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A One-Pot Synthesis of β-*C*-Glucopyranosides from *exo*-Glucal, *p*-Tolylsulfenyl Chloride, an α-Methoxyalkene, and an External Nucleophile

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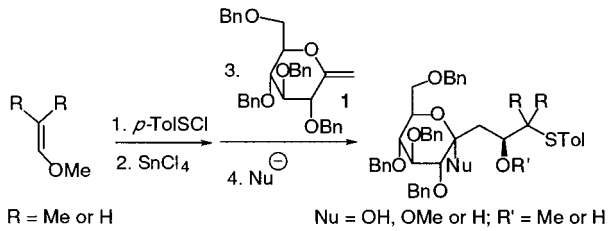
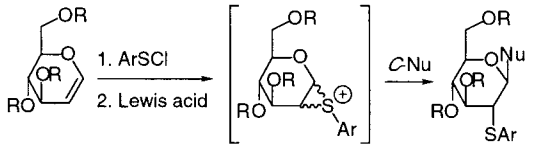
ABSTRACT



***β*-*C*-Glycosides were synthesized in one-pot experiments using the following sequence of four reactions: (i) addition of *p*-TolSCl to an α-methoxyalkene, (ii) generation of the episulfonium ion from a *β*-(arylsulfanyl)alkyl chloride, (iii) reaction of the episulfonium intermediate with benzylated *exo*-D-glucal to form a cyclic five-membered sulfonium salt, and (iv) quenching of the sulfonium salt with the external nucleophile: H_2O, CH_3OH, or $NaCNBH_3$.**

The development of new methods for the preparation of physiologically active compounds, including *O*- and *C*-glycosides, from simple, available, and inexpensive precursors is of unquestionable importance. One approach to making a new synthesis efficient is to carry out a reaction sequence as a one-pot procedure, where satisfactory yield of the desired compound must also be accompanied by a high level of stereoselectivity.[1,2] Previously, we have shown that ArSCl adducts of glycals can be readily converted to various *C*-glycosylic compounds (*C*-glycosides) using a convenient one-pot procedure (Scheme 1).[3−6] With tri-*O*-benzyl-D-glucal or tri-*O*-benzyl-D-galactal as the starting substrates, the reactions proceed in a highly stereoselective fashion providing 2-(arylsulfanyl)-substituted *β*-*C*-gluco- or

Scheme 1



β-*C*-glucopuranoside, major isomer

β-gluco:α-manno is from 5.3:1 to 99:1

C-Nu = TMS enol ethers, allylsilanes, TMSCN, RMgHal, aromatic and heteroaromatic compounds and vinyl ethers

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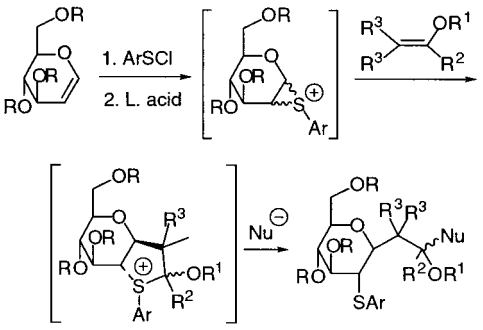
β-*C*-galactopyranosides, respectively. The major reason for the high stereoselectivity of these reactions is believed to be the formation of cyclic sulfur-stabilized intermediates: episulfonium ions and, in the case of vinyl ethers, five-membered sulfonium ions (Scheme 2). Following our interest

Scheme 2

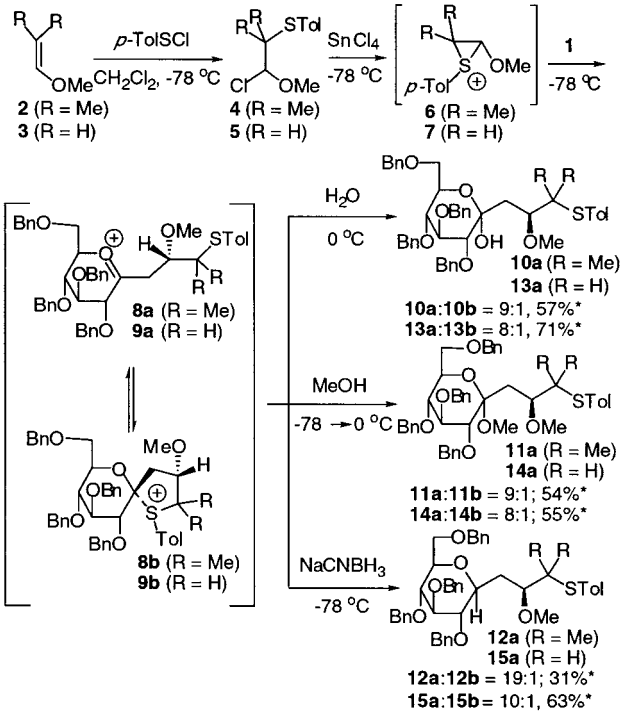


in the use of these and similar cyclic intermediates for synthesis of *C*-glycosides and related compounds, we have investigated the possibility of preparing these carbohydrate derivatives by reacting *exo*-glucal (**1**) with the episulfonium ions generated from β-(arylsulfanyl)alkyl chlorides. In this paper, we report the initial results of our study.

exo-Glucal[7] (**1**, 2,6-anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-D-glucohep-1-enitol) was synthesized from commercially available methyl α-D-glucopyranoside using the reaction sequence[8−13] proposed by the R. J. K. Taylor group and the Ramberg−Bäcklund rearrangement as a key step (Scheme 3).

The episulfonium ion **6** was prepared in situ from 1-chloro-1-methoxy-2-methyl-2-(*p*-tolylsulfanyl)propane (**4**) obtained by the addition of *p*-TolSCl to 1-methoxy-2-methylpropene (**2**, Scheme 3). The episulfonium salt reacted with *exo*-glucal **1** at −78 °C to form another intermediate that has either the oxonium (**8a**) or cyclic sulfonium (**8b**) structure or, most likely, is a mixture of **8a** and **8b** in equilibrium. The salts **8a** or **8b** could not be isolated; however, the intermediate of a similar ArSCl-mediated dimerization of two vinyl ethers

Scheme 3[a]



[a] Values with an asterisk are yields given for the mixtures of diasteromers.

was isolated, and its cyclic sulfonium structure was proven by X-ray crystallographic analysis.[1] Reactions of the sulfonium intermediates **8a**,**b** with H_2O at 0 °C and MeOH and $NaCNBH_3$ at −78 °C provided glycosides **10**−**12**, respectively.

Compounds **10**−**12** have two new chiral centers; thus, mixtures of up to four diastereomers could be expected. The analysis of ^{1}H and ^{13}C NMR spectra of **12** indicated that the glycoside was obtained predominantly in one diastereomeric form with traces (less than 5%) of another isomer. In the case of derivatives **10** and **11**, the reactions were less stereoselective and the mixtures of two isomers in a ratio of 9:1 (^{1}H NMR data) were obtained. Pure compounds **10a**, **11a**, **11b**, and **12a** were isolated using TLC.

It is known that, due to the anomeric effect, reactions of pyranoxonium intermediates with nucleophiles occur through attack of the latter from the bottom face furnishing predominantly, or exclusively, α-glycosides.[14] Since the oxonium intermediate **8a** has an alkyl group at C(1), its reaction with a hydride ion must lead to the β-*C*-glycoside **12a**. If a nucleophile reacted with the sulfonium salt **8b**, the other anomer, α-*C*-glucopyranoside, would be the major product. Cyclic sulfonium salt **8b** is formed as a result of the ArS group attacking from the bottom face, as directed by the anomeric effect. This suggests that the absolute configuration of the C(1) chiral center in the pyranose ring of the sulfonium

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salt is likely to be (*R*). Therefore, the sulfonium intermediate **8b** would be likely to react with a nucleophile by the S_N2 mechanism to form an α-*C*-glucopyranoside. In the ^{1}H NMR spectrum of **11a**, the large coupling constant, $J_{1,2} = 9.2$ Hz, is indicative of the *β*-*C*-D-gluco structure. The formation of this particular isomer suggested that the nucleophile reacted with the oxonium intermediate **8a**, rather than with the sulfonium intermediate **8b**.

The ^{1}H NMR signals of H(1a′) and H(1b′) in **12a** had large coupling constants $J_{1,1b'}$ and $J_{1a',2'}$ (Table 1), indicating the antiperiplanar orientation of H(1)/H(1b′) and H(1a′)/H(2′) (Figure 1). This suggested that the predominant conformation

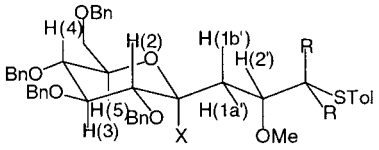


Figure 1. Stereochemistry of the major isomers of the synthesized *C*-glycosides **10**−**15**.

of the C(3)−C(2)−C(1)−C(1')−C(2')−C(3′) chain in the molecule has a zigzag shape.[15] The large value of $J_{1a',2'}$ and the low value of $J_{1b',2'}$ pointed to the (*S*) absolute configuration of the C(2′) stereogenic center.

The stereochemistry of **11a** and its diastereomer **11b** was determined using their NOESY spectra and the analysis of coupling constant values. According to the data obtained from the NOESY spectra, in both isomers the MeO group at the anomeric position is in close proximity to H(3) and H(5), whereas no NOE enhancements were observed between H(1a′,1b′) and H(3)/H(5). Therefore, both **11a** and **11b** are *β*-*C*-glucopyranosides and have the opposite absolute configurations of the C(2′) chiral center.

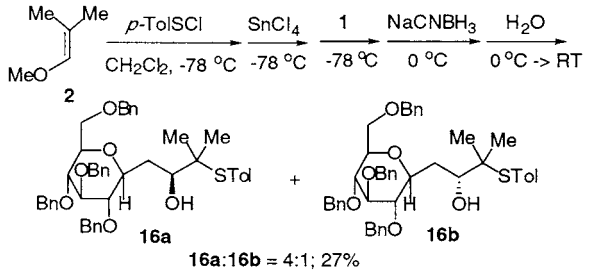
The NOESY spectrum of **11a** contained two signals indicating NOEs between H(1a′) and the anomeric OMe group and between H(1b′) and H(2); therefore, H(1b′) is anti to the MeO group. A large value for $J_{1a',2'}$ and a very low value for $J_{1b',2'}$ pointed to the (2′*S*) absolute configuration in **11a**. The combination of the NOESY data [a strong interaction between H(2) and H(1a′)] and characteristic coupling constant values (Table 1) obtained for minor isomer **11b** indicated that the absolute configuration of the C(2′) chiral center is (*R*).

The stereochemistry of **10a** was determined using 1D and 2D NMR spectroscopy data. As expected for the *β*-*C*-gluco structure, the NOESY spectrum showed no enhancement corresponding to interactions between H(1a′)/H(1b′) and H(3)/H(5). Only one of the C(1) hydrogens, H(1a′), with the chemical shift (*δ*) equal to 1.65 ppm, displayed a strong NOE with H(2); this placed H(1a') *anti* to the anomeric OH group. The signal of H(1a′) in the ^{1}H NMR spectrum appeared as a doublet of doublets with one large and one small coupling constants, whereas the signal of H(1b′) was a doublet of doublets with two large coupling constants (Table 1). These data are indicative of the (2′*S*) absolute configuration. Thus, NMR data for all major isomers **10a**, **11a**, and **12a** supported the same (*S*) absolute configuration of the C(2′) stereogenic center, as one could expect for the compounds prepared from the same intermediate **8a**.

Similar results were obtained when the episulfonium ion **7** obtained from the *p*-TolSCl adduct of methyl vinyl ether **3** was used in the reaction with *exo*-glucal **1** (Scheme 3). Upon treatment of intermediates **9a**,**b** with H_2O, MeOH, and $NaCNBH_3$, glycosides **13**−**15** were formed, respectively. The reactions proceeded with high stereoselectivity providing *β*-*C*-glycosides **13a**−**15a** as the major isomers. Their stereochemistry was determined based on analysis of coupling constant values and NOESY data using the same approach as described above for compounds **10a**−**12a**.

A rather unusual and unexpected result was obtained when the reaction mixture **8a**,**b** was treated with $NaCNBH_3$ at 0 °C. Instead of compounds **12a**,**b**, new products **16a** and **16b**, containing the OH group in the lateral chain, were isolated (Scheme 4). It is known that methyl ethers are usually inert

Scheme 4



in the presence of various hydrides, including borohydrides.[15] Several cases have been reported where the methoxy-substituted aromatic compounds were converted to the corresponding phenols using DIBAH.[16,17] However, removal of the methyl group from alkyl methyl ethers by metal hydrides is more unusual. We could find only one example[18] of this reaction type, which is highly selective and requires the formation of a specific cyclic intermediate. It also has been reported that $NaCNBH_3$ deprotects 4-methoxybenzyl ethers in the presence of $BF_3{\cdot}Et_2O$.[19] In our case, $NaCNBH_3$ did not remove the Bn groups of the pyranose ring. This suggested that the observed selective removal of the Me group in **16a** and **16b** was likely to take place through the

Scheme 5

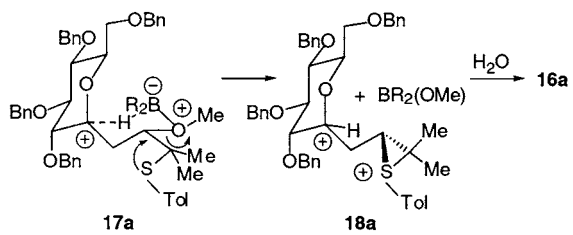


Table 1. Selected Chemical Shifts, δ (ppm), and Coupling Constants, $^3J_{HH}$ (Hz), in ^{1}H NMR Spectra ($CDCl_3$) of the Synthesized *C*-Glycosides

	10a (2′*S*)	**11a** (2′*S*)	**11b** (2′*R*)	**12a** (2′*S*)	**16a** (2′*S*)	**16b** (2′*R*)
H(1a′)	$\delta = 1.65$	$\delta = 2.10$	$\delta = 2.67$	$\delta = 1.92$	$\delta = 1.95$	$\delta = 1.61$
	$J_{1a',2'} = 2.8$	$J_{1a',2'} = 9.3$	$J_{1a',2'} = 1.2$	$J_{1a',2'} = 10.6$	$J_{1a',2'} = 5.8$ (5.6[a])	$J_{1a',2'} = 2.8$ (6.6[a])
	$J_{1a',1b'} = 14.3$	$J_{1a',1b'} = 15.3$	$J_{1a',1b'} = 14.9$	$J_{1a',1} = 2.3$	$J_{1a',1} = 2.8$ (3.8[a])	$J_{1a',1} = 2.0$ (4.4[a])
				$J_{1a',1b'} = 13.0$	$J_{1a',1b'} = 15.0$	$J_{1a',1b'} = 13.7$
H(1b′)	$\delta = 2.07$	$\delta = 2.44$	$\delta = 2.10$	$\delta = 1.97$	$\delta = 2.23$	$\delta = 1.83$
	$J_{1b',2'} = 11.5$	$J_{1b',2'} = 0$	$J_{1b',2'} = 10.9$	$J_{1b',2'} = 2.6$	$J_{1b',2'} = 4.9$ (6.0[a])	$J_{1b',2'} = 2.8$ (6.6[a])
				$J_{1b',1} = 10.6$	$J_{1b',1} = 7.9$ (7.2[a])	$J_{1b',1} = 10.6$ (4.4[a])

[a] Data are taken from the spectra recorded in [$^2H_6$]acetone.

sequential formation of two cyclic intermediates, **17a** and **18a** or **17b** and **18b**, respectively (Scheme 5).

According to the ^{1}H NMR data obtained for **16a** and **16b**, both isomers have the β-gluco configuration ($J_{1,2} = 9.2$ and 9.0 Hz, respectively) and, therefore, have opposite absolute configurations of the C(2′) stereogenic center. The values of coupling constants (Table 1) revealed that the minor isomer **16b** has one predominant conformation with the antiperiplanar orientation of H(1), H(1b′), and H(2′), whereas the major isomer **16a** with its coupling constants of medium value has no predominant conformation. The existence of one predominant conformation for **16b** can be explained by the presence of stabilizing intramolecular hydrogen bonding (Figure 2). The ^{1}H NMR spectrum of **16b** taken in

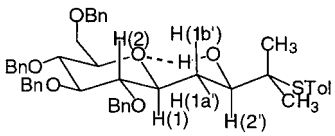


Figure 2. Intramolecular hydrogen bonding in **16b**.

[$^2H_6$]acetone, capable of breaking the intramolecular hydrogen bonding, had medium coupling constant values (Table 1); therefore, molecules of **16b** in this solvent had no predominant conformation.[15] All these data pointed to the (2′*R*) absolute configuration in **16b**. Thus, the removal of the MeO group took place with the retention of the absolute configuration at C(2′); this supported the idea of the episulfonium ion involvement in the reaction (Scheme 5).

In conclusion, we have shown that *exo*-glucal is a valuable substrate capable of reacting with episulfonium ions to form β-*C*-glucopyranosides, including those having a hydroxy or alkoxy group at the anomeric center. Currently we are investigating the scope and limitations of this method for stereoselective synthesis of various β-*C*-glycosides, including 1,1-dialkyl derivatives.

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Supporting Information Available: Full characterization for compounds **10a**−**16a**, **11b**, and **16b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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