Available online at www.sciencedirect.com
ScienceDirect
Carbohydrate Research 343 (2008) 18–30
Carbohydrate RESEARCH

C-2 Epimerization of aldonolactones promoted by magnesium iodide: a new way towards non-enzymatic epimerization

Julie Gratien,[a] Marie-Pierre Heck[a,*] and Charles Mioskowski[a,b]

[a]*CEA, DSV, iBiTecS, Service de Chimie Bioorganique et de Marquage (SCBM), Bât 547, Gif sur Yvette F-91191, France*
[b]*Université Louis Pasteur, Laboratoire de Synthèse BioOrganique, CNRS, 74 Route du Rhin, BP 24, F-67401 Illkirch, France*

Received 27 June 2007; received in revised form 2 October 2007; accepted 10 October 2007
Available online 17 October 2007

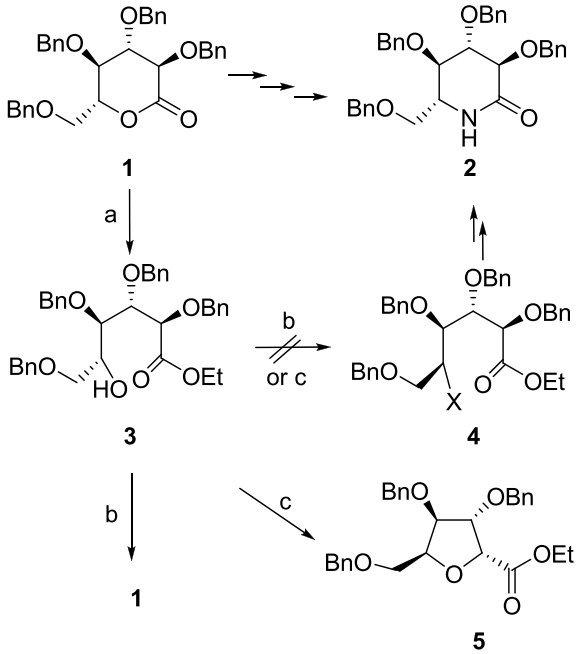
Dedicated to the memory of Dr. Charles Mioskowski[†]

Abstract—The first example of a non-enzymatic C-2 epimerization of aldonolactones is reported. The reaction of 2,3,4,6-tetra-*O*-benzyl-D-gluconolactone or 2,3,4,6-tetra-*O*-benzyl-D-mannonolactone with MgI_2 in EtOH afforded their respective C-2 epimer. Studies conducted in EtOD showing the incorporation of a deuterium atom only at the C-2 position of the epimerized product reveal an epimerization rather than a racemization reaction. A mechanism involving a chelation with a magnesium species is proposed to explain this C-2 inversion reaction.

Keywords: Aldonolactone; Mannonolactone; Gluconolactone; C-2 epimerization; Magnesium iodide

1. Introduction

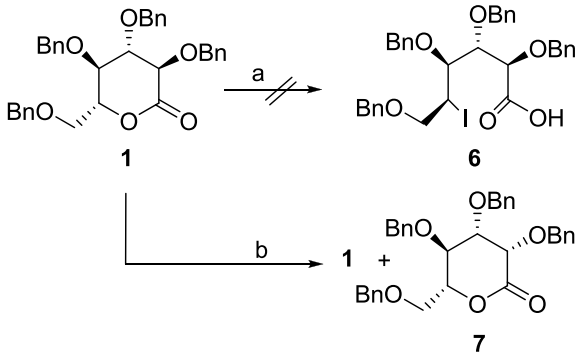
Recently we have reported the synthesis of a series of D-glycoamidines that show good inhibition toward mannosidases due to their favourable $B_{2,5}$ boat conformation.[1] In order to prepare other glycoamidine derivatives, we have focused our efforts on the improvement of our original synthesis. We were interested in saving steps in the transformation of 2,3,4,6-tetra-*O*-benzyl-D-gluconolactone (**1**)[2] into the corresponding 2,3,4,6-tetra-*O*-benzyl-D-gluconolactam (**2**)[3] (Scheme 1). The transesterification of lactone **1** with EtOH easily yielded hydroxyethyl ester **3**,[4] but its subsequent transformation into the bromo, tosyl, or mesyl ester **4** (X = Br, OTs or OMs) possessing the inverted C-5 configuration was never observed. When compound **3** was submitted to various substitution conditions,[4,5] an O-cyclization yielding gluconolactone **1**, or a S_N2 intramolecular



Scheme 1. Reagents and conditions: (a) EtOH, H_2SO_4 (cat.) reflux 12 h, (75%); (b) PBr_3, Et_2O, (X = Br, 66%), or PPh_3, DEAD, $Zn(OTs)_2$, (X = OTs, 81%); (c) MsCl, TEA, Et_2O; then LiOH, THF–H_2O (76% over two steps).

* Corresponding author. Fax: +33 1 69087991; e-mail: marie-pierre.heck@cea.fr
† Our exceptional supervisor and friend affectionately called 'Miko' died on June 2nd, 2007.

0008-6215/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.carres.2007.10.006



Scheme 2. Reagents and conditions: (a) MgI_2, toluene, CS_2, or Et_2O, rt to reflux, 8 h; (b) MgI_2 (1.2 equiv), EtOH, rt, 1 h, then H_2O–TFA cat. (40%).

cyclization by benzyloxy group participation at C-2 affording the polyoxygenated tetrahydrofuran **5** rather than the formation of compound **4** was observed.

The mild method reported by Garcia Martinez[6] for the non-hydrolytic cleavage of esters with magnesium iodide in aprotic non-polar solvents prompted us to study the reactivity of tetra-*O*-benzyl-D-gluconolactone (**1**). According to this methodology, lactone **1** was supposed to lead to iodo acid **6** bearing an inverted C-5 stereochemistry (Scheme 2, conditions (a)).

When 2,3,4,6-tetra-*O*-benzyl-D-gluconolactone (**1**) was subjected to reaction with MgI_2 under a variety of experimental conditions (time, temperature, solvent, equivalents of MgI_2 conditions (a) in Scheme 2), the iodo acid **6** was never observed and the starting lactone **1** was totally recovered (Scheme 2, conditions (a)). Surprisingly, the treatment of D-gluconolactone **1** with MgI_2 in EtOH afforded its C-2 epimer unambiguously identified as D-mannonolactone **7**[3b] (Scheme 2, conditions (b)).

Whereas the C-2 epimerization of aldoses with molybdate,[7] nickel,[8] cobalt[9] and calcium[10,8c] complexes has been extensively described, to date to our knowledge, neither a C-2 epimerization of aldonolactones promoted by a metal, nor a transformation of sugars catalyzed by magnesium has been reported. Furthermore, enzymes showing a C-2 epimerase activity,[11] especially δ-lactone epimerase,[12] are not well documented compared to C-3,[13] C-5,[13c] or C-4 epimerases.[14] To our knowledge only a C-2 epimerase extracted from *Acetobacter suboxydans* is reported[12] to catalyze the reversible epimerization of D-gluconolactone and D-mannonolactone. Based on these facts, we decided to study the mechanism of the reaction promoted by MgI_2. Herein we report our first results, our comments, and a possible mechanism for this epimerization.

2. Results and discussion

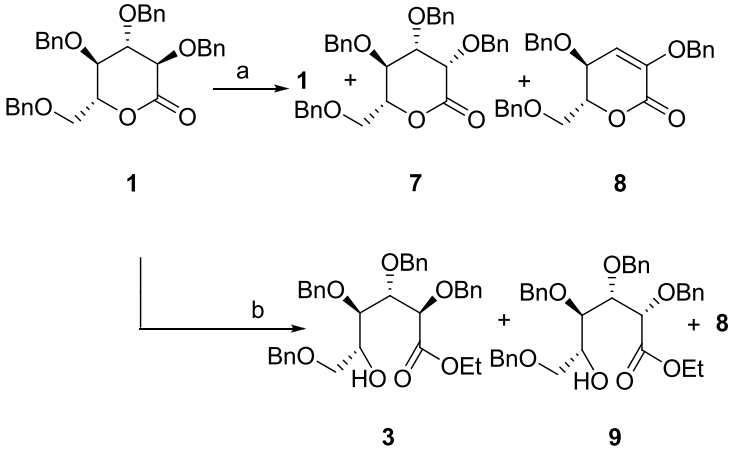
2.1. Studies of the epimerization reaction with MgI_2

We first investigated the potential of MgI_2 to transform 2,3,4,6-tetra-*O*-benzyl-D-gluconolactone (**1**) into 2,3,4,6-tetra-*O*-benzyl-D-mannonolactone (**7**) under various solvent and temperature conditions (Scheme 3). (A blank test showed that MgI_2 was indispensable to the epimerization reaction.)

When gluconolactone **1** was subjected to reaction with MgI_2 following conditions (a) in Scheme 3, lactones **1**, **7**, and **8** (identified as 2,4,6-tri-*O*-benzyl-3-deoxy-D-*erythro*-hex-2-enono-1,5-lactone)[15] were obtained. A treatment following conditions (b) afforded the corresponding hydroxy esters **3** and **9** and lactone **8** (Scheme 3).

In the following examples, conditions (a) were employed, and MgI_2 was prepared following the procedure reported by De la Pradilla[16a] (commercially available MgI_2 or that prepared from Mg/I_2 following the method reported in Fieser and Fieser's reagents[16b] did not give satisfactory results). The results are reported in Table 1.

We first carried out the reaction in EtOH and studied the quantity of MgI_2 and the conditions of time and



Scheme 3. Reagents and conditions: (a) MgI_2, see conditions Table 1 followed by a H_2O–TFA cat. work-up. (b) MgI_2, see conditions Table 1 followed by an aqueous treatment.

Table 1. Reactivity of D-gluconolactone **1** with MgI_2

Entry	MgI_2[a]	Conditions	Products **1**:**7**:**8**[b] **3**:**9**:**8**[c]
1	1.2	rt, 1 h, EtOH	60:40:0
2	1.2	rt, 6 h, EtOH	38:38:24
3	1.2	60 °C, 1 h, EtOH	20:20:60
4	2	rt, 1 h, EtOH	30:60:10
5	3.5	rt, 1 h, EtOH	26:58:16

[a] Number of equivalents.
[b] Products resulting from a treatment H_2O–cat. TFA.
[c] Products resulting from an aqueous treatment.

Table 2. Reaction of D-mannonolactone **7** with MgI_2

Entry	MgI_2[a]	Conditions[b]	Products[c] **7**:**1**:**8**
1	2	rt, 1 h, EtOH	85:15:0
2	6	rt, 1 h, EtOH	60:35:5
3	6	rt, 4 h, EtOH	55:35:10
4	10	rt, 1 h, EtOH	61:25:14

[a] Number of equivalents.
[b] Conditions followed by a treatment H_2O–TFA cat.
[c] Yields of lactones: 2,3,4,6-tetra-*O*-benzyl-D-mannonolactone (**7**), 2,3,4,6-tetra-*O*-benzyl-D-gluconolactone (**1**), α,β-unsaturated lactone **8**.

temperature to allow the epimerization reaction (Table 1, entries 1–5). The optimum conditions were obtained when reacting gluconolactone **1** with 2 equiv of MgI_2 at room temperature for 1 h affording mannonolactone **7** (60% yield), recovered lactone **1** (30% yield), and α,β-unsaturated lactone **8** (10% yield) (entry 4). When gluconolactone **1** was subjected to reaction with higher quantities of MgI_2, longer reaction times, or heated to 60 °C, unsaturated lactone **8** was obtained in higher yields (entries 2, 3 and 5, 16–60% yield). Surprisingly, gluconolactone **1** was totally recovered when conducting the reaction in MeOH. No reaction occurred in *tert*-BuOH regardless of the reaction conditions.

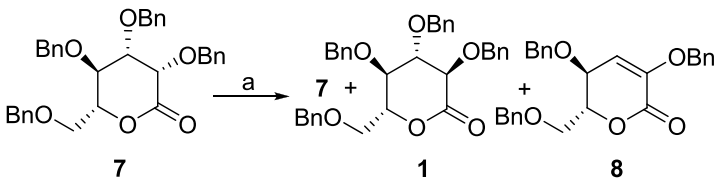
Then we studied the reaction of 2,3,4,6-tetra-*O*-benzyl-D-mannonolactone (**7**) with MgI_2 in EtOH to examine the possible reversibility of the reaction (Scheme 4 and Table 2).

When mannonolactone **7** was allowed to react with MgI_2, lactones **1** and **8** were obtained. The results are summarized in Table 2.

Under the optimum conditions obtained for the reaction of D-gluconolactone **1**, D-mannonolactone **7** yielded gluconolactone **1** (15% yield, entry 1). An excess of MgI_2 (6–10 equiv) allowed the formation of gluconolactone **1** in a higher yield (25–35%) together with α,β-unsaturated lactone **8** (5–14% yield) (entries 2–4). When the reaction was conducted with 6 equiv of MgI_2, mannonolactone **7** afforded gluconolactone **1** in the highest yield (35%, entry 2) and a low quantity of eliminated lactone **8** (5% yield). These results show that the epimerization reaction is reversible. The conversion of D-mannonolactone **7** into D-gluconolactone **1** proceeds in lower yields (35%) compared to the reverse reaction (60% yield). The similar ratio of lactones **1**:**7** obtained starting from lactone **1** or **7**, respectively (30:60 Table 1, entry 4 compared to 35:60 Table 2, entry 2), allowed us to envisage a possible thermodynamic control for this transformation. The lower yield of lactone **7** obtained along with a higher ratio of unsaturated lactone **8** from **1** (Table 1, entries 2–3) allows us to deduce that the elimination process affording **8** should be favoured in mannolactone **7** compared to gluconolactone **1**.

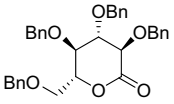
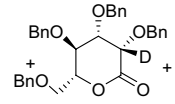
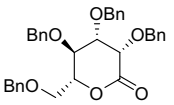
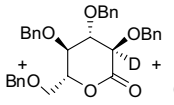
At this stage, we were interested in characterizing this C-2 transformation. Indeed, the reaction promoted by MgI_2 could proceed through an epimerization or a racemization mechanism. To differentiate these two processes, the reactions of lactones **1** and **7** were performed in EtOD under the optimum conditions. The results are summarized in Table 3.

Surprisingly, D-gluconolactone **1** subjected to reaction with MgI_2 in EtOD (Table 3, entry 1) afforded the C-2 deuterated mannonolactone **10** (60% yield) as the unique deuterated product, along with the recovery of undeuterated starting lactone **1** (30% yield) and unsaturated lactone **8** (10% yield). Analogously, D-mannonolactone **7** (Table 3, entry 2) generated the C-2 deuterated gluconolactone **11** (35% yield), recovery of starting undeuterated lactone **7** and lactone **8** (60% and 5%, respectively). The unique incorporation of a deuterium atom at the C-2 position of the epimerized product (lactone **10** starting from lactone **1** or lactone **11** starting from lactone **7**, respectively) allows us to suppose that the MgI_2 reaction is occurring via a C-2 inversion of configuration (epimerization). The unique deuteration that was obtained for lactone **10** (or **11**) shows that thermodynamic control, as envisaged above, is probably not occurring. (Thermodynamic control would have generated both deuterated lactones **10** and



Scheme 4. Reagents and conditions: (a) MgI_2, see conditions Table 2 followed by H_2O/TFA cat. work-up.

Table 3. Experiments in EtOD

Entry	Substrate	Conditions	Products
1	 **1**	2 equiv MgI_2, EtOD, rt, 1 h, H_2O/TFA	**1** (30%) +  + **8** (10%) **10** (60%)
2	 **7**	6 equiv MgI_2, EtOD, rt, 1 h, H_2O/TFA	**7** (60%) +  + **8** (5%) **11** (35%)

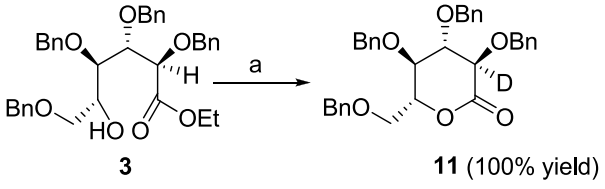
11 in the same ratio regardless of the starting lactone **1** or **7**.)

We had reported earlier in the discussion that the reaction of gluconolactone **1** with MgI_2 in EtOH afforded the transesterification products **3** and **9** when using an aqueous work-up (Scheme 3, conditions (b)). Therefore, the reaction of ethyl 2,3,4,6-tetra-*O*-benzyl-D-gluconate (**3**)[4] with MgI_2 in EtOD was studied (Scheme 5). Hydroxyethyl ester **9** resulting from the transesterification of mannonolactone **7** was not stable enough to be tested with MgI_2/EtOD.

Treatment of gluconate **3** with MgI_2 in EtOD under conditions (a) quantitatively yielded the C-2 deuterated D-gluconolactone **11** (Scheme 5). This result shows that the reactivity of gluconate **3** is different toward MgI_2 than gluconolactone **1**, and that the cyclic structure of aldonolactone is required to allow the MgI_2 epimerization to proceed.

In an effort to further explore this C-2 epimerization and to identify the involved reactive species, gluconolactone **1** and mannonolactone **7** were subjected to reaction with other potential chelating and/or basic reactants.

First, owing to the possible formation of magnesium ethoxide in the reaction mixture (MgI_2/EtOH), the reaction of lactones **1** and **7** was examined in the presence of commercially available or synthesized $Mg(OEt)_2$[17] (Table 4, entries 1–2). The reaction of D-gluconolactone **1** with $Mg(OEt)_2$ afforded the recovery of the starting lactone **1** and the corresponding hydroxyethyl ester **3** in a 1:1 ratio (entry 1). The reaction of D-mannonolactone **7** with $Mg(OEt)_2$ gave a recovery of the starting lactone



Scheme 5. Reagents and conditions: (a) MgI_2 (2 equiv), EtOD, 1 h, rt, and H_2O–cat. TFA.

7 and the formation of hydroxyethyl ester **9** in 65% and 35% yields, respectively (entry 2). These results show that $Mg(OEt)_2$ is promoting the transesterification of lactones **1** and **7** rather than their epimerization.

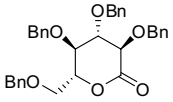
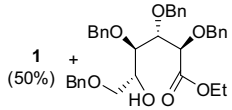
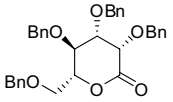
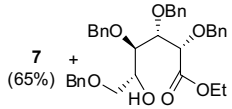
The reaction of lactones **1** and **7** with sodium acetate[18] only afforded the starting lactone, showing that the epimerization does not occur in this basic medium. Then, the reactivity of MgI_2 was compared to other Lewis acids: no reaction occurred when aldonolactones **1** and **7** were subjected to reaction with $BF_3{\cdot}OEt_2$, $ZnCl_2$, or $MgBr_2$ in EtOH.

Moreover, the reported reactivity of a metal halide with an alcohol yielding a halo alkoxy metal[19] led us to envisage that MgI_2 in EtOH could generate iodoethoxymagnesium MgI(OEt). To have more information on the magnesium species involved in the epimerization of the lactones, infrared studies of MgI_2, $Mg(OEt)_2$, and $MgI_2{\cdot}Et_2O$ previously subjected to EtOH, were carried out. The results reported in the experimental part confirm the possibility of MgI(OEt) acting as the reactive magnesium species in the epimerization reaction (crystallization of MgI(OEt) was unsuccessful).

Furthermore, the possible formation of hydrogen iodide during the reaction of MgI_2 in EtOH led us to evaluate the reactivity of this powerful acid toward aldonolactones. The reaction of lactones **1** and **7** with anhydrous HI[20] (DI) in EtOD did not afford their corresponding C-2 epimer, which allowed us to conclude that the MgI_2 epimerization reaction is not promoted by HI.

Finally, we decided to characterize the complexes formed by MgI_2 and the aldonolactones. The best results were obtained by NMR studies, running the reaction of lactones and MgI_2 in $CDCl_3$. ^1H and ^{13}C NMR spectra of the magnesium–lactone complexes showed important shifts at low field (for gluconolactone **1** δ 169.2 (C=O) compared to gluconolactone **1** + Mg species δ 179.8 (C=O); for mannonolactone **7** δ 168.3 (C=O) compared to mannonolactone **7** + Mg species δ 180.6 (C=O); the crystallization of the magnesium–lactone complex was unsuccessful). On the other hand as reported in the experimental part, mass spectral

Table 4. Reaction of aldonolactones **1** and **7** with $Mg(OEt)_2$

Entry	Substrate	Conditions	Products
1	 **1**	$Mg(OEt)_2$, 2 equiv, EtOH, rt, 1 h	**1** (50%) +  **3** (50%)
2	 **7**	$Mg(OEt)_2$, 2 equiv, EtOH, rt, 1 h	**7** (65%) +  **9** (35%)

analysis confirmed the formation of magnesium–lactone complexes.

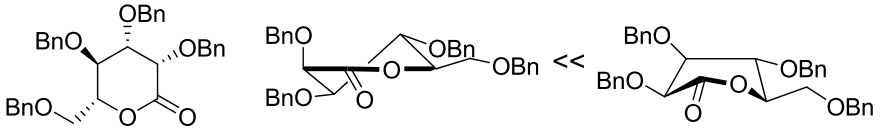
2.2. Conformational studies

To propose an epimerization mechanism, we studied the conformations in a solution of tetra-*O*-benzyl-D-gluconolactone (**1**) and tetra-*O*-benzyl-D-mannonolactone (**7**). Recent NMR investigations have shown that the conformations in a solution of unprotected D-gluconolactone and D-mannonolactone were strongly in favour of a chair $^4H_3$ and a boat $B_{2,5}$, respectively.[21] Conformational analysis carried out by X-ray crystallography and molecular modeling reported that 2-(*R*)-aldono-δ-lactam and 2-(*S*)-aldono-δ-lactam were in half-chair and boat conformations, respectively.[22] Recently, we have shown that the conformation of a bis cationic D-mannoamidine in solution was closer to a $B_{2,5}$ boat.[1] Moreover, NMR studies showed a significant NOE effect between H-2 and H-5 for D-mannonolactone **7**, proving that its conformation should be closer to a boat $B_{2,5}$ (Chart 1). The ^{1}H NMR coupling constants $J_{3,4}$ 3.9 Hz and $J_{2,3}$ 2.5 Hz were in accord with this proposed conformation.

Concerning D-gluconolactone **1**, the two significant NOE effects observed between H-3 and H-5 and between H-2 and H-4, and the ^{1}H NMR constants $J_{2,3}$ 6.7 Hz pointed out that the conformation of lactone **1** should be closer to a half-chair $^4H_3$ (Chart 2).

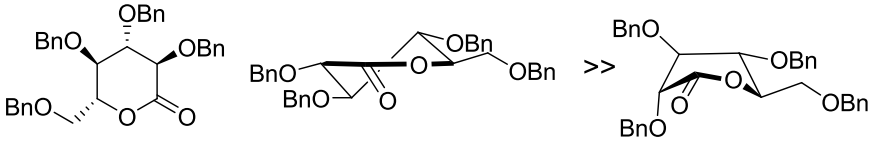
2.3. Proposed mechanism for the C-2 epimerization of D-glucono- and D-mannonolactones

In the epimerization reaction, D-mannonolactone **7** and D-gluconolactone **1** should adopt their favoured conformations (a $B_{2,5}$ boat and a $^4H_3$ chair conformation, respectively), and MgI(OEt) is presumed to be the reactive magnesium species. We have reported that at least 2 equiv of MgIOEt (MgI_2) were required in the optimized conditions. According to us, 1 equiv of MgIOEt is supposed to chelate the lactone, and the other equivalent should complex two *O*-benzyl groups in the C-4 and C-6 positions, yielding complexes **7a** and **1c** (five- and six-membered O–Mg–O chelates are well known



7 $^4H_3$ $B_{2,5}$

Chart 1. Conformations of 2,3,4,6-tetra-*O*-benzyl-D-mannonolactone (**7**).



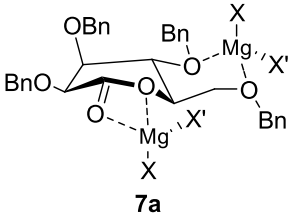
1 $^4H_3$ $B_{2,5}$

Chart 2. Conformations of 2,3,4,6-tetra-*O*-benzyl-D-gluconolactone (**1**).

in the literature)[23] (Chart 3). In complex **7a** (simplified **7b**) the equatorial C-2 OBn should force the magnesium to chelate the lactone function from the plane below the lactone ring. Similarly in complex **1c** (simplified **1d**), the presence of an equatorial C-2 OBn compelled the magnesium to chelate the lactone from the top of the molecule. We suggest that these two probable chelations of MgIOEt (see complexes **7a** and **1c**, Chart 3) should restrain the conformational changes of all proposed chelated intermediates favouring a possible kinetic control. On the following of the discussion to make clearer the proposed mechanisms and schemes, only one equivalent of MgIOEt will be represented. The simplified complexes are drawn as **7b** and **1d** (Chart 3).

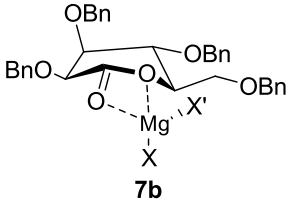
In light of our experimental results, we suggest a possible mechanism for the epimerization of D-mannonolactone **7** into deuterated D-gluconolactone **11** (Scheme 6). The initial step is supposed to be the chelation of magnesium species with mannonolactone **7** reacting as its $B_{2,5}$ conformation **7b** (see Chart 3). Then, a transesterification with EtOD would generate the chelated ester **7c**. The strong chelation of MgIOEt with glyconate led us to propose a further substitution of an iodide by EtOH, generating $Mg(OEt)_2$ as the chelating species in intermediate **7d**. Considering that an iodide ligand is a better nucleofuge than an ethoxide, $Mg(OEt)_2$ is supposed to be the chelating species rather than MgIOEt. Then, **7d** would be attacked by EtOD from the top side due to the Mg chelation. By way of a concerted mechanism, one ethoxide ligand on the magnesium would become a leaving group and would remove the H-2. Then, this C-2 position would be deuterated by EtOD from the opposite side following a S_N2-type reaction yielding complex **7e**. The axial 2-OBn in complex **7e** should prevent another attack of EtOD on the magnesium from the bottom of the molecule, avoiding a retro-epimerization process. The restricted conformational changes proposed above in the discussion could validate this hypothesis. Finally an aqueous treatment could generate hydroxyester **7f**, affording with TFA the corresponding C-2 deuterated gluconolactone **11**. This proposed mechanism could explain the transformation of tetra-*O*-benzyl-D-mannonolactone (**7**) into tetra-*O*-benzyl-D-gluconolactone (**11**) promoted by MgI_2.

Concerning the transformation of D-gluconolactone **1** into C-2 deuterated D-mannonolactone **10**, we proposed a similar mechanism (Scheme 7). Lactone **1** complexed with MgI_2 is supposed to react by way of its $^4H_3$ conformation **1d** (Chart 3). A transesterification of complex **1d** with EtOD would yield complex **1e** and then intermediate **1f**. An approach of EtOD from the bottom would attack the magnesium, and through a concerted mechanism, complex **1f** would afford intermediate **1g**. The presence of an axial C-2 OBn in complex **1g** would prevent a retro-epimerization from the top of the molecule as previously proposed. After hydrolysis, the corresponding hydroxy ester **1h** would be obtained and would yield with TFA treatment the C-2 deuterated mannonolactone **10**.



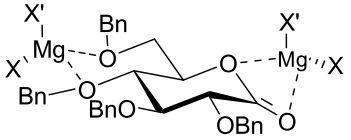
7a

7a: tetra-*O*-benzyl-mannonolactone $B_{2,5}$ complexed with MgXX'
X = OEt, X' = I or X = I, X' = OEt.



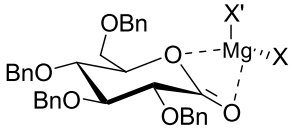
7b

7b: "simplified" tetra-*O*-benzyl-mannonolactone $B_{2,5}$ with MgXX'
X = OEt, X' = I or X = I, X' = OEt.



1c

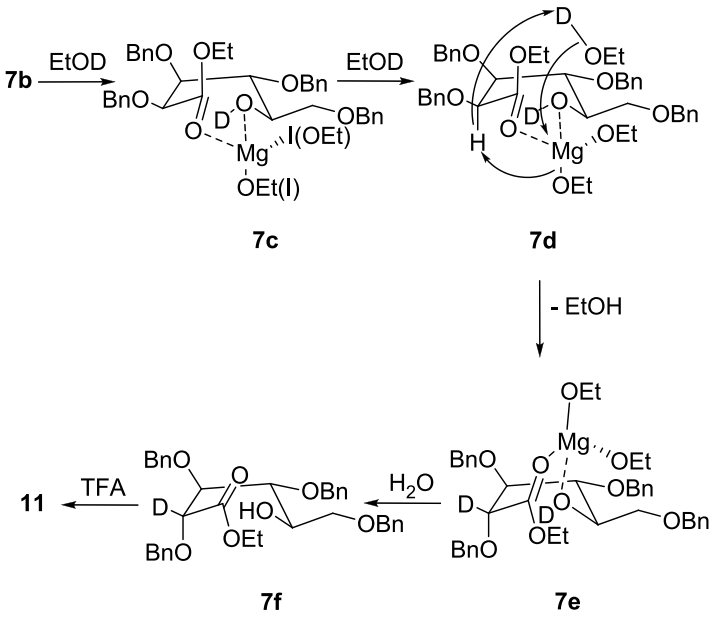
1c: tetra-*O*-benzyl-gluconolactone $^4H_3$ complexed with MgXX'
X = OEt, X' = I or X = I, X' = OEt.



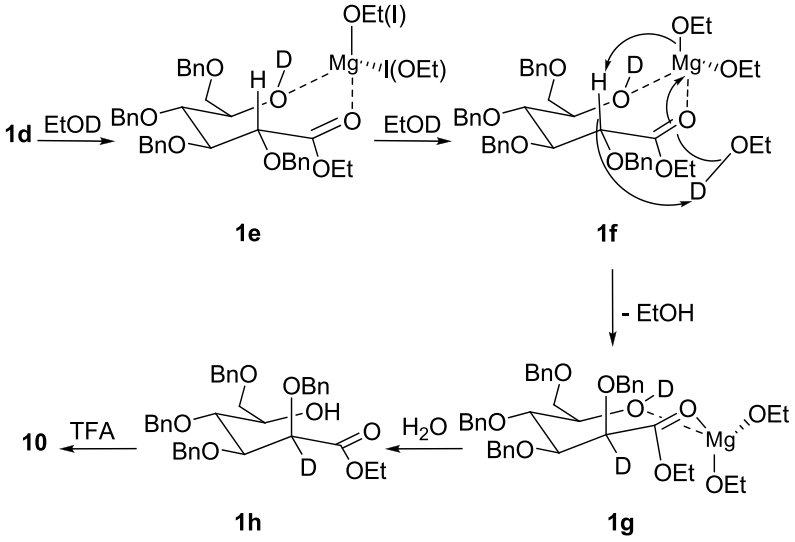
1d

1d: "simplified" tetra-*O*-benzyl-gluconolactone $^4H_3$ with MgXX'
X = OEt, X' = I or X = I, X' = OEt.

Chart 3. Possible chelation of MgIOEt with mannonolactone **7** and gluconolactone **1**.



Scheme 6. Proposed mechanism for epimerization of D-mannonolactone **7**.



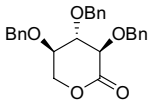
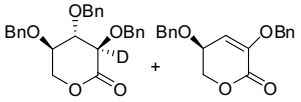
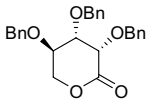
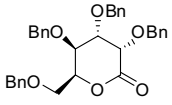
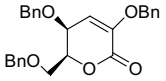
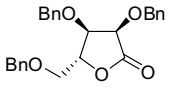
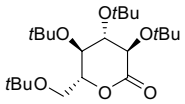
Scheme 7. Proposed mechanism for epimerization of D-gluconolactone **1**.

Since this epimerization methodology has no precedent in the literature, we submitted a variety of aldonolactones to MgI_2/EtOH conditions (Table 5).

2,3,4-Tri-*O*-benzyl-D-xylonolactone (**12**)[24] subjected to reaction with MgI_2/EtOH conditions afforded C-2 deuterated xylonolactone **13** and α,β-unsaturated lactone **14** in 80% and 20% yield, respectively (entry 1). Compound **14** was unambiguously identified to (*S*)-3,5-dibenzyloxy-5,6-dihydro-2-pyrone by comparison with its reported analytical data.[25] When 2,3,4-tri-*O*-benzyl-D-lyxonolactone (**15**), prepared by the oxidation of 2,3,4-tri-*O*-benzyllyxopyranose-1-ol,[26] was allowed to react under the same conditions, unsaturated lactone **14** and recovered starting lactone **15** were obtained in 10% and 90% yield, respectively (entry 2). Treatment of 2,3,4,6-tetra-*O*-benzyl-L-gulonolactone (**16**)[4] with MgI_2 afforded quantitatively the unsaturated lactone **17** (entry 3). 2,3,5-Tri-*O*-benzyl-D-ribofuranolactone (**18**)[27] subjected to reaction with similar conditions afforded only a recovery of starting product **18** (entry 4). No reaction occurred by reacting the hindered lactone 2,3,4,6-tetra-*O*-*tert*-butyl-D-gluconolactone (**19**) with MgI_2 either under standard conditions or under more drastic treatment (entry 5).

From the results reported in Table 5, we can deduce that the C-2 epimerization reaction of aldonolactones

Table 5. Reaction of various aldonolactones with MgI_2 in EtOD

Entry	Substrate	Cond[a]	Products
1	 **12**	a	 **13** (80%) **14** (20%)
2	 **15**	b	**15** + **14** (90%) (10%)
3	 **16**	b	 **17** (100%)
4	 **18**	b or c	**18** (100%)
5	 **19**	a or c	**19** (100%)

(a) MgI_2 (2 equiv), rt, 1 h, EtOD and workup H_2O–cat TFA.
(b) MgI_2 (6 equiv), rt, 1 h, EtOD and workup H_2O–cat TFA.
(c) MgI_2 (10 equiv), rt, 2 h, EtOD and workup H_2O–cat TFA.
[a] Cond = experimental conditions.

with MgI_2 in EtOH is occurring with 5-(*R*)-benzyloxy-six-membered-ring lactones, that five-membered ring lactone or *tert*-butyl protecting groups did not allow the epimerization to proceed. We suppose that these specificities should force the lactones to adopt a particular conformation probably required for the chelation with magnesium.

In summary, we have presented herein the first examples of a reversible non-enzymatic C-2 epimerization of aldonolactones promoted by MgI_2. 2,3,4,6-Tetra-*O*-benzyl-D-aldonolactone subjected to reaction with MgI_2 in EtOH afforded its corresponding C-2 epimer (60% yield from D-gluconolactone and 35% yield for D-mannonolactone). Subsequent mechanistic studies in EtOD have confirmed that the C-2 transformation promoted by MgI_2 was an epimerization reaction rather than a racemization. This epimerization process is supposed to involve a magnesium-chelated species. The magnesium species/aldonolactone complex seems to allow a specific recognition by EtOD, affording the deuterated C-2 epimer of the starting lactone.

This methodology allows access in one step to 2,3,4,6-tetra-*O*-benzyl-D-mannonolactone (**7**) starting from 2,3,4,6-tetra-*O*-benzyl-D-gluconolactone (**1**). Such a process can be very useful to prepare a series of aldonoderivatives avoiding a multistep synthesis starting from the corresponding commercially available mannopyranoside. Studies aimed at employing this new methodology for the synthesis of glycoamidines are ongoing. This original C-2 inversion should be a further interest in synthetic organic chemistry for the preparation of naturally rare and expensive carbohydrates from their commonly available C-2 epimer, and to develop new methods whereby magnesium could promote the transformation of sugars.

3. Experimental

3.1. General methods

All reagents were commercial grade and were used as received without further purification. All reactions were performed under inert atmosphere, and dry solvents were dried and distilled over appropriate desiccant prior to use. Thin-layer chromatography (TLC) and flash chromatography separations were, respectively, performed on precoated Silica Gel 60 F254 plates (0.25 mm) and on E. Merck Silica Gel 60 (230–400

mesh). ^{1}H NMR spectra were recorded at 400 MHz, and ^{13}C NMR spectra were obtained at 100 MHz in the specified solvent. IR spectra were recorded as thin films on NaCl plates using an FTIR instrument.

3.2. Preparation of 2,3,4,6-tetra-*O*-benzyl-D-glucono-1,5-lactone (1)

Compound **1** was prepared following the reported method. Physicochemical data were in accord with those reported.[2]

3.3. Preparation of 2,3,4,6-tetra-*O*-benzyl-D-mannono-1,5-lactone (7)

Lactone **7** was prepared following the reported method. Physicochemical data were in accord with those reported.[3b]

3.4. General procedure for the preparation of MgI_2

To dried magnesium turnings (7 mg, 0.23 mmol), stored overnight in an oven before use, was added a solution of 1,2-diiodoethane (53 mg, 0.19 mmol) in dry Et_2O (0.5 mL). The reaction mixture was stirred under reflux for 15 min until the solution became colorless. Then, the mixture was filtered through a cotton pad under N_2 to remove excess of magnesium. The resulting solution was concentrated under vacuum to yield MgI_2 as a white solid that was used directly in the aldonolactone epimerization reaction.

3.5. General procedure for the C-2 epimerization of D-gluconolactone

To MgI_2 (0.19 mmol), freshly prepared following the reported general procedure, was added a solution of 2,3,4,6-tetra-*O*-benzyl-D-gluconolactone (**1**) (50 mg, 0.09 mmol) in dry EtOH (1 mL). The mixture was stirred at room temperature for 1 h, then H_2O (1 mL) and TFA (10 mmol) were added. The solution was diluted with Et_2O (5 mL) and stirred at room temperature for 15 min. The organic layer was separated, washed with H_2O, dried over $MgSO_4$, and concentrated under vacuum. The crude products were purified by column chromatography (9:1 pentane–EtOAc) to yield compounds **1** (14 mg, 30% yield), **7** (27 mg, 60% yield), and **8** (4 mg, 10% yield).

3.6. General procedure for the C-2 epimerization of D-mannonolactone

To MgI_2 (0.5 mmol), freshly prepared following the reported general procedure, was added a solution of 2,3,4,6-tetra-*O*-benzyl-D-mannonolactone (**7**) (50 mg, 0.09 mmol) in dry EtOH (1 mL). The mixture was stirred at rt for 1 h, and H_2O (1 mL) and TFA (10 mmol) were added. The solution was diluted with Et_2O (5 mL) and stirred at room temperature for 15 min. The organic layer was separated, washed with H_2O, dried over $MgSO_4$, and concentrated under vacuum. The crude products were purified by column chromatography (9:1 pentane–EtOAc) to yield compounds **7** (27 mg, 60% yield), **1** (16 mg, 35% yield), and **8** (2 mg, 5% yield).

3.7. Preparation of ethyl 2,3,4,6-tetra-*O*-benzyl-D-gluconate (3)

Ester **3** was prepared following the reported method. Physicochemical data were in accord with those reported.[4]

3.8. Preparation of tri-*O*-benzyl-3-deoxy-D-*erythro*-hex-2-enono-1,5-lactone (8)

Lactone **8** was prepared following the reported method. Physicochemical data were in accord with those reported.[15]

3.9. Ethyl 2,3,4,6-tetra-*O*-benzyl-D-mannonate (9)

Treatment of D-gluconolactone following the general procedure for the C-2 epimerization yielded an unseparable mixture of compounds **3** (30%) and **9** (60%). Another procedure was used to prepare ester **9**: To a solution of lactone **7** (50 mg, 0.09 mmol) in anhyd EtOH (1 mL) was added $Mg(OEt)_2$ (0.18 mmol). The mixture was stirred at room temperature for 1 h and H_2O (1 mL) was added. The solution was diluted with Et_2O (5 mL) and stirred at room temperature for 15 min. The organic layer was separated, washed with H_2O, dried over $MgSO_4$, and concentrated under vacuum to yield a mixture of recovered lactone **7** and ester **9** (51 mg, ^{1}H NMR ratio 7/9:65/35). Ester **9** was not stable enough to be purified on column chromatography and was oxidized to the corresponding ketone **20** to allow further identification [see below the preparation and characterization of ethyl 2,3,4,6-tetra-*O*-benzyl-D-lyxo-5-hexulosonate (**20**)].

3.10. 2-(^{2}H)-2,3,4,6-Tetra-*O*-benzyl-D-mannono-1-5-lactone (10)

Lactone **1** (50 mg, 0.09 mmol) was subjected to reaction with MgI_2 (0.19 mmol) in EtOD (1 mL) to yield compound **10** (27 mg, 60% yield) following the general procedure reported for the C-2 epimerization of D-gluconolactone. ^{1}H NMR ($CDCl_3$) δ 7.42–7.09 (m, 20H,

Ph), 5.07 (d, $J = 11.9$ Hz, 1H, CH_2Ph), 4.85 (d, $J = 12.3$ Hz, 1H, CH_2Ph), 4.65 (d, $J = 12.3$ Hz, 1H, CH_2Ph), 4.61 (d, $J = 11.9$ Hz, 1H, CH_2Ph), 4.57 (d, $J = 11.4$ Hz, 1H, CH_2Ph), 4.54 (d, $J = 11.4$ Hz, 1H, CH_2Ph), 4.35 (d, $J = 11.4$ Hz, 1H, CH_2Ph), 4.27 (d, $J = 11.5$ Hz, 1H, CH_2Ph), 4.27–4.23 (m, 1H, H-5), 4.06 (d, $J = 1.6$ Hz, 1H, H-3), 3.80 (dd, $J = 1.6$, 7.2 Hz, 1H, H-4), 3.65 (d, $J = 4.6$ Hz, 2H, H-6); ^{13}C NMR ($CDCl_3$) δ 169.5 (C-1), 137.8 (2C, Ph), 137.4 (Ph), 136.9 (Ph), 128.6–127.9 (Ph), 78.7 (C-5), 76.7 (C-3), 76.2 (C-4), 73.6 (*C*H_2Ph), 73.1 (*C*H_2Ph), 73.0 (*C*H_2Ph), 72.3 (*C*H_2Ph), 69.3 (C-6); ^{13}C NMR DEPT 135 ($CDCl_3$) δ 128.6–127.9 (Ph), 78.7 (C-5), 76.7 (C-3), 76.3 (C-4), 73.6 (*C*H_2Ph), 73.1 (*C*H_2Ph), 73.0 (*C*H_2Ph), 72.0 (*C*H_2Ph), 69.3 (C-6); HRESIMS: m/z $[M+Na]^+$ 562.2335; calcd for $C_{34}H_{33}DO_6Na$: m/z 562.2316.

3.11. 2-(^{2}H)-2,3,4,6-Tetra-*O*-benzyl-D-glucono-1,5-lactone (11)

Lactone **7** (50 mg, 0.09 mmol) was subjected to reaction with MgI_2 (0.5 mmol) in EtOD (1 mL) to yield compound **11** (16 mg, 35% yield) following the general procedure reported for the C-2 epimerization of D-mannonolactone. ^{1}H NMR ($CDCl_3$) δ 7.43–7.16 (m, 20H, Ph), 4.99 (d, $J = 11.3$ Hz, 1H, CH_2Ph), 4.73 (d, $J = 11.4$ Hz, 1H, CH_2Ph), 4.71 (d, $J = 11.4$ Hz, 1H, CH_2Ph), 4.64 (d, $J = 11.4$ Hz, 1H, CH_2Ph), 4.59 (d, $J = 11.4$ Hz, 1H, CH_2Ph), 4.57–4.45 (m, 4H, H-5 and CH_2Ph), 3.96 (d, $J = 6.8$ Hz, 1H, H-3), 3.92 (dd, $J = 6.8$, 7.0 Hz, 1H, H-4), 3.73 (dd, $J = 2.5$, 10.9 Hz, 1H, H-6a), 3.67 (dd, $J = 3.3$, 10.8 Hz, 1H, H-6b); ^{13}C NMR ($CDCl_3$) δ 169.4 (C-1), 137.8 (Ph), 137.7 (2C, Ph), 137.1 (Ph), 128.8–128.0 (Ph), 81.0 (C-4), 78.3 (C-5), 76.3 (C-3), 74.1 (*C*H_2Ph), 73.8 (2C, *C*H_2Ph), 73.7 (*C*H_2Ph), 68.5 (C-6); HRESIMS: m/z $[M+Na]^+$ 562.2321, calcd for $C_{34}H_{33}DO_6Na$: m/z 562.2316.

3.12. 2,3,4-Tri-*O*-benzyl-D-xylono-1,5-lactone (12)

Compound **12** was prepared by the oxidation of 2,3,4-tri-*O*-benzyl-D-xylopyranose.[24b] To a solution of 2,3,4-tri-*O*-benzyl-D-xylopyranose (5.00 g, 11.9 mmol) in dry DMSO (25 mL) was added Ac_2O (15 mL, 262 mmol). The reaction was run for 12 h at room temperature. H_2O (50 mL) was added, and the mixture was stirred for an additional 1 h. The aqueous layer was then extracted with Et_2O (3×100 mL). The combined organic extracts were washed with H_2O (3×50 mL), dried under $MgSO_4$, and concentrated under vacuum to yield a solid. Recrystallization from MeOH gave compound **15** (4.74 g, 95% yield), as white needles. The NMR data and mp were in accord with those reported.[24a]

3.13. 2-(^{2}H)-2,3,4-Tri-*O*-benzyl-D-xylono-1,5-lactone (13)

Lactone **12** (50 mg, 0.12 mmol) was subjected to reaction with MgI_2 (0.24 mmol) in EtOD (1 mL) at rt for 1 h to yield compound **13** (40 mg, 80%), following the general procedure reported for the C-2 epimerization of D-gluconolactone. ^{1}H NMR ($CDCl_3$) δ 7.36–7.19 (m, 15H, Ph), 4.96 (d, $J = 11.6$ Hz, 1H, CH_2Ph), 4.59 (d, $J = 11.7$ Hz, 2H, CH_2Ph), 4.51 (d, $J = 11.7$ Hz, 1H, CH_2Ph), 4.50 (d, $J = 11.6$ Hz, 1H, CH_2Ph), 4.45 (d, $J = 11.9$ Hz, 1H, CH_2Ph), 4.33 (ddd, $J = 12.3$, 3.3, 1.5 Hz, 1H, H-5a), 4.30 (dd, $J = 2.0$, 12.4, 1H, H-5b), 3.82 (s, 1H, H-3), 3.71–3.69 (m, 1H, H-4); ^{13}C NMR ($CDCl_3$) δ 169.9 (C-1), 137.4 (Ph), 137.2 (Ph), 137.1 (Ph), 128.7–127.9 (Ph), 81.4 (C-3), 79.0 (t, $J = 20.7$ Hz, C-2), 75.3 (C-4), 73.4 (*C*H_2Ph), 72.9 (*C*H_2Ph), 70.7 (*C*H_2Ph), 65.8 (C-5); HRESIMS: m/z $[M+Na]^+$ 442.1755, calcd for $C_{26}H_{25}DO_5Na$: m/z 442.1741.

3.14. (*S*)-3,5-Dibenzyloxy-5,6-dihydro-2-pyrone (14)

Lactone **12** (50 mg, 0.12 mmol) was subjected to reaction with MgI_2 (0.24 mmol) in EtOD (1 mL) at rt for 1 h following the general procedure reported for the C-2 epimerization of D-gluconolactone and gave compound **14** (8 mg, 20%). The NMR data were in accord with those reported.[25]

3.15. 2,3,4-Tri-*O*-benzyl-D-lyxono-1,5-lactone (15)

Lactone **15** was prepared by the oxidation of 2,3,4-tri-*O*-benzyl-D-lyxopyranose.[26] To a solution of lactol (800 mg, 1.90 mmol) in dry DMSO (6 mL) was added Ac_2O (4 mL, 41.8 mmol). The reaction was run for 12 h at room temperature. H_2O (10 mL) was added, and the mixture was stirred for an additional 1 h. The aqueous layer was then extracted with Et_2O (3×20 mL). The combined organic extracts were washed with H_2O (3×10 mL), dried over $MgSO_4$, and concentrated under vacuum to yield **15** (637 mg, 80% yield), which was pure enough to be used in the next step without further purification. $[\alpha]_D^{20}$ −63.1 (*c* 1.14, $CHCl_3$); IR (neat, cm^{-1}) 2873, 1737, 1454, 1113, 699; ^{1}H NMR ($CDCl_3$) δ 7.36–7.09 (m, 15H, Ph), 5.03 (d, $J = 12.0$ Hz, 1H, CH_2Ph), 4.81 (d, $J = 12.1$ Hz, 1H, CH_2Ph), 4.59 (d, $J = 12.1$ Hz, 1H, CH_2Ph), 4.58 (d, $J = 12.1$ Hz, 1H, CH_2Ph), 4.49 (dd, $J = 4.0$, 12.4 Hz, 1H, H-5a), 4.42 (d, $J = 11.8$ Hz, 1H, CH_2Ph), 4.35 (d, $J = 11.8$ Hz, 1H, CH_2Ph), 4.36 (d, $J = 2.9$ Hz, 1H, H-2), 4.18 (dd, $J = 2.9$, 12.4 Hz, 1H, H-5b), 4.03 (dd, $J = 3.0$, 3.3 Hz, 1H, H-3), 3.75–3.73 (m, 1H, H-4); ^{13}C NMR ($CDCl_3$) δ 176.7 (C-1), 137.7 (Ph), 137.5 (Ph), 136.9 (Ph), 128.7–127.7 (Ph), 76.4 (C-3), 74.9 (C-2), 74.3 (C-4), 73.5 (*C*H_2Ph), 73.3 (*C*H_2Ph), 71.4 (*C*H_2Ph),

68.7 (C-5); HRESIMS: m/z $[M+Na]^+$ 441.1698, calcd for $C_{26}H_{25}O_5Na$: m/z 441.1678.

3.16. Preparation of 2,3,4,6-tetra-*O*-benzyl-L-gulonolactone (16)

Compound **16** was prepared following the reported method. Physicochemical data were in accord with those reported.[4]

3.17. 2,4,6-Tri-*O*-benzyl-3-deoxy-L-*erythro*-hex-2-enono-1,5-lactone (17)

Lactone **16** (50 mg, 0.09 mmol) was subjected to reaction with MgI_2 (0.54 mmol) in EtOD (1 mL) at rt for 1 h to yield compound **17** (39 mg, 98% yield) following the general procedure reported for the C-2 epimerization of D-gluconolactone. $[\alpha]_D^{20}$ −3.9 (c 0.16, $CHCl_3$); IR (neat, cm^{-1}) 2925, 1743, 1456, 1099, 698; ^1H NMR ($CDCl_3$) δ 7.38–7.18 (m, 15H, Ph), 5.71 (d, $J = 6.5$ Hz, 1H, H-3), 4.94 (d, $J = 12.4$ Hz, 1H, CH_2Ph), 4.88 (d, $J = 12.4$ Hz, 1H, CH_2Ph), 4.62 (d, $J = 11.8$ Hz, 1H, CH_2Ph), 4.59–4.55 (m, 1H, H-5), 4.55 (d, $J = 11.7$ Hz, 1H, CH_2Ph), 4.47 (d, $J = 11.9$ Hz, 1H, CH_2Ph), 4.39 (d, $J = 12.0$ Hz, 1H, CH_2Ph), 4.16 (dd, $J = 2.7$, 6.5 Hz, 1H, H-4), 3.91 (dd, $J = 7.3$, 9.7 Hz, 1H, H-6a), 3.81 (dd, $J = 6.0$, 9.7 Hz, 1H, H-6b); ^{13}C NMR ($CDCl_3$) δ 159.8 (C-1), 146.4 (C-2), 137.9 (Ph), 137.8 (Ph), 135.3 (Ph), 128.9–127.4 (Ph), 109.2 (C-3), 79.0 (C-4), 73.8 (C-5), 70.7 (*C*H_2Ph), 70.5 (*C*H_2Ph), 67.8 (*C*H_2Ph), 67.3 (C-6); HRESIMS: m/z $[M+Na]^+$ 453.1699, calcd for $C_{27}H_{26}O_5Na$: m/z 453.1678.

3.18. Preparation of 2,3,5-tri-*O*-benzyl-D-ribofurano-1,4-lactone (18)

Compound **18** was prepared following the reported method.[27a] Physicochemical data were in accord with those reported.[27b]

3.19. 2,3,4,6-Tetra-*O*-*tert*-butyl-D-glucono-1,5-lactone (19)

To a suspension of commercially available D-gluconolactone (5 g, 28.1 mmol) in dried CH_2Cl_2 (30 mL) in a pressure flask at −78 °C was condensed isobutene (50 mL). After addition of concd H_2SO_4 (0.8 mL), the flask was closed and stirred for 24 h at 50 °C. After cooling, a stream of nitrogen was passed through the resulting solution. The reaction mixture was hydrolyzed with satd aq $NaHCO_3$ (50 mL) and extracted with Et_2O (2 × 30 mL). The organic layers were separated, dried ($MgSO_4$) and concentrated under vacuum. The crude product was purified on column chromatography (95:5 pentane–EtOAc) to give compound **19** (5.9 g, 60% yield). $[\alpha]_D^{20}$ −44.1 (c 1.29, $CHCl_3$); IR (neat, cm^{-1}); 2973, 1789, 1368, 1101, 566; ^1H NMR ($CDCl_3$) δ 4.83 (d, $J = 9.7$ Hz, 1H, H-2), 4.45 (dd, $J = 2.3$, 7.6 Hz, 1H, H-4), 4.24 (dd, $J = 7.6$, 9.7 Hz, 1H, H-3), 3.89 (ddd, $J = 2.3$, 5.4, 7.7 Hz, 1H, H-5), 3.77 (dd, $J = 7.8$, 9.2 Hz, 1H, H-6b), 3.43 (dd, $J = 5.4$, 9.2 Hz, 1H, H-6b), 1.27 (s, 9H, t-Bu), 1.24 (s, 9H, t-Bu), 1.20 (s, 9H, t-Bu), 1.18 (s, 9H, t-Bu); ^{13}C NMR ($CDCl_3$) δ 175.2 (C-1), 77.1 (C-4), 75.4 (C-5), 75.0 (2C, C-2 and C-3), 74.8 (t-Bu), 73.8 (t-Bu), 72.8 (t-Bu), 71.6 (t-Bu), 62.4 (C-6), 28.6 (2C, t-Bu), 28.2 (t-Bu), 27.6 (t-Bu); HRESIMS: m/z $[M+Na]^+$ 425.2887, calcd for $C_{22}H_{42}O_6Na$: m/z 425.2879.

3.20. Ethyl 2,3,4,6-tetra-*O*-benzyl-D-lyxo-5-hexulosonate (20)

To a stirred solution of $(COCl)_2$ (16 μL, 0.18 mmol) in CH_2Cl_2 (0.6 mL) was added DMSO (26 μL, 0.36 mmol). After stirring at −78 °C for 10 min, the crude mixture resulting from the treatment of compounds **9** and **7** in CH_2Cl_2 (0.9 mL) was added. After stirring at −78 °C for 30 min, Et_3N (76 μL, 0.54 mmol) was added, and the mixture was allowed to warm to room temperature and stirred for 1 h. The reaction mixture was diluted with Et_2O (5 mL), washed with H_2O, dried under $MgSO_4$, and concentrated under vacuum. The crude mixture was purified by column chromatography (9:1 pentane–EtOAc) to yield ketone **20** (17 mg, 95% yield for the oxidation) and lactone **7** (33 mg). $[\alpha]_D^{20}$ −35.8 (c 0.02, $CHCl_3$); IR (neat, cm^{-1}) 2871, 1737, 1454, 1098, 698; ^1H NMR ($CDCl_3$) δ 7.34–7.22 (m, 20H, Ph), 4.55–4.21 (m, 13H, H-2, H-3, H-4, H-6 and CH_2Ph), 4.12 (t, $J = 7.2$ Hz, 2H, H-7), 1.22 (t, $J = 7.2$ Hz, 3H, H-8); ^{13}C NMR ($CDCl_3$) δ 207.9 (C-5), 171.1 (C-1), 137.4 (2C, Ph), 136.9 (Ph), 136.8 (Ph), 128.6–127.9 (Ph), 83.7 (C-4), 80.7 (C-3), 77.7 (C-6), 74.9 (C-2), 74.4 (2C, *C*H_2Ph), 73.3 (*C*H_2Ph), 72.5 (*C*H_2Ph), 61.4 (C-7), 14.2 (C-8); HRESIMS: m/z $[M+Na]^+$ 605.2530, calcd for $C_{36}H_{38}O_7Na$: m/z 605.2515.

3.21. Studies of the magnesium-complexed aldonolactones: NMR, IR, and SM studies

3.21.1. Analysis of the MgI_2–gluconolactone complex compared to 2,3,4,6-tetra-*O*-benzyl-D-gluconolactone (1)

3.21.1.1. 2,3,4,6-Tetra-*O*-benzyl-D-gluconolactone (1). IR (neat, cm^{-1}) 2869, 1773, 1453, 1074, 699; ^1H NMR ($CDCl_3$) δ 7.35–7.12 (m, 20H, Ph); 4.95 (d, $J = 11.3$ Hz, 1H, CH_2Ph); 4.70–4.42 (m, 7H, CH_2Ph); 4.43–4.39 (m, 1H, H-5); 4.08 (d, $J = 6.5$ Hz, 1H, H-2); 3.91 (dd, $J = 6.9$, 8.2 Hz, 1H, H-4); 3.87 (dd, $J = 6.5$, 6.8 Hz, 1H, H-3); 3.68 (dd, $J = 2.5$, 11.1 Hz, 1H, H-6a); 3.62 (dd, $J = 3.3$, 11.1 Hz, 1H, H-6b); ^{13}C NMR ($CDCl_3$) δ 169.2 (C-1), 137.8 (Ph), 137.7 (2C, Ph), 137.1 (Ph), 128.4–127.8 (Ph), 81.2 (C-4), 78.3 (C-5),

77.6 (C-2), 76.3 (C-3), 74.1 (CH_2Ph), 73.9 (2C, CH_2Ph), 73.7 (CH_2Ph), 68.4 (C-6).

3.21.1.2. MgI_2-complexed gluconolactone. IR (neat, cm^{-1}) 3396, 1644, 1453, 1094; ^1H NMR ($CDCl_3$) δ 7.47–7.13 (m, 20H), 5.34 (br s, 1H), 5.28 (br s, 1H), 4.84 (br s, 1H), 4.76 (br s, 1H), 4.55–4.07 (m, 6H), 3.61–3.59 (m, 1H), 3.50–3.40 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 179.8, 136.3–136.5, 129.3–127.8, 84.0, 80.1, 77.2, 75.2, 74.4, 73.4, 72.7, 67.7, 53.4; ESITOF-MS $(M+EtOMgI+H)^+$, m/z 735.

3.21.2. Analysis of the MgI_2-complexed mannonolactone compared to 2,3,4,6-tetra-*O*-benzyl-D-mannono-1,5-lactone (7)

3.21.2.1. 2,3,4,6-Tetra-*O*-benzyl-D-mannono-1,5-lactone (7). IR (neat, cm^{-1}) 2868, 1755, 1453, 1094, 698; ^1H NMR ($CDCl_3$) δ 7.39–7.09 (m, 20H, Ph), 5.07 (d, $J = 11.9$ Hz, 1H, CH_2Ph), 4.84 (d, $J = 11.2$ Hz, 1H, CH_2Ph), 4.65 (d, $J = 11.2$ Hz, 1H, CH_2Ph), 4.59 (d, $J = 11.9$ Hz, 1H, CH_2Ph), 4.54 (s, 2H, CH_2Ph), 4.29 (d, $J = 2.7$ Hz, 1H, H-2), 4.30–4.16 (m, 2H, CH_2Ph), 4.20–4.16 (m, 1H, H-5), 3.99 (dd, $J = 1.7$, 2.6 Hz, 1H, H-3), 3.73 (dd, $J = 1.6$, 7.2 Hz, 1H, H-4), 3.58 (d, $J = 4.6$ Hz, 2H, H-6); ^{13}C NMR ($CDCl_3$) δ 169.3 (C-1), 137.7 (2C, Ph), 137.2 (Ph), 136.8 (Ph), 128.4–127.7 (Ph), 78.6 (C-5), 77.0 (C-3), 76.1 (C-4), 75.7 (C-2), 73.7 (CH_2Ph), 72.9 (2C, CH_2Ph), 71.3 (CH_2Ph), 69.2 (C-6).

3.21.2.2. MgI_2-complexed mannonolactone. IR (neat, cm^{-1}) 3416, 1630, 1453, 1092, 619; ^1H NMR ($CDCl_3$) δ 7.68–7.54 (m, 2H), 7.44–6.95 (m, 18H), 5.51–5.38 (m, 1H), 5.21–5.09 (m, 1H), 4.93 (br s, 1H), 4.56–4.36 (m, unclear), 3.85–3.75 (m, 1H), 3.64 (d, $J = 9.5$ Hz, 1H), 3.52 (dd, $J = 4.1$, 11.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 180.6, 136.9, 135.9, 135.6, 132.9, 130.1–127.8, 83.3, 82.0, 77.5, 75.7, 74.5, 74.2, 73.3, 72.3, 71.8, 71.2, 67.4; ESITOF-MS $(M+OMg_2I_2+H)^+$: m/z 857.

3.22. Infrared spectral studies

Commercially available MgI_2: IR (neat, cm^{-1}) 3402, 2357, 1591, 671; Commercially available $Mg(OEt)_2$: IR (neat, cm^{-1}) 2848, 2359, 1382, 1119, 880; Freshly prepared $Mg(OEt)_2$: IR (neat, cm^{-1}) 2965, 2359, 1379, 1059, 883; Freshly prepared $Mg(I)_2{\cdot}Et_2O$: IR (neat, cm^{-1}) 3280, 2979, 2359, 1400, 1033, 874.

Freshly prepared magnesium species in the epimerization reaction: MgI_2 (0.19 mmol prepared from the general procedure) was stirred in EtOH (1 mL) for 1 h 30 min at room temperature. Then EtOH was evaporated under vacuum, and the resulting solid was dried and submitted to FTIR analysis. FTIR (neat, cm^{-1}) 3376, 2972, 2359, 1608, 1386, 1026, 770. These results allow us to propose MgIOEt as the reactive Mg species involved in the epimerization reaction.

Supplementary data

^1H and ^{13}C NMR spectra of **1**, **7**, **10**, **11**, **13**, **15**, **17**, **19**, **20**, and NMR spectra of the magnesium–aldonolactone complexes. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2007.10.006.

References

1. Heck, M.-P.; Vincent, S. P.; Murray, B. W.; Bellamy, F.; Wong, C.-H.; Mioskowski, C. *J. Am. Chem. Soc.* **2004**, *126*, 1971–1979.
2. (a) Kuzuhara, H.; Fletcher, H. G. *J. Org. Chem.* **1967**, *32*, 2531–2534; (b) Hoos, R.; Naughton, A. B.; Vasella, A. *Helv. Chim. Acta* **1992**, *75*, 1802–1807.
3. (a) Overkleeft, H. S.; van Wiltenburg, J.; Pandit, U. K. *Tetrahedron Lett.* **1993**, *34*, 2527–2528; (b) Overkleeft, H. S.; van Wiltenburg, J.; Pandit, U. K. *Tetrahedron* **1994**, *50*, 4215–4224.
4. Monthiller, S.; Heck, M.-P.; Mioskowski, C.; Lafargue, P.; Lellouche, J.-P.; Masella, M. *Bull. Soc. Chim. Fr* **1997**, *134*, 145–151.
5. (a) Ermet, P.; Vasella, A. *Helv. Chim. Acta* **1991**, *74*, 2043–2053; (b) Martin, O. G.; Yang, F.; Xie, F. *Tetrahedron Lett.* **1995**, *33*, 47–50.
6. Garcia Martinez, A.; Barcina, J. O.; Hidalgo del Veccio, G.; Hanack, M.; Subramanian, L. R. *Tetrahedron Lett.* **1991**, *32*, 5931–5934.
7. (a) Bilik, V.; Stancovik, L. *Chem. Zvesti* **1973**, *27*, 544–546; (b) Hayes, M. L.; Pennings, N. J.; Serianni, A. S.; Barker, R. *J. Am. Chem. Soc.* **1982**, *104*, 6764–6769, and Refs. 2–5 therein; (c) Kolarie, S.; Gelo, M.; Sankovic, M.; Sunjie, V. *J. Mol. Catal.* **1994**, *89*, 247–256; (d) Clark, E.; Hayes, M. L.; Barker, R. *Carbohydr. Res.* **1986**, *153*, 263–270.
8. (a) Tanase, T.; Kurihara, K.; Yano, S.; Kobayashi, K.; Sakurai, T.; Yoshikawa, S.; Hidai, M. *Inorg. Chem.* **1987**, *26*, 3134–3139; (b) Tanase, T.; Shimizu, F.; Kuse, M.; Yano, S.; Hidai, M.; Yoshikawa, S. *Inorg. Chem.* **1988**, *27*, 4085–4094; (c) Osanai, S.; Inaba, K.; Yoshikawa, S. *Carbohydr. Res.* **1990**, *209*, 233–239.
9. Tanase, T.; Takei, T.; Hidai, M.; Yano, S. *J. Chem. Res.* **1992**, 252–253.
10. Yanagihara, R.; Soeda, K.; Shiina, S.; Osanai, S.; Yoshikawa, S. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2268–2272.
11. (a) Seeholzer, S. H. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 1237–1241; (b) Finlay, T. H.; Adams, E. *J. Biol. Chem.* **1970**, *245*, 5248–5260; (c) Sala, R. F.; Morgan, P. M.; Tanner, M. E. *J. Am. Chem. Soc.* **1996**, *118*, 3033–3034; (d) Maru, I.; Ohnishi, J.; Ohta, Y.; Tsukada, Y. *Carbohydr. Res.* **1998**, *306*, 575–578.
12. Posternak, Th.; Waegell, P. *Helv. Chem. Acta* **1961**, *44*, 257–267.
13. (a) McDonough, M. W.; Wood, W. A. *J. Biol. Chem.* **1961**, *236*, 1220–1224; (b) Sultana, I.; Mizanur, R. M. D.; Takeshita, K.; Takada, G.; Izumori, K. *J. Biosci. Bioeng.* **2003**, *95*, 342–347; (c) Major, L. L.; Wolucka, B. A.;

Naismith, J. H. *J. Am. Chem. Soc.* **2005**, *127*, 18309–18320.
14. (a) Davis, N.; Lee, N.; Glaser, L. *J. Biol. Chem.* **1972**, *247*, 5862–5866; (b) Deupree, J. D.; Wood, W. A. *J. Biol. Chem.* **1972**, *24*, 3093–3097; (c) Lee, L. V.; Poyner, R. R.; Vu, M. V.; Cleland, W. W. *Biochemistry* **2000**, *39*, 4821–4830; (d) Lee, L. V.; Vu, M. V.; Cleland, W. W. *Biochemistry* **2000**, *39*, 4808–4820.
15. Csuk, R.; Kühn, M.; Ströhl, D. *Tetrahedron* **1997**, *53*, 1311–1322.
16. (a) De la Pradilla, R. F.; Alhambra, A.; Castellanos, A.; Fernandez, J.; Manzano, P.; Montero, C.; Urena, M. C.; Viso, A. *J. Org. Chem.* **2005**, *70*, 10693–10700; (b) Fieser, L. F.; Fieser, M.. In *Reagents for Organic Synthesis*; Wiley: New York, 1967; Vol. 1, p 630.
17. Zhang, T.; Guo, K. P.; Qiu, L.; Shen, Y. *Synth. Commun.* **2006**, *36*, 1367–1372.
18. Bruce, I.; Fleet, G. W. J.; Girdhar, A.; Haraldsson, M.; Peach, J. M.; Watkin, D. J. *Tetrahedron* **1990**, *46*, 19–32.
19. Ayen, R. J.; Burk, J. H.; Greco, C. C. Preparation of insoluble metal alkoxides. U.S. US4681959, 1987.
20. Chervin, S. M.; Abada, P.; Koreeda, M. *Org. Lett.* **2000**, *2*, 369–372.
21. Walaszek, K.; Horton, D.; Ekiel, I. *Carbohydr. Res.* **1982**, *106*, 193–201.
22. Nishimura, Y.; Adachi, H.; Satoh, T.; Shitara, E.; Kakamura, H.; Kojima, F.; Takeuchi, T. *J. Org. Chem.* **2000**, *65*, 4871–4882.
23. (a) Muxfeldt, H.; Weigele, M.; Van Rheenen, V. *J. Org. Chem.* **1965**, *30*, 3573–3574; (b) Baker, S. R.; Crombie, L. *J. Chem. Soc., Chem. Commun.* **1980**, 213–214; (c) Crombie, L.; Games, D. E.; James, A. W. G. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2715–2724.
24. (a) Lopez, R.; Fernandez-Mayoralas, A. *J. Org. Chem.* **1994**, *59*, 737–745; (b) Nadein, O. L.; Kornienko, A. *Org. Lett.* **2004**, *6*, 831–834.
25. Bigorra, J.; Font, J.; Ochoa de Echagüen, C.; Ortuno, R. M. *Tetrahedron* **1993**, *49*, 6717–6728.
26. Lucero, C. G.; Woerpel, K. A. *J. Org. Chem.* **2006**, *71*, 2641–2647.
27. (a) Jensen, H. S.; Limberg, G.; Pedersen, C. *Carbohydr. Res.* **1997**, *302*, 109–112; (b) Mangholz, S. E.; Vasella, A. *Helv. Chim. Acta* **1995**, *78*, 1020–1035.