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Stereoselective protecting group free synthesis of D,L-gulose ethyl glycoside via multicomponent enyne cross metathesis—hetero Diels–Alder reaction

Daniele Castagnolo [a], Lorenzo Botta [a], Maurizio Botta [a,b,*]

[a] Dipartimento Farmaco Chimico Tecnologico, Università degli Studi di Siena, via A. de Gasperi 2, 53100 Siena, Italy
[b] Sbarro Institute for Cancer Research and Molecular Medicine, Center for Biotechnology, College of Science and Technology, Temple University, BioLife Science Bldg., Suite 333, 1900 N 12th Street, Philadelphia, PA 19122, USA

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ABSTRACT

An efficient and stereoselective synthesis of D,L-gulose was described. The key step of the synthetic route is represented by a multicomponent enyne cross metathesis—hetero Diels–Alder reaction which allows the formation of the pyran ring from cheap and commercially available substrates in a single synthetic step. The synthesis of D,L-gulose was accomplished without the use of protecting groups making this approach highly desirable also in terms of atom economy.

1. Introduction

L-Hexoses, which are known as rare sugars in the natural resources, sometimes play important roles in the microbial world. As notable examples, L-gulose **1**, the C-3 epimer of galactose **2**, is the key building block of the carbohydrate moiety of antitumor antibiotic bleomycin A2[1] and L-iduronic acid **3** is a typical component of mammalian dermatan sulfate, heparan sulfate and heparin[2] (Fig. 1). Gulose is an unnatural monosaccharide that exists as a syrup with a sweet taste. Both the D- and L-forms are not fermentable by yeast. L-Gulose is commercially available but it is very expensive. Syntheses of L-gulose[3] have been reported so far as well as the synthesis of D-gulose which has been prepared in a multistep process from D-glucose.[4] However, most of these synthetic approaches showed low convenience because they require creating new stereocentres by various reactions and making a large use of protecting groups. Hence, it is clear that the development of new and efficient methodologies that makes rare sugars 'common' are highly desirable. Herein we describe a novel and practical stereoselective synthesis of D,L-gulose ethyl glycoside through a multicomponent enyne cross metathesis—hetero Diels–Alder reaction carried out in a few minutes under microwave irradiation.[5] The synthesis was accomplished without the use of protecting groups making this approach also desirable for its 'atom economy' benefits.

2. Results and discussion

We first focused on the synthesis of the pyran ring through the reaction of trimethylsilylacetylene **4** with ethylvinyl ether **5** and ethyl glyoxalate **6** in the presence of Grubbs' 2nd generation catalyst. The multicomponent enyne cross metathesis—hetero Diels–Alder reaction was performed under microwave irradiation and was completed in only 20 min (2 runs × 10 min) leading to dihydropyrans **7a**–**b** as a mixture of *trans*/*cis* diastereoisomers in a 2:1 ratio. The diastereomeric mixture **7a**–**b** was equilibrated with $ZnCl_2$ affording **7a** as the single isomer.[6] Allylic oxidation of **7a** with SeO_2 in the presence of pyridine[7] led to diol **8** which was isolated as a mixture of diastereoisomers. Epimerization at C5 occurred due to the basic environmental reaction conditions (Scheme 1).

Hence, compound **7a** was reduced to alcohol **9** with $LiAlH_4$. The proton at C5 of **9** in fact is less acidic than the corresponding hydrogen at C5 of **7a** and as a consequence it is less inclined to

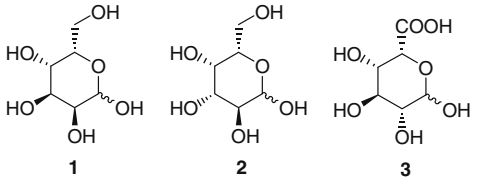

Figure 1. L-Hexoses.

* Corresponding author.
E-mail address: botta@unisi.it (M. Botta).

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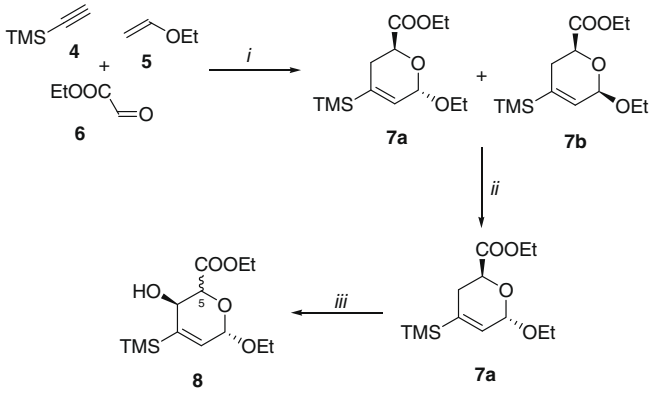
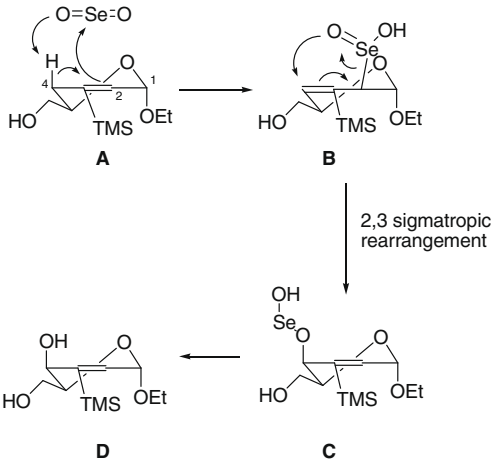


Scheme 1. Reagents and conditions: (i) Grubbs' cat. 2nd gen. 10 mol %, toluene, 80 °C, μW, 20 min; (ii) $ZnCl_2$, DCM, 24 h; (iii) SeO_2, pyridine, dioxane, reflux, 2 h.

epimerize during the allylic oxidation step. Reaction of **9** with SeO_2 in pyridine led in fact to diol **10** as a single diastereoisomer. The relative stereochemistry was determined by 2D-NOESY experiment. Compound **10** was reacted with TBAF and ^{t}BuOK with the aim to obtain derivative **11**. In both cases only starting material was recovered from the reaction mixtures and no traces of **11** were detected. On the contrary, dihydroxylation of **10** with OsO_4 and NMO led to compound **12**[8] which was then converted into D,L-gulose ethyl glycoside **13** through TBAF desilylation (Scheme 2).[9] In this case desilylation occurred due to the presence of the hydroxy moiety on C3 which favours the cleavage of carbon-silicon bond.[9a] The relative stereochemistry of was determined by 2D-NOESY experiment. No cross peak between H-2 and H-4 was observed.[8]

The observed stereoselectivity of the SeO_2 oxidation step was explained as follows: dihydropyran **9** reacted with SeO_2 leading to intermediate **B**. The attack of selenium on the double bond occurred at C2 on the less hindered face,[10] namely opposite to the ethoxy moiety. Subsequent 2,3 sigmatropic rearrangement and hydrolysis of **C** led in a stereoselective way to the diol **10** having the hydroxy moiety at C4 and *anti* as regards to the ethoxy group (Scheme 3).

In conclusion an efficient and stereoselective synthesis of D,L-gulose ethyl glycoside **13** was accomplished. Compound **13** was obtained stereoselectively in a few steps and high yields starting from cheap substrates. Moreover the complete synthetic route



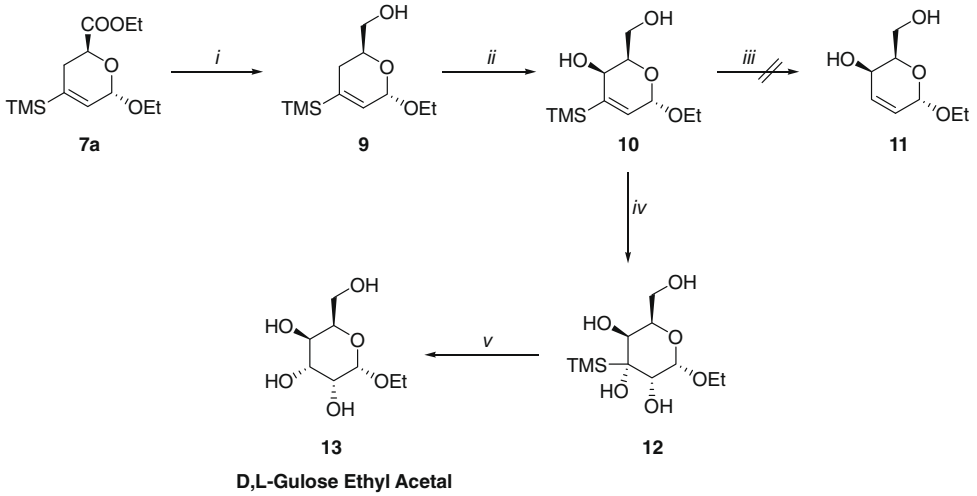
Scheme 3. Mechanism of the SeO_2 mediated hydroxylation step.

was completed without the use of protecting groups making this approach highly desirable also in terms of atom economy.

3. Experimental

3.1. General methods

Reagents were obtained from commercial suppliers and used without further purification. Anhydrous reactions were run under a positive pressure of dry argon. Silica gel 60 was used for flash chromatography (23–400 mesh). ^{1}H NMR and ^{13}C NMR spectra were measured on a 400 MHz spectrometer. Chemical shifts for protons are reported in parts per million (δ scale) and internally referenced to the $CDCl_3$ signal at δ 7.24 ppm. Chemical Shifts for carbon are reported in parts per million n (δ scale) and referenced to the carbon resonances of the solvent ($CDCl_3$: δ 77.76 ppm, the middle peak). Mass spectral (MS) data were obtained using a LC/MSD VL system with a 0.4 mL/min flow rate using a binary solvent system of 95:5 methyl alcohol/water. UV detection was monitored at 254 nm. Mass spectra were acquired in positive and negative mode scanning over the mass range. Elemental analyses (C, H, N) were performed in house.



Scheme 2. Reagents and conditions: (i) $LiAlH_4$, THF, rt, 3 h; (ii) SeO_2, pyridine, dioxane, reflux, 2 h; (iii) TBAF, THF, rt; (iv) OsO_4, NMO, THF, rt, 48 h; (v) TBAF, THF, rt, 3 h.