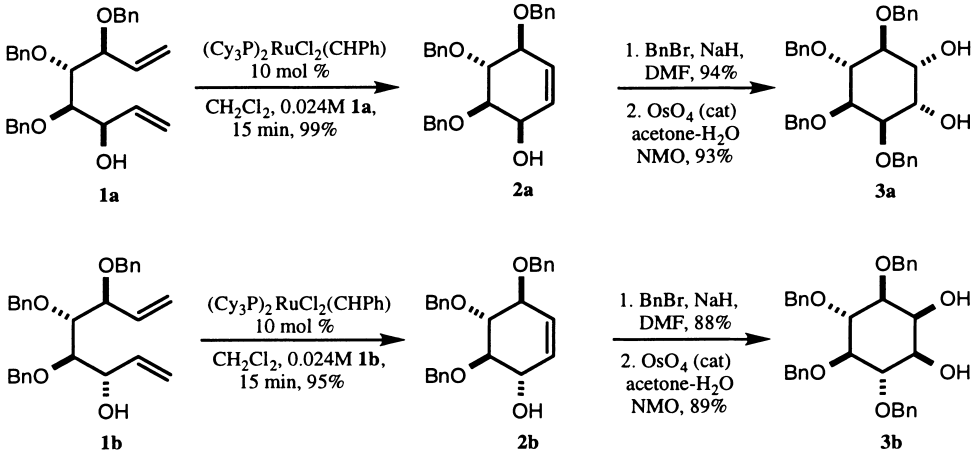
Unfortunately, **1a** and **1b** were not easily separable. For the purpose of this study, we used the pure compounds obtained by triisopropylsilylation of the mixture, chromatographic separation of the diastereomers, and desilylation.[6] However, since the diastereomeric products of the ring-closing metathesis (**2a** and **2b**) are well resolved chromatographically,[8] separation of **1a** and **1b** is unnecessary.

Reaction of **1a** or **1b** under Grubbs olefin metathesis conditions[7] provided conduritols **2a**[8,11a] and **2b**,[11c] respectively (Scheme 2). The facility with which these reactions proceeded is noteworthy. The cyclizations were complete in 15 min with 10 mol% of the Grubbs catalyst affording high yields of **2a** and **2b**. Benzylation and subsequent dihydroxylation of **2a** or **2b** provided L-*chiro*- or *myo*-inositol **3a**[9] or **3b**[10], respectively, in good yield as the only observed products.



Scheme 2.

Since both D- and L-xylose are commercially available, this strategy provides a short and practical approach to either enantiomer of conduritols **2** and inositols **3**. Since both antipodes of conduritols **2** have been useful intermediates in a number of syntheses[11] including the recent total synthesis of (+)-cyclophellitol by Trost and coworkers,[12] we believe that the RCM approach to inositols and conduritols will be found useful in the synthesis of a variety of important natural products and their analogues.

Acknowledgements

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