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Microwave-assisted stereoselective α-2-deoxyglycosylation of hex-1-en-3-uloses

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ABSTRACT

α-2-Deoxyglycosides were successfully synthesized by means of microwave-assisted glycosylation. Hex-1-en-3-uloses were treated with a catalytic amount of $AlCl_3$ and various *O*-nucleophiles including alcohols and sugars under microwave conditions. The desired α-2-deoxy-ulosides products were obtained in good to excellent yields with high stereoselectivity (α/β ⩾ 88/12).

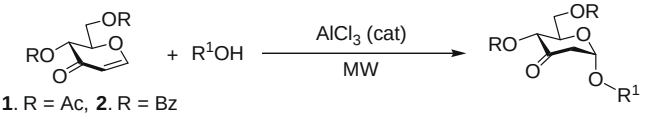
1. Introduction

Many antibiotic and antitumor natural products contain one or more 2-deoxyglycosides in their scaffolds, such as the angucycline family of antibiotics (landomycin A), the aureolic acid antibiotics (olivomycin A, chromomycin A_3), the enediynes (calicheamycin γ_1^I, esperamicins A_1 and C), the avermectins (avermectin B_{1a}, ivermectin), cholestane glycosides (OSW-1) and cardiac glycosides.[1] The carbohydrate moieties were necessary in these compounds for their bioactivity.

In the literature, several reports were made previously on the synthesis of α-2-deoxy-ulosides by means of the acid-mediated conjugate addition[2], the base-catalyzed Michael-type reaction,[3] the enolate alkylation,[4] the rhodium(I)-catalyzed 1,4-addition,[5] the organocopper addition[6,7] and the palladium-catalyzed addition.[8] However, long reaction time and low stereoselective result were required in these cases. In this work, we reported a new microwave-assisted methodology for the synthesis of *O*-2-deoxyglycoside by reacting hex-1-en-3-uloses with *O*-nucleophiles in the presence of $AlCl_3$ as the catalyst. In this new microwave-assisted method, the reaction provided the corresponding α-2-deoxyglycosylation as the high kinetic stereoselective products.

2. Result and discussion

Hex-l-en-3-uloses are attractive starting materials for glycosylations via Michael-type additions.[2–8] Hex-l-en-3-uloses **1** and **2** were synthesized from 3,4,6,-tri-*O*-acetyl-D-glucal through deprotection with methanolic sodium methoxide,[9] oxidation by pyridinium dichromate[10] and acetylation[11] or benzoylation. Many methods were reported to synthesize α-2-deoxy-ulosides.[2–8] However, their syntheses are not straightforward and smooth for the reaction time and the quantitative yield. In this Letter, we first used the microwave-assisted reaction and $AlCl_3$-catalyzed conjugation addition of acetyling hex-1-en-3-ulose (**1**) and benzoyling hex-1-en-3-ulose (**2**) to synthesize α-2-deoxyglycosylation; representative examples are shown in Scheme 1. In the microwave-assisted method, the reliable molding procedure involved the treatment of acetyling hex-1-en-3-ulose (**1**) with a catalytic amount of $AlCl_3$ and various alcohol reactants, such as benzyl alcohol, cyclohexanol, isopropanol and *n*-hexyl alcohol, at 60 °C with 100 W of



1. R = Ac, **2**. R = Bz

Scheme 1.

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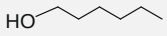
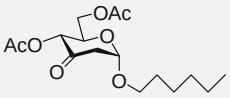
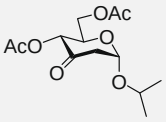
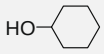
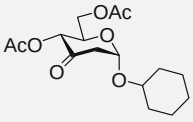
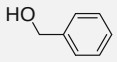
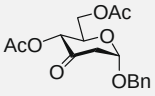
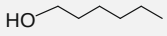
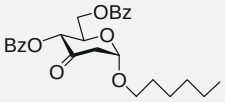
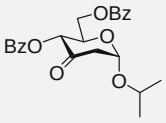
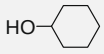
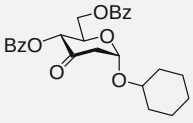
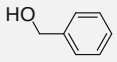
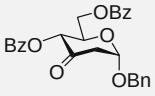
Table 1
Glycosylation of Hex-1-en-3-uloses (**1** and **2**) with simple alcohols

Entry	Substrate	Nucleophile	Product		α/β ratio[a]	Yield (%)
a	**1**			**3**	94/6	92
b	**1**			**4**	91/9	76
c	**1**			**5**	89/11	72
d	**1**			**6**	93/7	89
e	**2**			**7**	92/8	92
f	**2**			**8**	88/12	74
g	**2**			**9**	94/6	68
h	**2**			**10**	96/4	90

[a] The α/β ratios were determined by ^{1}H NMR.

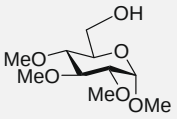
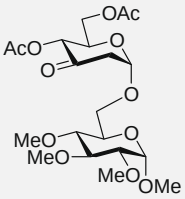
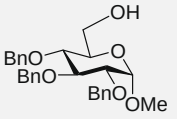
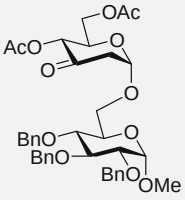
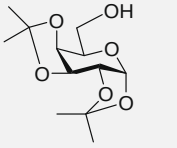
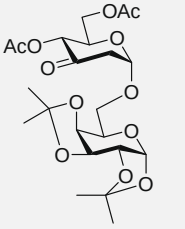
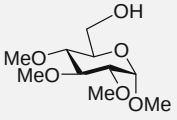
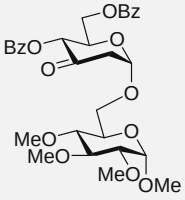
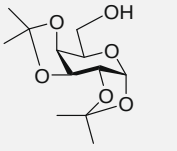
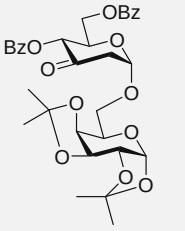
microwave energy within 6–10 min. After the reaction was completed, the reaction mixture was worked-up and purified by column chromatography on silica gel to give the desired *O*-2-deoxyglycoside products in good yields (**3**–**6**, 72–92%, see Table 1). All the products were fully characterized by spectroscopic methods. For example, the ^{1}H NMR spectrum of compound **4** showed a doublet of doublets at 5.30 ppm for the characteristic peak at the anomeric centre and a multiplet at 3.83 ppm for –C*H*(Me)$_2$ peak. The ^{13}C NMR spectrum possessed a characteristic peak at 197.96 ppm for the –C=O group, at 96.53 ppm for the C-1 and at 46.56 ppm for the C-2 of hex-3-ulose. The IR absorptions of **4** provided main peaks at 1741 cm^{-1} for stretching of the –C=O group. The synthetic strategy is applicable to the benzoylated hex-1-en-3-ulose (**2**) as the substrate under the same condition to afford the corresponding *O*-2-deoxyglycoside products **7**–**10** in 68–92% yields (see Table 1).

We have also compared the stereoselective behaviour of various alcohols in the Michael glycosylation, α-2-deoxy-ulosides were predominantly generated as the main isomeric products. The α/β 2-deoxy-uloside stereoselectivity was determined by ^{1}H NMR and the ratios were greater than 88/12 (α/β, see Table 1).

A few reported literatures[2,3] provided the direct and smooth method by using hex-l-en-3-uloses as substrates to generate disaccharides with high α-stereoselectivity and in moderate yields. Herein, we explored the newly developed method towards sugar alcohols **11**–**13**. When we treated a CH_2Cl_2 solution of acetyling hex-1-en-3-ulose (**1**) with a catalytic amount of $AlCl_3$ at 50 °C with 100 W of microwave energy within 25–30 min, the corresponding products **14**–**16** were produced in 59–72% yields and the ratios of α/β 2-deoxy-uloside stereoselectivity were more than 93/7 (α/β, see Table 2). Furthermore, we tried to prolong the reaction time under the same microwave process, the reaction results were not optimized clearly. When applying sugar alcohols **11**–**13** under the same conditions to benzoylated hex-1-en-3-ulose (**2**), we obtained the α-2-deoxy-uloside products **17**–**18** in 63–71% yields (see Table 2). During the study of the synthesis of α-disaccharides, we found that the high stereoselectivity could be accomplished in our new method. All of the product structures were determined by DEPT, NOESY and other spectroscopic spectra.

In conclusion, we have found a practical methodology for the synthesis of α-2-deoxyglycosides by using a catalytic quantity of

Table 2
Glycosylation of Hex-1-en-3-uloses (**1** and **2**) with sugar alcohols

Entry	Substrate	Nucleophile		Product		α/β ratio[a]	Yield (%)
a	**1**		**11**		**14**	93/7	68
b	**1**		**12**		**15**	95/5	59
c	**1**		**13**		**16**	96/4	72
d	**2**		**11**		**17**	96/4	63
e	**2**		**13**		**18**	93/7	71

[a] The α/β ratios were determined by ^{1}H NMR.

$AlCl_3$ under microwave irradiation condition. The newly developed method could be applied to *O*-nucleophile alcohols, including aliphatic, benzyl and sugar alcohols. The 2-deoxyglycoside products can be obtained with high α-stereochemistry and in good yields.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.10.049.

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