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Reaction of Vinyl Ethers with ArSCl Adducts of D-Glucal

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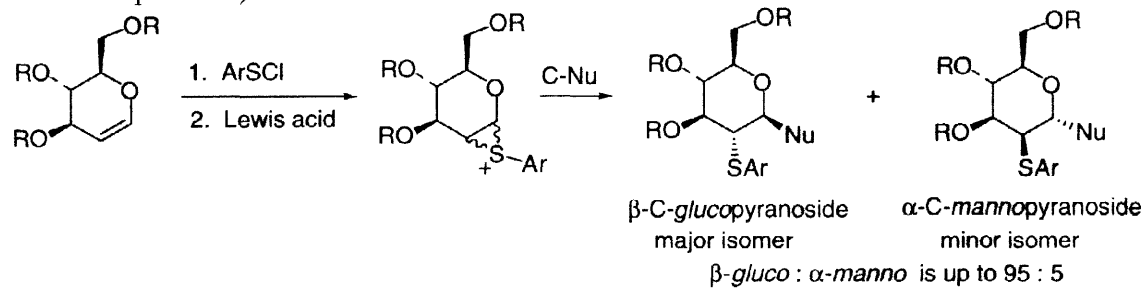
Abstract: Lewis acid mediated reactions of vinyl ethers with ArSCl adducts of benzyl protected D-glucal followed by quenching of the five-membered sulfonium salt intermediates with external nucleophiles, H_2O, MeOH, and *n*-Bu_4NBH_4, lead to a highly stereoselective formation of β-*C*-*gluco*pyranosides with different functional groups in the lateral chain.

Keywords: *C*-glycosides, glycals, vinyl ethers, sulfonium salts.

Introduction

During the past two decades the synthesis of *C*-glycosides has been an intriguing topic in both carbohydrate and organic chemistry.[1] Compounds of this type have been found in nature and often possess a variety of physiological activities.[2] As non-hydrolyzable analogs of *O*-glycosides, carbon-linked glycosides have been used as enzyme inhibitors[3,4] and substrates for carbohydrate-binding proteins.[3] Numerous methods have been proposed for the synthesis of *C*-glycosides, but the majority of these procedures give mixtures of α- and β-anomers with predominant formation of α-*C*-glycosides.[1,5,6] Recently we have reported that, in the presence of a Lewis acid, ArSCl adducts of tri-*O*-benzyl-D-glucal are capable of reacting with a number of *C*-nucleophiles including TMSCN, silyl enol ethers, silyl ketene acetals, allylsilanes, and Grignard reagents (Scheme 1).[7] These reactions provide β-*C*-*gluco*pyranosides with high stereoselectivity (the β-*gluco* : α-*manno* ratio is up to 95:5).



Scheme 1.

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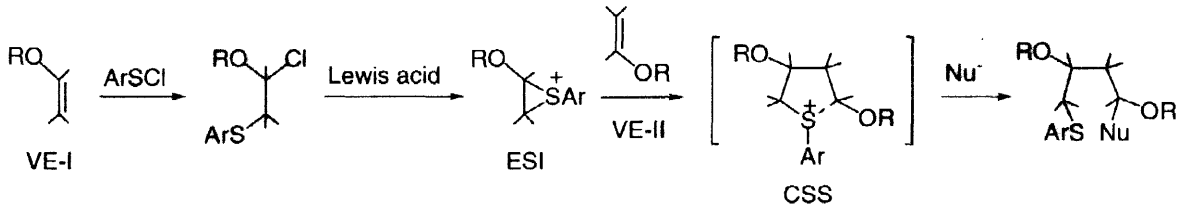
Vinyl ethers have not been used in organic synthesis as broadly as silyl enol ethers or other enols. To the best of our knowledge, vinyl ethers have not been used as carbon nucleophiles in the synthesis of *C*-glycosides and related compounds. Previously we reported the ArSCl mediated condensation of two vinyl ethers, in which the first vinyl ether was used as a precursor of a *C*-electrophile (an episulfonium ion) and the second vinyl ether was employed as a *C*-nucleophile.[8] The reaction proceeds through the formation of two intermediates, the episulfonium ion and the cyclic sulfonium salt (CSS). The later intermediate was isolated and its structure was established by X-ray crystallographic analysis.[8g] The cyclic sulfonium salt is capable of reacting with various nucleophiles (Scheme 2). Here we would like to report the application of this methodology for the synthesis of *C*-glycosides.

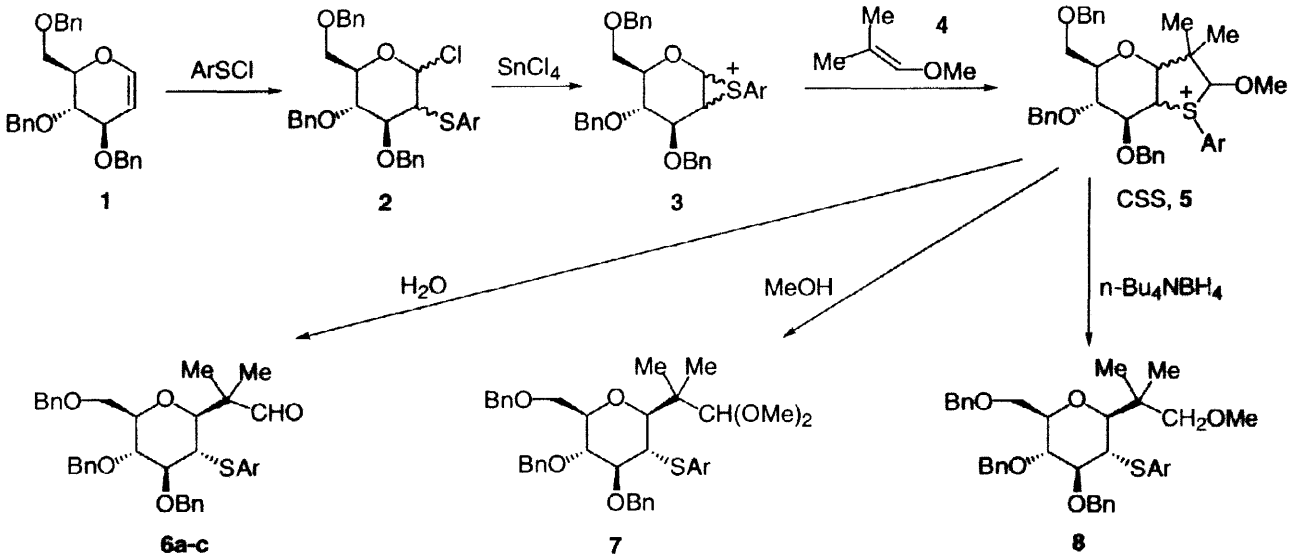


Scheme 2.

Results and Discussion

The commercially available tri-*O*-benzyl-D-glucal (**1**) has been chosen as a model glycal for the present study. Reaction of **1** with p-TolSCl was carried out as described previously.[7a] The products of this reaction (CH_2Cl_2, room temperature) are three isomeric chlorides (**2**), β-*gluco*-**2**, α-*gluco*-**2**, and α-*manno*-**2**, in a ratio of 88:12 (*gluco* : *manno*).[7a] It was found that, in the presence of $SnCl_4$, the reaction of chloride mixture **2** (prepared *in situ* in CH_2Cl_2 at room temperature) with 1-methoxy-2-methyl-1-propene (**4**) at -78 °C in CH_2Cl_2 followed by quenching the reaction mixture with water resulted in the formation of aldehyde **6a** as a mixture of β-*gluco* and α-*manno* isomers in a ratio of 87:13 in a combined yield of 87% (Scheme 3). The high yield and the absence of products of vinyl ether oligomerization suggest to us that the reaction is likely to take place through the formation of the stabilized intermediate, the cyclic sulfonium salt **5**, as it was observed in the ArSCl mediated dimerization of vinyl ethers.[8,9] To support this, we quenched the reaction mixture with other nucleophiles, MeOH and *n*-Bu_4NBH_4.[10] The use of MeOH led to the formation of acetal **7**, while treatment of the reaction mixture with *n*-Bu_4NBH_4 gave rise to reduced product **8**.

In order to determine the scope and limitations of the reaction, other vinyl ethers have also been employed. Thus, the reaction of adduct mixture **2** with methyl vinyl ether after quenching with water provides a mixture of two isomeric aldehydes **11** (β-*gluco* : α-*manno* ratio is 91:9) in a combined yield of 63%. The use of MeOH and *n*-Bu_4NBH_4 instead of H_2O as the final nucleophile in the same reaction provided the corresponding *C*-glycosides having acetal and ether functional groups in the lateral chain (see Table 1). Aldehyde **11** has also been synthesized in the same yield by the reaction of chloride mixture **2** with ethyl vinyl ether. The use of the bulkier nucleophile, propyl vinyl ether, led to the formation of the same *C*-glycoside but in the low yield of 18%. Our numerous attempts to obtain aldehyde **11** using *n*-butyl vinyl ether



Ar = p-Tol (**6a**), p-ClC_6H_4 (**6b**), 2,4,6-$Me_3C_6H_2$ (**6c**)

β-*gluco* : α-*manno* ratios are up to 99:1 (see Tables 1,2, and 3).

Scheme 3

were unsuccessful. The main product of the latter reaction was 3,4,6-tri-*O*-benzyl-2-(p-tolylsulfanyl)-D-glucose although some other unidentified compounds have been isolated as well. One could suggest that in the case of a rather bulky alkoxy group, such as n-butyl, the five-membered sulfonium salt intermediate is very unstable or can not be formed at all. However, the reaction of ethylene glycol methyl vinyl ether with adduct mixture **2** provided two isomers of *C*-glycoside **11** in a good yield (see Table 1).

The use of 2-methoxypropene, an α-substituted vinyl ether, as a *C*-nucleophile did not provide the desired *C*-glycoside. However, another vinyl ether with the bulky electron-releasing trimethylsilyl group in the α-position (**17**) smoothly reacted with adducts **2a-c** to give *C*-glycoside **18** in a yield of 59%.

The reactions with two cyclic vinyl ethers, 1-methoxycyclohexene (**19**) and 1-methoxycyclopentene, gave contrary results. The use of **19** provided a mixture of only two isomeric *C*-glycosides (**20**, 10:1) in a good yield (61%). In the contrast to other vinyl ethers, these two isomeric compounds both have β-*gluco* configuration (^{1}H NMR data) and differ in the configuration of the chiral center in the lateral chain. The (S)-configuration of the chiral center of the major isomer **20** has been established using a single crystal crystallographic analysis of the corresponding sulfone. The reaction with 1-methoxycyclopentene did not provide any traces of the expected *C*-glycoside. An examination of molecular models of the required sulfonium salt intermediate for this reaction indicates a significant angle strain.

We also studied the stereoselectivity of the last step of the reaction sequence: the reaction of a final nucleophile with the second intermediate, the five-membered sulfonium salt. To examine stereoselectivity, *n*-Bu_4NBD_4 was used as the final nucleophile. The product of this reaction was a mixture of two isomeric *C*-glycosides (**9**) (β-*gluco* : α-*manno* = 95:5). The main β-*gluco* isomer was isolated as a mixture of two diastereomers (ca. 1:1) which differ in the configuration at the chiral center in the lateral chain (NMR data).

Table 1. Reaction of p-TolSCl Adducts of Glucal 1 with Vinyl Ethers.[a]

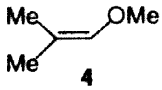
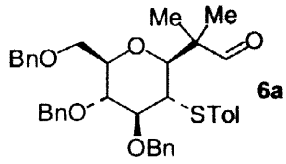
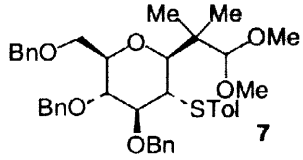
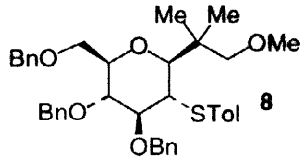
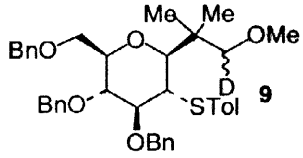
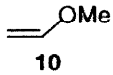
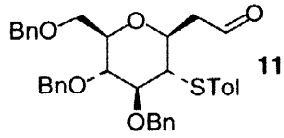
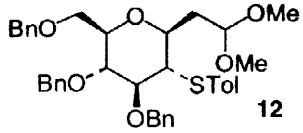
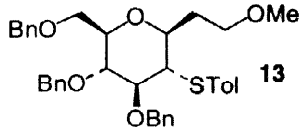
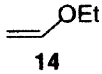
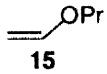
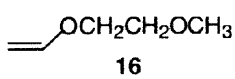
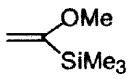
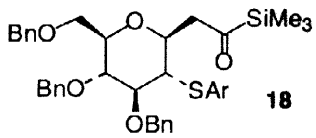
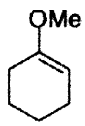
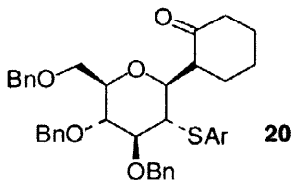
Entry	VE	Nu	Product	Yield, %[b]	Ratio β-*gluco* : α-*manno*
1	 **4**	H_2O	 **6a**	87	87:13
2	**4**	MeOH	 **7**	76	87:13
3	**4**	n-Bu_4NBH_4	 **8**	84	87:13
4	**4**	n-Bu_4NBD_4	 **9**	58	92:8
5	 **10**	H_2O	 **11**	63	91:9
6	**10**	MeOH	 **12**	34	91:9
7	**10**	n-Bu_4NBH_4	 **13**	23	91:9
8	 **14**	H_2O	**10**	63	95:5
9	 **15**	H_2O	**10**	18	88:12
10	 **16**	H_2O	**10**	42	91:9

Table 1 - Continuation

Entry	VE	Nu	Product	Yield, %	Ratio β-*gluco* : α-*manno*
11	 **17**	H_2O	 **18**	59	94:6
12	 **19**	H_2O	 **20**	61	90:10

[a] All reactions were carried out in CH_2Cl_2 in the presence of 1.2 equiv of $SnCl_4$ at -78 °C.

[b] Combined yield of β-*gluco* and α-*manno* isomers

Table 2. Effect of Lewis Acid on the Stereoselectivity of the Reaction of p-TolSCl Adducts of Glucal **1** with Vinyl Ether **4**.

Entry	Lewis Acid	β-*gluco*-**6a** : α-*manno*-**6a** ratio	Yield, %
1	$SnCl_4$	87:13	87
2	$TiCl_4$	93:7	32
3	$BF_3.OEt_2$	87:13	93
4	$ZnCl_2$	95:5	95

Table 3. Effect of ArS Substituent on the Stereochemistry of the Reaction of ArSCl Adducts of Glucal **1** with Vinyl Ether **4**.

Entry	ArS Group	β-*gluco*-**6** : α-*manno*-**6** ratio	Yield, %
1	p-TolSCl	87:13	87
2	p-ClC_6H_4SCl	85:15	90
3	2,4,6-$(CH_3)_3C_6H_2SCl$	99:1	90

The effects of various factors, such as the nature of the Lewis acid, electronic and steric properties of the arylthio group, temperature and polarity of the solvent, have been examined in the reaction of adducts **2** with vinyl ether **4**. It is well known that stereoselectivity and sometimes even regioselectivity of electrophilic alkylations are sensitive to the Lewis acid used.[11] It has also been reported that the choice of Lewis acid may control the stereoselectivity of episulfonium ion reactions.[12] In the reaction studied, the Lewis acid is directly involved in the generation of an electrophile (which presumably has an episulfonium-like structure, *vide infra*) from adducts **2**. The structure of this electrophile and, consequently, reaction stereoselectivity and reactivity of the reactions of this intermediate may depend on the nature (e.g., acid strength, size, metal affinity to oxygen and sulfur) of the Lewis acid. We found, however, that the use of different Lewis acids does not lead to dramatic changes in the stereoselectivity of the glycosidation. In all cases, the reaction between **2** (Ar = p-Tol) and **4** proceeds with a high stereoselectivity with a predominant formation of the β-*gluco* isomer of **6a**. The best Lewis acid as judged by the stereoselectivity and combined yield of two isomers was $ZnCl_2$ (see Table 2).

One can speculate about the exact structure of the intermediate formed upon the action of a Lewis acid on the ArSCl adducts of D-glucal, but the involvement of ArS group in the stabilization of the species is obvious. The presence of different substituents on the aryl ring may change the bridging capacity of the sulfur and, therefore the intermediates with different structures could possibly alter the stereoselectivity of the reaction with vinyl ethers. Three different ArSCl have been used in the reaction: p-TolSCl, p-ClC_6H_4SCl, and 2,4,6-$Me_3C_6H_2SCl$ (see Table 3). We found that differences in the electronic properties of the substituents on the aromatic ring do not significantly affect the stereoselectivity of the reaction. However, the use of the bulky 2,4,6-$Me_3C_6H_2S$ group turned out to be very successful: only the β-*gluco* isomer of **6c** has been identified and isolated. These observations are in line with data for similar reactions of episulfonium ions.[7a,13]

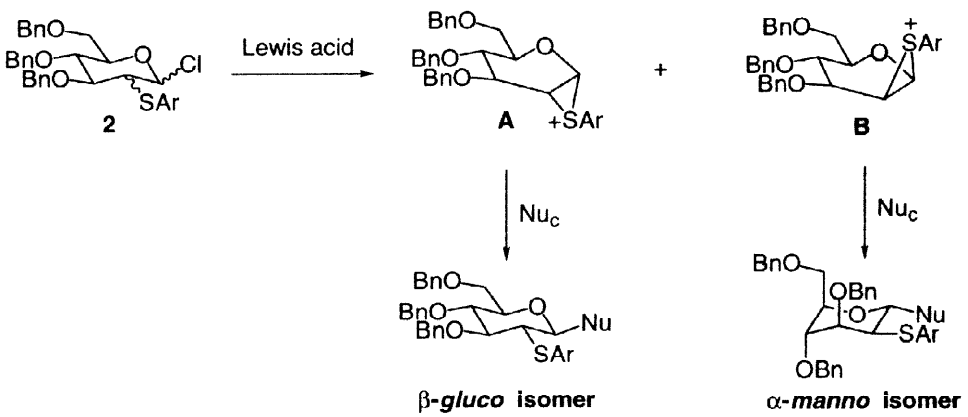
To determine the possible effect of temperature, the reaction of **2** (Ar = p-Tol) with **4** in the presence of $SnCl_4$ has been conducted at -78, -25, and 20 °C. In all three cases the stereoselectivity of glycosidation was the same (β-*gluco* : α-*manno* = 87:13).

We found that tri-*O*-acetyl-D-glucal (**21**) can also be employed instead of the benzyl protected analog, although the use of the former is much less practical. The addition of ArSCl to glucal **21** occurs at a sufficient rate only in CH_3CN which has to be removed before adding a Lewis acid and a nucleophile.[14] The overall yield of *C*-glycoside **22** prepared by reacting vinyl ether **4** with ArSCl adducts of tri-*O*-acetyl-D-glucal was 51% (β-*gluco* : α-*manno* = 78:22).

The structures of all the synthesized *C*-glycosides were determined using ^1H NMR, ^{13}C NMR (DEPT), ^1H-^1H homonuclear decoupling, and, in some cases, 2D ^1H-^1H homonuclear COSY and 2D ^1H-^{13}C heteronuclear correlations. The composition of the compounds was confirmed by HRMS data and, in some cases, elemental analysis. The purity of the compounds (not less than 95%) has been estimated by NMR spectroscopy. The ratios of β-*gluco* and α-*manno* isomers were determined from ^1H NMR spectra. For compounds **6a**, **6b**, and **20** the minor isomers have been isolated and their α-*manno* configuration and conformation, as shown in Scheme 4, were unambiguously established upon analysis of the coupling constants in the ^1H NMR spectra. In the cases of **7**, **8**, **10-13**, and **18** the minor isomers have not been isolated and their

structure as α-*manno* derivatives was accepted by analogy. It is significant that, in contrast to 2-ArS substituted α-*O*-*manno*pyranosides,[13] the corresponding *C*-glycosides have the conformation with axial substituents at C-3, C-4, and C-5 and an equatorial ArS group at C-2 and an equatorial alkyl chain at C-1 (see ^{1}H NMR data for α-*manno*-**6a**, α-*manno*-**6b**, and α-*manno*-**22** in Experimental Section).

In all the reactions we performed, only two isomeric C-glucosides, β-*gluco* and α-*manno*, have been obtained. Both of them are the result of the *trans* addition of the ArS group and the carbon nucleophile across the double bond of the glucal. The *trans* configuration of the C-glycosides suggests that the intermediates formed upon the action of a Lewis acid on a mixture of the ArSCl adducts are likely to have the episulfonium ion structure. The comparison of the ratio of (α-*gluco* + β-*gluco*) : α-*manno* isomers for p-TolSCl adducts of D-glucal (88:12, CH_2Cl_2) with the ratio of two isomeric *C*-glycosides **6a** (β-*gluco* : α-*manno* = 87:13, CH_2Cl_2) initially suggested that the stereoselectivity of glycosidation solely depends on the ratio of ArSCl adducts of D-glucal. However, when CH_3NO_2 was used in the reaction sequence, the ratio of TolSCl adducts (α-*gluco* : α-*manno* = 64:36, ^{1}H NMR data) did not coincide with the isomer ratio of **6a** (β-*gluco* : α-*manno* = 49:51). Moreover, in the presence of $SnCl_4$ and in a solution of CH_3NO_2, vinyl ether **4** reacted with the mixture of adducts **2** ([α-*gluco* + β-*gluco*] : α-*manno* = 88:12) prepared in CH_2Cl_2 (the latter was removed before the reaction with compound **4**) to give β-*gluco* and α-*manno* isomers of **6** in a ratio of 62:38. These data indicate that, if the reaction intermediate is the episulfonium ion, there is an interconversion between two forms of the intermediate, A and B (Scheme 4).[7a] The equilibrium of two episulfonium ions is considered to be rather unique[13] but it has been reported for a similar glucal-based episelenium species.[15] One can suggest that the interconversion of intermediates A and B takes place through the formation of the glucal and the ArS^+.[7a] However, the glucal and the ArS^+ would react with carbon nucleophiles but no products of these reactions have been detected. Another possible explanation of epimerization at C-2 would be the formation of the 2-arylsulfanyl substituted glucal as an intermediate. A recent theoretical study of 1-methoxy-2-sulfanylethan-1-yl cation does not exclude this possibility.[16] However, the later mechanism cannot satisfactory explain the exclusive formation of the *trans* (β-*gluco* and α-*manno*) isomers.



Scheme 4.

It is noteworthy that the reaction studied requires special care to avoid traces of water. It is known that, under conditions when traces of water are not removed completely, episulfonium ions react with H_2O to give β-(arylsulfanyl)alkyl alcohols.[12] In the case of using vinyl ethers as nucleophiles, the presence of H_2O in the reaction mixture resulted in the formation of *O*-glycosides instead of *C*-glycosides. For example, the reaction of adducts **2** with methyl or ethyl vinyl ether in the presence of $ZnCl_2$, which was exposed to the air for a few minutes, provided the α and β-anomers of methyl or ethyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-(phenylsulfanyl)-β-D-*gluco*pyranoside as the major product in yield of 73% and 49%, respectively, as well as up to 10% of 3,4,6-tri-*O*-benzyl-2-(p-tolylsulfanyl)-D-glucose. It seems apparent that the vinyl ethers reacted with H_2O to give the corresponding aldehydes and alcohols (MeOH or EtOH) and the alcohol formed then reacted with the episulfonium-like intermediate to yield the *O*-glycoside instead of the *C*-glycoside.

In summary, we have shown that the reaction of vinyl ethers with ArSCl adducts of D-glucal can be used for the highly stereoselective synthesis of β-*C*-glucosides. The reaction takes place through the formation of the five-membered sulfonium salt that can be quenched with H_2O, MeOH, or *n*-Bu_4NBH_4 to give an aldehyde, an acetal, or a vinyl ether, respectively.

Experimental Section

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ unless stated otherwise. Coupling constants, *J*, are reported in Hz. Preparative TLC were carried out by using glass plates, 200 x 200 mm, with an unfixed layer of Merck silica gel 60 (230-400 mesh). Analytical TLC were performed on Merck precoated 0.2 mm plates of silica gel 60 F_{254}. All reactions were carried out under an atmosphere of dry nitrogen using flame-dried glassware and freshly distilled and dried solvents.

Arylsulfenyl chlorides were obtained from the corresponding thiophenols by using SO_2Cl_2.[16] Methyl vinyl ether was synthesized from n-butyl vinyl ether and MeOH in the presence of $Hg(OAc)_2$.[17] 1-Methoxy-2-methyl-1-propene, 1-methoxy-1-cyclohexene, and 1-methoxy-1-cyclopropene were prepared by pyrolysis of 1,1-dimethoxy-2-methylpropane, 1,1-dimethoxycyclohexane, and 1,1-dimethoxycyclopentane, respectively, in the presence of p-toluenesulfonic acid.[18] Ethylene glycol methyl vinyl ether was synthesized from ethylene glycol vinyl ether.[19] Other chemicals are commercially available (Aldrich).

2-(3,4,6-Tri-*O*-benzyl-2-deoxy-2-(p-tolylsulfanyl)-β-D-*gluco*pyranosyl)-2-methylpropanal (β-*gluco*-6a) and 2-(3,4,6-Tri-*O*-benzyl-2-deoxy-2-(p-tolylsulfanyl)-β-D-*gluco*pyranosyl)-2-methylpropanal (α-*manno*-6a). To a solution of 159 mg (1.0 mmol) p-TolSCl in 10 mL CH_2Cl_2 at room temperature was added 416 mg (1 mmol) 3,4,6-tri-*O*-benzyl-D-glucal (the color changed from yellow to colorless). After 10 min the mixture was cooled to -78 °C and a solution of 103 mg (1.2 mmol) 2-methyl-1-methoxypropene in 2 mL CH_2Cl_2 was introduced. Then a solution of 0.14 mL (1.2 mmol) $SnCl_4$ in 2 mL CH_2Cl_2 was added dropwise. The mixture was stirred 30 min at -78 °C, quenched with an aqueous saturated solution of $NaHCO_3$, extracted with ether, and dried over Na_2SO_4. Preparative TLC (ether - hexane, 1 : 4) of the crude material after solvent removal in vacuo afforded two isomers (β-*gluco* : α-*manno* = 87 : 13). Yield 530 mg (76 %). Data for β-*gluco*-**6a**. TLC: R_f (ether - hexane, 1 : 1) = 0.50. $[\alpha]^{21}_D$ = -52.2 (c 2.46, $CHCl_3$).

^{1}H NMR (300 MHz): 0.90, 1.14 (two s, 6 H), 2.32 (s, 3 H), 3.07 (t, J = 10.8, 1 H), 3.48 (ddd, J = 9.8, 4.0, 2.5, 1 H), 3.60 (d, J = 10.8, 1 H), 3.67 (m, 2 H), 3.78 (dd, J = 11.0, 4.0, 1 H), 3.77 (dd, J = 11.0, 2.5, 1 H), 4.56, 4.62 (two d, J = 12.5, 2 H), 4.67, 4.89 (two d, J = 10.5, 2 H), 4.91, 5.05 (two d, J = 10.5, 2 H), 7.28 (m, 19 H), 9.72 (s, 1 H). ^{13}C NMR (75 MHz): 15.7, 21.1, 22.0, 50.1, 54.6, 69.2, 73.5, 75.1, 76.6, 79.7, 79.9, 92.2, 95.9, 127.6, 127.7, 127.8, 128.0, 128.3, 128.4, 128.5, 128.6, 130.0, 130.7, 131.6, 137.0, 138.4, 199.7. HRMS: calcd for $C_{38}H_{42}SO_5$ (M^+) m/e 610.2753, found m/e 610.2760. Data for α-*manno*-**6a**. TLC: R_f (ether - hexane, 1 : 1) = 0.56. $[\alpha]_D^{21}$ = + 70.9° (c 0.186, $CHCl_3$). ^{1}H NMR (300 MHz): 0.995, 1.08 (two s, 6 H), 2.185 (s, 3 H), 3.52 (dd, J = 10.5, 3.2, 1 H), 3.63 (dd, J = 3.8, 2.0, 1 H), 3.69 (dd, J = 10.0, 6.4, 1 H), 3.83 (dd, J = 10.0, 7.5, 1 H), 3.90 (br.t, J = 3.2, 1 H), 4.08 (d, J = 10.5, 1 H), 4.175 (br.t, J = 6.8, 1 H), 4.53 (m, 6 H), 7.30 (m, 19 H), 9.61 (s, 1 H). ^{13}C NMR (75 MHz): 16.0, 20.8, 21.2, 50.0, 50.2, 68.1, 71.9, 73.0, 73.8, 73.1, 73.2, 75.0, 78.3, 127.8, 127.8, 127.9, 128.1, 128.3, 128.5, 128.6, 129.6, 130.1, 131.1, 201.6. HRMS calcd for $C_{38}H_{42}SO_5$ (M^+) m/e 610.2753, found m/e 610.2756.

2-(3,4,6-Tri-*O*-benzyl-2-deoxy-2-((p-chlorophenyl)sulfanyl)-β-D-*gluco*pyranosyl)-2-methylpropanal (β-*gluco*-6b) and 2-(3,4,6-Tri-*O*-benzyl-2-deoxy-2-((p-chlorophenyl)sulfanyl)-α-D-*manno*pyranosyl)-2-methylpropanal (α-*manno*-6b). Both compounds were synthesized using p-ClC_6H_4SCl by method described for **6a** with a combined yield of 90% (β-*gluco*-**6b** : α-*manno*-**6b** = 85 : 15, ^{1}H NMR data). Data for β-*gluco*-**6b**. TLC: R_f (ether - hexane, 1 : 1) = 0.54. IR (neat): 1718 cm^{-1}. ^{1}H NMR (500 MHz): 0.86, 1.13 (two s, 6 H), 3.10 (br.t, J = 10.7, 1 H), 3.55 (ddd, J = 10.0, 4.0, 2.3, 1 H), 3.65 (d, J = 10.7, 1 H), 3.66 (m, 2 H), 3.72 (dd, J = 11.0, 2.3, 1 H), 3.74 (dd, J = 11.0, 4.0, 1 H), 4.62, 4.68 (two d, J = 12.5, 2 H), 4.75, 4.96 (two d, J = 11.0, 2 H), 5.00, 5.06 (two d, J = 10.5, 2 H), 7.35 (m, 19 H), 9.76 (s, 1 H). ^{13}C NMR (125 MHz): 15.4, 21.9, 50.0, 54.8, 68.9, 73.4, 75.1, 76.7, 79.6, 79.7, 81.7, 85.8, 127.5, 127.6, 127.6, 127.8, 127.8, 127.9, 128.2, 128.3, 128.4, 128.5, 129.1, 131.7, 133.0, 133.5, 138.0, 138.3, 199.3. HRMS calcd for $C_{37}H_{39}SO_5Cl$ (M^+) m/e 630.2207, found m/e 630.2227. Data for α-*manno*-**6b**. TLC: R_f (ether - hexane, 1 : 1) = 0.57. IR (neat): 1717 cm^{-1}. ^{1}H NMR (500 MHz): 0.955, 1.07 (two s, 6 H), 3.50 (dd, J = 10.0, 3.0, 1 H), 3.63 (dd, J = 3.7, 1.9, 1 H), 3.68 (dd, J = 10.0, 6.2, 1 H), 3.81 (dd, J = 10.0, 7.1, 1 H), 3.90 (br. t, J = 3.7, 3.0, 1 H), 4.07 (d, J = 10.0, 1 H), 4.175 (br.t, J = 6.4, 1 H), 4.52 (m, 6 H), 7.30 (m, 19 H). ^{13}C NMR (125 MHz): 15.8, 20.7, 49.9, 50.1, 67.9, 71.9, 73.1, 73.7, 72.7, 72.9, 74.8, 78.2, 127.4, 127.6, 127.7, 127.7, 127.8, 127.9, 128.0, 128.2, 128.4, 128.5, 129.3, 131.8, 133.1, 137.4, 137.9, 138.1, 201.3. HRMS calcd for $C_{37}H_{39}SO_5Cl$ (M^+) m/e 630.2207, found m/e 630.2240.

2-(3,4,6-Tri-*O*-benzyl-2-deoxy-2-(mesitylsulfanyl)-β-D-*gluco*pyranosyl)-2-methylpropanal (β-*gluco*-6c). This derivative was synthesized by the method described for **6a** with a yield of 90%. TLC: R_f (ether - hexane, 1 : 1) = 0.53. IR (neat): 1724 cm^{-1}. ^{1}H NMR (500 MHz): 1.17, 1.26 (two s, 6 H), 2.27 (s, 3 H), 2.49 (s, 6 H), 3.47 (dd, J = 6.7, 4.6, 1 H), 3.53 (dd, J = 9.0, 2.9, 1 H), 3.56 (br. t, J = 4.6, 2.9, 1 H), 3.63 (dd, J = 11.0, 5.4, 1 H), 3.68 (dd, J = 11.0, 2.4, 1 H), 3.76 (ddd, J = 9.0, 5.4, 2.4, 1 H), 3.84 (d, J = 6.7, 1 H), 4.10, 4.13 (two d, J = 11.7, 2 H), 4.20, 4.26 (two d, J = 11.2, 2 H), 4.58, 4.60 (two d, J = 11.2, 2 H), 6.87, 7.09, 7.28, 7.35 (four m, 17 H), 9.70 (s, 1 H). ^{13}C NMR (75 MHz): 18.5, 19.1, 21.0, 23.5, 45.0, 50.5, 70.1, 71.1, 72.3, 73.4, 78.0, 78.3, 80.4, 83.6, 127.4, 127.5, 127.6, 127.7, 127.8, 127.9, 128.0, 128.3, 128.4, 137.8, 137.9, 138.2, 138.4, 142.7, 203.3. HRMS calcd for $C_{40}H_{46}SO_5$ (M^+) m/e 638.3066, found m/e 638.3082.

2-(3,4,6-Tri-*O*-benzyl-2-deoxy-2-(p-tolylsulfanyl)-β-D-*gluco*pyranosyl)-1,1-dimethoxyethane (7) was prepared by the method described for **6a** but the reaction mixture was quenched with MeOH and K_2CO_3. Preparative TLC (ether - hexane, 1 : 4) afforded a mixture of β-*gluco* and α-*manno* isomers in a ratio of 87 : 13 in a combined yield of 76%. Data for β-*gluco*-**7**. TLC: R_f (hexane - ether, 1 : 1) = 0.55. ^{1}H NMR (C_6D_6, 250 MHz): 1.27, 1.52 (two s, 6 H), 1.98 (s, 3 H), 3.34, 3.39 (two s, 6 H), 3.60 (m, 6 H), 3.83 (d, J = 9.5, 1 H), 4.37, 4.43 (two d, J = 11.8, 2 H), 4.51, 4.77 (two d, J = 11.8, 2 H), 4.71, 4.95 (two d, J = 11.3, 2 H), 7.15 (m, 19 H). ^{13}C NMR (C_6D_6, 50 MHz): 18.4, 19.0, 20.7, 45.1, 52.2, 57.4, 58.6, 70.1, 73.1, 73.7, 75.1, 78.7, 79.7, 82.9, 84.6, 110.9, 127.5, 127.6, 127.7, 127.9, 128.3, 129.1, 134.6, 136.2, 139.8. HRMS calcd for $C_{40}H_{48}SO_6$ (M^+) m/e 656.3159, found m/e 656.3177.

Methyl 2-(3,4,6-Tri-*O*-benzyl-2-deoxy-2-(p-tolylsulfanyl)-β-D-*gluco*pyranosyl)-2-methylpropyl Ether (8) was synthesized by analogy to **6a** using Bu_4NBH_4 (3 mmol) as a final nucleophile. After introducing Bu_4NBH_4, the mixture was stirred at -20 °C for 1 hour and poured into an aqueous saturated solution of $NaHCO_3$, extracted with ether, and dried over Na_2SO_4. Preparative TLC (ether - hexane, 1 : 4) of the crude material afforded a mixture of β-*gluco* and α-*manno* isomers (87:13) in a yield of 84%. Data for β-*gluco* -**8**. TLC: R_f (hexane - ether, 2 : 1) = 0.55. ^{1}H NMR (300 MHz): 1.02, 1.11 (two s, 6 H), 2.36 (s, 3 H), 3.385 (dd, J = 9.5, 8.5, 1 H), 3.69 (dd, J = 11.5, 2.5, 1 H), 3.465 (ddd, J = 9.5, 4.8, 2.5, 1 H), 3.61 (dd, J = 9.5, 7.0, 1 H), 3.71 (dd, J = 8.5, 7.0, 1H), 3.74 (dd, J = 4.8, 2.5, 1 H), 4.54, 4.72 (two d, J = 10.5, 2 H), 4.60, 4.65 (two d, J = 12.5, 2 H), 4.69, 4.87 (two d, J = 11.0, 2 H). ^{13}C NMR (50 MHz): 21.1, 22.3, 22.7, 40.0, 51.1, 59.1, 69.9, 73.4, 73.9, 75.0, 80.6, 78.8, 79.5, 82.4, 84.2, 127.6, 127.8, 128.0, 128.3, 128.4, 128.5, 129.9, 131.0, 136.5, 138.4, 138.5. HRMS calcd for $C_{39}H_{46}SO_5$ (M^+) m/e 626.3066, found 626.3058.

2-(3,4,6-Tri-*O*-benzyl-2-deoxy-2-(p-tolylsulfanyl)-β-D-*gluco*pyranosyl)ethanal (10) was synthesized by the method described for **6a** using excess of methyl vinyl ether and 2 equiv. of $SnCl_4$. The preparative TLC (hexane - ether, 3:1) afforded a mixture of two isomers (β-*gluco* and α-*manno*) in a ratio of 10 : 1 (^{1}H NMR data) and combined yield of 63%. Data for β-*gluco* -**10**. TLC: R_f (hexane - ether, 1 : 1) = 0.45. $[\alpha]^{21}_D$ = -17.14° (c 0.7, $CHCl_3$). IR ($CHCl_3$): 1726. ^{1}H NMR (300 MHz): 2.31 (s, 3 H), 2.59 (ddd, J = 12.7, 9.2, 2.7, 1 H), 2.94 (t, J = 10.4, 1 H), 3.12 (ddd, J = 12.7, 3, 1.5, 1 H), 3.50 (m, 5 H), 3.90 (ddd, J = 10.4, 9.2, 3, 1 H), 4.47, 4.57 (two d, J = 12.3, 2 H), 4.57, 4.86 (two d, J = 10.8, 2 H), 4.89, 5.07 (two d, J = 10.4, 2 H), 7.27 (m, 19 H), 9.75 (dd, J = 2.7, 1.5, 1 H). ^{13}C NMR (75 MHz): 21.1, 41.8, 46.9, 56.9, 73.7, 75.1, 76.3,76.5, 79.1, 79.6, 84.5, 127.6, 127.8, 127.7, 128.5, 130.0, 132.4, 137.7, 138.0, 138.1, 138.4, 184.9. HRMS calcd for $C_{36}H_{38}SO_5$ (M^+) m/e 582.2430, found m/e 582.2423.

2-(3,4,6-Tri-*O*-benzyl-2-deoxy-2-(p-tolylsulfanyl)-β-D-*gluco*pyranosyl)-1,1-dimethoxyethane (11). The compound was synthesized by the method described for **6a** using methyl vinyl ether (ca. 3 mmol) as a carbon nucleophile and MeOH as a final quencher. The combined yield of two isomers (β-*gluco* and α-*manno* in a ratio of 91 : 9, ^{1}H NMR data) is 34%. Data for β-*gluco*-**11**. R_f (ether-hexane, 1:1) = 0.42. $[\alpha]^{21}_D$ = -31.1° (c 0.74, $CHCl_3$). ^{1}H NMR (300 MHz): 1.62 (m, 1H), 2.32 (s, 3H), 2.60 (m, 1H), 2.93 (t, J = 10.6, 1H), 3.33 (s, 3H), 3.37 (s, 3H), 3.41 (ddd, J = 9.1, 2.9, 1.9, 1H), 3.48 (ddd, J = 10.6, 2.9, 1.9, 1H), 3.57 (dd, J = 10.6, 8.7, 1H), 3.67 (dd, J = 9.1, 8.7, 1H), 3.72 (d, 2H), 4.70 (dd, J = 8.9, 2.8, 1H), 4.55, 4.63 (two d, J = 12.3, 2H), 4.62, 4.86 (two d, J = 10.8, 2H), 4.90, 5.08 (two d, J = 19.3, 2H), 7.25 (m, 19H). ^{13}C NMR (75

MHz): 21.0, 35.8, 52.3, 53.3, 57.3, 68.3, 73.3, 74.3, 76.1, 77.2, 78.5, 79.7, 84.8, 102.0, 127.3, 127.6, 127.8, 128.3, 128.4, 129.7, 129.7, 131.6, 132.2, 137.1, 138.1, 138.2, 138.4. HRMS calcd for $C_{38}H_{44}SO_6$ (M^+) m/e 628.2859, found m/e 628.2854.

Methyl 2-(3,4,6-Tri-*O*-benzyl-2-deoxy-2-(p-tolylsulfanyl)-β-D-*gluco*pyranosyl)ethyl Ether (12). The compound was synthesized by the method described for **6a** using methyl vinyl ether (ca. 3 mmol) as a carbon nucleophile and *n*-Bu_4NBH_4 as a final quencher. A combined yield of two isomers (β-*gluco* and α-*manno* in a ratio of 91 : 9, ^{1}H NMR data) is 23%. Data for β-*gluco*-**12**. R_f (ether-hexane, 1:1) = 0.44. $[\alpha]^{21}_D$ = - 53.0° (c 0.42, $CHCl_3$). ^{1}H NMR (300 MHz): 1.62 (m, 1H), 2.30 (s, 3H), 2.51 (m, 1H), 2.89 (t, *J* = 10.4, 1H), 3.30 (s, 3H), 3.36 (ddd, *J* = 8.9, 3.4, 3.2, 1H), 3.44 (m, 2H), 3.53 (t, *J* = 10.4, 8.9, 1H), 3.54 (t, 1H), 3.63 (t, *J* = 8.9, 1H), 3.70 (m, 2H), 4.53, 4.60 (two d, *J* = 12.2, 2H), 4.58, 4.84 (two d, *J* = 10.8, 2H), 4.88, 5.06 (two d, *J* = 10.3, 2H), 7.28 (m, 19H). ^{13}C NMR (75 MHz): 21.0, 32.6, 57.3, 58.5, 69.0, 69.2, 73.4, 74.9, 76.1, 76.6, 78.6, 79.8, 84.8, 127.5, 127.6, 127.7, 127.8, 128.0, 128.3, 128.4, 129.7, 131.6, 132.3, 137.1, 138.2, 138.5. HRMS calcd for $C_{37}H_{42}SO_5$ (M^+) m/e 598.2753, found m/e 598.2747.

Methyl 1-Deuterio-2-(3,4,6-Tri-*O*-benzyl-2-deoxy-2-(p-tolylsulfanyl)-β-D-*gluco*pyranosyl)-2-methylpropyl Ether (13). The ether was formed as a mixture of two isomers (β-*gluco* : α-*manno* = 92:8) in 59% combined yield using n-Bu_4NBD_4 as a final nucleophile. Data for pure β-*gluco* isomer. TLC: R_f (ether-hexane, 1:2) = 0.52. ^{1}H NMR (300 MHz): 1.00 (s, 3H), 1.09 (s, 3H), 2.33 (s, 3H), 3.30 (s, 3H), 3.36 (dd, *J* = 9.4, 7.9, 1H), 3.38 (dd, *J* = 13.8, 4.3, 1H), 3.44 (ddd, *J* = 9.2, 4.3, 2.6, 1H), 3.51 (d, *J* = 9.4, 1H), 3.57 (dd, *J* = 9.2, 6.8, 1H), 3.68 (m, 3H), 4.52, 4.84 (two d, *J* = 10.8, 2H), 4.56, 4.62 (two d, *J* = 12.2, 2H), 4.65, 4.70 (two d, *J* = 11.1, 2H), 7.25 (m, 19H). ^{13}C NMR (75 MHz): 21.3, 22.4, 22.5, 22.8, 51.2, 59.1, 70.1, 73.5, 74.1, 75.2, 80.3, 78.9, 79.6, 82.5, 84.3, 127.6, 127.7, 127.9, 128.1, 128.3, 128.4, 128.5, 128.6, 129.9, 131.1, 136.5, 138.5, 138.6, 138 9. HRMS calcd $C_{39}H_{45}DO_5SNa$ (M^++Na^+) m/e 650.3026, found (M^++Na^+) 650.3043.

[2-(3,4,6-Tri-*O*-benzyl-2-deoxy-2-(p-tolylsulfanyl)-β-D-*gluco*pyranosyl)-1-(oxoethyl)]trimethylsilane (18) was synthesized by the method described for **6a** using (1-methoxyvinyl)trimethylsilane as a carbon nucleophile. The preparative TLC (hexane-ether, 3:1) afforded a mixture of two isomers (β-*gluco* and α-*manno*:) in a ratio of 95:5 and a combined yield of 59%. Data for β-*gluco*-**18**. TLC: R_f (hexane - ether, 1 : 1) = 0.60. $[\alpha]^{22}_D$ = -15.9° (c 0.22, $CHCl_3$). ^{1}H NMR (300 MHz): 0.21 (s, 9H), 2.97 (dd, *J* = 16.1, 8.5, 1H), 2.98 (t, *J* = 10.2, 1H), 3.22 (dd, *J* = 16.1, 2.7, 1H), 3.38 (ddd, *J* = 9.7, 1.9, 3.4, 1H), 3.57 (dd, *J* = 10.0, 3.4, 1H), 3.58 (dd, *J* = 10.2, 9.0, 1H), 3.67 (dd, *J* = 9.7, 9.0, 1H), 3.72 (dd, *J* = 10.0, 1.9, 1H), 3.98 (ddd, *J* = 10.2, 8.5, 2.7, 1H), 4.51, 4.61 (two d, *J* = 12.2), 4.63, 4.87 (two d, *J* = 10.7), 4.93, 5.08 (two d, *J* = 10.4), 7.28 (m, 19H). ^{13}C NMR (75 MHz): -3.3, 21.1, 51.0, 56.5, 68.8, 73.4, 74.9, 75.8, 75.9, 76.7, 79.6, 84.5, 127.6, 129.8, 132.3, 137.3, 138.1, 138.2, 138.5, 246.3. HRMS calcd $C_{39}H_{47}SiO_5S$ (MH^+) m/e 655.2915, found $(MH)^+$ 655.2922.

2-(3,4,6-Tri-*O*-benzyl-2-deoxy-2-(p-tolylsulfanyl)-β-D-*gluco*pyranosyl)cyclohexanone (20) was synthesized by the method described for **6a** using 1-methoxy-1-cyclohexene as a carbon nucleophile. The product was obtained as a mixture of two diastereomers (both are β-*gluco* isomers) in a ratio of 10 : 1 and a combined yield of 61%. Data for the major isomer (with (S)-configuration at the chiral center in the lateral chain). Mp 104-105 °C. TLC: R_f (hexane - ether, 1 : 1) = 0.43. $[\alpha]^{21}_D$ = - 53.9° (c 1.19, $CHCl_3$). IR

($CHCl_3$): 1714 cm^{-1}. ^1H NMR (500 MHz): 1.65, 2.30 (two m, 6 H), 2.33 (s, 3 H), 3.12 (b.t, J = 11.3, 9.6, 1 H), 3.10 (b.dd, J = 12.1, 6.0, 1 H), 3.47 (m, J = 9.6, 3.3, 1, 1 H), 3.61 (t, J = 9.6, 1 H), 3.69 (t, J = 9.6, 9.5, 1 H), 3.70 (dd, J = 11.0, 1, 1 H), 3.785 (dd, J = 11.0, 3.3, 1 H), 4.11 (dd, J = 11.3, 1.0, 1 H), 4.51, 4.60 (two d, J = 12.1, 2 H), 4.69, 4.86 (two d, J = 10.7, 2 H), 4.93, 5.06 (two d, J = 10.3, 2 H), 7.30 (m, 19 H). ^{13}C NMR (50 MHz): 21.0, 24.1, 24.7, 25.7, 41.8, 50.2, 53.7, 68.8, 73.1, 74.8, 76.1, 76.7, 78.8, 79.8, 84.5, 127.3, 127.5, 127.55, 127.6, 127.8, 127.9, 128.0, 128.2, 128.3, 129.7, 129.8.0, 131.0, 132.7, 137.5, 138.3, 138.5, 209.8. HRMS calcd for $C_{40}H_{44}SO_5$ (M^+) m/e 636.2898, found for m/e 636.2923. **Anal.** Calcd for $C_{40}H_{44}SO_5$: C, 75.44; H, 6.96; S, 5.03. Found: C, 75.38, H, 6.93; S, 4.97. Data for the minor isomer. R_f (hexane-ether, 1:1) = 0.50. ^1H NMR (500 MHz): 1.6 (m, 6 H), 2.28 (s, 3 H), 3.07 (b.t, J = 8.5, 1 H), 3.36 (m, J = 9.8, 5.2, 2.1, 1 H), 3.39 (dd, J = 10.7, 1.8, 1 H), 3.52 (dd, J = 10.7, 8.9, 1 H), 3.62 (b.t, J = 10.7, 8.9, 1 H), 3.66 (dd, J = 11.0, 5.2, 1 H), 3.71 (dd, J = 11.0, 2.1, 1 H), 3.805 (b.t, J = 10.7, 9.8, 1 H), 4.52, 4.58 (two d, J = 12.1, 2 H), 4.58, 4.82 (two d, J = 10.9, 2 H), 4.84, 5.00 (two d, J = 10.4, 2 H), 7.30 (m, 19 H). ^{13}C NMR (75 MHz): 20.9, 21.3, 21.6, 24.3, 42.2, 49.9, 52.9, 69.2, 73.1, 74.9, 75.7, 79.5, 79.6, 81.2, 85.3, 127.3, 127.6, 127,75, 127.8, 128.0, 128.1, 128.2, 128.2, 128.3, 129.6, 129.8, 131.2, 131.5, 132.7, 136.6, 138.1, 138.4, 209.5.

2-(3,4,6-Tri-*O*-acetyl-2-deoxy-2-(p-tolylsulfanyl)-β-D-*gluco*pyranosyl)-2-methylpropanal (β-*gluco*-22) and 2-(3,4,6-Tri-*O*-acetyl-2-deoxy-2-(p-tolylsulfanyl)-α-D-*manno*pyranosyl)-2-methylpropanal (α-*manno*-22). To a solution of 159 mg (1.00 mmol) p-TolSCl in 3 ml CH_3CN at 0 °C was added 272 mg (1.00 mmol) 3,4,6-tri-*O*-acetyl-D-glucal (**21**) (the color changed from yellow to colorless). After 10 min the solvent was evaporated and the residue was dissolved in 20 mL CH_2Cl_2. This solution was cooled to -78 °C and a solution of 103 mg (1.2 mmol) 1-methoxy-2-methyl-1-propene in 2 mL CH_2Cl_2 was introduced. After that a solution of 0.14 mL (1.2 mmol) $SnCl_4$ in 2 mL CH_2Cl_2 was added dropwise. The mixture was stirred 30 min at 0 °C, quenched with a saturated solution of $NaHCO_3$ in water, extracted with ether, and dried over Na_2SO_4. Preparative TLC (ether - hexane, 1:2) of the crude material after solvent removal in vacuo afforded **22** as a mixture of β-*gluco* and α-*manno* isomers in a ratio of 78:22 and a combined yield of 51%. Data for β-*gluco*-**22**. TLC: R_f (hexane - ether, 1:1) = 0.25. IR (neat): 1748 cm^{-1}. ^1H NMR (250 MHz): 0.96, 1.11 (two s, 6 H), 1.92, 2.03, 2.07 (three s, 9 H), 2.31 (s, 3 H), 3.15 (t, J = 10.8, 1 H), 3.66 (d, J = 10.8, 1 H), 3.68 (m, J = 9.5, 5.3, 2.6, 1 H), 4.12 (dd, J = 12.2, 2.6, 1 H), 4.22 (dd, J = 12.2, 5.3, 1 H), 4.97 (t, J = 9.5, 1 H), 5.23 (dd, J = 10.8, 9.5, 1 H), 7.16 (m, 4 H), 9.66 (s, 1 H). ^{13}C NMR (62.5 MHz): 15.3, 20.6, 20.6, 20.7, 20.9, 21.5, 49.9, 51.9, 62.2, 69.7, 75.5, 75.7, 81.3, 129.9, 130.5, 132.6, 137.4, 169.4, 169.8, 170.5, 199.2. HRMS calcd for $C_{23}H_{30}O_8S$ (M^+) m/e 466.1661, found m/e 466.1673. Data for α-*manno*-**22**. TLC: R_f (hexane - ether, 1:1) = 0.28. IR (neat): 1745 cm^{-1}. ^1H NMR (500 MHz): 1.11, 1.13 (two s, 6 H), 2.055, 2.06, 2.08 (3 s, 9 H), 2.32 (s, 3 H), 3.43 (dd, J = 9.5, 3.7, 1 H), 4.08 (d, J = 9.5, 1 H), 4.12 (m, 2 H), 4.75 (m, J = 11.6, 4.0, 1.5, 1 H), 4.88 (dd, J = 4.9, 1.5, 1 H), 5.22 (br.t, J = 4.9, 3.7, 1 H), 7.19 (m, 4 H), 9.61 (s, 1 H). ^{13}C NMR (125 MHz): 16.4, 19.5, 20.6, 20.7, 20.8, 21.1, 48.0, 50.1, 60.1, 67.7, 69.8, 72.6, 74.2, 130.0, 132.6, 138.4, 170.4, 169.4, 201.5. HRMS calcd for $C_{23}H_{30}O_8S$ (M^+) m/e 466.1661, found m/e 466.1671.

Crystallographic Data Sulfone of the Major Isomer of 20. The compound was crystallized by dissolving in benzene and then layering with hexane. Colorless plate crystals were grown of diffraction quality. Data was collected using a Siemens SMART CCD (charge coupled device) based diffractometer

equipped with an LT-2 low-temperature apparatus operating at 213 °K. A suitable crystal was chosen and mounted on a glass fiber using grease. Data were measured using omega scans of 0.3 ° per frame for 30 seconds, such that a hemisphere was collected. A total of 1271 frames were collected with a final resolution of 0.90 A. The first 50 frames were recollected at the end of data collection to monitor for decay. Cell parameters were retrieved using SMART[20] software and refined using SAINT on all observed reflections. Data reduction was performed using the SAINT software[21] which corrects for Lp and decay. Absorption corrections were applied using SADABS.[22] The structures are solved by the direct method using the SHELXS-90 program[23] and refined by least squares method on F^2, SHELXL-97,[24] incorporated in SHELXTL-PC V 5.03.[25] The structure was solved in the space group P1 (#1) by analysis of systematic absences. All non-hydrogen atoms are refined anisotropically. The Flack parameter, 0.1(3) and refinement of the other enantiomer suggested the reported conformation. The crystal used for the diffraction study showed no decomposition during data collection.

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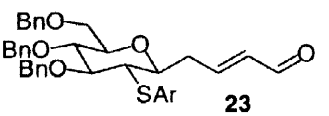
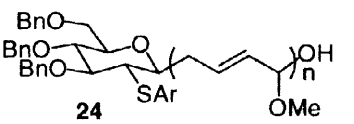
9. Another fact supporting the formation of the five-membered sulfonium salt is the result of the reaction of adducts **2** with 1-methoxybutadiene. In this case, the formation of the cyclic intermediate is impossible. Compound **23** was isolated in a low yield of 3%, other products were oligomers **24** (ca. 40%).



23



24

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