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Synthesis of C-disaccharides via a hetero-Diels–Alder reaction and further stereocontrolled transformations

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Abstract—The partial *de novo* synthesis of two new C-disaccharides containing D-glucosamine is described. The strategy is based on a hetero-Diels–Alder reaction leading to a 1:1 mixture of separable cycloadducts, which have been stereoselectively functionalized and converted into α-D-Gal*p*-(1→3)-*C*-D-Glc*p*NAc and α-L-Gal*p*-(1→3)-*C*-D-Glc*p*NAc.

Keywords: C-Glycoside; D-Glucosamine; Krapcho reaction; cis-Dihydroxylation

1. Introduction

Numerous studies have been devoted to the synthesis of C-glycosides,[1,2] the carbon-linked analogues of naturally occurring sugars, because these compounds are stable toward both enzymatic and chemical hydrolysis, and show biological properties similar[3] and even better[4] than those of the parent O-glycosides. To this end, several methodologies were developed by some of us, for example, the condensation of the carbanion of β-diketones and a formyl group of unprotected sugars in aqueous medium,[5] the indium-promoted condensation of bromoenopyranosides with formyl C-glucoside,[6] or the Mukaiyama aldol reaction of the latter with silyl enol ethers.[7]

The partial *de novo* synthesis of C-disaccharide analogues may offer the advantage of allowing stereochemical variation leading to molecular diversity. Because important naturally occurring oligosaccharides feature a *N*-acetyl-glucosamine moiety substituted at the position 3 by a galactose unit, we planned on synthesizing carbon linked analogues of the disaccharides D-sugar-(1→3)-Glc*p*NAc. In particular, oligosaccharides related to the antigenic determinant of the O-specific side chain of the human pathogen *Shigella dysenteriae* type 1 contain an α-linked 2-acetamido-2-deoxy-D-glucopyranosyl residue.[8] Many studies have been carried out to achieve the synthesis of the oligosaccharides that constitute the repeating units of this lipopolysaccharide to better understand the interactions between this antigen and antibodies, with the final goal of developing a synthetic vaccine.[9] Our approach to a C-mimetic of part of this antigenic determinant is based on a hetero Diels–Alder reaction using diene **1**,[10] which could be prepared efficiently in large scale, followed by stereo-controlled transformations.

2. Results and discussion

To construct the heterocycle from diene **1**,[10] we first envisaged the use of diethyl mesoxalate as the dienophile because, due to its symmetry, only two diastereoisomers resulting from the facial selectivity of the diene can be obtained. Numerous examples of hetero-Diels–Alder reactions involving diethyl mesoxalate have been described,[11] some of them being the key step of syntheses of sugars.[12] The hetero-Diels–Alder reaction between **1** and diethyl mesoxalate was carried out in toluene at 100 °C for 48 h to afford a 1:1 mixture of cycloadducts **2** and **3** in 82% yield (Scheme 1). The diastereoisomers were separated by column chromatography followed

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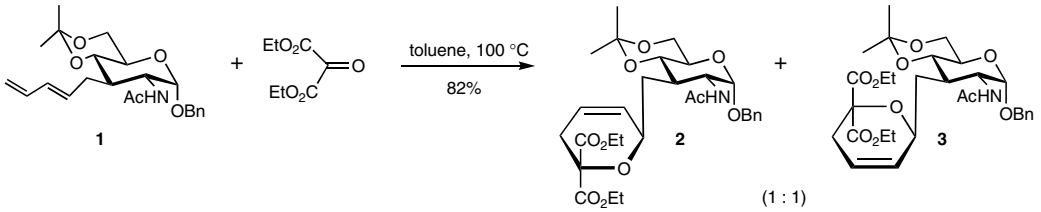
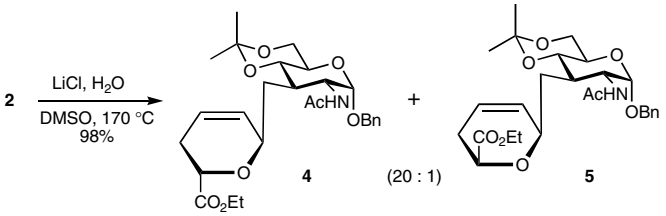


Scheme 1. Hetero Diels–Alder reaction of diene **1** with diethyl mesoxalate.

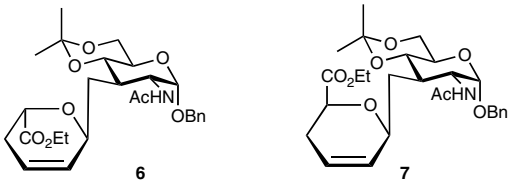


Scheme 2. Krapcho decarbethoxylation of compound **2**.

by crystallization. The stereochemistry at C-1′ for both compounds was deduced from NOE experiments and then confirmed by X-ray analysis.

The geminal diester **2** was then subjected to the Krapcho decarbethoxylation (Scheme 2).[13] Under classical conditions (LiCl, H_2O, DMSO, 170 °C), the reaction was very clean and gave the two diastereoisomers, **4** and **5**, in 98% total yield and in a 20:1 ratio as shown by ^1H NMR analysis. The major diastereoisomer, **4**, was obtained in a pure form by column chromatography, whereas **5** was recovered together with trace amounts of **4**.

Having proven the absolute configuration at the anomeric carbon (C-1′) of their precursor **2**, the stereochemical outcome of the decarbethoxylation was deduced from NMR experiments. In the case of **4**, the presence of NOEs between H-7b and H-3, H-7a and H-1′, H-1′ and H-3 suggested the preferred relative orientation of the two sugar units (Fig. 1). The NOE observed between H-7b and H-5′ allowed us to establish a trans disposition of the substituents at positions 1′ and 5′ of the enopyranoside ring, which adopts a ^5H_O half chair conformation (Fig. 1, $R_1 = H\text{-}5'$, $R_2 = CO_2Et$). In fact, the alternative half chair conformation shown in Figure 1, that is, $^OH_5$, was not compatible with the above-mentioned NOEs. From these observations, we could conclude that the newly formed ring belonged to the D stereochemical series. Therefore, **4** was bearing an α-D-enopyranosidic moiety and **5** was bearing a β-L unit.



Treated under the same conditions, the geminal diester **3** afforded a 20:1 mixture of **6** and **7** in 98% yield. The two products were isolated in a pure form by chromatography. The NOE experiments, confirmed by the

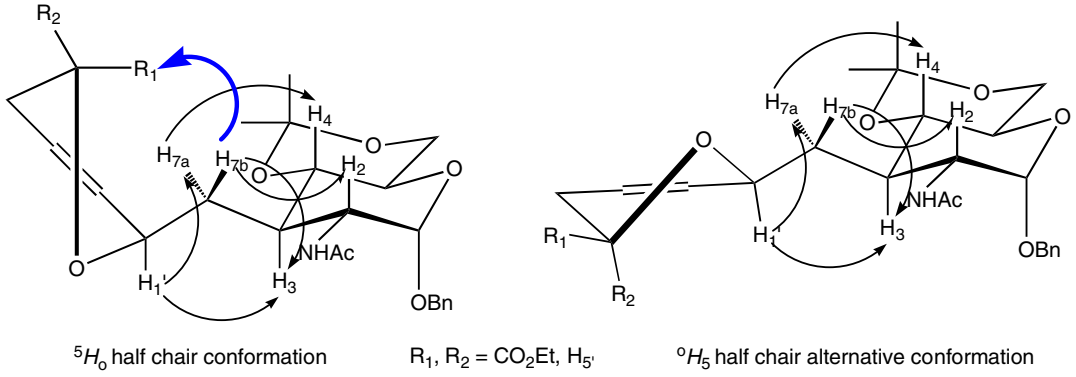


Figure 1. Structure determination of compound **4** by NOE experiments.