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Lifetime of the Glucosyl Oxocarbenium Ion and Stereoselectivity in the Glycosidation of Phenols with 1,2-Anhydro-3,4,6-tri-*O*-methyl-α-D-glucopyranose

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Abstract: The glycosidation of para substitued phenols with 1,2-anhydro-3,4,6-tri-*O*-methyl-α-D-glucopyranose, $ZnCl_2$ catalyzed, gives predominatly the corresponding α-anomers. In the presence of an amino base, 1,1,3,3-tetramethylguanidine, however, enhances the β-selectivity, which becomes practically complete when the reaction is carried out under basic conditions, by addition of K_2CO_3 and 18-crown-6. A rationaliation based on the lifetime of the oxocarbenium ion intermediate and on the nucleophilicity of the phenols is proposed. © 1997 Elsevier Science Ltd.

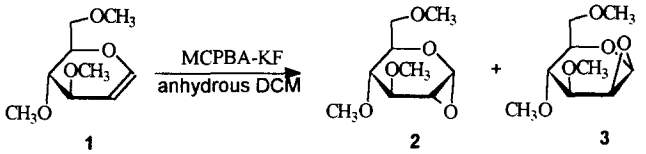
O-Aryl glucosides are widely found in natural products having important biological activities, generally in antibiotics with chemotherapeutic and antitumor action,[1] and are known to form ordered macrostructures such as micelles and liquid crystalline phases.[2] The carbon-oxygen bond formation employing activated sugars and phenols has been, therefore, extensively studied,[3] and of particular relevance has been the development of coupling reactions able to give high yields and high stereoselectivity.[4-6] It is noteworthy that, although the Lewis acid catalyzed addition of aliphatic alcohols to 1,2-anhydrosugars represents an important way to prepare β–glycosides with a high stereoselectivity,[7] it has been recently reported[8] that the reaction of 1,2-anhydro-3,4,6-tri-*O*-benzyl-α-D-glucopyranose with phenol gives a 1.8:1 ratio of the corresponding α- and β-glucosides, and stereospecific synthesis of aryl β-glucosides can be obtained[8] only using phenolate anions. The lack of stereoselectivity in the glycosidation of phenols under acid conditions has been tentatively attributed to a possible S_N1-like component to reaction.[8] Moreover, even the reactions of phenols with 2,3,4,6-tetra-*O*-acetyl-α–D-glucopyranosyl fluoride in the presence of $BF_3{\cdot}Et_2O$ give predominantly the α–anomers.[9] In this case, however, the α–selectivity has been related to the lesser acidity of the phenolic protons in the equatorial adducts, arising from the kinetically controlled attack of the phenolic oxygen on the oxocarbenium ion intermediate, which should favour, through the interconversion between the equatorial and axial adducts, the formation of the thermodynamically more stable α–anomers.[9]

In order to obtain more informations about the factors affecting the stereochemical course of the oxirane ring opening of 1,2-anhydro sugars we have investigated the reaction 1,2-anhydro-3,4,6-tri-*O*-methyl-α-D-glucopyranose with para substitued phenols under different conditions. The product distribution data, obtained with phenol, *p*-nitrophenol and *p*-methoxyphenol in the presence of $ZnCl_2$, with and without the addition of an amine base, and using K_2CO_3 in the presence of 18-crown-6, have shown that the stereochemical outcome of the reaction is due to different factors, affecting either the nucleophilic attack of the

phenol on the oxirane ring and the subsequent proton loss, some of which can be easily modulated in order to obtain selectively the α or β anomers.

RESULTS

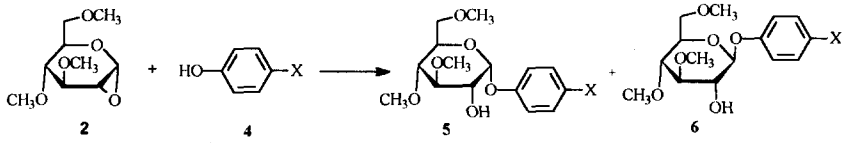
The suitable 3,4,6-tri-*O*-methyl-D-glucal (**1**), used as the starting material in this work, was prepared from commercial 3,4,6-tri-*O*-acetyl-D-glucal by deacetylation[10] followed by exhaustive methylation with CH_3I/NaH in DMF. The epoxidation of **1** was carried out with MCPBA-KF in anhydrous CH_2Cl_2, a reaction which has been shown[11] to proceed with a high diastereoselection.



1 **2** **3**

d.e.> 90:10

The crude 1,2-anhydro-3,4,6-tri-*O*-methyl-α-D-glucose (**2**), containing *ca.* 5% of the corresponding β anomer **3**, was then subjected to oxirane ring opening by treatment with para substitued phenols in the presence of $ZnCl_2$.



2 **4** **5** **6**

X = CH_3O, or H, or NO_2

The reactions were carried out in 1,2-dichloroethane (DCE), in the presence of molecular sieves as a moisture scavenger, using the inverse addition order of the reagents reported by Kong.[12] It has been indeed recently shown[12] that, although 1,2-anhydro sugar derivatives have been proved to be very good glycosyl donator for oligosaccharide and other glycoside synthesis,[7] even with aliphatic alcohols, solvent catalyst and order of reagent addition can seriously affect the yield of the process. Molecular sieves have been therefore added in order to reduce the amount of water, which could compete with the phenols in the oxirane ring opening, while the inverse addition of the reagents has been used to reduce the possible competive attack of the formed glucosides, having a free hydroxy group at C-2. The results are summarized in Table 1.

It is noteworthy that, while the products arising from water attack were always < 5%, larger amounts, around 20%, of disaccharides have been isolated by column chromatography in all reactions carried out in the presence of $ZnCl_2$. Furthermore, being known[13] that Lewis acids can catalyze the conversion of *O*-aryl glycosides to the correspoding *C*-derivatives, the stability of the α- and β-glucosides, **5** and **6**, has been preliminary checked. All compounds **5** and **6** were quantitatively recovered after exposure to $ZnCl_2$ under conditions identical to those employed in the reactions reported in Table 1. This excluded any product loss by

$ZnCl_2$-promoted *O*- → *C*-glycoside interconversion and assured that the measured α/β ratios were actually obtained under kinetic control.[14]

All reactions carried out in the presence of $ZnCl_2$ (runs 1-3) showed a selectivity towards the α-glycosides **5** which increased on passing from electron donating methoxy substituent to the electron withdrawing nitro group.

Table 1. Glycosidation of phenols (**4**) with 1,2-anhydro-3,4,6-tri-*O*-methyl-α-D-glucose (**2**).

Run	**4** X	Reaction Conditions	Yields %[a]	**5** : **6**[b]
1	*p*-OCH_3	$ZnCl_2$, DCE	62	55 : 45
2	H	$ZnCl_2$, DCE	40	65 : 35
3	*p*-NO_2	$ZnCl_2$, DCE	60	78 : 22
4	*p*-OCH_3	$ZnCl_2$, TMG, DCE	73	20 : 80
5	H	$ZnCl_2$, TMG, DCE	61	20 : 80
6	*p*-NO_2	$ZnCl_2$, TMG, DCE	83	60 : 40
7	*p*-NO_2	TMG, DCE	60	50 : 50
8	*p*-OCH_3	K_2CO_3, THF, 18-Crown-6	73	5 : 95
9	H	K_2CO_3, THF, 18-Crown-6	87	5 : 95
10	*p*-NO_2	K_2CO_3, THF, 18-Crown-6	60	5 : 95

[a] After column chromatography. [b] Determined by ^1H NMR before purification.

On the other hand, when an amine base, 1,1,3,3-tetramethylguanidine (TMG) was added prior to the Lewis acid, in agreement with the glycosidation of phenols with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl fluoride,[9] a significant enhacement of the β-glycosides **6** was observed in particular with phenol and *p*-methoxyphenol. It must be remarked that UV experiments, carried out under indentical conditions with those reported in Table 1, runs 4-6, have shown that at least in the case of phenol and methoxyphenol the base is not able to produce a detectable ionization of the hydroxy group. An ionization around 70 % has been instead calculated for the para nitro derivative and, taking into account the nucleophilic character of the *p*-nitrophenoxy anion, the reaction with **2** was also carried out in the absence of $ZnCl_2$ (run 7). A small increase in the β-anomer was observed under these conditions. Finally a significant enhacement in the β-glycoside **6** was obtained, in agreement with the previously reported data,[8] when the reactions were carried out under basic condition, in the presence of K_2CO_3 and 18-crown-6, independently of the nature of the substituent in the para position (runs 8-10).

DISCUSSION

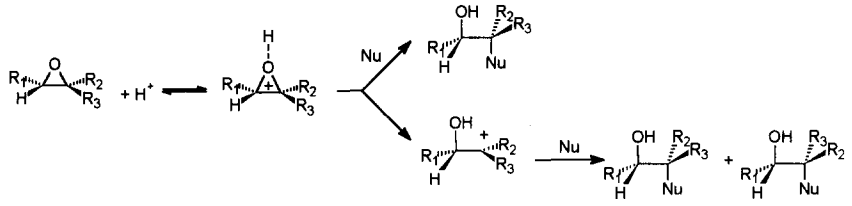
The mechanism of oxirane ring opening and its regio- and stereoselectivity has been areas of great interest in the organic chemistry and the reaction has been extensively studied in basic, acid and neutral media.[15] In basic medium, the reaction is a substitution of S_N2 type, the mechanism and stereochemistry of which have been reasonably well clarified. The mechanism of the opening in acidic medium is instead not so simple. The reaction is indeed influenced to a great extent by the structure of the oxirane, the steric and electronic effects of the substituents, and the solvent also play an important role.

In acidic medium, the first step is considered the preequilibrium addition of a proton (or a Lewis acid) to the oxirane ring with formation of an oxonium ion intermediate which can react further in two ways, by S_N2 or

S_N1 mechanism (Scheme 1). The nucleophilic attack occurs, however, always to the carbon bearing the larger number of substituents, with inversion of configuration in the first case and in a syn and anti way in the latter.

Distinctions between mechanisms of chemical reactions in solution are concerned in large part with the sequence in which reactants are assembled and dispersed in relaction to the bond-making and -breaking steps. It has been suggested that a clear-cut distinction between reaction mechanisms is impossible and generally there is a gradual transformation, for example, of an S_N2 into an S_N1 mechanism with no sharp borderline as the transition state develops more carbocation character.[16]

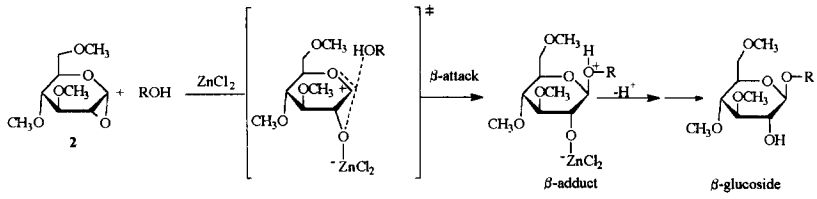
Scheme 1



The mechanism change observed as the structure of the reactants or the reaction conditions are modified can therefore be due, to not only to the possibility that the two mechanisms can exist concurrently, as suggested for the acid catalyzed oxirane ring opening, but also to the fact that a machanism becomes the other.[17] In particular, it has been stated[17] that this transformation can takes place when the intermediate in a stepwise process becomes progressively less stable, so that the well corresponding to the intermediate disappears and the reaction becomes concerted. The lifetime of the intermediate rather than the character of the transition state has been therefore considered as an important criterium for a clear distinction between mechanisms.[17]

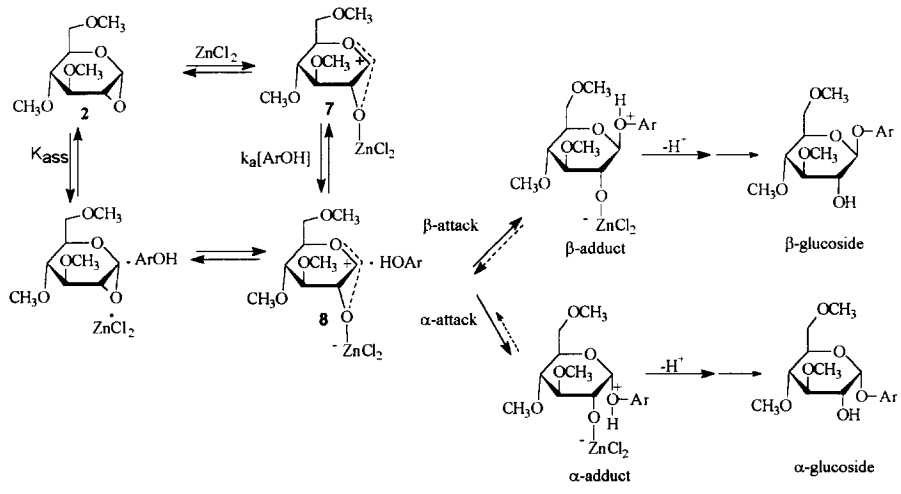
Although substitution and solvolysis reactions at the anomeric carbon atom of sugars have been widely believed to proceed through an oxocarbenium ion intermediate, it has been more times stressed[17-18] by Jencks, on the basis of studies about the reactions of nucleophiles with glucopyranosides, that these intermediates exist for a short time in water but they have no significant lifetime when are in contact with a strong nucleophile, so that these reactions proceed through a "preassociation mechanism" or through a "concerted mechanism". Taking into account these results, the product distribution data reported in Table 1 for the glycosidation of **2**, carried out in the presence of $ZnCl_2$, can be rationalized on the basis of the mechanisms sketched in Schemes 2 and 3. In agreement with the high reactivity of 1,2-anhydro sugars and taking into account the different stereochemical course of the process when the nucleophile is an alcohol or a phenol, it is possible that the coordination of the Lewis acid with the oxirane oxygen of **2** does not lead, through a preequilibrium step, to a fully developed oxocarbenium ion intermediate, but rather it is concerted with the more or less asynchronous addition of the nucleophile (practically the reaction occurs through a general acid-catalyzed mechanism). Furthermore, according to the nucleophilicity of the ROH species the mechanism can shift from a completely concerted and synchronous process, i.e. the C-1 atom of the sugar interacts with both the leaving group and the entering group in an highly symmetric even if loose transition state (Scheme 2), to a stepwise process, in which the oxirane bond breaking gives, with or without nucleophilic assistance, the oxocarbenium ion intermediate (Scheme 3). When ROH is an aliphatic alcohol the reaction probably occurs through Scheme 2 to give stereospecifically the β-adduct, which then undergoes to a very fast proton loss to give the corresponding β-glucoside. The formation of the β-adduct can be therefore considered an irreversible process.

Scheme 2



On the other hand, when ROH is a phenol, being this one a weaker nucleophile than alcohol, the reaction probably occurs through Scheme 3. The nucleophilic attack probably occurs on the oxocarbenium ion intermediate (**8**), whose formation can be or not nucleophilically assisted by the phenol, from the equatorial (β) or axial (α) face to give the corresponding β- and α-adducts. It is noteworthy that in this case the subsequent proton loss can be sufficiently slow, in particular in the less acid β-adducts, so that, in the absence of a proton captor, the formation of the β- and α-adducts can be a reversible process, which gives through their interconversion the thermodynamically more stable α-glycosides. In other words, with phenols the stereochemical control can take place at the stage of nucleophilic attack and/or at the sequent proton loss step.

Scheme 3



The results obtained in this work in the presence of $ZnCl_2$, with and without TMG, seem to indicate that in the case of the unsubstituted phenol, or when an electron donating substituent is present on the phenyl ring, the low product-stereoselectivity is essentially determined at the stage of proton loss. The addition of an amine base, which rapidly removes the proton from the β-adduct, indeed significantly increases the selectivity towards the β-glycosides. The diastereoisomeric ratio observed under these conditions can be therefore attributed to the involvement of an open intermediate (**8**) having a short but significant lifetime, which is probably generated by a preassociation mechanism in which all of the reagents are assembled in an encounter complex before the first covalent change occurs. Although front-side substitution is not usually expected for

nucleophilically assisted S_N1 reactions, the relatively small fraction of reaction (around 20%) which goes with retention of configuration can be attributed to the involvement of open, "exploded" trasition states having weak interactions with both the entering and leaving group, as previously suggested for solvolysis of sugars.[18]

Finally, when the strong electron withdrawing nitro group is present on the phenyl ring the addition of an amine base produces only a moderate enhacement in the β-glycoside (runs 3 and 6) showing that the stereochemical control is essentially affected by the nucleophilic step. In this case an open oxocarbenium ion intermediate, having a longer lifetime and whose formation is not nucleophilically assisted by the entering group, is probably involved. The diastereoisomeric ratio arises therefore from the selectivity of the nucleophilic attack for the α or β face which is affected by the anomeric effect,[19] stabilizing the transition state for the axial substitution, and by the stereoelectronic effect which disfavour the β attack having a transition state boatlike.[19]

In the presence of K_2CO_3 and 18-crown-6 the reaction involves the more nucleophilic potassium phenoxide salts which directly bring to the displacement of the epoxide to give, with high stereoselection and through an S_N2 mechanism, the β-glycosides. It is noteworthy that in the case of *p*-nitrophenol although the reactions reported in runs 7 and 10 of Table 1 involve the corresponding phenoxy anion they are characterized by a different stereoselectivity, which could be related to ion pairs dissociation phenomena. Indeed, when the *p*-nitrophenoxy anions are generated by treatment of the phenol with K_2CO_3 and 18-crown-6 highly nucleophilic "naked" anions are present in solution and the reaction occurs through the direct attack of these anion on the oxirane ring of **2** to give selectively the trans addition product. On the other hand, when the ionization of the phenol takes place in the low polar DCE by addition of TMG, the formed *p*-nitrophenoxy anion, in equilibrium with the undissociated phenol, is probably present in solution as ion pair with tetramethylguanidinium cation and the electrostatic interaction between the two species significantly reduces the reactivity of the phenoxy anion. The nucleophilic attack of the *p*-nitrophenoxy anion probably occurs on the protonated oxirane ring, the excess of phenol can indeed act as an acid, and therefore even in this case a shift from a concerted mechanism, like S_N2, to a stepwise process can be proposed to rationalized the stereochemical results.

In conclusion, the product distribution data reported in this work not only show that it is possible, independently of the nature of the substituent on the phenyl ring, to obtain *O*-aryl glycosides with high stereoselection, but also take on new informations about the mechanism of glycosidation through 1,2-anhydro sugars.

EXPERIMENTAL

Melting points were measured on a Kofler apparatus and are uncorrected. Optical rotations were measured at 20±2°C with a Perkin-Elmer 241 polarimeter. NMR spectra were registered with a Bruker AC 200 instrument using tetramethylsylane as internal standard. All reactions were followed by TLC Alugram^R sil G/UV$_{254}$ with detection by UV or with ethanolic 10% sulphuric acid and heating. Kieselgel Macherey-Nagel (70-230 or 230-400 mesch) was used for column. Solvents were distilled and stored over 4Å molecular sieves activated by heating for 24 h at 400°C. Reactions in anhydrous conditions were carried out under an argon atmosphere.

3,4,6-Tri-*O*-methylglucal (**1**) was prepared from commercial 3,4,6-tri-*O*-acetylglucal by deacetylation[10] followed by methylation according to the reported[20] procedure.

1,2-Anhydro-3,4,6-tri-O-methyl-α-D-glucopyranose (2) and 1,2-anhydro-3,4,6-tri-O-methyl-β-D-mannopyranose (3). Anhydrous KF, obtained by heating at 120 °C and 0.1 mm Hg for 2 h, (2.84 g, 49 mmol)

was added to a dichloromethane solution (245 ml) of 70% *m*-chloroperoxybenzoic acid (6.04 g, 24.5 mmol), previously dried over Sikkon and $MgSO_4$, and the mixture was stirred at room temperature for 30 min. **1** (1.84 g, 9.8 mmol) was then added and the mixture was stirred at room temperature for 24 h. The insoluble complexes were then filtered off, and the solvent was removed under reduced pressure to give, in 95% yield, a *ca.* 95:5 mixture of **2** and the corresponding diastereomeric epoxide **3**, which were identified on the basis of the ^1H and ^{13}C NMR spectra by comparison with those previously reported[11] for the analogous 1,2-anhydro-3,4,6-tri-O-benzyl D-glucopyranoses. **2:** ^1H-NMR ($CDCl_3$) δ: 2.97 (d, 1 H, J=2.4 Hz, H-2); 3.40 (s, 3 H, CH_3O); 3.50 (s, 3 H, CH_3O); 3.54 (s, 3 H, CH_3O); 3.50-3.70 (m, 5H); 4.93 (d, 1 H, J=2.4 H-1). ^{13}C-NMR ($CDCl_3$) δ: 52.5 (C-2); 58.2 (OCH_3); 59.6 (OCH_3), 60.4 (OCH_3); 69.5; 71.0 (C-6); 76.1; 77.8; 81.0 (C-1). (Anal. Calc. for $C_9H_{16}O_5$: %C=52.93, %H=7.90; Found: %C=53.01, %H=7.85).

Glycosidation in the presence of $ZnCl_2$.

Without 1,1,3,3-Tetramethylguanidine. A suspension of powdered 4Å molecular sieves (300 mg) and the proper phenol **4** (7.3 mmol) in dry DCE (3 ml) was stirred at room temperature. After 15 min a solution of the crude epoxidation product (300 mg, 1.47 mmol) in 1 ml of dry DCE was added, the mixture was cooled -30°C and a solution (1 M, 2.2 ml) of $ZnCl_2$ in ethyl ether was added. The reaction mixture was then allowed to warm to room temperature and stirred for 24 h. After filtering, the mixture was washed with water and with a saturated $NaHCO_3$ solution. The organic phase was dried ($MgSO_4$) and evaporated in vacuo to give a residue which was purified by column chromatography over silica gel (6:4 hexane/AcOEt). Yields and diasteroisomeric ratios are reported in Table 1.

p-*Methoxyphenyl-3,4,6-tri-O-methyl-α-D-glucopyranoside* $[\alpha]_D$= +175.0 (c 1.53, $CHCl_3$). M.p. 129-131 °C ^1H-NMR ($CDCl_3$) δ: 3.39 (s, 3 H, OCH_3), 3.56 (s, 3 H, OCH_3), 3.72 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 3.30-3.80 (m, 6 H), 5.43 (d, 1 H, J=3.7 Hz, H-1), 6.80-7.05 (AA'BB', 4 aromatic H) . ^{13}C-NMR ($CDCl_3$) δ: 55.56 (OCH_3); 59.07 (OCH_3); 60.31 (OCH_3); 60.89 (OCH_3); 70.51; 70.85; 72.16; 78.91; 84.29; 98.02 (C-1); 114.55 and 118.03 (aromatic C); 150.38 and 155.14 (aromatic >C<). Anal. Calc. for $C_{16}H_{24}O_7$: %C=58.53, %H=7.37. Found: %C=58.43, %H=7.40.

p-*Methoxyphenyl-3,4,6-tri-O-methyl-β-D-glucopyranoside.* $[\alpha]_D$= -21.4 (c 1.19, $CHCl_3$). M.p. 74-76 °C. ^1H-NMR ($CDCl_3$) δ: 3.39 (s, 3 H, OCH_3), 3.56 (s, 3 H, OCH_3), 3.68 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 3.30-3.80 (m, 6 H), 4.71 (d, 1 H, J=7.8 Hz, H-1), 6.80-7.05 (AA'BB' , 4 aromatic H) . ^{13}C-NMR ($CDCl_3$) δ: 55.60 (OCH_3); 59.35 (OCH_3); 60.38 (OCH_3); 60.83 (OCH_3); 70.99; 73.77; 75.13; 79.30; 85.87; 101.92 (C-1); 114.45 and 118.41 (aromatic CH); 151.20 and 155.30 (aromatic >C<). Anal. Calc. for $C_{16}H_{24}O_7$: %C=58.53, %H=7.37. Found: %C=58.62, %H=7.42.

P*henyl-3,4,6-tri-O-methyl-α-D-glucopyranoside.* $[\alpha]_D$= +193.9 (c 1.16, $CHCl_3$). M.p. 125-127 °C. ^1H-NMR ($CDCl_3$) δ: 3.30 (s, 3 H, OCH_3), 3.48 (s, 3 H, OCH_3), 3.65 (s, 3 H, OCH_3), 3.28-3.70 (m, 6 H), 5.48 (d, 1 H, J=3.7 Hz, H-1), 7.00-7.25 (m , 5 aromatic H). ^{13}C-NMR ($CDCl_3$) δ: 58.92 (OCH_3); 60.20 (OCH_3); 60.75 (OCH_3); 70.34 (C-6); 70.79; 71.86; 78.74; 84.07; 97.01 (C-1); 116.59, 122.43, 129.38 (5 aromatic CH); 156.30 (aromatic >C>). Anal. Calc. for $C_{15}H_{22}O_6$: %C=60.39, %H=7.43. Found: %C=60.28, %H=7.49.

P*henyl-3,4,6-tri-O-methyl-β-D-glucopyranoside.* $[\alpha]_D$= -22.5 (c 1.75, $CHCl_3$). M.p. 72-74 °C ^1H-NMR ($CDCl_3$) δ: 3.38 (s, 3 H, OCH_3), 3.55 (s, 3 H, OCH_3), 3.68 (s, 3H, OCH_3), 3.26-3.70 (m, 6 H), 4.82 (d, 1 H, J=7.8 Hz, H-1), 7.00-7.30 (m , 5 aromatic H) . ^{13}C-NMR ($CDCl_3$) d: 59.32 (OCH_3); 60.35 (OCH_3); 60.82 (OCH_3); 70.97 (C-6); 73.64; 75.00; 79.05; 85.92; 100.75 (C-1); 116.77, 122.67, 129.40 (5 aromatic CH); 157.16 (aromatic >C<). Anal. Calc. for $C_{15}H_{22}O_6$: %C=60.39, %H=7.43. Found: %C=60.47, %H=7.38.

p-*Nitrophenyl-3,4,6-tri-O-methyl-α-D-glucopyranoside.* $[\alpha]_D$= 224.8 (c 2.63, $CHCl_3$). M.p. 116-118 °C. ^1H-NMR ($CDCl_3$) δ: 3.39 (s, 3 H, OCH_3), 3.56 (s, 3 H, OCH_3), 3.74 (s, 3 H, OCH_3), 3.37-3.74 (m, 6 H), 5.68 (d, 1 H, J=3.6 Hz, H-1), 7.20-8.24 (AA'BB' , 4 aromatic H). ^{13}C-NMR ($CDCl_3$) d: 59.00 (OCH_3); 60.30 (OCH_3); 60.79 (OCH_3); 70.19; 71.31; 71.45; 78.56; 83.48; 96.89 (C-1); 116.32 and 125.55 (4 aromatic CH); 142.41 and 161.12 (aromatic >C<). Anal. Calc. for $C_{15}H_{21}NO_8$: %C=52.48, %H=6.17. Found: %C=52.34, %H=6.21.

p-*Nitrophenyl-3,4,6-tri-O-methyl-β-D-glucopyranoside* $[\alpha]_D$= -35.9 (c 1.33, $CHCl_3$). M.p. 84-86 °C. ^1H-NMR ($CDCl_3$) δ: 3.39 (s, 3 H, OCH_3), 3.56 (s, 3 H, OCH_3), 3.74 (s, 3 H, OCH_3), 3.37-3.74 (m, 6 H), 4.97(d, 1 H, J=7.6 Hz, H-1), 7.20-8.24 (AA'BB' , 4 aromatic H) . ^{13}C-NMR ($CDCl_3$) δ: 59.33 (OCH_3); 60.40

(OCH_3); 61.00 (OCH_3); 70.73; 73.33; 75.29; 78.88; 85.72; 99.87 (C-1); 116.42 and 125.71 (4 aromatic CH); 142.64 and 161.75 (aromatic >C<). Anal. Calc. for $C_{15}H_{21}NO_8$: %C=52.48, %H=6.17; Found: %C=52.66, %H=6.0.

With 1,1,3,3-Tetramethylguanidine. A suspension of powdered 4Å molecular sieves (300 mg) and the proper phenol **4** (5.15 mmol) in dry DCE (3 ml) was stirred at room temperature. After 15 min a solution of the crude epoxidation product (210 mg, 1.03 mmol) in 1 ml of dry DCE and 1,1,3,3-tetramethylguanidine (237 mg, 0.26 ml, 2.06 mmol) were added, the mixture was cooled at -30°C and a solution (1 M, 1.5 ml) of $ZnCl_2$ in ethyl ether was added. The reaction mixture was then allowed to warm to room temperature and stirred for 24 h. After filtering, the mixture was washed with water and with a saturated $NaHCO_3$ solution. The organic phase was dried ($MgSO_4$) and evaporated in vacuo to give a residue which was purified by column chromatography over silica gel (6:4 hexane/AcOEt). Yields and diasteroisomeric ratios are reported in Table 1.

Glycosidation in the presence of K_2CO_3 and 18-crown-6. The crude epoxidation product (0.5 g, 2.45 mmol) dissolved in 10 ml of THF was added to a refluxing solution of the proper phenol **4** (12.25 mmol) in the same solvent (30 ml), containining K_2CO_3 (3.4 g, 24.5 mmol) and 18-crown-6 (65 mg, 0.245 mmol). After 4 hours the mixture was cooled at room temperature, washed with a saturated Na_2CO_3 solution and extracted with AcOEt. The organic phase was dried ($MgSO_4$) and evaporated in vacuo to obtain a residue, which was purified by column chromatography over silica gel (6:4 hexane/AcOEt). Yields and diasteroisomeric ratios are reported in Table 1.

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