DOI: 10.1002/adsc.201000614

Stereoselective Tandem Epoxidation–Alcoholysis/Hydrolysis of Glycals with Molybdenum Catalysts

Irene Marín,[a] M. Isabel Matheu,[a] Yolanda Díaz,[a,*] and Sergio Castillón[a,*]

[a] Departament de Química Analítica i Química Orgànica, Universitat Rovira i Virgili, C/Marcel·lí Domingo s/n, 43007 Tarragona, Spain
Fax: (+34)-977-558-446; e-mail: yolanda.diaz@urv.cat or sergio.castillon@urv.cat

Received: July 30, 2010; Revised: November 2, 2010; Published online: December 7, 2010

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201000614.

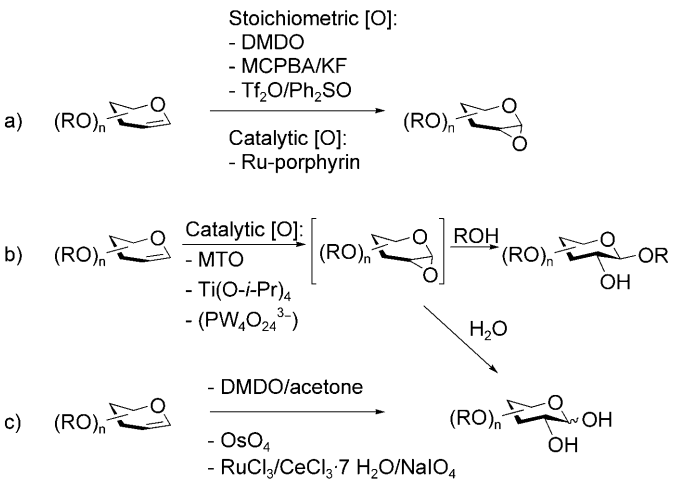
Abstract: Molybdenum catalysts are efficient and selective catalysts for the tandem epoxidation/alcoholysis or epoxidation/hydrolysis of glucal and galactal derivatives. In glucal derivatives the selectivity is mainly controlled by the allylic substituent at position 3 of the glycal, obtaining in general the products derived from the initial formation of the α-epoxide (*gluco*) when this hydroxy group is protected, while products derived from the β-epoxide (*manno*) are mainly obtained when it is unprotected. In galactal derivatives the estereoselectivity is always high to give the α-epoxide (*galacto*) and independent of the protecting groups.

Keywords: carbohydrates; dihydroxylation; directing effect; molybdenum; oxidation; stereoselectivity

Introduction

Glycoconjugates play an important role in many biological processes such as immune response, inflammation, pathogen recognition, etc.[1] This fact has spurred the research for new synthetic methodologies looking for an easy and selective access to these compounds. In this way glycals are versatile building blocks for the synthesis of oligosaccharide motifs,[2] 2-deoxyglycosides,[3] *C*-glycosides,[4] nucleosides[5] and other biologically important molecules.[6–8] Glycals are usually activated by epoxidation,[9] to furnish 1,2-anhydro sugars, which are used as glycosyl donors[2] or as precursors of more stable glycosyl donors.[10] Glycals are also activated by dihydroxylation to give protected sugar 1,2-diols, which have been used in the synthesis of *O*-glycosides,[11] *C*-glycosides[12] and in intramolecular *O*-glycosylations.[13]

The most common epoxidation method uses dimethyldioxirane[9] (DMDO). However, DMDO is unstable and explosive and its use presents serious drawbacks. Other stoichiometric reagents include *m*-chloroperbenzoic acid (*m*CPBA)/KF[14] and diphenyl sulfoxide/Tf_2O.[15] Epoxides *trans* to the substitutent at C-3 are obtained as the major product (Scheme 1a). The need of atomic economy and environmental awareness fuelled the development of new catalytic epoxidation methods. Catalysts for epoxidation of glycals have only recently been identified. Thus, Ru-porphyrin,[16] CH_3ReO_3 (MTO),[17,18] Ti(O-*i*-Pr)$_4$[19] and Venturello's peroxotungstate ($PW_4O_{24}^{3-}$)[19] have been used in the sequential epoxidation–alcoholysis or epoxidation–hydrolysis of glycals. The epoxides initially obtained are opened *in situ* to give 2-hydroxy glycosides or dihydroxy derivatives in the presence of the epoxidation catalysts, depending on whether the reaction is carried out in the presence of alcohols or



Scheme 1.

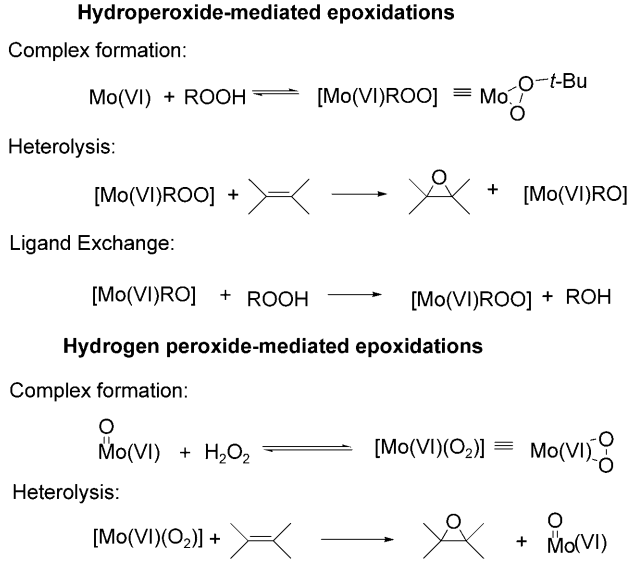
water, respectively (Scheme 1b). Other methods for synthesising 1,2-diols from glycals are based on the dihydroxylation reaction by OsO_4-NMO,[11b,c] and $RuCl_3/CeCl_3{\cdot}7H_2O/NaIO_4$,[20] and on the one-pot epoxidation–hydrolytic opening using DMDO in acetone (Scheme 1c).[21] Sugar 1,2-diols can also be classically prepared by hydrolysis of orthoesters.[22]

The transition metal-catalyzed processes aforementioned mostly afford products mainly derived of the epoxidation *trans* to the C-3 substituent (Scheme 1b). Interestingly, the dihydroxylation (epoxidation/hydrolysis) of unprotected glucal using MoO_3 as a catalyst in water as a solvent affords mainly mannose, in a process that involves directed β-epoxidation, probably *via* a hydrogen bond between the neighbouring allylic hydroxy group and the catalyst.[23] Only Venturello's peroxotungstate ($PW_4O_{24}^{3-}$)[19] provided a similar selectivity in unprotected glycals.

However, in spite of the results previously mentioned using MoO_3 and the facts that molybdenum complexes are readily available and one of the most active and efficient catalysts for alkene epoxidation,[24] no systematic investigations of their use in glycal epoxidation–alcoholysis or epoxidation–hydrolysis have been carried out. In this report we show that a variety of molybdenum complexes catalyze these processes with high conversions and selectivities.

Results and Discussion

The general mechanism for the molybdenum-catalyzed epoxidation reaction has been extensively studied and can summarily be viewed as a stepwise process (Scheme 2).[25] Using alkyl hydroperoxides as terminal oxidant, the first step is a rapid and reversible reaction in which the active catalyst, which is presumably a peroxy-molybdenum, is formed.



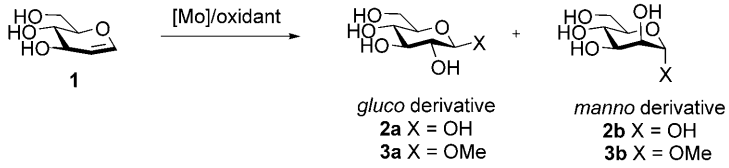
Scheme 2.

Thereafter, the intact active complex can react with the alkene, to irreversibly form the epoxide and alkoxo-substituted metal complex. Substitution of the alkoxo-substituted complex by fresh hydroperoxide could re-form the active catalyst and complete the catalytic cycle. The analogous H_2O_2-mediated process involves the intermediacy of an Mo-peroxo complex. Since the discovery by Mimoun et al.[26] that peroxo-Mo complexes can stoichiometrically epoxidize alkenes under anhydrous conditions in organic solvents, the mechanism of the oxygen transfer process has been a subject of intensive debate. The long-standing controversy about the mechanism of olefin epoxidation with η^2-diperoxomolybdenum complexes $[MoO(O_2)_2(OPr_3)]$ has recently been settled with the help of density functional methods.[27] The theoretically predicted energies of the transition states and the calculated intrinsic reaction coordinates show that the oxygen transfer takes place in a single-step reaction *via* a direct attack of the alkene to the peroxo group as proposed by Sharpless,[28] thus ruling out Mimoun's metalla-2,3-dioxolane model.[26]

We initially evaluated the epoxidation of unprotected glucal (**1**) under similar conditions to those previously explored,[23] using two molybdenum catalysts in polar solvents such as water and methanol and using different oxidizing reagents. The results are collected in Table 1. The key role of the molybdenum complex in the oxygen transfer process was first established by the lack of reactivity of the oxidant towards **1** in its absence (results not displayed in Table 1).

When the reaction was carried out in water with readily available MoO_3 as a catalyst precursor and H_2O_2 as stoichiometric oxidant, mannose (**2b**) was almost exclusively obtained, in agreement with that reported by Bilik[23] et al. (Table 1, entry 1). Note that in no case was the epoxide obtained, as a consequence of the high reactivity of the anhydro sugar in the presence of nucleophilic solvents. The use of methanol as solvent and working in similar conditions allowed us to obtain exclusively methyl α-mannopyroside (**3b**) as consequence of an epoxidation–methanolysis process (entries 2 and 3), although the reaction rate was lower than in water. In order to seek for more general oxidation conditions that would involve protected or partially protected glycals, less polar solvents and more soluble oxidizing agents should also be explored. With this purpose in mind, oxidation reactions of **1** using *tert*-butyl hydroperoxide (TBHP) as a terminal oxidant were explored next. Reactions with this oxidant driven in methanol took place with complete conversion although they required higher temperatures than with H_2O_2 (entries 4 and 5). Interestingly, the stereoselectivity was observed to depend on the solvent for solubilizing TBHP. Thus, an almost

Table 1. Tandem epoxidation–hydrolysis/glycosylation of glucal with molybdenum catalysts.



Entry	Catalyst	Peroxide	Solvent	Temp. [°C]	Time [h]	Conv. [%][a,b]	Products	Ratio[a]
1[c]	MoO_3	H_2O_2 in H_2O	H_2O	r.t.	48	>98	**2a/2b**	4:96
2[c]	MoO_3	H_2O_2 in H_2O	MeOH	r.t.	48	50	**3b**	
3[c]	MoO_3	H_2O_2 in H_2O	MeOH	r.t.	96	>98	**3b**	
4[d]	MoO_3	TBHP 5.5 M in C_9H_{20}	MeOH	50	72	>98	**3a/3b**	45:55
5[d]	MoO_3	TBHP 70 wt% in H_2O	MeOH	50	72	>98	**3a/3b**	9:91
6[d]	$Mo(CO)_6$	TBHP 5.5 M in C_9H_{20}	MeOH	50	72	>98	**3a/3b**	55:45
7[d]	$Mo(CO)_6$	TBHP 70 wt% in H_2O	MeOH	50	72	>98	**3a/3b**	9:91

[a] Determined by integration in the ^{1}H NMR spectrum of anomeric proton signals of compounds in the final reaction crude.
[b] Selectivity > 98%.
[c] *Conditions:* 1.71 mmol glycal, 1% mol catalyst, 2.5 mL H_2O_2 (5%) in the solvent.
[d] *Conditions:* 0.36 mmol glycal, 5 mol% catalyst, 1.2 mL TBHP, 2 mL MeOH.

1:1 mixture of methyl β-glucopyranoside (**3a**) and methyl α-mannopyranoside (**3b**) was obtained when TBHP was dissolved in nonane, while the stereoselectivity was 9:91 when TBHP in water was used (entries 4 and 5). The anomeric configuration of the *gluco* derivative **3a** is β, while it is α for the *manno* derivative **3b**. This is a consequence of the selective *trans* opening of the *gluco* and *manno* epoxides initially formed under the reaction conditions. The use of TBHP with more soluble molybdenum catalysts such as $Mo(CO)_6$ provided similars results to those from MoO_3 (entries 6 and 7).

A general trend of these epoxidation reactions with polar solvents is the long reaction times. This deactivating effect has been already observed,[26,28,29] and two reasons have been proposed, depending on the oxidant used. On the one hand, coordination of a basic ligand (solvent molecule) to a peroxo-Mo complex induces a decrease of electrophilicity of the peroxo group due to donation of electron density from the basic solvent *via* the metal center, thus lowering its reactivity.[30] On the other hand, the coordinating solvent may compete with the stoichiometric TBHP oxidant for the substitution of the alcohol ligand in the final molybdenum complex thus slowing down the generation of the catalytic species.[25b,c]

In order to assess the factors influencing the activity of the catalyst, reactivity of the starting glycals, protecting group effect and influence on the facial selectivity in product formation, a range of differently protected or partially unprotected glucals (**4**–**10**), and galactals (**11**–**14**) were prepared using standard literature procedures and used as starting materials for the epoxidation reaction (Figure 1).

Table 2, Table 3, Table 4 and Table 5 summarize the results obtained in the molybdenum-catalyzed epoxidation/hydrolysis or epoxidation/alcoholysis of protected glycals with *tert*-butyl hydroperoxide as an oxidant. Different [Mo]/TBHP catalytic systems and different solvents were explored using tri-*O*-acetyl-D-glucal (**4**) as a substrate (Table 2, entries 1–7). Thus, the reaction of **4** with $Mo(CO)_6$ in MeOH gave a mixture of compounds **15a(β)/15b(α)** in a 70:30 ratio as a consequence of a tandem epoxidation–*trans* epoxide opening process (Table 2, entry 1). The reaction needed 36 h for completion, in line with the results of Table 1. The *gluco* derivative **15a** was now principally obtained, in agreement with that reported for other oxidation catalysts, and on the contrary to that observed in the reaction of unprotected glucal.[17–19,23] The use of less polar solvents such as toluene did not prevent epoxide opening, probably due to the Lewis

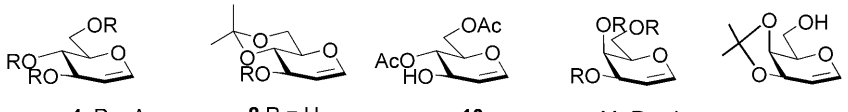
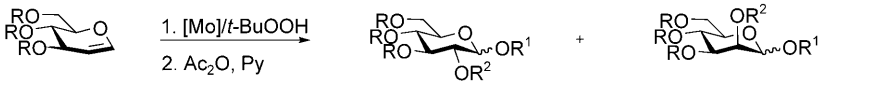
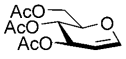
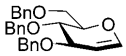
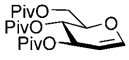
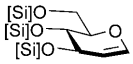


Figure 1. Structures of glycals **4**–**14** used in Mo/TBHP dihydroxylation.

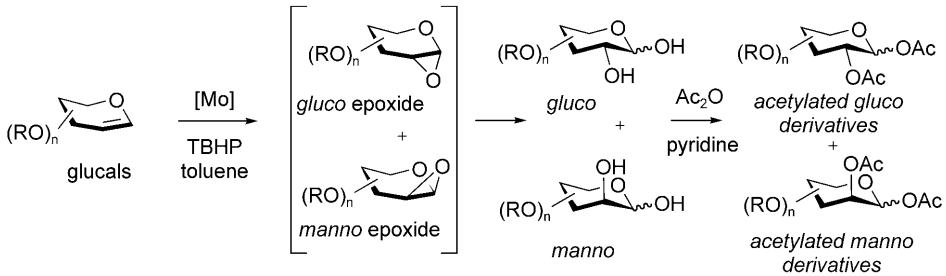
Table 2. [Mo]-catalyzed oxidation of glucals (**4**–**7**). Influence of the solvent.[a]



Entry[a)]	Substrate	Catalyst	Solvent	Temp. [°C]	Time [h]	Conv [%]	Products	Ratio[b]
1		$Mo(CO)_6$	MeOH	50	36	>98	**15a/15b**	70:30
2		$MoO_2(acac)_2$	MeOH	50	36	>98	**15a/15b**	70:30
3[c]		$MoO_2(acac)_2$	CH_2Cl_2	r.t.	6	>98	**16a/16b**	65:35
4[c]		$MoO_2(acac)_2$	toluene	30	3	>98	**16a/16b**	65:35
5[c]	**4**	$Mo(CO)_6$	toluene	40	96	>98	**16a/16b**	67:33
6[c]		$Mo(CO)_6$	toluene	80	1	>98	**16a/16b**	65:35
7[c]		MoO_2Cl_2	toluene	50	2	>98	**16a/16b**	62:38
8[c]		$Mo(CO)_6$	toluene	80	1	>98	**17a/17b**	82:18
9[c]		$MoO_2(acac)_2$	toluene	30	3	>98	**17a/17b**	75:25
10[c]	**5**	MoO_2Cl_2	toluene	50	3	>98	**17a/17b**	77:23
11[c]		$Mo(CO)_6$	toluene	80	21	>98	**18a/18b**	96:4
12[c]		$MoO_2(acac)_2$	toluene	30	24	>98	**18a/18b**	94:6
	6							
13[c,d]		$Mo(CO)_6$	toluene	80	21	0	**19a/19b**	–
14[c,d]		$MoO_2(acac)_2$	toluene	30	72	0	**19a/19b**	–
	7							

[a] *Conditions:* 0.36 mmol glycal, 5 mol% catalyst, 1.2 mmol TBHP 5.5 M in nonane, 2 mL solvent.
[b] Determined by NMR by integration of the anomeric protons in the crude reaction mixture.
[c] The reaction crude was acetylated to give the corresponding acetyl derivatives.
[d] [Si] = TIPS.

acidity of the own catalyst (Table 2, entries 4–7). For practical reasons, the crude reaction mixture was analyzed after acetylation of the free hydroxy groups in the resulting oxidation products (Scheme 3) to afford around 2:1 mixtures of **16a/16b**. Thus, the diastereoselectivity of this reaction and subsequent reactions were calculated by integration of the ^{1}H NMR signals of the anomeric protons of the crude product mixture after acetylation. The spectral data obtained were assigned by comparison with those reported in the literature.[31] Although the opening of epoxides is expected to be *trans*, an α/β mixture was observed in each case as a result of an anomerization process. Two signals corresponded to *gluco* derivatives, derived from the α-epoxide (attack from the bottom face of the double bond), and other two signals to the *manno* derivatives, resulting from the β-epoxide, (attack from the upper face of the double bond). In all cases epoxidation–hydrolysis reactions were carefully monitored by TLC and the reported reaction times correspond to the disappearance of starting glycal. The stereochemistry at position 2 in the final acetate products



Scheme 3. Tandem epoxidation–hydrolysis of glycals with [Mo] catalysts.

reflects the stereoselectivity in the initial epoxide formation.

The temperature conditions seemed to be crucial when $Mo(CO)_6$ was used as a catalyst in apolar solvents and temperatures of 80 °C are required for complete conversion of **4** in reasonable reaction times (entries 5 and 6). As an Mo(0) species, $Mo(CO)_6$ requires an induction period prior to any epoxidation, in which the molybdenum complex is oxidized by the alkyl hydroperoxide or the oxygen peroxide to its highest oxidation state, the active Mo(VI)[25a,32] Most probably, the dissociation of the carbonyl ligands in the starting complex in apolar solvents is the limiting process for activation of the complex at low temperature.

The nature of the oxidant reagent solution in the stereoselectivity outcome of the epoxidation reaction was also explored starting from **4** and using $Mo(CO)_6$ as a catalyst precursor, but there were not significant differences between the use of TBHP 5.5 M in nonane (Table 2, entry 6) and the use of TBHP 70 wt% in water (98% conversion, 2 h, *gluco/manno* ratio = 55:45, results not displayed in Table 2).

The reaction was then tried using another soluble catalyst, $MoO_2(acac)_2$, in different solvents. In the presence of MeOH, the corresponding methyl glycosides **15a** and **15b** were obtained with a similar stereoselectivity to that from $Mo(CO)_6$ (entry 2). Reaction in dichloromethane or toluene led to **16a/16b** with slightly lower stereoselectivities than with methanol (entries 3 and 4). Accordingly to the previous results obtained with $Mo(CO)_6$, the use of non-coordinating solvents led to shorter reaction times.

Other (dioxo)Mo(VI) catalyst precursors, like MoO_2Cl_2, allowed performance of the reaction in short reaction times but with virtually the same stereoselectivity (Table 2, entry 7). The use of MoO_3 was not considered with protected glycals as a consequence of its insolubility problems in non-polar solvents.

In general, epoxidation–hydrolysis of glycal **4** proceeded with poor selectivities, probably as a consequence of steric and conformational factors. Glycals are well known to be conformationally flexible.[33] Moreover, the conformational preference between the normal half-chair ($^4H_5$ conformation) and the conformationally inverted isomer ($^5H_4$ conformation) is known to be sensitive not only to configuration but also to hydroxy group protection.[34] More importantly, this $^4H_5/^5H_4$ distribution can affect the stereoselectivity of addition reaction at the glycal alkene. In fact, reported data on electrophilic addition reactions of glucals locked in a $^4H_5$ conformation have usually shown low diastereofacial selectivities, with a slight preference for the addition from the α face.[35] On the basis of conformational NMR-based studies, describing the $^4H_5$ half-chair as the most stable conformation in glucal **4** (and other glucal derivatives), with all its substituents in a *pseudo*-equatorial orientation,[36] low stereoselectivities should be expected, as it is the case.

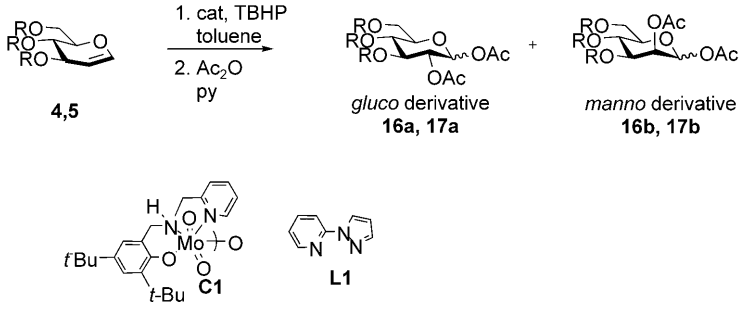
In comparison, reaction with the more hindered glucal **5** afforded better stereoselectivities (Table 2, entries 8–10), obtaining *gluco* derivative **17a** as a major product. Considering that tri-*O*-benzyl is conformationally more biased towards the $^4H_5$ half-chair conformation than the tri-*O*-acetyl glucal itself, the increase in α-epoxidation might be explained by steric hindrance of the protecting benzyl moiety. The existence of a π-stacking interaction of the aryl group of the benzyl group at C-3 or C-6 and the π system in the glycal thus blocking the β face could not be discarded either.

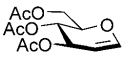
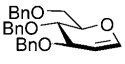
Glucals **6** and **7**, with bulkier protecting groups were then tested. Glucal **6** afforded the *gluco* derivative **18a** with excellent stereoselectivity when $Mo(CO)_6$ and $MoO_2(acac)_2$ were used as catalyst (Table 2, entries 11 and 12).

Unexpectedly, reaction of **7** did not occur, neither with $Mo(CO)_6$ nor with $MoO_2(acac)_2$ (Table 2, entries 13 and 14). This lack of reactivity can be attributed to the significant steric demand of the bulky TIPS groups, which destabilize the $^4H_5$ conformation due to a serious *gauche* interaction between the protecting groups at positions 3 and 4 and force 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 peroxy-molybednum species to the double bond.[19]

Following previous experiments, we decided to carry out the dihydroxylation of **4** and **5** with N-heterocyclic ligands-containing [Mo] complexes in order to modulate the reactivity and selectivity of the oxidation (Table 3).[17b,37] It is well known that this kind of Mo complexes presents better solubilities in apolar solvents and lower Lewis acidity, preventing the formation of diols. In our experiment, the use of the complex **C1**/TBHP[38] or the MoO_3/**L1**/TBHP catalytic system did not prevent epoxide opening and only diol derivatives were obtained as the main reaction products. Moreover, reactions were in general slower (Table 3 *versus* Table 2) in agreement with reported epoxidation reactions catalyzed by *N*,*N*-bidentate ligand-containing Mo complexes.[39] This deactivating effect is in line with that previously stated for the effect of coordinating solvents in the decrease of electrophilicity of the Mo-peroxo or alkylperoxo-Mo complex and has been also determined by theoretical studies on peroxo-Mo complexes.[32,40] Higher stereoselectivies in comparison with the unmodified catalytic systems could be obtained although catalytic performance was random. Thus, in terms of stereoselectivity, the MoO_3/**L1**/TBHP catalytic system worked best with glycal **4** (Table 3, entry 2), whereas oxida-

Table 3. Sequential epoxidation–hydrolysis of glucals **4** and **5** catalyzed by Mo/ligand catalytic systems.



Entry[a]	Substrate	Catalyst	Temp. [°C]	Time [h]	Conv. [%][b,c]	Products	Ratio[b]
1		complex **C1**	50	48	>98	**16a/16b**	55:45
2	**4**	MoO_3/**L1**	80	24	>98	**16a/16b**	76:24
3		complex **C1**	50	6	>98	**17a/17b**	88:12
4	**5**	MoO_3/**L1**	80	24	50	**17a/17b**	nd

[a] *Conditions:* 0.36 mmol glycal, 5 mol% catalyst, 1.2 mmol TBHP 5.5 M in nonane, 2 mL solvent.
[b] Determined by NMR by integration of the anomeric protons of acetylated compounds of the crude reaction mixture.
[c] Selectivity > 98%.

tion of glycal **5** was more efficient with complex **C1** (Table 3, entry 3).

Epoxidation–hydrolysis reactions from differently protected glucals **2–7** showed diastereoselectivities mainly governed by steric factors, so that the initial epoxidation occurs preferentially by attack from the opposite face to that of OR group at C-3. After these initial results, and taking into account that the epoxidation–hydrolysis of unprotected glucal affords mannose (see Table 1) which involves electrophilic oxygen transfer *syn* to the C-3 hydroxy moiety, we decided to investigate next the reaction of glucals containing a free hydroxy group on that position.

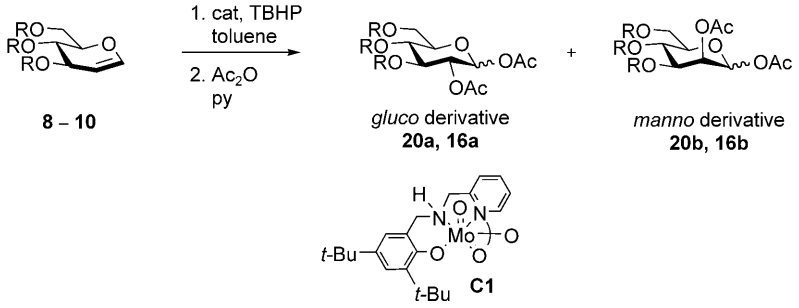
Thus, **8** was treated with TBHP (Table 4, entries 1 and 2) in the presence of $MoO_2(acac)_2$ and complex **C1**, to obtain **20b** (*manno*) as the major product, with a stereoselectivity *gluco*:*manno* 30:70. The goal of using conformationally-restricted **8**, which is locked in a $^4H_5$ on account of its isopropylidene group, is to gain insight into the parameters that govern the selectivity in oxygen transfer mechanism. Compared to results in Table 1 or Table 2, epoxidation of a glucal **8** occurs with reversed selectivity, leading preferentially to a mannose derivative, thus showing the implication of the allylic hydroxy group in the oxygen transfer process. This fact was confirmed by epoxidation of the acetyl-protected derivative **9** (Table 4, entry 3). In this case, the products derived from the *gluco* epoxide **20a** were predominantly formed, as expected for an epoxidation reaction dominated by steric factors.

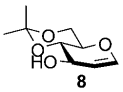
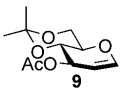
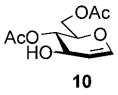
With the aim of testing the influence of the conformational freedom in the stereoselectivity of the epoxidation-hydrolysis, the diacetyl glucal **10** was reacted under the optimized reaction conditions (Table 4, entry 4) to furnish **16a/16b** (*gluco/manno* ratio, *ca.* 20:80) with the *manno*-configured pyranosyl acetates as the major products. Note that the *manno* selectivity increased in comparison to the results obtained from conformationally-fixed glucal **8**, and that it is practically reversed in comparison to the obtained from compound **4** (Table 2, entry 4).

To continue studying the effect of glycal configuration in the stereoselectivity, the reaction of differently protected galactals **11–14** with [Mo]/TBHP was tested. The reaction of tri-*O*-acetyl-D-galactal (**11**) with TBHP in the presence of $MoO_2(acac)_2$ afforded, after acetylation, compound **21a** as the only product (Table 5, entry 1). The reaction is much more stereoselective from galactal **11** than from glucal derivative **4** (Table 5, entry 1 *vs.* Table 2, entry 4). This is in agreement with that previously observed by other groups,[19] and indicates that the configuration at C-4 plays a major role in determining the degree of stereoselection, with the OR group at C-4 directing the attack of oxygen preferentially to the opposite face when it is placed in an axial position.

The reaction of tri-*O*-benzyl-D-galactal (**12**) and tri-*O*-pivaloyl-D-galactal (**13**) under similar conditions also provided compounds **22a** and **23a** with an excellent stereoselectivity (Table 5, entries 2 and 3). Especially significant results were obtained in the reaction of galactal **14**, which has the 6-OH unprotected. The reaction was considerably slower and finished after 24 h to give **24a**/**24b** with a stereoselectivity *galacto*:*ta-*

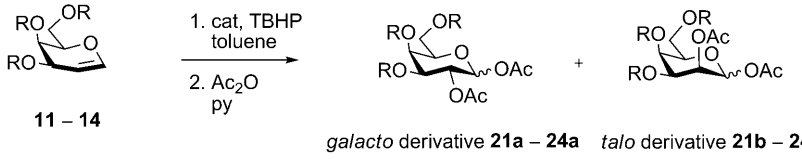
Table 4. Mo-catalyzed sequential epoxidation–hydrolysis of partially protected glycals **8**–**10**.[a]

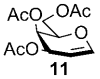
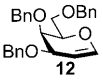
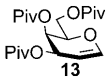
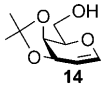


Entry[a]	Substrate	Catalyst	Temp. [°C]	Time [h]	Conv. [%][b,c]	Products	Ratio[b]
1	 **8**	$MoO_2(acac)_2$	30	24	>98	**20a/20b**	30:70
2		complex **C1**	50	48	50	**20a/20b**	28:72
3	 **9**	$MoO_2(acac)_2$	50	53	>98	**20a/20b**	65:35
4	 **10**	$MoO_2(acac)_2$	30	24	>98	**16a/16b**	20:80

[a] *Conditions:* 0.36 mmol glycal, 5 mol% catalyst, 1.2 mmol TBHP 5.5 M in nonane, 2 mL toluene.
[b] Determined by integration in the ^{1}H NMR spectrum of the anomeric protons of acetylated compounds in the crude reaction mixture.
[c] Selectivity > 98%.

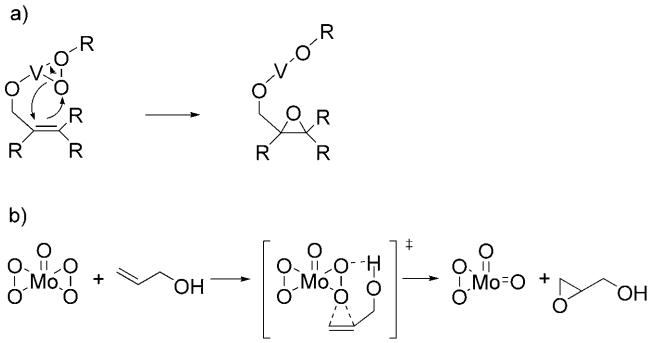
Table 5. Mo-catalyzed sequential epoxidation–hydrolysis of differently protected galactal derivatives **11**–**14**.



Entry[a]	Substrate	Catalyst	Temp. [°C]	Time [h]	Conv. [%][b,c]	Products	Ratio[b]
1	 **11**	$MoO_2(acac)_2$	30	4	>98	**21a/21b**	>98:2
2	 **12**	$MoO_2(acac)_2$	30	3	>98	**22a/22b**	97:3
3	 **13**	$MoO_2(acac)_2$	30	7	>98	**23a/23b**	97:3
4	 **14**	$MoO_2(acac)_2$	30	24	>98	**24a/24b**	70:30

[a] *Conditions:* 0.36 mmol glycal, 5 mol% catalyst, 1.2 mmol TBHP 5.5 M in nonane, 2 mL solvent.
[b] Determined by integration in the ^{1}H NMR spectrum of the anomeric protons of acetylated compounds in the crude reaction mixture.
[c] Selectivity > 98%.

lo ratio 70:30 (Table 5, entry 4). The increase in the percentage of isomer **24b**, resulting from the epoxidation by the *endo* face, may be indicative of a directing effect of the hydroxy group at C-6.



Scheme 4.

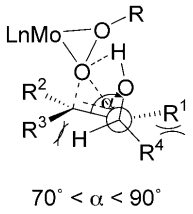


Figure 2. Modified Adam's model for transitions-state structures of the Mo-catalyzed epoxidation of allylic alcohols.

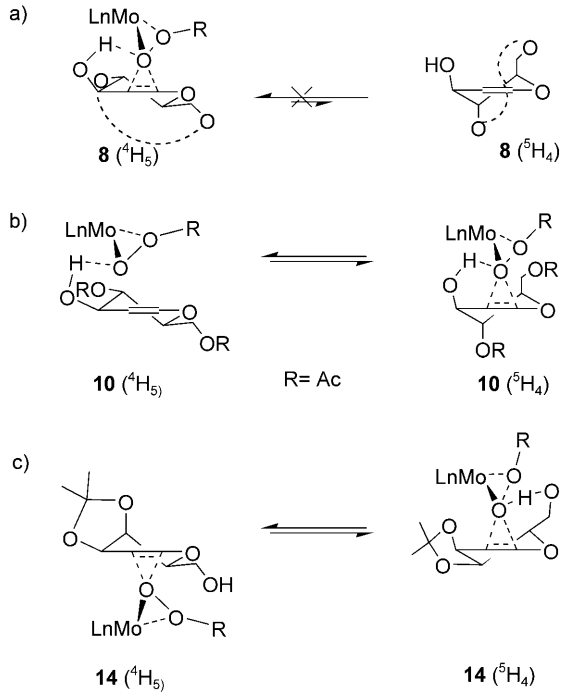
According to the literature, it seems clear that the reaction of TBHP with an oxo-Mo complex leads to the formation of an Mo(VI) alkylperoxo complex, which then transfers oxygen to the olefin.[38,41] Several studies previously attempted to isolate the intermediate Mo(VI)-*tert*-butyl peroxide complex without success.[42] In order to gain insight in the nature of the active catalytic species in the Mo-catalyzed epoxidation of glycals, we decided to monitor the process by solution phase IR, also without success.

Another interesting issue, the role of the allylic hydroxylic group in the metal-catalyzed directed epoxidation reactions of allylic alcohols, has been already studied.[43,44] Di Furia et al. used geraniol and linalool as probe substrates for gaining insight into the mechanism of the Mo-catalyzed epoxidation of alkenes.[44c] Based on previous experiments, the same authors had already proposed that the Mo-catalyzed epoxidation reaction of geraniol with hydrogen peroxide was consistent with an intermolecular rather than intramolecular oxygen transfer that involved the formation of a hydrogen bond between the peroxo-Mo complex and the alcohol moiety in the allylic alcohol (Scheme 4b).[45] Further experimentation led them to conclude that the moderate activation of Mo-catalyzed epoxidation of allylic alcohols compared with the very large one observed for V systems might not be due to a coordinated substrate as in V (Scheme 4a), but is more reasonable to propose the involvement of a transition state effect, i.e., a hydrogen-bonding assistance in the oxygen transfer process.[44c] Moreover, Sheldon et al. arrived at similar conclusions when using pinane hydroperoxide (PHP) as mechanistic probe in the metal-catalyzed epoxidation of alkenes to distinguish between oxometal and peroxometal pathways.[44d] In the late 1990s, Adam et al. proposed a transition state structure for the Ti- and Mo-TBHP epoxidation of chiral allylic alcohols, mainly dominated by ^{1,3}A strain, where the preferred dihedral angle α for the epoxidation of the peroxy complex lies between 70° and 90°. On the basis on the similar diastereoselectivity ratios of Ti and Mo systems of the epoxidation reactions of chiral allylic alcohols and relating them with the regio- and diastereoselective epoxidation of 1-methylgeraniol with Ti, they proposed for both metals, a metal-alcoholate complex model.[44e] However, this proposal is in disagreement with the non-coordinative model proposed by Di Furia and others.

Notwithstanding, since Adam's proposal for the Mo-catalyzed transition state structures is mainly based on the observed *erythro/threo* diastereoselectivities of chiral allylic alcohols, we believe that such a model can still be valid in terms of dihedral angle of the transition state, as long as the metal-alkoxo bond would be replaced with a hydrogen bond between the peroxy oxygen atom and the hydroxy group in the allylic alcohol (Figure 2).

Taking into account all these pieces of evidence, the most obvious result extracted from Table 4 is the *syn*-epoxidation of partially protected glycals with the allylic group unmasked. This is indeed indicative of some kind of directing effect by the hydroxy group. The precedent information stated above, altogether with the experimental stereoselectivity ratios obtained in this work, which are moderately high, tend to point to a hydrogen-bond assistance model rather than the coordinative metal-alkoxo model. A qualitative conformational analysis of glycal derivatives altogether with the adjustement to the previous described intermolecular Mo-catalyzed epoxidation model *via* hydrogen-bond activation may also give some justification to the degree of stereoselection of the process.

As stated above, the optimum dihedral angle α for Mo-catalyzed epoxidation transition state conformation of allylic alcohols was determined to be in the range of 70–90°, which would fit more consistently with the glycal $^5H_4$ half-chair conformation, where the allylic alcohol is in a pseudo-axial position, rather than in the $^4H_5$ conformation, in a pseudo-equatorial position. Conformationally fixed glycals (**8**), though, cannot attain the $^5H_4$ conformation, and therefore the resulting transition state structure will not benefit from the same stabilization degree that should have in the inverted $^4H_5$ conformation (Scheme 5a).[46] On the other hand, conformationally mobile glycal **10** is most likely to be preferentially in the $^4H_5$ conformation. Nevertheless, if epoxidation is agreed to proceed



Scheme 5. Conformational equilibrium of glucals **8** (restricted, a), **10** (unrestricted, b) and galactal **14** (c), and directed intermolecular epoxidation through hydrogen-bond assistance.

under Curtin–Hammet conditions, ground state conformations are not determinant of the product distribution but rather the relative energies of transition state structures. In this case, $^5H_4$ half-chair is not the most populated conformation but is the conformation that benefits from the greatest stabilization in the transition state structure, with dihedral angles in the range of what is considered an optimum value. The slight increase in the *manno* selectivity obtained with glycal **10** compared to that obtained with **8** is consistent with this appreciation (Scheme 5b).

Analogous considerations might be applied to epoxidation of galactal **14** unprotected at position 6. Simultaneous protection of hydroxy groups at positions 3 and 4 as an isopropylidene acetal is not expected to prevent conformational equilibrium between half-chair conformations. On one hand, epoxidation of **14** from the most stable half-chair $^4H_5$ conformation might be expected to proceed from the α face, based on the steric interaction with the isopropylidene acetal group. In such a conformation, the hydroxymethyl chain in a pseudo-equatorial position is in a too distal position to establish any activating effect. The $^5H_4$ isomer conformation, though, may benefit from intermolecular hydrogen assistance from the hydroxymethyl moiety in a pseudo-axial position (Scheme 5c).

Table 6 displays a comparison of the selectivities in epoxidation/alcoholysis or epoxidation/hydrolysis of glycals obtained in this work using molybdenum catalysts, with those obtained with other catalysts, particularly MTO, titanium tetraisopropoxide and Venturello's catalysts. Although glycosides or hydroxy derivatives are obtained depending on the papers, it is assumed that the *gluco/manno* ratio depends on the selectivity of the epoxidation step.

Stereoselectivity in the epoxidation of tri-*O*-acetyl-D-glucal (**4**) or tri-*O*-benzyl-D-glucal (**5**) is moderate with all the catalysts except with Ti(O-*i*-Pr)$_4$, which provides excellent selectivities (entries 2 and 3). An important improvement in the selectivity using TMO was obtained when the reaction was carried out in the presence of nitrogen ligands. A similar effect, although less significant was obtained with molybdenum catalysts. More important, however, is the effect of the protecting groups. Thus, the presence of bulky protecting groups such as the pivaloyl allows us to reach very high selectivities using molybdenum catalysts (entry 4); although the presence of TIPS precludes the reaction. A really different behaviour

Table 6. Comparison of selectivity α/β epoxide in the tandem epoxidation-alcoholysis or hydrolysis with different catalysts.

Entry	Substrate		MTO[a],[18]	MTO[17]	MTO[b,c] modif.[17]	Ti(O-*i*-Pr)$_4$[a],[19]	Venturello's method[a],[19]	[Mo] (this work)
1	glucal	unprotected	66:33			40:60	<2:98	0:100
2		3,4,6-*O*-Ac	66:33	64:36	77:23	94:6	86:14	70:30
3		3,4,6-*O*-Bn	86:14	85:15	93:7	>98:2	86:14	86:14
4		3,4,6-*O*-Si-*t*-BuMe$_2$ (a), 3,4,6-*O*-Piv (b)				94:6(a)		96:4(b)
5		4,6-*O*-isopropylidene	66:33					28:72
6		4,6-*O*-Ac						20:80
7	galactal	OAc	75:25	95:5	>98:2	>98:2	>98:2	>98:2
8		OBn		>98:2	97:3	>98:2	>98:2	97:3
9		OPiv						97:3

[a] Reactions performed in methanol and consequently the methyl glycoside was obtained.
[b] Tandem epoxidation/phosphorylation in ionic liquids.
[c] Tandem epoxidation phosphorylation in the presence of nitrogen ligands (mainly pyridine).

among the compared catalysts is observed in the epoxidation of unprotected glucal, $Ti(O\text{-}i\text{-}Pr)_4$ catalyst afforded very low selectivity, while Venturello's and molybdenum catalysts provided almost complete stereoselectivity in the *manno* epoxide (entry 1). This effect is also observed with molybdenum catalysts in partially protected derivatives. Thus, compounds derived from the *manno* epoxide are mainly formed when 3-OH is unprotected (entries 5 and 6). Concerning galactal derivatives all the studied catalysts provide excellent selectivities (entries 7–9).

Conclusions

Highly stereoselective one-pot epoxidation–hydrolysis or epoxidation–alcoholysis of glucal and galactal derivatives was achieved using H_2O_2 or TBHP and molybdenum catalysts. The stereoselectivity in the epoxidation-hydrolysis of glucal derivatives depends on the presence or absence of the protecting groups. In the absence of protecting groups the *manno* epoxide is preferently obtained. Thus, mannose and methyl mannopyranoside can be easily and stereoselectively obtained from D-glucal using molybdenum catalysts and performing the reaction in water or methanol, respectively.

However, when the reaction is carried out in a protected glucal the *trans* epoxide is mainly obtained. The better stereoselectivities in this last case were obtained when pivaloyl groups were present. Modified molybdenum catalysts allowed increases, in some cases, of the stereoselectivity of the process.

In 4,6-diprotected glucal derivatives, the hydroxy group at position 3 directs the stereoselectivity. Thus, the *gluco* derivative is obtained in fully protected glucals (*anti* attack), while the *manno* derivative is mainly obtained (*syn* attack) when 3-OH is unprotected.

A similar behaviour to that observed for protected glucals was stated for the protected galactal derivatives, although in this case the stereoselectivity is always good independently of the protecting groups present, and the *galacto* derivative is almost exclusively obtained in all cases.

In conclusion, molybdenum salts and complexes efficiently catalyze the epoxidation of glycals and the subsequent epoxide opening to afford glycosides or hydroxy derivatives depending on whether the solvent is an alcohol, water or other organic solvent. The stereoselectivities obtained are similar to those of the best catalysts reported. A directing effect was observed in unprotected or partially protected glycals that seems to be consistent with a hydrogen-bond assistance model.

Experimental Section

General Experimental Methods

All chemicals used were reagent grade and used as supplied. Glucals **1a** and **1b** and galactals **11a** and **11b** were commercially available. Glucal **9** was obtained through a conventional procedure for acetylation. All other glycals were synthesized according to literature procedures: **6**,[47] **7**,[48] **8**,[49] **10**,[49] **13**,[48] **14**.[50] HPLC grade dichloromethane (CH_2Cl_2), tetrahydrofuran (THF), dimethylformamide (DMF) and diethyl ether were dried using a solvent purification system (Pure SOLV system-4®). The other solvents were purified using standard procedures.[51] ^1H and ^{13}C NMR spectra were recorded on a Varian® Mercury 400 and Varian® 400-MR, (both at 400 MHz and 100 MHz, respectively) spectrometer in $CDCl_3$ as solvent, with chemical shifts (δ) referenced to internal standards $CDCl_3$ (7.27 ppm ^1H, 77.23 ppm ^{13}C) or Me_4Si as an internal reference (0.00 ppm), unless otherwise specified. 2D correlation spectra (TOCSY, gCOSY, NOESY, gHSQC, gHMBC) were visualized using the VNMR program (Varian®). ESI-MS were run on an Agilent® 1100 Series LC/MSD instrument. Optical rotations were measured at room temperature in a Perkin–Elmer® 241 MC apparatus with 10 cm cells. Elemental analysis (C, H, N, S) was performed on a Carlo Erba® EA 1108 Analyser in the Servei de Recursos Cientifics (SRCiT-URV). Analytical thin layer chromatography (TLC) was performed on Merck® silica gel 60 F_{254} glass or aluminium plates. Compounds were visualized by UV (254 nm) irradiation or dipping the plate in a suitable developing solution. Flash column chromatography was carried out using forced flow or by gravity of the indicated solvent on Fluka® or Merck® silica gel 60 (230–400 mesh). Radial chromatography was performed on 1, 2, or 4 mm plates of Kieselgel 60 PF_{254} silica gel, depending on the amount of product.

General Procedure for Catalytic Dihydroxylation using Mo(VI)/TBHP Systems in Water – Acetylation

To a solution of glycal (1.71 mmol) in 5% aqueous or methanolic hydrogen peroxide (2.5 mL), the corresponding [Mo] catalyst (1.0 mol%) was added. After 48 h at room temperature, undissolved oxide was removed, and the excess of hydrogen peroxide was decomposed by treatment for 24 h at 22 °C with 5% palladized charcoal (5–10 mg). The filtered mixture was then evaporated under vacuum. The resulting residue was analyzed by ^1H NMR.[24] The ratio of isomers was determined by integration of anomeric protons of the corresponding acetyl derivatives.

General Procedure for Catalytic Dihydroxylation using Mo(VI)/TBHP Systems in Organic Solvents – Acetylation

To a solution of glycal (0.36 mmol) in dry toluene (2 mL) the corresponding [Mo] catalyst (5.0 mol%) and TBHP (5.5 M in nonane, 0.4 mL, 1.2 mmol) were added. The mixture was heated between 30–80 °C over a 1–96 h period. The reaction was monitored by TLC. When the reaction was completed the solution was concentrated under vacuum. The resulting residue was dissolved in pyridine (2 mL) and acetic anhydride (1 mL) was added. The resulting solution

was stirred at room temperature for 2–3 h. The reaction mixture was quenched by adding MeOH. The solution was extracted with CH_2Cl_2 and washed successively with brine, saturated aqueous $NaHCO_3$ and water. The solution was dried over $MgSO_4$ and then the solvent was removed under reduced pressure. The resulting residue was analyzed by ^1H NMR. The ratio of isomers was determined by integration of the anomeric protons of the corresponding acetylated products. When the solvent is methanol, the acetylation was not needed.

Acknowledgements

Financial support of DGI (CTQ2008-01569-BQU), Consolider Ingenio 2010 (CSD2006-0003) (Ministerio de Ciencia y Tecnología, Spain) and technical assistance from the Servei de Recursos Cientifics (URV) are gratefully acknowledged. I.M. thanks MICINN for a fellowship.

References

[1] a) A. Varki, *Glycobiology* **1993**, *3*, 97–130; b) Y. C. Lee, R. T. Lee, *Acc. Chem. Res.* **1995**, *28*, 321–327; c) R. A. Dwek, *Chem. Rev.* **1996**, *96*, 683–720; d) S. Hakomori, *Adv. Cancer Res.* **1989**, *52*, 257–331; e) P. M. Rudd, T. Elliott, P. Cresswell, I. A. Wilson, R. A. Dwek, *Science* **2001**, *291*, 2370–2376.

[2] a) S. J. Danishefsky, M. T. Bilodeau, *Angew. Chem.* **1996**, *108*, 1482–1522; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1380–1419; b) J. Y. Roberge, X. Beebe, S. J. Danishefsky, *J. Am. Chem. Soc.* **1998**, *120*, 3915–3927; c) F. E. McDonald, H. Y. H. Zhu, *J. Am. Chem. Soc.* **1998**, *120*, 4246–4247; d) J. Thiem, M. Gerken, *J. Org. Chem.* **1985**, *50*, 954–958.

[3] a) D. Hou, T. L. Lowary, *Carbohydr. Res.* **2009**, *344*, 1911–1940; b) A. Kirschning, M. Jesberger, K.-U. Schöning, *Synthesis* **2001**, 507–540; c) A. Veyrières, in: *Carbohydrates in Chemistry and Biology*, (Eds.: B. Ernst, G. W. Hart, P. Sinaÿ), Wiley, Weinheim **2000**, Part I, Vol. I, pp 367–405; d) H. Marzabadi, R. W. Franck, *Tetrahedron* **2000**, *56*, 8385–8417; e) J. C. Castro-Palomino, R. R. Schmidt, *Synlett* **1998**, 501–503; f) K. Toshima, K. Tatsuta, *Chem. Rev.* **1993**, *93*, 1503–1531.

[4] a) S. N. Thorn, T. Gallagher, *Synlett* **1996**, 856; b) S. Hosokawa, B. Kirschbaum, M. Isobe, *Tetrahedron Lett.* **1998**, *39*, 1917–1920.

[5] a) R. Robles, C. Rodríguez, I. Izquierdo, M. T. Plaza, A. Mota, *Tetrahedron: Asymmetry* **1997**, *8*, 2959–2965; b) Y. Díaz, A. El-Laghdach, S. Castillón, *Tetrahedron* **1997**, *53*, 10921–10938; c) Y. Díaz, A. El-Laghdach, M. I. Matheu, S. Castillón, *J. Org. Chem.* **1997**, *62*, 1501–1505; d) Q. Chao, J. Zhang, L. Pickering, T. S. Jahnke, V. Nair, *Tetrahedron* **1998**, *54*, 3113–3124; e) F. Bravo, M. Kassou, Y. Díaz, S. Castillón, *Tetrahedron Lett.* **2001**, *42*, 83–97.

[6] For use in cyclopropanation and ring expansion see: C. V. Ramana, R. Murali, M. Nagarajan, *J. Org. Chem.* **1997**, *62*, 7694–7703.

[7] For use in a novel class of glycosylations based in a [4+2]cycloaddition see: a) G. Capozzi, A. Dios, R. W. Frank, A. Geer, C. H. Marzabadi, S. Menichetti, C. Nativi, M. Tamarez, M. *Angew. Chem.* **1996**, *108*, 805–807; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 777–779; b) R. W. Franck, C. H. Marzabadi, *J. Org. Chem.* **1998**, *63*, 2197–2208.

[8] For the synthesis of thionucleosides from thioglycals see: K. Haraguchi, A. Nishikawa, E. Sasakura, H. Tanaka, K. T. Nakamura, T. Miyasaka, *Tetrahedron Lett.* **1998**, *39*, 3713–3716.

[9] R. L. Halcomb, S. J. Danishefsky, *J. Am. Chem. Soc.* **1989**, *111*, 6661–6666.

[10] D. M. Gordon, S. J. Danishefsky, *Carbohydr. Res.* **1990**, *206*, 361–366.

[11] a) L. Shi, Y.-J. Kim, D. Y. Gin, *J. Am. Chem. Soc.* **2001**, *123*, 6939–6940; b) W. J. Sanders, L. L. Kiessling, *Tetrahedron Lett.* **1994**, *35*, 7335–7338; c) A. B. Charette, J. F. Marcoux, B. Cote, *Tetrahedron Lett.* **1991**, *32*, 7215–7218.

[12] a) M. Carpintero, I. Nieto, A. Fernandez-Mayoralas, *J. Org. Chem.* **2001**, *66*, 1768–1774; b) T. Vidal, A. Haudrechy, Y. Langlois, *Tetrahedron Lett.* **1999**, *40*, 5677–5680; c) S.-C. Hung, C.-H.; Wong, *Angew. Chem.* **1996**, *108*, 2829–2832; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2671–2674.

[13] a) M. Bols, *J. Chem. Soc. Chem. Commun.* **1992**, 913–914; b) G. Stork, G. Kim, *J. Am. Chem. Soc.* **1992**, *114*, 1087–1088; c) F. Barresi, O. Hindsgaul, *J. Am. Chem. Soc.* **1991**, *113*, 9376–9377.

[14] G. Bellucci, G. Catelani, C. Chiappe, F. D′Andrea, *Tetrahedron Lett.* **1994**, *35*, 8433–8436.

[15] E. Honda, D. Y. Gin, *J. Am. Chem. Soc.* **2002**, *124*, 7343–7352.

[16] a) C.-J. Liu, W.-Y. Yu, S.-G. Li, C.-M. Che, *J. Org. Chem.* **1998**, *63*, 7364–7369; b) X.-Q Yu, J.-S. Huang, W.-Y Yu, C.-M Che, *J. Am. Chem. Soc.* **2000**, *122*, 5337–5342.

[17] a) G. Soldaini, F. Cardona, A. Goti, A. *Tetrahedron Lett.* **2003**, *44*, 5589–5592; b) G. Soldaini, F. Cardona, A. Goti, A. *Org. Lett.* **2005**, *7*, 725–728; c) A. Goti, F. Cardona, G. Soldaini, C. Crestini, C. Fiani, R. Saladino, *Adv. Synth. Catal.* **2006**, *348*, 476–486.

[18] E. C. Boyd, R. V. H. Jones, P. Quayle, A. J. Waring, *Green Chem.* **2003**, *5*, 679–681.

[19] P. Levecque, D. W. Gammon, H. H. Kinfe, P. Jacobs, D. De Vos, B. Sels, *Adv. Synth. Catal.* **2008**, *350*, 1557–1568.

[20] P. Tiwari, A. K. Misra, *J. Org. Chem.* **2006**, *71*, 2911–2913.

[21] S. Rani, Y. D. Vankar, *Tetrahedron Lett.* **2003**, *44*, 907–909.

[22] a) F. W. Lichtenthaler, T. Schneider-Adams, *J. Org. Chem.* **1994**, *59*, 6728–6734; b) W. Broder, H. Kunz, *Carbohydr. Res.* **1993**, *249*, 221–241; c) R. R. Schmidt, F. Effenberger, *Carbohydr. Res.* **1987**, *171*, 59–79; d) E. Wu, Q. Wu, *Carbohydr. Res.* **1993**, *250*, 327–333; e) R. U. Lemieux, A. R. Morgan, *Can. J. Chem.* **1965**, *43*, 2198–2204.

[23] V. Bilik, S. Kucar, *Carbohydr. Res.* **1970**, *13*, 311–313.

[24] K. B. Sharpless, T. R. Verhoeven, *Aldrichimica Acta* **1979** *12*, 63–74.

[25] a) G. R. Howe, R. R. Hiatt, *J. Org. Chem.* **1971**, *36*, 2493–2497; b) A. O. Chong, K. B. Sharpless, *J. Org. Chem.* **1977**, *42*, 1587–1590; c) T. N. Baker, G. J. Mains, M. N. Sheng, J. K. Jajacek, *J. Org. Chem.* **1973**, *38*, 1145–1148; d) W. J. Thiel, *J. Mol. Catal. A* **1997**, *117*, 449–454.
[26] H. Mimoun, S. de Roch, L. Sajus, *Tetrahedron* **1970**, *26*, 37–50.
[27] D. V. Deubel, J. Sundermeyer, G. Frenking, *J. Am. Chem. Soc.* **2000**, *122*, 10101–10108.
[28] K. B. Sharpless, J. M. Towsend, D. R. Williams, *J. Am. Chem. Soc.* **1972**, *94*, 295–296.
[29] a) G. Amato, A. Arcoria, F. P. Ballisteri, G. A. Tomaselli, O. Bortolini, V. Conte, F. Di Furia, G. Modena, G. Valle, *J. Mol. Catal* **1986**, *37*, 165–175; b) H. Mimoun, *Angew. Chem.* **1982**, *94*, 750–766; *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 734–750.
[30] D. V. Deubel, J. Sundermeyer, G. Frenking, *Eur. J. Org. Chem.* **2001**, 1819–1827.
[31] For triacetylated and tribenzylated *gluco* derivatives, see: Ref.[20] For triacetylated and tribenzylated *manno* derivaties, see: a) J.-R. Ella-Menye, X. Nie, G. Wang, *Carbohydr. Res.* **2008**, *343*, 1743–1753; b) S. Valerio, A. Pastore, M. Adinolfi, A. Iadonisi, *J. Org. Chem.* **2008**, *73*, 4496–4503.
[32] G. R. Haas, J. W. Kolis, *Organometallics* **1998**, *17*, 4454–4460, and references cited therein.
[33] M. Rico, M. Santoro, *Org. Mag. Resonance* **1976**, *8*, 49–55.
[34] a) J. Thiem, P. Ossowski, *J. Carbohydr. Chem.* **1984**, *3*, 287–313; b) W. R. Roush, D. P. Sebesta, C. E. Bennett, *Tetrahedron* **1997**, *53*, 8825–8836.
[35] G. Grewal, N. Kaila, R. W. Franck, *J. Org. Chem.* **1992**, *57*, 2084–2092.
[36] A. A. Chalmers, R. H. Hall, *J. Chem. Soc. Perkin Trans. 2* **1974**, 728–732.
[37] P. Ferreira, W.-M. Xue, E. Bencze, E. Herdtweck, F. Kühn, *Inorg. Chem.* **2001**, *40*, 5834–5841.
[38] J. M. Mithcell, N. S. Finney, *J. Am. Chem. Soc.* **2001**, *123*, 862–869.
[39] P. Carreiro, C. Monteiro, G. Yong-en, A. J. Burke, A. I. Rodrigues, *J. Mol. Catal. A* **2006**, *260*, 295–298.
[40] C. Di Valentin, P. Gisdakis, I. V. Yudanov, N. Rösch, *J. Org. Chem.* **2000**, *65*, 2996–3004.
[41] a) F. E. Kühn, M. Groarke, É. Bencze, E. Herdtweck, A. Prazeres, A. M. Santos, M. J. Calhorda, C. C. Romão, I. S. Gonçalves, A. D. Lopes, M. Pillinger, *Chem. Eur. J.* **2002**, *8*, 2370–2383; b) A. Al-Ajlouni, A. A. Valente, C. D. Nunes, M. Pillinger, A. M. Santos, J. Zhao, C. C. Romão, I. S. Gonçalves, F. E. Kühn, *Eur. J. Inorg. Chem.* **2005**, 1716–1723; c) A. M. Al-Ajlouni, A. Günyar, M.-D. Zhou, P. N. W. Baxter, F. E. Kühn, *Eur. J. Inorg. Chem.* **2009**, 1019–1026.
[42] a) P. Chaumette, L. Mimoun, L. Saussine, J. Fischer, A. Mitschler, *J. Organomet. Chem.* **1983**, *250*, 291-310; b) M. Groarke, I. S. Gonçalves, W. A. Herrmann, F. E. Kühn, *J. Organomet. Chem.* **2002**, *649*, 108–112; c) see also Refs.[25d,38]
[43] A. H. Hoveyda, D. A. Evans, G. C. Fu, *Chem. Rev.* **1993**, *93*, 1307–1370.
[44] a) M. N. Sheng, J. G. Zajacek, *J. Org. Chem.* **1970**, *35*, 1839–1843; b) K. B. Sharpless, R. C. Michaelson, *J. Org. Chem.* **1973**, *37*, 6136–6137; c) A. Arcoria, F. P. Ballistreri, G. A. Tomaselli, F. *Di* Furia, G. Modena, *J. Org. Chem.* **1986**, 51, 2374–2376; d) H. E. B. Lempers, I. Ripollès, A. Garcia, R. E. Sheldon, *J. Org. Chem.* **1998**, *63*, 1408–1413; e) W. Adam, T. With, *Acc. Chem. Res.* **1999**, *32*, 703–710; f) W. Adam, C. M. Mitchell, R. Paredes, A. K. Smerz, L. A. Veloza, *Liebigs Ann. Recueil* **1997**, 1365–1369.
[45] O. Bortolini, F. Di Furia, G. Modena, *J. Mol Catal.* **1983**, *19*, 319–329.
[46] Another experimental evidence that underscores the different mode of action between V and Mo is that the reaction glycal **8** with $VO(acac)_2$ and TBHP did not led to even traces of the epoxidation–hydrolysis product.
[47] Y. Matsushita, K. Sugamoto, Y. Kita, T. Matsui, *Tetrahedron Lett.* **1997**, *38*, 8709–8712.
[48] K. H. Dötz, F. Otto, M. J. Nieger, *J. Organomet. Chem.* **2001**, *621*, 77–88.
[49] E. W. Holla, *Angew. Chem.* **1989**, *101*, 222–223; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 220–221.
[50] T. Toyokuni, S. Cai, B. Dean, *Synthesis* **1992**, 1236–1238.
[51] D. D. Perrin, W. L. F. Armarego, *Purification of Laboratory Chemicals*, 3rd edn., Pergamon Press, Oxford, **1989**.

