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Tandem Epoxidation-Alcoholysis or Epoxidation-Hydrolysis of Glycals Catalyzed by Titanium(IV) Isopropoxide or Venturello's Phosphotungstate Complex

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Abstract: Venturello's phosphotungstate complex and titanium(IV) isopropoxide [Ti(O-*i*-Pr)$_4$] were successfully used as catalysts for the epoxidation-alcoholysis of glycals using hydrogen peroxide [H_2O_2]. Reaction substrates included a range of variously protected glycals and different alcohols were used as solvents. Ti(O-*i*-Pr)$_4$ was only effective in methanol as solvent, but gave methyl glycosides in high yields and high selectivities. The Venturello complex proved to be a very versatile and efficient catalyst. Apart from epoxidation-alcoholysis in alcoholic solvents it also showed activity in biphasic conditions to allow for glycosylation of long-chain alcohols and was very effective in the stereoselective dihydroxylation of benzylated glucal.

Keywords: dihydroxylation; epoxidation-alcoholysis; glycals; hydrogen peroxide; titanium isopropoxide; Venturello's complex

Introduction

Oligosaccharides and glycoconjugates are now known to play essential roles in biological systems, in diverse areas such as protein folding, tissue structure, blood coagulation, immune response, cell-cell recognition, pathogen-cell recognition, and inflammation.[1] These advances in glycobiology were the basis for the discovery of a number of sugar-based drugs and vaccines[1a] and are fuelling interest in the development of chemical tools to manipulate the sugar entities in order to acquire a better understanding of their functions. Because of their versatility, glycals have often been used as building blocks in the synthesis of these oligosaccharides and glycoconjugates. Different strategies for activation of the double bond in glycals are known,[1e,f,2,3,4,5] of which epoxidation[5a] is probably the most common. Epoxidation of glycals yields 1,2-anhydro sugars which are good glycosyl donors. Regiospecific opening of the epoxide with a suitable nucleophile leaves O-2 unprotected and hence available for further manipulation, while the C-1 can carry a glycosidic substituent or can further be activated. In addition to obvious applications in the synthesis of oligosaccharides, the use of long-chain alcohols as nucleophiles can provide an 'anchoring' chain on C-1 and allows synthesis of artificial cell membrane components. A further application is the stereoselective production of sugar 1,2-diols. These are useful synthetic intermediates in several organic transformations, such as the synthesis of chiral polyols, *O*-glycosides, *C*-glycosides and in intermolecular *O*-glycosylations.[6]

The most common epoxidation method uses dimethyldioxirane[5] (DMDO). However, the instability and explosivity of DMDO are serious drawbacks. Other proposed methods include *m*-chloroperbenzoic acid/KF[7] and Tf_2O with diphenyl sulfoxide.[8] These methods all use stoichiometric amounts of reagents, resulting in large amounts of waste. However, the economic and environmental realities calling for sustainable processes are fuelling the current interest in incorporating catalysts in synthetic pathways. Catalysts for epoxidation of glycals have only recently been identified, including Ru-porphyrin[9] and CH_3ReO_3 (MTO).[10,11]. The latter has also been applied in a heterogeneous version.[10c] Apart from epox-

idation with DMDO, followed by hydrolysis, a different set of methodologies exists to perform the dihydroxylation of unsaturated sugars. In one of the earliest reports on the matter, Bilik et al.[12] used a range of metal oxides among which MoO_3 gave the best results. Other methods include the use of oxone-acetone,[13] OsO_4-NMO[14] and the bimetallic system $RuCl_3/CeCl_3/NaIO_4$.[15]

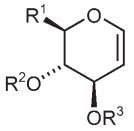
Against this background we here present a methodology for the selective formation of α-epoxides from protected glycals, followed by *in situ* opening of the epoxides to give either 2-hydroxyglycosides or sugar 1,2-diols. The method uses either Ti(O-*i*-Pr)$_4$ or Venturello's peroxotungstate $PW_4O_{24}^{3-}$ as catalysts, and hydrogen peroxide as benign and cheap oxidant in alcoholic solvents. Biphasic conditions are applied to the Venturello complex to allow for incorporation of long-chain alcohols or to selectively obtain sugar 1,2-diols. The Venturello complex, in particular, has been shown to be a highly efficient and versatile catalyst, with potential use in the production of a wide range of high-value products.

Results and Discussion

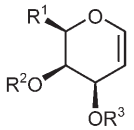
We recently described the use of Venturello's peroxophosphotungstate compound, $Q_3PW_4O_{24}$, as well as Ti(O-*i*-Pr)$_4$ as efficient catalysts for H_2O_2-mediated epoxidations of simple cyclic enol ethers (Q = quaternary ammonium ion)[16]. Small quantities of dry NaA zeolite were used to suppress the undesired acid-catalyzed alcohol addition to the double bond. We here report on an investigation of the applicability of these methods to selective tandem epoxidation-alcoholysis or epoxidation-hydrolysis of glycals (1,2-anhydro sugars) to give the corresponding glycosides or glycoses (**I**→**II**→**III**, Scheme 1).

Selection and Preparation of Glycals

In order to assess the factors influencing activity of the catalyst, reactivity of the starting glycals and selectivity in product formation, a range of variously protected or selectively unprotected glucals (**1**–**7**), xylal (**8**) and galactals (**9**, **10**) was prepared using standard literature procedures and used as substrates in reactions with a variety of alcohols. It is known that the reactivity of glycals is influenced by the nature of the protecting groups,[17] with esters providing an electron-withdrawing effect on the double bond which is deactivating in view of the electrophilic mechanism of epoxidation using peroxometal catalysts,[18] but also potentially a "participating" effect on reactions at the anomeric centre, while ether protecting groups are electron donating and thus activating.



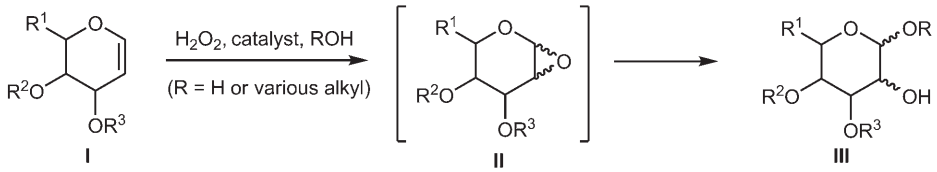
	R^1	R^2	R^3
1	CH_2OAc	Ac	Ac
2	CH_2OBn	Bn	Bn
3	CH_2OMe	Me	Me
4	$CH_2OTBDMS$	TBDMS	TBDMS
5	$CH_2OTBDPS$	H	H
6	CH_2OH	Bn	Bn
7	CH_2OH	H	H
8	H	OBn	OBn



	R^1	R^2	R^3
9	CH_2OAc	Ac	Ac
10	CH_2OBn	Bn	Bn

Epoxidation-Alcoholysis of Glycals

The results of reactions of glycals with H_2O_2 and catalysts in either methanol, ethanol or propanol as nucleophilic solvents are summarized in Table 1, for Ti(O-*i*-Pr)$_4$ as the catalyst, and in Table 2, for the Venturello compound as the catalyst. In all cases 2-hydroxyglycosides were formed; the initially formed epoxide is unstable under these reaction conditions, and the stereochemistry of the products reflects the stereose-



Scheme 1. Generalized reaction scheme for tandem epoxidation-alcoholysis or epoxidation-hydrolysis of variously protected glycals.

lectivity in initial epoxide formation. In some instances product identification was facilitated by acetylation of the 2-hydroxyglycosides to give 2-*O*-acetyl products, with resultant downfield shift of the H-2 signal in the ^{1}H NMR spectrum. In all cases reactions were carefully monitored by TLC and where the reaction went to completion, the reported reaction times correspond to the disappearance of starting material. In cases of incomplete conversion the reaction times reflect the time of reaction quenching and the conver-

Table 1. Results of epoxidation-methanolysis of various glycals with Ti(O-*i*-Pr)$_4$.[a]

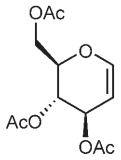
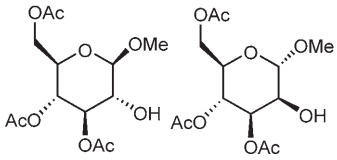
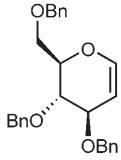
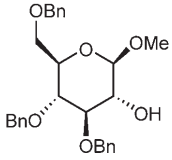
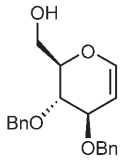
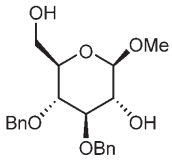
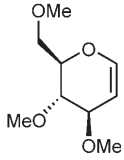
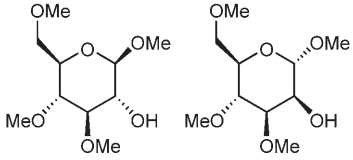
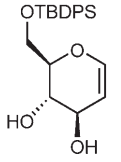
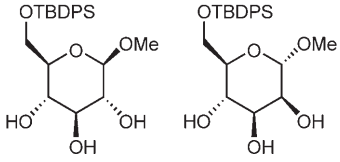
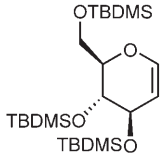
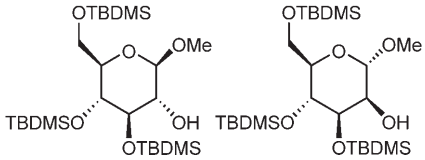
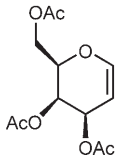
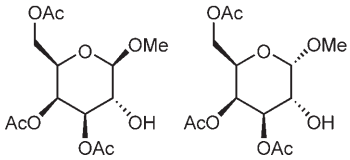
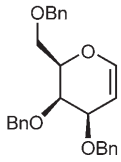
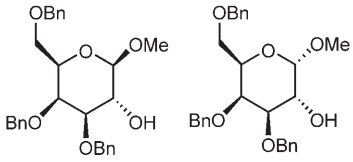
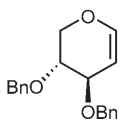
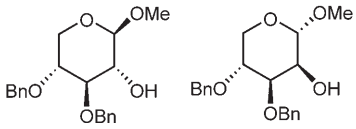
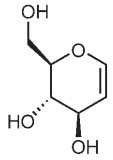
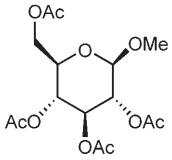
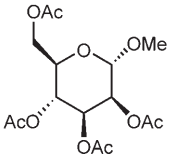
Entry	Substrate	Time [h]	Conv. [%]	Products	Ratio α:β epoxide[b]	Ratio opening epoxide (*trans*:*cis*)
1		170	70		16:1[c]	*trans* mainly
2		≤50	100		α only	*trans* only
3		80	55		α only	*trans* only
4		120	100		6:1	*trans* only
5		70	95		3:1	*trans* only
6		100	20		16:1	*trans* only
7		140	100		α only	10:1
8		≤50	100		α only	6:1
9		135	60		3:4	*trans* only

Table 1. (Continued)

Entry	Substrate	Time [h]	Conv. [%]	Products	Ratio α:β epoxide[b]	Ratio opening epoxide (*trans:cis*)
10		170	90	 	1:1.5[d]	*trans* only

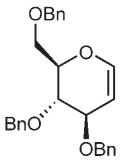
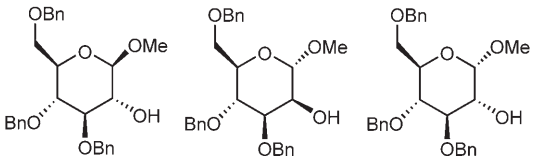
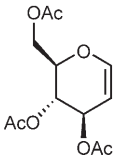
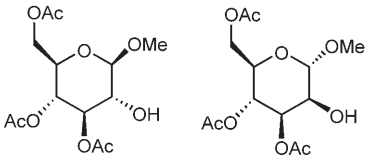
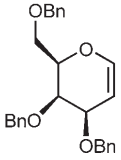
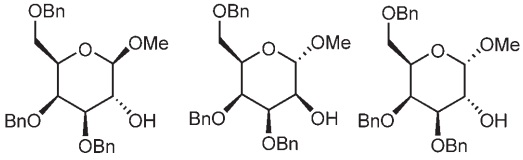
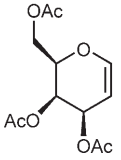
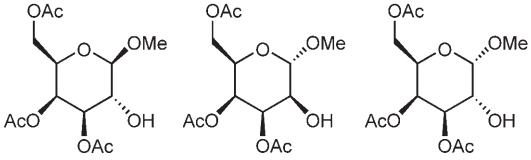
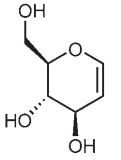
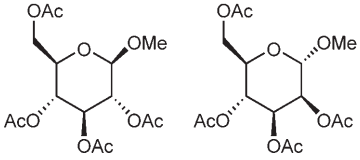
[a] *Conditions:* glycal: 0.1 M in MeOH, Ti(O-*i*-Pr)$_4$: 2 mM (0.02 equiv., based on substrate), NaA (dry): 15 mg/10 mL, H_2O_2: 4 M (4 equiv.), 323 K. The alkaline nature of the zeolite is needed to suppress the acid-catalyzed addition of alcohols to the double bond.

[b] All ratios were determined by integration of selected signals in the ^{1}H NMR spectra of the crude reaction mixture.

[c] Another isomer, presumably *cis* opened α epoxide, was also detected. However yield was very low (under 5%).

[d] Products were obtained by immediate acetylation on completion of reaction.

Table 2. Comparison of results with Ti(O-*i*-Pr)$_4$ with those in the literature.

Substrate	Products	Catalyst	Ratio	Time	Ref
		Ti(O-*i*-Pr)$_4$-H_2O_2	1:0:0	50 h	This paper
		MTO-H_2O_2	11:1:21	?	[11]
		MTO-UHP	5.3:1:0	15 h	[10c]
		Ti(O-*i*-Pr)$_4$-H_2O_2	16:1	170 h	This paper
		MTO-H_2O_2	2:1	2 h	[11]
		MTO-UHP	2:1	?	[11]
		MTO-UHP	1.9:1	20 h	[10c]
		Ti(O-*i*-Pr)$_4$-H_2O_2	6:0:1	50 h	This paper
		MTO-H_2O_2	-	-	[11]
		MTO-UHP	1.7:1:0	3.5 h	[10c]
		Ti(O-*i*-Pr)$_4$-H_2O_2	10:0:1	140 h	This paper
		MTO-H_2O_2	3:1:0	?	[11]
		MTO-UHP	7.5:1:0	19 h	[10c]
		Ti(O-*i*-Pr)$_4$-H_2O_2	1:1.5	170 h	This paper
		MTO-H_2O_2	2:1	?	[11]

sion percentages were calculated from ^{1}H NMR spectra of crude product mixtures.

A full comparison of the activity of the two catalysts is limited by their complementary solubilities in the solvents investigated. Ti(O-*i*-Pr)$_4$ could only be used in methanol due to the formation of precipitates in ethanol or propanol, whereas the Venturello compound was not completely soluble in methanol. However, it is immediately apparent from the results in Table 1 and Table 2 that the Venturello compound is more active and versatile as a catalyst than Ti(O-*i*-Pr)$_4$, with the former tolerating a wider range of alcohols in generally shorter reaction times.

Reactions using Ti(O-*i*-Pr)$_4$

Ti(O-*i*-Pr)$_4$ proved to only be effective as a catalyst when reactions were conducted in methanol, and required long reaction times. However, these drawbacks were offset by the excellent selectivity in reactions of protected glucals, which yielded predominantly or sometimes exclusively the β-glucosides (entries 1, 2 and 3, Table 1). The implication is that with this catalyst epoxidation from the α-face is favoured, with subsequent concerted β-face nucleophilic attack at the anomeric carbon and opening of the C-1−O bond. Exclusive α-selectivity in epoxide formation is retained when the 6-OH is free (entry 3) and drops only marginally with the TBDMS-protected glucal (entry 6). However, the selectivity dropped more markedly with Me-protected glucal (entry 4), deteriorated further with the 2,3-unprotected glucal (entry 5), and was reversed to favour β-epoxide formation with unprotected D-glucal (entry 10). In addition, the protected xylal derivative (entry 9), which can be thought of as a glucal derivative from which C-6 has been removed, gave a mixture of α- and β-epoxides. Overall, these results suggest that facial selectivity in epoxide formation is influenced by a subtle interplay between the nature and steric bulk of the substituent at C-5, the nature of the protecting groups in general, and whether the allylic hydroxy group at C-3 is protected or not, with the latter having a *syn*-directing effect on the epoxidation. In addition, a free 6-OH in an otherwise protected glucal appears to result in α-epoxide formation. The stereochemistry at C-4 appears to have a limited effect on the stereoselectivity of epoxide formation in acetylated glycals: acetylated glucal (entry 1) yields α- and β-epoxide in a ratio 16:1, while only α-epoxide is formed from acetylated galactal (entry 7). In the case of benzylated glycals, the product distributions indicate exclusive α-epoxide formation from both glucal and galactal. However, a significant difference is seen in the stereoselectivity of the subsequent opening of the epoxides. Whereas the glucal derivatives all exhibit almost exclusive selectivity towards formation of 1,2-*trans* glycosides, the galactal derivatives give significant proportions of 1,2-*cis* glycosides, suggesting that the substituent at C-4 may assist in stabilizing a carbenium ion at C-1 formed by opening of the epoxide.

The results of reactions with Ti(O-*i*-Pr)$_4$ in methanol can be compared with similar tandem catalytic oxidations in methanol using methyltrioxorhenium (MTO) as catalyst and either H_2O_2 or urea-hydrogen peroxide (UHP) as oxidant, as reported independently by Quayle and co-workers[11] and Goti and co-workers[10a] and summarized in Table 2. While reaction times for the Ti(O-*i*-Pr)$_4$-catalyzed reactions were significantly longer than for the other reactions, the selectivities towards α-epoxides were markedly superior in most cases. However, in the case of galactal the opening of the epoxide seems less selective. Remarkably, the reaction of the unprotected glucal proceeded with reversed selectivity compared to the one achieved with MTO-H_2O_2.

Reactions using Venturello's Complex

The Venturello complex is significantly more active than Ti(O-*i*-Pr)$_4$ as a catalyst in epoxidation-alcoholysis reactions, giving high conversions in a range of solvents, in reaction times generally shorter than 24 h (Table 3). While epoxidation from the α-face was again favoured for the fully protected glycals, exclusive α-epoxidation was only achieved in selected reactions of galactal derivatives (Table 3, entries 19 and 20), and all glucal derivatives gave mixtures which included small proportions of products derived from β-epoxide intermediates.

As before, reactivity was lower for acetylated glucals (entries 11 and 19) than for their ether-protected counterparts (entries 14 and 21). The influence of the nature of the protecting groups and pattern of protection can be evaluated by comparing results for reactions in ethanol. For fully protected glucals, reactivity decreases in the order Bn > Me > TBDMS (entries 13, 16, 18). The low reactivity of the TBDMS-protected glucal can be attributed to the significant steric demand of the bulky TBDMS groups which forces the glucal into the $^5H_4$ conformation, where the substituents at C-3, C-4 and C-5 are in a *pseudo*-axial orientation. These inhibit access of the electrophilic oxygen species to the double bond between carbons 1 and 2. Selectivities towards α-epoxidation are comparable for these three protecting groups, although in the opening of the epoxide some 1,2-*cis* glycoside formation is observed with methyl- or TBMDS-protected glucals. Removal of the benzyl group at O-6 (entry 15) results in significantly enhanced selectivity in epoxide formation (α:β = 25:1, compared to 7:1 in benzylated glucal, entry 13). The benzylated xylal derivative (entry 22, Table 2) gives selectivities comparable to those of the benzylated glucal (entry 13), a result in marked contrast to the β-selectivity in epoxidation of benzylated xylal with Ti(O-*i*-Pr)$_4$ as catalyst (Table 1, entry 9). The selectivity using the Venturello complex is reversed to favour products arising from β-epoxidation in the 3,4-unprotected glucal (entry 17), while in a remarkable result, the fully unprotected D-glucal (entry 23) gives exclusively the product resulting from β-epoxide formation. As in the case of the Ti(O-*i*-Pr)$_4$-catalyzed reaction, these results clearly suggest a participatory role for the allylic alcohol in directing β-face epoxidation.

An indication of the influence of the solvent on reactivity and selectivity is obtained from comparison of

Table 3. Results of epoxidation-alcoholysis of various glycals with Venturello's compound.[a]

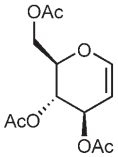
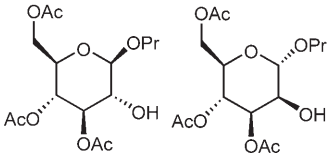
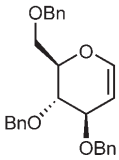
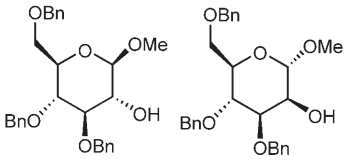
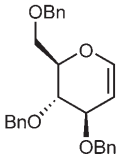
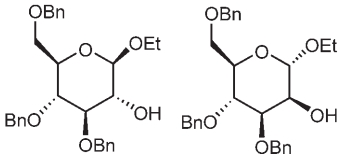
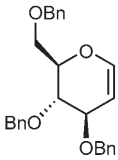
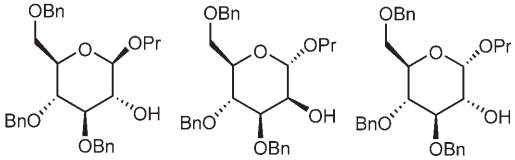
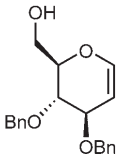
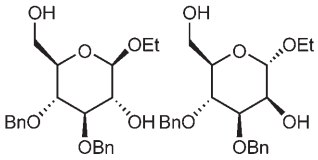
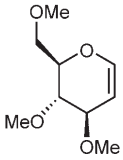
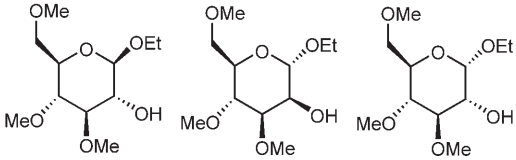
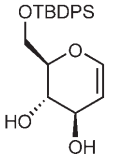
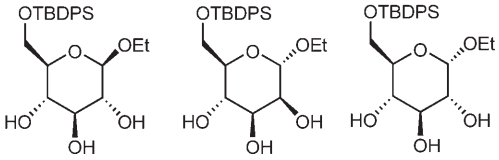
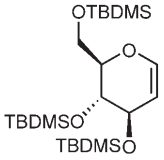
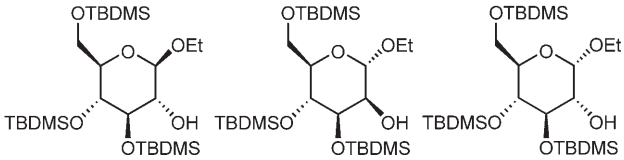
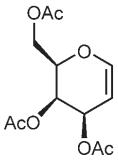
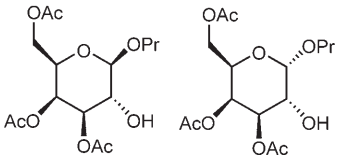
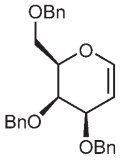
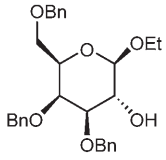
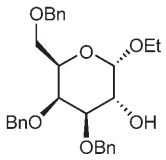
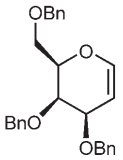
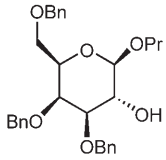
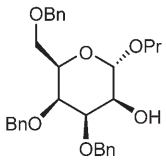
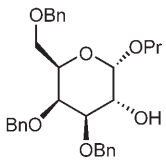
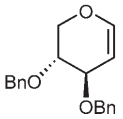
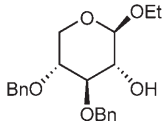
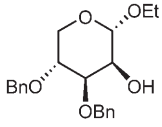
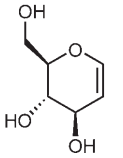
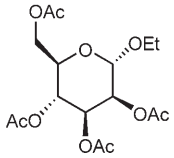
Entry	Substrate	Solvent	Time [h]	Conv. [%]	Product(s)	Ratio α:β epoxide[b]	Ratio opening epoxide (*trans:cis*)
11		*n*-PrOH	22	100		8:1[c]	*trans* only
12		MeOH/ 1,4-di-oxane	170	≥99		8:1	*trans* only
13		EtOH	2	100		7:1	*trans* only
14		*n*-PrOH	≤1	100		4:1	3:1
15		EtOH	8	≥99		>25:1	*trans* only
16		EtOH	≤14	100		12:1	9:1
17		EtOH	1.5	100		1:2.7	10:1
18		EtOH	24	100		8.5:1	27:1
19		*n*-PrOH	22	100		α only	2.5:1

Table 3. (Continued)

Entry	Substrate	Solvent	Time [h]	Conv. [%]	Product(s)	Ratio α:β epoxide[b]	Ratio opening epoxide (*trans:cis*)
20		EtOH	2	100	 	α only	2.5:1
21		*n*-PrOH	4.5	100	  	6:1	2:1
22		EtOH	20	≥95	 	10:1	*trans* only
23		EtOH	3.5	100		β only[d]	*trans* only

[a] *Conditions:* glycal: 0.1 M in selected solvent, $Q_3PW_4O_{24}$: 2 mM (0.02 equiv., based on substrate), NaA (dry): 5 mg/10 mL, H_2O_2: 4 M (4 equiv.), 323 K. The alkaline nature of the zeolite is needed to suppress the acid catalyzed addition of alcohols to the double bond.

[b] All ratios were determined by integration of the NMR signals of the crude reaction mixture.

[c] Another isomer, presumably *cis* opened α epoxide, was also detected. However yield was very low (under 5%).

[d] Products were obtained by immediate acetylation on completion of reaction.

reactions of the benzylated glucal and galactal in ethanol and propanol. In the case of the glucals (entries 13 and 14) a change from ethanol to propanol results in a slight lowering of the selectivity towards α-epoxide formation, and appearance of an additional α-glucoside product resulting from non-stereospecific opening of the α-epoxide. With galactals (entries 20 and 21) exclusive α-epoxidation is achieved in ethanol, while in propanol some β-epoxide formation is observed.

General Comments on the Epoxidation-Alcoholysis

It is clear from these results that starting from the fully protected glycals, the α-epoxide is formed predominantly and in some cases exclusively with both catalytic systems, a result which has general synthetic significance. Selective formation of one epoxide has been reported for some stoichiometric methods, but is highly dependent on the substrate[5] or the type of reagent.[8] Liu et al. and Yu et al. managed to selectively obtain the α-epoxide with a homogeneous and a heterogeneous Ru-porphyrin catalyst,[9] but this was only achieved with acetylated glucal and the heterogeneous reaction gave no result with benzylated glucal. Another general feature of these methods is the high yield obtained, in the range of 85 to 90%. Similar yields have been achieved with MTO for a few substrates,[10–11] and in the work of Danishefsky and others using DMDO[5] but most other methods are associated with yields under 80%.

While the $Ti(O\text{-}i\text{-}Pr)_4$ protocol is limited to methanol, the Venturello compound appears to be effective in a broader range of alcoholic solvents. For protected glucals the reaction is faster with *n*-propanol than with ethanol and methanol. As epoxides are not detected in the product mixtures, it is safe to assume that the epoxidation is the rate-limiting step, rather than the epoxide opening. Thus, it appears that the epoxidation is faster in *n*-propanol. Tests with the Venturello compound in different solvents with 3,4-dihydro-2*H*-pyran showed the same phenomenon,[16] suggesting that the rate differences are due to different solvation of the transition states in the various solvents, or to a different solubility of the catalyst itself.

With the protected galactals (entries 20 and 21) the order *n*-propanol/ethanol is surprisingly reversed.

The stereochemical outcome of the epoxidations is directed by a number of different factors. Firstly there are the steric and stereoelectronic considerations taking into account the orientation of the ring substituents and the preferred conformation ($^4H_5$ *vs.* $^5H_4$) of the glycals, as noted above for both the Ti and Venturello catalytic systems. Secondly, a free OH group on C-3 may direct the epoxidation, either by coordination of the alcohol group to a metal catalyst, or by hydrogen bonding. In the case of hydrogen bonding, the oxirane transition state is stabilized by intramolecular hydrogen bonding with an adjacent OH group, causing a *syn*-directing effect for the epoxidation reaction. The use of polar, alcoholic solvents, however, partly cancels this *syn*-directing effect by disturbing the hydrogen bonding.[5b,11] Coordination of a substrate allylic alcohol on the metal centre has a similar *syn*-directing effect. As the α-epoxide was obtained predominantly from all substrates with a protected O-3, it seems that the epoxide is formed preferentially on the opposite face of the C-3 substituent. Since all our compounds have the C-3 in an upper face β-orientation, this outcome was expected.

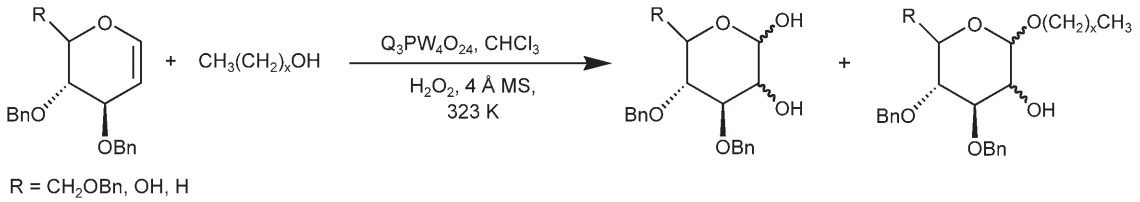
For 6-*O*-TBDPS-D-glucal both hydrogen bonding or coordination, and steric effects come into play. The OH group on C-3 can direct the epoxide to the β-face, although this effect may be cancelled out by the use of alcoholic solvents and the steric factors which favour α-epoxide formation. The directing effect of the OH group is, however, particularly clear in the reaction catalyzed by Venturello complex, where β-face attack predominates (entries 17 and 23). Steric effects are dominant for the Ti(O-*i*-Pr)$_4$ reaction, with a 3:1 α:β ratio (entry 5).

Regarding the stereochemistry of epoxide opening, the high proportion of the 1,2-*trans*-products and hence the β-configuration at C-1 after opening of the epoxides suggests that a concerted or S_N2-type mechanism predominates in many cases. To rule out the possibility that the *trans*/*cis* ratios detected here are caused by Lewis acid-catalyzed isomerization of the *trans*-product, the crude product mixture of a reaction of benzylated glucal and the Venturello compound in ethanol was concentrated under vacuum and then reacted for 36 h in the Ti(O-*i*-Pr)$_4$ conditions. The products were acetylated and their NMR spectrum compared with that of the acetylated Venturello product mixture, with no change in the *trans/cis* ratio observed. This confirms that the ratios obtained are not caused by acid-catalyzed rearrangement. As *cis* opening of the epoxide is hardly discussed in the literature it is difficult to make a thorough comparison with literature.

For reactions with the Venturello catalyst, 1,2-*cis*-disubstituted compounds are particularly formed when the substituents or the nucleophile are bulky. Thus, more *cis* opening is obtained from a glucal with bulky TBDMS substituents than from the benzylated glucal (entries 18 *vs.* 13). *cis*-Opened products are also abundant in the reactions of the galactals, in which the crowding at the β-side favours nucleophile attack *via* the α-side, even on an α-epoxide (entries 19–21). On closer examination it appears that the group on the C-5 position exerts a significant influence. When a C-5 substituent is absent (xylal derivative, entry 22) or is an unprotected hydroxymethyl group (entry 15), only *trans*-opening of the epoxide is observed, presumably due to the easy access to the β-face of the α-epoxide. With an acetyl protecting group on O-6, only a small degree of *cis* opening is detected, even with propanol (entry 11). Obviously, the size of the alcohol also determines the stereochemical outcome of the epoxide opening. *cis*-Product formation from glucal and galactal derivatives are more pronounced with *n*-propanol. *cis*-Opening of the epoxide was observed less frequently in the Ti-catalyzed reactions; only in reactions of galactals, are 1,2-*cis*-disubstituted compounds observed, with selectivities between 10 and 15% (entries 7 and 8).

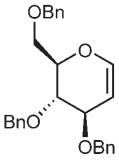
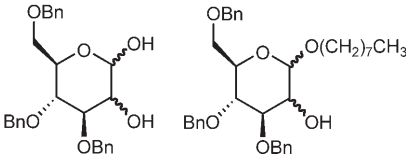
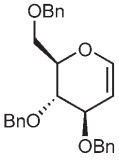
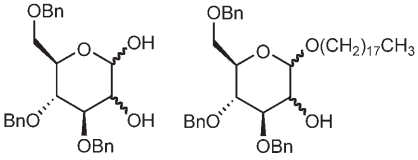
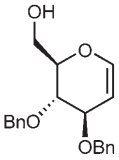
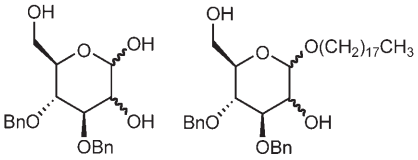
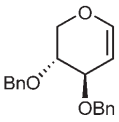
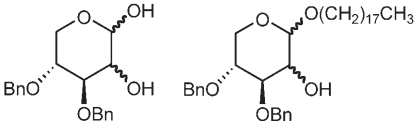
Incorporation of Long-Chain Alcohols using Biphasic Conditions

To broaden the scope of possible nucleophiles beyond alcohol solvents, we decided to test the Venturello compound in biphasic conditions on a range of glycals (Scheme 2). $CHCl_3$ was used as solvent and aqueous H_2O_2 as oxidant. Octanol or octadecanol were added as a nucleophile. This protocol is similar to the one that we previously successfully used for the oxidative incorporation of long alcohols in a more simple cyclic



Scheme 2. General scheme for incorporation of long-chain alcohols with Venturello's compound.

Table 4. Incorporation of long alcohols by applying Venturello's compound in biphasic conditions.[a]

Entry	Substrate	Nucleophile	Time	Conv. [%]	Products	Diol:Ether
24		Octanol	8 h	100		2:1
25		Octadecanol	5 h	100		3.5:1
26		Octadecanol	2 h	100		4:1
27		Octadecanol	3 h	100		1.7:1

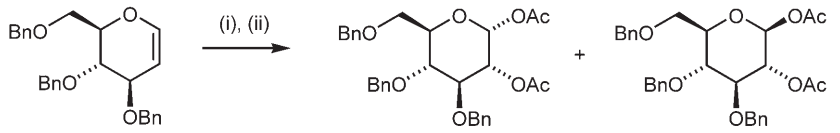
[a] *Conditions:* glycal: 25 mM in $CHCl_3$, $Q_3PW_4O_{24}$: 1 mM (0.04 equiv., based on substrate), NaA (dry): 2.5 mg/10 mL, nucleophile: 50 mM (2 equiv.), H_2O_2: 37.5 mM (1.5 equiv.), 323 K.

enol ether such as 3,4-dihydro-2*H*-pyran.[16] From the results obtained (Table 4) it is immediately clear that protocols based on the use of aqueous hydrogen peroxide are not applicable to the glycals, as the latter are much more sterically encumbered than 3,4-dihydro-2*H*-pyran. Due to the lower reactivity of the long aliphatic alcohols, water is a competitive nucleophile in opening the epoxide, leading to the formation of 1,2-diol as the major product. Only with the benzylated xylal (entry 27) was it possible to achieve an almost 1:1 ratio of desired product and diol. In order to exclude water as much as possible the same reaction was performed with the urea-hydrogen peroxide adduct (UHP) as the oxidant instead of hydrogen peroxide. The reaction only went to completion with addition of 3 equivalents of UHP, but no significant enhancement of the selectivity towards the desired products was observed. Apparently, the molar equivalent of water formed during the epoxidation competes efficiently with long aliphatic alcohols in the nucleophilic opening of the epoxide. In a second set of experiments the use of selectively unprotected pyranosides as nucleophiles was attempted in order to explore the potential for disaccharide synthesis under these conditions. In all cases complete conversion of the starting material was observed but a complex mixture of products was obtained and even after chromatographic separation on silica gel it was not possible to unambiguously identify disaccharide products.

Selective Dihydroxylation of 1,2-Glycals

As incorporation of long alcohols was unsuccessful because of the competing formation of glycal diols, attention was turned to adaptation of the reaction protocol in order to selectively obtain 1,2-diols from glycals (Scheme 3). Although these diols are synthetically very useful compounds (*vide supra,* Introduction), only a few methods for their selective preparation have been reported[6b,d,12–14]. The existing methods for direct dihydroxylation of glycals all have drawbacks such as the removal of Os salts[12–14] problems in scale-up in the case of DMDO,[13] formation of C-2 epimers or use of high mol% of metal.[14]

In a first approach, the same reaction conditions as for the incorporation of long-chain alcohols were used, but the nucleophile was replaced by an excess of water. Diol was formed only as minor product. This is presumably due to the low polarity of the chloroform. To overcome this problem, 1,4-dioxane was employed as solvent, and water added in excess. The desired *gluco*-diol was obtained within 24 h in 86% selectivity and in a 1:1 α:β ratio. A subsequent attempt in a mixture of acetonitrile-ethyl acetate-water (based on Tiwari et al.[14]) led to *gluco*-diol being obtained with improved selectivity (95%) and α:β ratio (1.35:1), while the reaction time was similar. The formation of only *gluco*-products in all reactions confirms that the Venturello catalyst selectively forms



1 – 1.35 1

i) $Q_3PW_4O_{24}$, 1,4-dioxane:H_2O (6:1) or CH_3CN:EtOAc:H_20 (3:3:1), H_2O_2 (2 equiv.), 323 K, 24 h
ii) Pyr, Ac_2O, r.t., 15 h.

Scheme 3. Selective dihydroxylation of benzylated glucal.

the α-epoxide and that it is an effective catalyst for selective synthesis of 1,2-diols from benzylated glucal.

Conclusions

New catalytic protocols have been developed for the epoxidation-alcoholysis and dihydroxylation of unsaturated sugars using H_2O_2 as environmentally benign oxidant. Both Ti isopropoxide and a Venturello compound have been shown to be effective catalysts in reactions on a range of glycals differing in configuration and protecting group patterns. Both catalysts gave exceptionally high selectivity for α-epoxide formation, as inferred from the stereochemistry of products derived from *in situ* opening of the epoxides. The Venturello compound in particular proved to be a very versatile catalyst. It tolerates a wide range of solvents and protecting groups in the substrates, and can also work in biphasic conditions for the dihydroxylation of glycals.

Experimental Section

General Remarks

Commercially obtained compounds were used as received. Solvents used were AR grade or dried according to common procedures. Reaction progress was followed by TLC. NMR spectra were recorded on a Bruker AMX 300 or a Varian Mercury 300 (300 MHz) and a Varian Unity 400 (400 MHz).

Substrates

D-Glucal and tri-*O*-acetyl-D-glucal were commercially obtained. All other glycals and the glycosides used as nucleophiles were synthesized according to known literature procedures: tri-*O*-benzyl-D-glucal,[17] 3,4-di-*O*-benzyl-D-glucal,[18,19] tri-*O*-methyl-D-glucal,[20] 6-*O*-TBDPS-D-glucal,[18] tri-*O*-TBDMS-D-glucal,[19] tri-*O*-acetyl-D-galactal,[22] tri-*O*-benzyl-D-galactal,[18] di-*O*-benzyl-D-xylal,[21,23] 2,3,4-tri-*O*-benzyl-D-methylglucoside,[24] 2,3,4,6-tetra-*O*-benzyl-D-glucoside.[20a,25]

Catalysts

$Ti(O\text{-}i\text{-}Pr)_4$ was commercially obtained. Venturello's phosphotungstate complex was prepared as described in a literature report.[26]

Venturello Complex

H_2WO_4 (10 g) was added to 35 wt% aqueous H_2O_2 (28 mL). The yellow mixture was stirred for 1.5 h at 333 K and then filtered to remove insoluble WO_3 particles. The filtrate was allowed to cool to room temperature and H_3PO_4 (1.2 mL) added. Doubly distilled H_2O was added to the mixture to a combined weight of 120 g. After stirring for 30 min at room temperature a solution of Aliquat 336 (8.56 g) in CH_2Cl_2 (180 mL) was added dropwise over 15 min. The resulting mixture was stirred vigorously for 1 h after which the organic phase was separated, washed once with H_2O then dried with $MgSO_4$ and concentrated under vacuum to give the complex as a sticky transparent yellow syrup; yield: 11 g (70%). IR (KBr): $\nu = 1050$ (P–O), 975 (W=O), 856 and 846 cm^{-1} (W-O-O). The data agree with reported values.[26b]

Reaction Protocols

Epoxidation-alcoholysis using the Venturello compound: A typical procedure for the epoxidation-alcoholysis of the glycal compounds with the Venturello complex is as follows: glycal (1.0 mmol), $Q_3PW_4O_{24}$ (0.02 mmol), H_2O_2 (50 wt% solution in H_2O, 4.0 mmol) and dry powdered NaA (5.0 mg) were combined and stirred in a selected solvent (10 mL) at 323 K. Reaction progress was monitored by TLC. On completion of the reaction, the mixture was filtered and the filtrate is taken up in CH_2Cl_2 and washed 3 times with water. The organic phase was dried with $MgSO_4$, filtered and concentrated under vacuum. The identity of products and ratios of diastereomers in product mixtures were determined by ^1H- and ^{13}C NMR, including COSY, HSQC and DEPT analysis. In some instances products were acetylated using acetic anhydride and pyridine.

Epoxidation-alcoholysis using the Ti catalysts: A typical procedure for the epoxidation-alcoholysis of the glycal compounds with Ti isopropoxide is as follows: glycal (1 mmol), $Ti(O\text{-}i\text{-}Pr)_4$ (0.02 mmol), H_2O_2 (50 wt% solution in H_2O, 4 mmol), and dry powdered NaA (15 mg) were combined in methanol (10 mL), with stirring at 323 K. Progress of reactions was monitored by TLC. On completion of the reaction, the mixture was filtered and the filtrate taken up in CH_2Cl_2 and washed 3 times with water. The organic phase was dried with $MgSO_4$, filtered and concentrated under vacuum. Prod-

ucts and their stereochemistry were determined by ^{1}H, ^{13}C NMR, COSY, HSQC and DEPT analysis. With complex mixtures, the products were acetylated (Ac_2O, pyridine) and analyzed by NMR.

Biphasic reaction using the Venturello compound: To a solution of 0.01 mmol of $Q_3PW_4O_{24}$ in $CHCl_3$ (10 mL) was added glycal (0.25 mmol), dry NaA (2.5 mg), nucleophile (2 equiv.) and H_2O_2 (0.375 mmol of 50 wt% solution in H_2O; 1.5 equiv. against glycal). The reaction was stirred at 323 K and monitored by TLC. On completion of the reaction, the mixture was filtered and the filtrate taken up in CH_2Cl_2 and washed 3 times with water. The organic phase was dried with $MgSO_4$, filtered and concentrated under vacuum, and then acetylated (Ac_2O, pyridine). The identity of products and the ratio of stereoisomers was determined by analysis of the mixtures by ^{1}H and ^{13}C NMR, and COSY, HSQC and DEPT analysis. Where necessary, separation and purification of products was achieved by chromatography on a column of silica gel using mixtures of ethyl acetate and hexane as eluent.

Dihydroxylation using the Venturello compound: To a solution of $Q_3PW_4O_{24}$ (0.005 mmol) in 1,4-dioxane (2.5 mL) (A) or CH_3CN (1.5 mL) and EtOAc (1 mL) (B) was added H_2O (0.5 mL), H_2O_2 (0.190 mmol, 1.5 equiv. against glycal) and glycal [0.125 mmol dissolved in 0.5 mL 1,4-dioxane (A) or EtOAc (B)]. The reaction was stirred at 323 K and monitored by TLC. When the reaction was complete, the mixture was diluted with EtOAc, dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was acetylated (Ac_2O, pyridine) and the mixture of products analyzed by ^{1}H NMR and ^{13}C NMR spectroscopy, using COSY, HSQC and DEPT analysis.

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