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MICHAEL-Type Additions in the Synthesis of α-*O*- and -*S*-2-Deoxyglycosides

Katja Michael and Horst Kessler*

Institut für Organische Chemie und Biochemie, Technische Universität München,
Lichtenbergstr. 4, D-85747 Garching, Germany

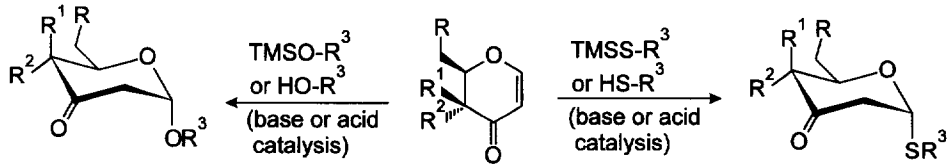
Abstract: *O- and S-Nucleophiles including galactose, serine and cysteine derivatives undergo MICHAEL-type additions to hex-1-en-3-uloses to furnish stereoselectively the α-2-deoxy-ulosides. The keto function at C-3 can be reduced stereoelectively with $NaBH_4$. Both configurations can be obtained depending on the presence or absence of $CeCl_3$. Glycosylation takes place either base catalyzed with DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) or KCN/18-crown-6 or acid catalyzed by ZnI_2.*

2-Deoxyglycosides are common structural elements of natural products, especially antibiotics with anti tumor activity, such as the anthracycline antibiotic daunorubicin,[1] the endiine antibiotic calicheamycin [2] or olivomycin A,[3] a member of the aureolic acid family. Both, α- or β-glycosidic linkages to the aglycon are found. While the specific therapeutic effect is thought to be caused by the aglycon, the carbohydrate residue is assumed to be responsible mainly for regulating the pharmacokinetics. The introduction of an *S*-glycosidic linkage or glycosylation of a drug with unnatural or rare 2-deoxy sugars instead of those common in eucaryots, can be used as a tool for enhancing the chemical stability or the resistance towards enzymatic degradation, thus increasing the half life of a pharmacon *in vivo*.

Here we present the use of hex-1-en-3-uloses in the synthesis of *O*- and *S*-2-deoxyglycosides (Scheme 1). Hex-1-en-3-uloses have a keto function at C-3 and differ in that point from glycals, often used in 2-deoxyglycoside syntheses.[4-12] The direct addition of nucleophiles to glycals under acid catalysis usually results in the formation of 2,3-unsaturated glycosides by migration of the allylic double bond, the FERRIER rearrangement.[13] Only the application of very mild, weakly acidic reaction conditions,[8,9] β-D-glycosidase in organic solvents [10] or some acylated 3-aminoglycals in the presence of TMSOTf (trimethylsilyl trifluoromethanesulfonate) [11,12] allows the direct one step-synthesis of 2-deoxyglycosides without loss of the substituent at C-3. However, hex-1-en-3-uloses are attractive starting materials for glycosylations via MICHAEL-type additions because FERRIER rearrangements cannot take place due to the lack of a leaving group at C-3. It is possible to use acid [14] as well as base catalysis for the MICHAEL-type addition, therefore the protecting groups involved can be suited. The resulting glycosylation products are α-configurated 3-ulosides, which can be reduced stereoselectively at C-3.

The hex-1-en-3-uloses [15] used in these studies were synthesized by allylic oxidation of D-glucal and D-galactal derivatives. 3,4,6-Tri-*O*-acetyl-D-glucal was either oxidized directly by KOSER's reagent,

[hydroxy(tosyloxy)-iodo]benzene [16] to give **1**, or after complete deprotection with methanolic sodium methoxide, by manganese dioxide or pyridinium dichromate [17] with subsequent acetylation. 4,6-Di-*O*-benzyl-D-galactal was synthesized by benzylation of D-galactal. Due to the higher reactivity of OH-4 versus OH-3 in D-galactal, a regioselective benzylation takes place.[6] Hexenulose **2** was obtained after oxidation of the unprotected OH-3 applying dimethyl sulfoxide/acetanhydride.[18] Alternatively, 4,6-*O*-isopropylidene-D-glucal was oxidized by pyridinium dichromate to give hexenulose **3.**



4 (R = OAc, R^1 = H, R^2 = OAc, R^3 = Bn)
5 (R = OAc, R^1 = H, R^2 = OAc, R^3 = Z-Ser-OBn)
6 (R = OBn, R^1 =H, R^2 = OBn, R^3 = 1,2:3,4-di- *O*-isopropylidene-D-galactose
7 (R, R^2 = 4,6-*O*-isopropylidene, R^1 = H, R^3 = Bn)

1 (R = OAc, R^1 = H, R^2 = OAc)
2 (R = OBn, R^1 = OBn, R^2 = H)
3 (R, R^2 = 4,6-*O*-isopropylidene, R^1 = H)

8 (R = OAc, R^1 = H, R^2 = OAc, R^3 = n-Bu)
9 (R = OAc, R^1 = H, R^2 = OAc, R^3 = All)
10 R = OAc, R^1 = H, R^2 = OAc, R^3 = Z-Cys-OAll)

Scheme 1: Synthesis of 2-deoxyglycosides via MICHAEL-type addition (Ac = acetyl, All = allyl, Bn = benzyl, n-Bu = n-butyl, TMS = trimethylsilyl, Z = benzyloxycarbonyl).

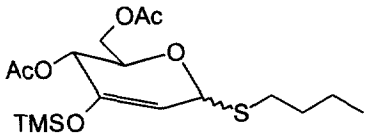
As previously reported, the MICHAEL-type addition of methanol (methanolic sodium methoxide) to a hex-1-en-3-ulose gives stereoselectively the α-*O*-ulosides.[19,20] In these reactions the alcohol served as aglycon and reaction medium as well. In contrast, for the synthesis of glycoamino acids or disaccharides approximately equimolar amounts of the glycosyl donor and acceptor are required. PEYVÁS et al. reported the MICHAEL-type addition of benzylmercaptane to a hex-1-en-3-ulose using equimolar amounts of the reactants in a mixture of pyridine and triethylamine.[21] We have found that DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) catalyzes MICHAEL-type reactions of *O*-nucleophiles and hexenuloses to produce predominantly the α-configurated ulosides in about 20 % yield (Table 1, entries 1-4).

Table 1: Results of the MICHAEL-type additions leading to α-2-deoxyglycosides.

entry	enone	*O*- or *S*-nucleophile	catalyst	glycosylation product	yield after column chromatography (%)
1	**1**	BnOH	DBU [22]	**4**	22
2	**1**	Z-Ser-OBn	DBU [22]	**5**	16
3	**2**	1,2:3,4-di-O-isopropylidene-D-galactose	DBU [22]	**6**	19
4	**3**	BnOH	DBU [22]	**7**	7
5	**1**	n-BuSTMS	KCN/18-crown-6 [23]	**8**	46
6	**1**	BnOTMS	KCN/18-crown-6 [23]	**4**	44
7	**1**	Z-Ser(TMS)-OBn	KCN/18-crown-6 [23]	**5**	3
8	**1**	AllSH	ZnI_2	**9**	22
9	**1**	BnOTMS	ZnI_2	**4**	35
10	**1**	Z-Cys-OAll	ZnI_2 [24]	**10**	41
11	**1**	n-BuSTMS	ZnI_2	**11**	76 (crude)

The yields could be increased up to 45 % when potassium cyanide/18-crown-6 (entries 5 and 6) or zinc iodide (entries 8-11) was used as catalyst. Originally, the latter two catalysts were utilized to protect ketones and aldehydes as thioketals by reaction of alkyltrimethylsilyl thioethers under mild conditions.[25] With α,β-unsaturated ketones and aldehydes the reaction resulted exclusively in 1,4-addition. Our results obtained with these catalysts in glycosylation reactions indicate, that a silylation of the mercapto species is not necessary. Allylmercaptane as well as the cysteine derivative Z-Cys-OAll reacted comparably well (entries 8 and 10).

In presence of potassium cyanide/18-crown-6 an inversion at C-4 of the galactose derived hex-1-en-3-ulose **2** (entry 3) took place during the glycosylation reaction. NMR studies revealed the equatorial position of the benzyl group of disaccharide **6**.



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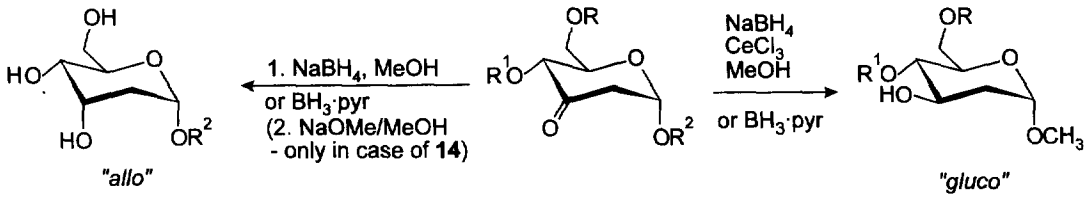
It is suggested that enol ethers are formed as reaction intermediates which could be confirmed by the isolation of the silylated glycoside **11** (entry 11).

The reduction of the keto function of some initial MICHAEL-type adducts was investigated with respect to the stereochemical outcome (Scheme 2). Reduction of uloside **4** with sodium borohydride and subsequent deacetylation gave the unprotected *allo*-configurated α-2-deoxy-benzylglycoside **14**. If the reduction of the acetylated methyluloside **12** was carried out in the presence of LUCHE reagent, cerium trichloride,[26,27] the *gluco*-configurated α-2-deoxy-methylglycoside **16** was obtained. In contrast to the acetylated compound **12**, the unprotected methyluloside **13** showed a different behaviour: Independently of cerium trichloride, reduction with sodium borohydride gave the *allo*-configurated glycoside **15**. When diborane pyridine complex was used as a reducing agent for **13**, the *allo*- and *gluco*-configurated glycosides **15** and **17** were obtained in a 2:1 mixture.



14 (R^2 = Bn)
15 (R^2 = CH_3)

4 (R = Ac, R^1 = Ac, R^2 = Bn)
12 (R = Ac, R^1 = Ac, R^2 = CH_3)
13 (R = H, R^1 = H, R^2 = CH_3)

16 (R = Ac, R^1 = Ac)
17 (R = H, R^1 = H)

Scheme 2: Reduction of the ulosidic keto-function. (The acetylated α-2-deoxy-methyl uloside **12** was synthesized by MICHAEL-type addition of methanol to hexenulose **1**.[19]
Subsequent deacetylation with sodium methylate/methanol gave the unprotected α-2-deoxy-methyluloside **13**.)

In conclusion, a new access to α-2-deoxy-*O*- and *S*-glycosides was developed by the use of hex-1-en-3-uloses as acceptors in MICHAEL-type additions of alcohols and mercaptanes including galactose, serine and cysteine. ZnI_2, DBU and KCN/18-crown-6 were suitable catalysts for the glycosylation reactions leading to the α-configurated ulosides in yields between 20 and 45 %. The ulosidic keto functions can be reduced stereoselectively with $NaBH_4$. Provided that the uloside was acylated, in the presence of $CeCl_3$ a 2-deoxy-*gluco*-configurated product was obtained, while in the absence of $CeCl_3$ 2-deoxy-*allo*-configurated glycosides were produced.

ACKNOWLEDGEMENT

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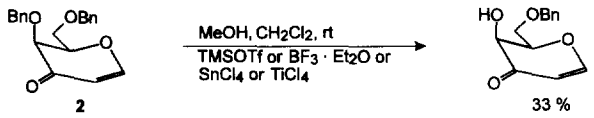
14. Unexpectedly, the attempt to add methanol to the 4,6-di-*O*-benzylated hex-1-en-3-ulose **2** under TMSOTf-, $BF_3 \cdot Et_2O$-, $SnCl_4$- or $TiCl_4$-catalysis, no addition product was observed. Instead, regioselective cleavage of the axial benzyl group at C-4 took place.



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23. For the reactions under KCN/18-crown-6 catalysis dichloromethane was used as a solvent just enough to dissolve the reactants.
24. A typical reaction procedure is examplified in the synthesis of glycoamino acid **10** (benzyloxycarbonyl-cysteine[(*S*)-2-deoxy-4,6-di-*O*-acetyl-α-D-erythro-hexopyranoside-3-ulosyl]-allylester): Enone **1** (13.6 mg, 0.060 mmol), Z-Cys-OAll (15.4 mg, 0.052 mmol) and ZnI_2 (5.0 mg, 0.016 mmol) were dissolved in 100 µL diethyl ether. The reaction mixture was stirred at room temperature for 24 h. After addition of 3 µL triethylamine, the solvent was removed in vacuo and the remaining raw material was purified by flash chromatography with acetone/hexane (1:2). 11.3 mg (44 %) of the target compound **10** was obtained as a colorless syrup. $R_f = 0.27$ in acetone/hexane (3:6); ^{1}H NMR (250 MHz, $CDCl_3$, 300 K): δ 7.40-7.28 (5H, m, aromat. H); 5.90 (allyl. methine H); 5.62 (1H, d, H-1); 5.32, 5.27 [2H, olef. CH_2 (allyl)]; 5.17 (1H, d, H-4); 4.71 (m, H-α); 4.67 (m, allyl., aliphat. CH_2); 4.58 (1H, m, H-5); 4.44-4.23 (2H, m, H-6, H-6'); 3.22, 3.06 (2H, m, H-β, H-β'); 3.16 (1H, m, H-2); 2.66 (1H, d, H-2'); 2.18, 2.08 (2 · 3H, 2s, 2 OAc) ppm.
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