δ-Galactonolactone: Synthesis, Isolation, and Comparative Structure and Stability Analysis of an Elusive Sugar Derivative

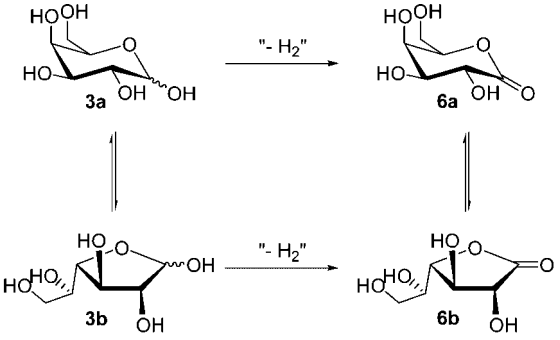
Matthias Bierenstiel[a] and Marcel Schlaf*[a]

Keywords: Carbohydrates / Homogeneous catalysis / Isomerization / Lactones

δ-D-Gluconolactone, δ-D-mannonolactone, and — for the first time — the thermodynamically unstable δ-D-galactonolactone have been prepared and isolated from DMF solution by oxidizing the corresponding sugars with Shvo's catalyst $[(C_4Ph_4CO)(CO)_2Ru]_2$ and a hydrogen acceptor. The preferred conformation of δ-D-galactonolactone in [D_6]DMSO solution has been determined by ^{1}H NMR spectroscopy experiments and DFT calculations to be $^4H_3$ and is compared to those of the previously established conformations of δ-D-gluconolactone ($^4H_3$) and δ-D-mannonolactone ($B_{2,5}$). The conformations of the lactones suggest an explanation for their relative rates of isomerization to their respective γ-D-lactones by an intramolecular mechanism.

Introduction

Lactones are the first oxidation products of reducing sugars, such as the naturally abundant hexoses, D-glucose (**1**), D-mannose (**2**), and D-galactose (**3**), and are formally obtained by the dehydrogenation of their hemiacetal function. In principle, as illustrated in Scheme 1 for D-galactose, two lactone isomers can be obtained: the 1,5-pyrano (δ) lactone or the 1,4-furano (γ) lactone. Again, in principle, either isomer can be formed by either the direct oxidation of the pyranose (**a**) or the furanose (**b**) form or by interconversion of the two lactone isomers following the initial oxidation of either form.



Scheme 1. Possible pathways for the oxidation of galactose (**3**) to the lactones **6a**,**b**

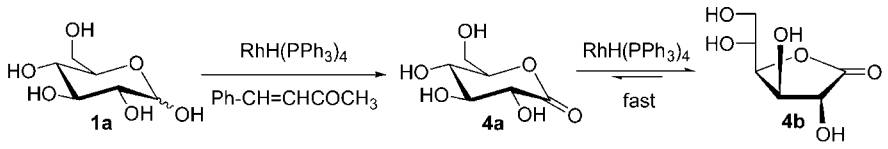
In solution, all three sugars are present predominantly as an anomeric mixture of their pyranose forms,[1] which also have been shown to be the actual oxidation substrates.[2,3] The lactones are typically synthesized by oxidation with bromine followed by fractional crystallization.[2,4] For glucose, the kinetic oxidation product, δ-D-gluconolactone (**4a**), is readily isolated,[5] but in all cases the γ-lactones, i.e., the furanose forms, are the thermodynamically stable oxidation products. δ-D-Gluconolactone has been fully characterized structurally by X-ray crystallography;[6] it is produced on an industrial scale by an enzymatic process and finds widespread use as food additive.[7,8] In aqueous solutions, the unproctected δ-lactones of D-mannose and D-galactose are reportedly much less stable against isomerization to the γ-form, but δ-mannonolactone has been isolated in moderate yield from a solution of calcium mannonate in aqueous oxalic acid by rapid fractional crystallization at low temperature.[9] In contrast, δ-galactonolactone has, to the best of our knowledge, never been isolated or structurally characterized,[10] but has been observed only as the transient immediate product of the enzymatic dehydrogenation by D-galactose dehydrogenase, during which — under the buffered aqueous reaction conditions required by the enzyme — it rapidly rearranges to the γ-lactone with k = 1.0 min^{-1}, which establishes $K_{eq}(\gamma/\delta) > 100$.[11]

An alternative method for the preparation of sugar lactones are transition metal-catalyzed transfer dehydrogenation reactions, which have been demonstrated for both protected and unprotected alditols as well as reducing sugars. 2,3,4-Protected L-*arabino* and L-*lxyono* lactones can be prepared from the corresponding α,ω-diols using *cis*-$[RuH_2(PPh_3)_4]$ as the catalyst and benzalacetone (*trans*-4-phenyl-3-buten-2-one) as the hydrogen acceptor.[12] Using the same hydrogen acceptor, Beaupère and co-workers em-

[a] Guelph-Waterloo Centre for Graduate Work in Chemistry (GWC)^2, Department of Chemistry and Biochemistry, University of Guelph,
Guelph, Ontario, Canada, N1G 2 W1
E-mail: mschlaf@uoguelph.ca

Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.

  DOI: 10.1002/ejoc.200300761



Scheme 2. Oxidation and isomerization of D-glucose to the δ- and γ-lactones

ployed [$RhH(PPh_3)_4$] as the catalyst in the dehydrogenation of a variety of C_4, C_5, and C_6 reducing sugars and unprotected alditols under mild conditions in DMF. Excellent yields of the corresponding γ-lactones were obtained using this method, but in no case were the corresponding δ-lactones isolated. NMR-scale reactions of D-glucopyranose in [D_7]DMF have established that the initial oxidation products are in fact the δ-lactones, but control experiments with the readily accessible δ-D-gluconolactone (see above) showed that, under the same reaction conditions, the rhodium catalyst isomerizes them rapidly to the thermodynamically more stable γ-form (Scheme 2).[13,14]

We have now discovered that Shvo's catalyst system, which is based on the dimeric ruthenium complex [$(C_4Ph_4CO)(CO)_2Ru]_2$ (**7**),[15,16] also efficiently catalyzes the dehydrogenation of D-gluco-, D-manno-, and D-galactopyranoses to the corresponding δ-lactones, but, with the exclusion of water, it does not effect the δ → γ isomerization of the kinetic to thermodynamic products.

For the first time, this process allows the isolation of the elusive δ-D-galactonolactone, the first oxidation product of one of the most abundant pyranoses in the biosphere, in useful quantities and its structural characterization and conformational analysis by NMR spectroscopy and DFT calculations.

Results and Discussion

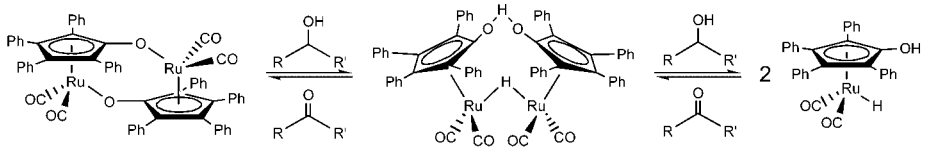
Rationale for the Selection of Catalyst

The complex [$(C_4Ph_4CO)(CO)_2Ru]_2$ (**7**) reacts with alcohols to give the hydrogen-loaded dimer [$(C_4Ph_4CO$-$HOCC_4Ph_4)(\mu$-$H)(CO)_4Ru_2$] (**8**) and the monomeric ruthenium hydride complex [$(C_4Ph_4COH)(CO)_2RuH$] (**9**) (Scheme 3), and it has also been shown to be an active catalyst for the dehydrogenation of primary alcohols to esters,[17] the disproportionation of aldehydes to esters,[16] and the oxidation of secondary alcohols to ketones.[18−20] All three complexes, as well as the coordinatively unsaturated, monomeric 16-electron complex [$(C_4Ph_4CO)(CO)_2Ru$] (**10**), have been shown to be part of the catalytic cycle, either as reactive intermediates (**9** and **10**) or catalyst resting states (**7** and **8**).[21]

The disproportionation of aldehydes to esters by the Shvo catalyst system follows the steps shown in Scheme 4,[16] i.e., it involves the formation of hemiacetals as intermediates. Therefore, we postulated that Shvo's catalyst would also be a highly effective catalyst for the oxidation of the hemiacetal function in reducing sugars, possibly under very mild conditions.

Scheme 4

This hypothesis was tested by a simple NMR-scale experiment: Shvo catalyst dimer **7** (0.02 mmol = 0.04 mmol ruthenium) was dissolved in [D_7]DMF (1.5 mL) to give a clear orange/yellow solution, the ^1H NMR spectrum of which displays only the previously reported signals of the phenyl protons of **7**.[15] Addition of α-D-glucose (0.2 mmol, five-fold excess with respect to ruthenium) to this solution at room temperature leads to an instantaneous color change to deep red. The ^1H NMR spectrum of this solution displays two singlets of 1:1 intensity at δ = 10.2 and −9.7 ppm, which we assign to the hydride ligand and hydroxy proton of the hydrogenated monomer complex **9**, respectively, along with the overlapping signals of a mixture of **1** and **4a**. Addition of benzalacetone (0.2 mmol) to the sample and heating at 100 °C for 6 h results in a color change back to orange/yellow and the disappearance of the peaks assigned to **9**, which indicates that the equilibrium depicted in Scheme 3 has shifted back to complex **7**. Because of the presence of the large amount of hydrogen acceptor, the other regions of the ^1H NMR spectrum of the resulting solution do not lend themselves to detailed analysis, but the ^{13}C NMR spectrum indicates, judging from the



Scheme 3

signals for the C-1 carbon atoms at δ = 172.0 and 175.7 ppm, respectively, that an 8:1 mixture of δ- and γ-gluconolactone had formed and no starting material remained, i.e., the sugar was converted quantitatively into the δ-lactone with only a small amount of subsequent isomerization to the γ-lactone occurring. In a control experiment, heating of a solution of authentic δ-gluconolactone in [D_7]DMF in the presence of **7** (10 mol%) at 60 °C for 2 h did not result in any measurable formation of γ-lactone. We conclude from these experiments that the Shvo system is indeed a viable hydrogen-transfer catalyst for the transformation of pyranose sugars into their corresponding δ-lactones, but — in contrast to [$Rh(PPh_3)_4$] — it does not, or only marginally does, catalyze their isomerization to the γ-lactones when it is in the hydrogen-deficient state (**7**) that is prevalent under oxidizing conditions.

Synthesis and Isolation of δ-Lactones

A systematic study of the reaction of various carbonyl-based hydrogen acceptors with **1a** as the substrate established that a solution of cyclohexanone in DMF results in optimized yields, reaction times, and γ:δ ratios.[22] Reaction and isolation procedures based on decantation and centrifugation, which were designed to minimize thermal stress on the material and, hence the γ:δ ratio, are detailed in the Exp. Sect. Table 1 summarizes isolated yields and γ:δ ratios of the lactones obtained from the oxidation of **1**, **2**, and **3** using these protocols (Methods A and B). Method A, which is undertaken at room temperature (21 °C), constitutes an empirically determined compromise between the reaction rate of oxidation and the rate of δ → γ isomerization and is optimized for the maximum amount of labile δ-lactones **5a** and **6a** present in the isolated material, rather than overall yield.

Method B indicates that the oxidations can, in fact, be carried out in a cyclohexanone suspension, without using DMF as solvent, by exploiting the marginal solubilities of the sugars in the acceptor itself. The method is an excellent one for the oxidation of **1**, but it is not practical for **2** and **3**, since the oxidation reactions at 21 °C in the absence of DMF are very slow, while the γ-lactones **5b** and **6b** dominate the product distribution at 45 °C.

NMR Spectroscopic and Conformational Analyses

^1H and ^{13}C NMR spectra of δ-galactonolactone (**6a**) isolated in > 95% isomeric purity (Table 1) were recorded in [D_6]DMSO at 400 and 100 MHz, respectively. A combination of COSY, HSQC, and APT techniques allowed us to assignment all the resonances unambiguously.[24] Table 2 lists the NMR spectroscopic data of all three δ-lactones, **4a**, **5a**, and **6a**, obtained in this study at 294 K and from the literature.[23] The slight differences in chemical shifts for **4a** and **5a** between those reported in the literature and those observed by us are due to the fact that the former were

Table 1. Oxidation of sugars with the Shvo catalyst system, using cyclohexanone as the hydrogen acceptor, at 45 °C

Entry	Sugar	Method[a]	Time [h]	*T* [°C]	Conversion [%][b]	Isolated yield [%]	δ/γ ratio of isolated product[c]
1	Glc	B	16 h	45	98	86	99.9:0.1
2	Man	A	87 h	21	91	41	94:6
3	Gal	A	87 h	21	92	54	93:7

[a] See Exp. Sect. [b] Determined by quantitative GC analysis of the cyclohexanol formed; estimated error ≤ 5%. [c] Determined by ^1H NMR spectroscopy.

Table 2. Comparison of the NMR spectroscopic data for δ-D-galactonolactone (**6a**) with those of δ-D-gluconolactone (**4a**) and δ-D-mannonolactone (**5a**) in [D_6]DMSO (Author: qui = quintuplett; o = octuplett).

^1H δ [ppm]	H-2	H-3	H-4	H-5	H-6	H-6′		OH-2	OH-3	OH-4	OH-6
Glc	3.79 dd	3.54 m	3.54 m	4.00 m	3.65 ddd	3.56 m		5.81 d	5.43 m	5.43 m	4.89 t
Glc (ref.)[a]	3.79 m	3.53 m	3.51 m	4.01 o	3.65 q	3.55 m		[b]	[b]	[b]	[c]
Man	4.45 dd	3.81 m	3.54 m	4.01 ddd	3.63 ddd	3.50 m		5.36 d	5.31 d	5.52 d	4.89 t
Man (ref.)[a]	4.93 dd	4.31 dd	4.03 dd	4.49 o	4.12 q	3.98 q		[b]	[b]	[b]	[c]
Gal	4.01 dd	3.71 ddd	3.89 qi (br)	4.21 t (br)	3.55 m	3.55 m		5.72 d	5.32 d	5.24 d	4.88 dd
J [Hz]	$^3J_{2,3}$	$^3J_{3,4}$	$^3J_{4,5}$	$^3J_{5,6}$	$^3J_{5,6'}$	$^2J_{6,6'}$	$^4J_{2,5}$	$^3J_{2,OH2}$	$^3J_{3,OH3}$	$^3J_{4,OH4}$	$^3J_{6,OH6}$
Glc (ref.)[a]	8.5[a]	7.5[a]	8.1[a]	2.5[a]	4.4[a]	−12.2[a]	0.5[a]	5.6	m	m	5.6
Man (ref.)[a]	3.4 [a]	1.2[a]	8.3[a]	2.6[a]	5.4[a]	−12.6[a]	0.5[a]	6.3	3.5	5.6	5.8
Gal	9.8	2.5	1.5	6.2[c]	6.2[c]	−11.0[c]	< 0.5	6.2	5.2	4.4	5.628; 5.738
^{13}C δ [ppm]	C-1	C-2	C-3	C-4	C-5	C-6					
Glc	172.0	72.5	67.9	73.9	81.4	60.2					
Glc (ref.)[a]	172.2	71.4	73.6	67.8	81.4	60.3					
Man	173.0	69.9	68.4	75.2	80.8	61.0					
Man (ref.)[a]	172.4	69.7	74.9	68.1	80.7	60.8					
Gal	172.6	69.9	71.8	69.9	79.8	67.6					

[a] Value as reported by Walaszek et al.[23] and measured in the presence of CF_3CO_2H. [b] Not reported by the authors because of the presence of CF_3CO_2H. [c] Determined from Spinworks 2.2 simulation.

recorded in the presence of CF_3COOH, which presumably also precluded the authors from reporting the shifts and coupling constants of the protons of the hydroxy functions. A spectrum of **6a** cannot be obtained in the presence of CF_3COOH because even traces of acids or bases lead to the rapid isomerization **6a** → **6b**.

The conformations of **4a** and **5a** in [D_6]DMSO have been determined previously by the calculation of dihedral bond angles using various forms of the Karplus equation.[23] This analysis suggested that the conformational equilibrium lies strongly in favor of a $^4H_3$(*gg*) half-chair for **4a**, essentially the same conformation as exists in the solid state, as determined by single-crystal X-ray crystallography,[6] and a $B_{2,5}$(*gg*) boat conformation for **5a**.

We hypothesize that the molecular shape of the individual δ-lactones in solution determines the pronounced differences in their stabilities with respect to the δ → γ isomerization and, therefore, we carried out a conformational analysis of **6a**, on the basis of the NMR spectroscopic data obtained, following the same rationale as Walaszek et al.[23] To verify the coupling constants obtained from the experimental spectrum and to extract coupling constants (as listed in Table 3) for the broad resonances for H-5 at δ = 4.21 ppm, H-4 at δ = 3.89 ppm, and the multiplet for H-6 and H-6′ at δ = 3.55 ppm, we simulated the spectrum of **6a** using the *Spinworks* program by Marat.[25]

Figure 1 displays the simulated (top) and experimental (bottom) spectra. The small additional peaks in the experimental spectrum represent small amount of the γ-lactone **6b**[26] formed on the time-scale of the NMR spectroscopy experiment.

With the experimental constants for $J_{2,3}$ and $J_{3,4}$ in hand, as well as the simulation-derived coupling constant for $J_{4,5}$, we determined the dihedral angles for these pairs of protons in **4a**, **5a**, and **6a** using the classical Karplus[27,28] and Altona−Haasnoot equations.[29] The latter takes into account the effect of the chemical nature of the substituents and their orientations relative to each other on the observed

Table 3. Calculated dihedral angles and coupling constants for δ-lactones **4a**, **5a**,[23] and **6a**

J_{xy}[a]	*J* [Hz] exp.	[°] X-ray	[°] calcd. by G98	[°] calcd. from *J* Karplus	[°] calcd. from *J* Altona[b]	*J* [Hz] calcd. from X-ray [°] Karplus	*J* [Hz] calcd. from X-ray [°] Altona	*J* [Hz] calcd. from G98 [°] Karplus	*J* [Hz] calcd. from G98 [°] Altona
Glu									
2,3	8.5	167.3	176.7	164.0	147.0	8.8	9.7	9.2	9.5
3,4	7.5	178.3	175.7	154.8	164.0	9.2	8.8	9.2	8.6
4,5	8.1	170.9	176.8	159.9	158.0	9.0	8.9	9.2	9.1
Man									
2,3	3.4	n/a	45.7	49.0	53.0	n/a	n/a	3.9	4.3
3,4	1.2	n/a	135.9	113.0	81.0	n/a	n/a	4.6	3.7
4,5	8.3	n/a	177.7	162.0	160.0	n/a	n/a	9.2	9.1
Gal									
2,3	9.8	n/a	176.4	n/a[c]	168.8[d]	n/a	n/a	9.2	9.6
3,4	2.5	n/a	54.2	55.0	57.0	n/a	n/a	2.6	2.8
4,5	1.5	n/a	35.0	63.0	78.0	n/a	n/a	5.4	6.3

[a] Geometry- and frequency-optimized using the *m*PW1PW91 method with the 6−31(d,p) basis set and a reaction-field solvent model in DMSO. [b] Calculated numerically. [c] Mathematically not defined. [d] Mathematically the maximum possible value equivalent to *J* = 9.7 Hz.

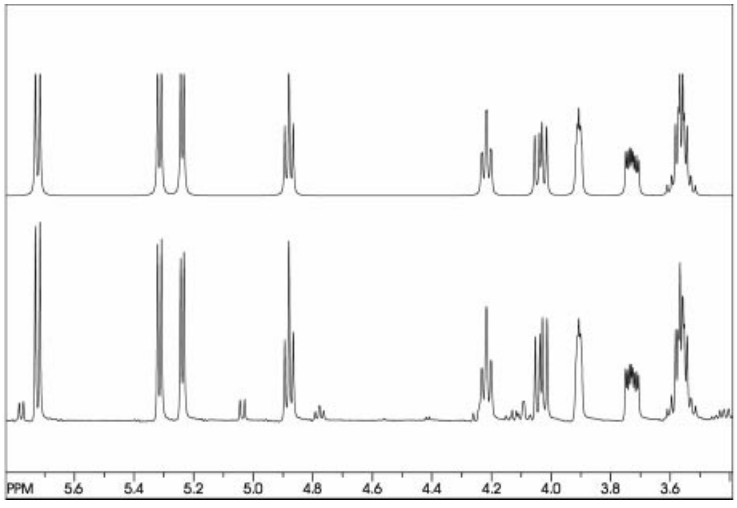


Figure 1. Simulated and experimental ^{1}H NMR spectra of **6a**, displaying the range between δ = 3.4 and 5.8 ppm, using TMS as an internal standard

coupling constants through purely empirically derived, position-dependent substituent constants, rather than group electronegativities.[30] While the Altona−Haasnoot equation is mathematically uniquely defined only to express *J* as a function of the associated dihedral angle φ, values for φ can readily be determined as a function of the observed value of *J* through a numeric analysis using standard spreadsheet programs.

We also determined the energy-minimum structures of the lactones through Gaussian 98/03 calculations using the *m*PW1PW91 method[31] with the 6−31(d,p) basis set and a continuous solvent sphere model in DMSO as implemented in the Gaussian 98 and 03 programs.[32−34] With these geometries we carried out the "reverse" calculations, i.e., we determined the coupling constants *J* for from the dihedral angles that define the geometry of the pyranose ring. Table 3 summarizes this data for all three δ-lactones.

Making the reasonable assumption that the solid-state structure of **4a** is the true energy minimum of the pyranose ring, or is very close to it, the X-ray data for **4a** provides a reference point for a comparison and assessment of the quality of the angles obtained from the Karplus and Altona−Haasnoot analyses on one hand and the quantum mechanical calculations on the other. The data in Table 3 indicate that the dihedral angles obtained from the DFT calculation provide a better overall fit to the X-ray structure than the ones calculated from the NMR spectroscopic coupling constants, which indicates either the limitations of the Karplus and Altona methods or, as suggested by Walaszek et al.,[23] an equilibrium with other conformers of the lactone in solution or — even more likely — both. By extension, we postulate with high confidence that the same situation is true for the structures of **5a** and **6a**, i.e., the geometries obtained from the DFT calculation represent energy minima that, in solution, are in equilibrium with other minor conformers whose presence impacts the observed values of *J* and, hence, the dihedral angles calculated from them. Figure 2 presents the geometries of all three δ-lactones as determined by DFT calculations.

The DFT calculations recreate the $^4H_3$ conformation for **4a** and the $B_{2,5}$ conformation for **5a** determined previously by a Karplus analysis[23] and result in a $^4H_3$ conformation for **6a** that is congruent with the combined results of the Karplus and Altona analyses for this compound. The comparatively large discrepancies between the DFT and NMR spectroscopy results for the 3,4 dihedral angle in **5a** and the 4,5 dihedral angle in **6a** point to the contribution in solution of a twist conformer for **5a** and a somewhat more-flattened half-chair for **6a**, but do not change the overall geometric preference of the pyranose rings. The top view of the lactones (bottom row of structures in Figure 2) reveals an ordered arrangement of the hydroxy functions in **4a** and **6a** and, to a lesser extent, in **5a** that — at least in the reference frame of the solvent model used — suggests the presence of a weak intramolecular hydrogen bond network at the static energy minimum determined by the DFT calculation. A similar situation is found for the γ-lactones **4b**, **5b**, and **6b** (not shown). Since the energies involved in such bonds are on the order of 2−4 *RT* (≈ 5−10 kJ/mol), the situation must be more dynamic in [D_6]DMSO solution and only a small portion of the lactones will display this type of network. SIMPLE (i.e., H/D isotope exchange) and variable-temperature NMR spectroscopy studies on monosaccharides conducted by Angyal, Christofides, and Vasella and co-workers[35−37] have suggested that at any given time only 5−10% of the sugar is internally hydrogen bonded with other C−O−H and $C^5-C^6H_2-O-H$ rotamers dominating, whose energies are accessible by thermal molecular motion at 294 K. This hypothesis explains why the DFT minimum energy structures of **4a**, and probably **6a**, do not represent the *gg* conformation proposed to dominate for the C^5-C^6 bond.[23] We cannot, however, make a definite statement for **6a**, as the reported coupling constant, $J = 6.2$ Hz, is derived from the simulation, as are the values of both $J_{5,6}$ and $J_{5,6'}$. The true constants could be significantly different, but we are unable to extract them from the current data, as the signal for H-5 at δ = 4.21 ppm is a broad pseudo-triplet and the simulated spectrum already provides an excellent match with the second-order multiplet at δ = 3.55 ppm for H-6/H6′, i.e., the amount of information obtainable from the experimental spectrum and the simulation is exhausted.

In summary, the DFT-derived structures, as well as the comparison of the NMR spectroscopic coupling constants between **4a**, **5a**, and **6a**, suggest that the δ-galactonolactone (**6a**) assumes the same $^4H_3$ conformation as the δ-gluconolactone (**4a**), a fact intimately related to its rapid isomerization to the γ-isomer (**6b**) that, to date, had precluded its structural characterization.

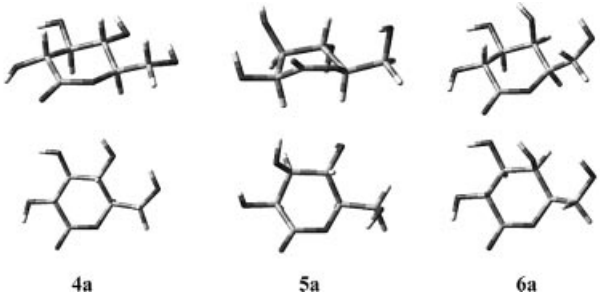


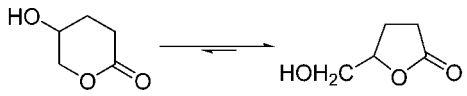
Figure 2. "Side" and "top" views of the minimum energy conformations of δ-gluco (**4a**), δ-manno (**5a**), and δ-galactono (**6a**) lactones determined by DFT [*m*PW1PW91/6−31(d,p)] calculations

Isomerization Reactions

Thermodynamic Considerations

Considering the parent compounds, γ-butyrolactone and δ-valerolactone, as models, the pronounced greater stability of the γ-lactones over the δ-lactones can be rationalized on the basis of a difference in ring strain between the pyrano and furano lactones, which, uniquely for alicyclic compounds, is larger for the six- than for the five-membered ring.[38] Matching the conformational behavior of sugar lactones **4a** and **6a**, δ-valerolactone also has a high preference

for the half-chair conformation, while γ-butyrolactone exists as a single conformer. The ring strains in γ-butyrolactone and δ-valerolactone have been determined to be 36.8 and 46.8 kJ/mol, respectively, resulting in a value of K_{eq} = [γ]/[δ] of ca. 60 on the basis of the release in ring strain alone. Similar behavior has been inferred in the equilibrium of the model compounds 4-hydroxy-δ-valerolactone and 4-hydroxymethyl-γ-butyrolactone (Scheme 5).[39,40] In addition, there is an unfavorable steric interaction for the lactones **4a** and **6a** between the equatorial substituent on C-2 and the ester functionality in the $^4H_3$ conformation adopted by these lactones (Figure 2).[3]



Scheme 5

The actual equilibrium γ:δ ratios of the three lactones in dry [D$_6$]DMSO were determined by averaging the integrals of their sharp and well-separated hydroxy group resonances in their ^{1}H NMR spectra. To ensure that equilibrium had been attained, individual samples were heated to 333 K for several days (**4a/b**, **6a/b**) or weeks (**5a/b**) and then cooled slowly to 294 K before the spectra were acquired. Table 4 lists the experimentally determined ratios and free enthalpies calculated by van't Hoff's equation for the δ→γ isomerization. It should be noted that the experimentally determined isomer distributions presented here cannot be compared directly with any previously published data,[3,11,41] since all of them were obtained in (buffered) aqueous solutions and, thus, include hydrolysis to the free aldonic acids, which is not observed in the dry DMSO medium employed in our study.

Table 4. Experimental γ:δ ratios of the lactones in DMSO at 294 K

Lactone (γ:δ ratio)	Experimental (Δ +/− 2%)[a]	$\Delta G_{exp.}$ (δ→γ) [kJ/mol][b]
Gluconolactone	89:11	−5.1
Mannonolactone	54:46	−0.4
Galactonolactone	100:0	< −9.5[c]

[a] By integration of signals in ^{1}H NMR spectra. [b] By $\Delta G = -RT \ln K$. [c] Based on an assumed maximum integration error for NMR spectroscopy of ± 2%, which results in γ:δ = 98:2.

Mechanistic Considerations

The δ→γ isomerizations of the lactones in dry [D$_6$]DMSO (water content << 0.01 equiv./lactone, as determined by ^{1}H NMR spectroscopy) follow simple first-order kinetics. By dissolving the δ-lactones (10 mg) in [D$_6$]DMSO (0.6 mL), we observed rate constants of $k_{obsd} = 1.41 \times 10^{-4}$ s^{-1} and $k_{obsd.} = 1.73 \times 10^{-4}$ s^{-1} at 333 K for **4a** and **6a**, respectively, but **5a** isomerizes too slowly for k to be measured reliably by ^{1}H NMR spectroscopy. Experimentally, the equilibrium distributions listed in Table 4 are reached within ca. 7 h for **6a/b** and ca. 10 h for **4a/b** (i.e., seven half-lives each), while **5a/b** requires weeks to attain its equilibrium. Overall, the isomerization process in [D$_6$]DMSO is orders of magnitudes slower than the value of k = 1 min^{-1} = 1.67×10^{-2} s^{-1} observed for **6a** in aqueous solution buffered at pH = 6.8,[11] which suggests that, in aqueous solution, the isomerization is susceptible to the general acid/base catalysis that is also observed in the hydrolysis of the lactones and precludes the isolation of **6a** from aqueous solution.[42] In addition, the relative rates of isomerization for the lactones **4a** and **5a** observed by us in [D$_6$]DMSO are opposite to those previously noted in the literature. This finding probably occurs because the only known previous preparation of **5a** was carried out by dissolving calcium mannonate in excess aqueous oxalic acid solution, i.e., under conditions of general acid catalysis, and this reaction probably follows a mechanism involving the free aldonic acid, which, thus, provides an alternative rapid isomerization pathway.[9,43]

The fact that there is essentially no water and no free acid present in our solutions and that first-order kinetics are observed immediately suggest an intramolecular δ→γ rearrangement mechanism involving a nucleophilic attack of OH-4 on the carbonyl carbon atom as originally proposed for **4a/b** by Jermyn.[41] In addition, Ueberschaer et al. have determined that — even in buffered aqueous solution — the δ→γ rearrangement of **6a** to **6b** is faster than the hydrolysis of **6a** to free galactonic acid.[11] Figure 3 depicts the three ester hemiketals that can be postulated to occur as intermediates on the reaction coordinate to effect the change from the δ-1,5 to the γ-1,4 linkage.

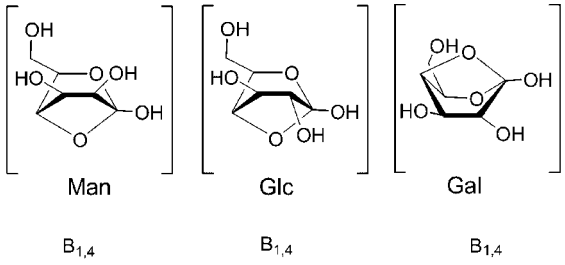


Figure 3. Structures of the proposed bicyclic intermediates in the γ → δ isomerization reactions of mannono-, glucono-, and galactonolactone

Starting from the known dominant conformations of **4a** and **5a**[23] and the newly determined conformation of **6a** (this work, cf. Table 3), and applying the *principle of least molecular motion* and assuming that the formation of the bicyclic intermediates is the rate-determining elementary step, it is then evident that the experimentally observed order of isomerization rates, $k_{Gal} > k_{Glu} >> k_{Man}$, is a direct consequence of the relative structural similarities or dissimi-

larities between the postulated ester hemiketal intermediates and the native conformation of the δ-lactones in [D_6]DMSO. The $^4H_3$ conformation of **6a** (Figure 2) is structurally most closely related to that of the $B^{1,4}$ conformation of the intermediate requiring motion of only the C(1)=O group [and, to a lesser extent, the C(3)−OH-3 group] from below to above the plane defined by the C(2)−C(5)−O atoms, i.e., the δ-galactonolactone is structurally "set-up" to attain the geometry required to isomerize to the γ-form, which results in a low activation barrier for this process. Starting from the same $^4H_3$ conformation, the equatorial position of the OH-4 unit in **4a** requires that the 1,4-linkage is established below the C(2)−C(5)−O plane to give a $B_{1,4}$ conformation, which requires motion of both the C(1) and C(4) centers and, thus, leads to a higher activation barrier and a slower rearrangement. In comparison, an even-more-extensive molecular motion is required for the $B_{2,5} \rightarrow B_{1,4}$ conformational change that **5a** has to undergo to establish the 1,4-linkage. In addition, there is an unfavorable *cis* interaction between the OH-2 and OH-3 groups present in the ester hemiketal intermediate that we also assume to be present in the actual transition state of the similar structure that further raises the activation barrier and results in the comparatively very slow rate of the **5a** → **5b** rearrangement in [D_6]DMSO.

Conclusions

δ-Galactonolactone can be prepared and isolated from DMF solutions by transfer dehydrogenating D-galactopyranose using Shvo's catalyst and cyclohexanone as the hydrogen acceptor. In [D_6]DMSO, δ-galactonolactone exists predominantly in the $^4H_3$ conformation, a structure closely related to a bicyclic ester hemiketal postulated to be the intermediate in its rearrangement to the corresponding γ-lactone, which explains its instability against this isomerization. In comparison, δ-D-glucono and δ-D-mannonolactone are much more stable against this isomerization since their native conformations do not, or less closely, resemble the shapes of their corresponding ester hemiketal intermediates.

Experimental Section

NMR spectra (400 MHz, ^1H; 100 MHz, ^{13}C) were measured in [D_6]DMSO with DMSO (δ = 2.49 ppm, ^1H; δ = 39.5 ppm, ^{13}C) and deuterated chloroform (δ = 7.24 ppm, ^1H; δ = 77.0 ppm, ^{13}C) as internal references. DMSO was stored inside a dry-box under Ar over 4-Å activated molecular sieves. For variable-temperature measurements, the spectrometer temperature controller unit was calibrated using a bimetal thermometer directly inserted into the probe. The γ:δ ratios of the lactones were determined by integration of their signals in their ^1H NMR spectra. Simulations of NMR spectra were carried out using the SpinWorks program (Version 2.2).[25] DFT calculations were carried on a PC using the Gaussian 98 and Gaussian 03 suite of programs. No imaginary frequencies were observed in the calculations. GC analyses were performed on a PEG column (30 m × 0.25 mm). The GC FID was calibrated for cyclohexanol using naphthalene as an internal standard. All experimental preparations were conducted in a dry-box under Ar and/or using usual Schlenk technique on a vacuum line. Acetone, cyclohexanone, and *n*-heptane were dried by distillation under Ar from anhydrous $CaCl_2$, anhydrous $MgSO_4$, and potassium, respectively, and then degassed and stored under Ar. DMF was dried over BaO and distilled under reduced pressure, and then it was degassed and stored under an Ar atmosphere. Cyclohexanol, cyclohexanone, D-galactose, D-glucose, D-mannose, naphthalene, tetraphenyl-cyclopentadienone, acetone, chloroform, *n*-heptane, and $Ru_3(CO)_{12}$ were purchased from commercial sources. All chemicals were reagent grade and used as obtained without further purification unless otherwise noted. Shvo's catalyst (**7**) was prepared according to literature procedures.[15] The best results were obtained when the synthesis was carried out inside the dry-box. Oil-pump vacuums applied in the isolation of the lactones were ≤ 30 mTorr.

General Procedure A — Oxidation of D-Galactose: D-Galactose (396 mg, 2.20 mmol), Shvo's catalyst (1.25 mol %, 30 mg), dry cyclohexanone (20 mL), and dry DMF (10 mL) were combined in a 50-mL Schlenk flask under Ar. Naphthalene (50 mg) was added as an internal GC standard. The reaction was stirred at 21 °C and monitored by GC by following the appearance of a peak for cyclohexanol. Once the reaction was complete, the mixture was transferred to a 50-mL one-necked flask and the solvents were evaporated under an oil-pump vacuum at ≤ 45 °C. Anhydrous acetone (10 mL) was added to the remaining solids and then the mixture was sonicated for 1 min, transferred to a centrifuge tube, and centrifuged at 2500 rpm for 3 min. The supernatant solution was carefully removed using a Pasteur pipette. The acetone extraction was repeated, usually three times, until the supernatant solution was colorless. The residual white solid was dried under an oil-pump vacuum to constant weight. Isolated yield: 206.4 mg (54%). The reaction can be performed at one- or two-thirds of this scale and carried out analogously for α-D-mannose. See text for the γ/δ ratio.

General Procedure B — Oxidation of D-Glucose: D-Glucose (132 mg, 0.73 mmol), Shvo's catalyst (1.25 mol %, 10 mg), and dry cyclohexanone (10 mL) were combined in a 15-mL Schlenk tube under an Ar atmosphere. Naphthalene (50 mg) was added as an internal GC standard. The suspension was stirred at 45 °C and monitored by GC by following the appearance of a peak for cyclohexanol. After completion of the reaction, the mixture was transferred to a centrifuge tube and centrifuged at 2500 rpm for 1 min. The supernatant orange solution was carefully removed using a Pasteur pipette and the residual white solid was dried under an oil-pump vacuum. In cases where the solids were slightly colored, anhydrous acetone (10 mL) was added and the extraction procedure repeated. See the text for isolated yields and γ/δ ratios.

General Procedure for the NMR Spectroscopy Experiments: Sugar lactone (10 mg) was dissolved in [D_6]DMSO (0.6 mL; stored under inert amosphere over activated 4-Å molecular sieves). The ^1H NMR spectra were recorded at the desired temperature after allowing the solution to equilibrate for approximately 10 min at each temperature.

Supporting Information (see also the footnote on the first page of this article): A comprehensive collection of ^1H and ^{13}C NMR spectroscopic data (COSY, HSQC), with images of spectra for all lactones. Atomic-coordinate data from the Gaussian 98/03 DFT calculations for all lactones (total 65 pages).

Acknowledgments

We are grateful to Professors John D. Goddard and Michael K. Denk for many helpful discussions and interventions during the DFT study and are indebted to Valerie Robertson and Leslie Fowley for assistance with the NMR spectroscopy studies. Funding for this work was provided by NSERC Canada, the Canadian Foundation for Innovation, the Ontario Innovation Trust Fund, VARIAN Canada Inc., and DuPont Canada through an ATE grant. M.B. thanks the Ernst Schering Research Foundation, Berlin, Germany, for a doctoral fellowship.

[1] P. Collins, R. Ferrier, *Monosaccharides*, John Wiley & Sons, Toronto, **1995**.
[2] H. S. Isbell, C. S. Hudson, *Bureau of Standards Journal of Research* **1932**, *8*, 327.
[3] B. Capon, *Chem. Rev.* **1969**, *69*, 407.
[4] H. Kiliani, *Ann.* **1880**, *205*, 182.
[5] H. S. Isbell, H. L. Frush, *Methods in Carbohydrate Chemistry*, Academic Press, New York, **1962**, vol. 2, p. 16.
[6] M. L. Hackert, R. A. Jacobson, *J. Chem. Soc., Chem. Commun.* **1960**, 1179.
[7] J. A. Kent, *Riegel's Handbook of Industrial Chemistry*, Chapman & Hall, Toronto, **1992**, p. 945.
[8] Kirk-Othmer, *Encyclopedia of Chemical Technology*, John Wiley & Sons, Toronto, **1998**.
[9] H. S. Isbell, H. L. Frush, *Bureau of Standards Journal of Research* **1933**, *11*, 649.
[10] A search of the CA database revealed no synthetic procedures or structural data for this compound.
[11] K.-H. Ueberschär, E.-O. Blachnitzky, G. Kurz, *Eur. J. Biochem.* **1974**, *48*, 389.
[12] M. Saburi, Y. Ishii, N. Kaji, T. Aoi, I. Sasaki, S. Yoshikawa, Y. Uchida, *Chem. Lett.* **1989**, 563.
[13] I. Isaac, I. Stasik, D. Beaupère, R. Uzan, *Tetrahedron Lett.* **1995**, *36*, 383.
[14] I. Isaac, G. Aizel, I. Stasik, A. Wadouachi, D. Beaupère, *Synlett* **1998**, 475.
[15] M. J. Mays, M. J. Morris, P. R. Raithby, Y. Shvo, D. Czarkie, *Organometallics* **1989**, *8*, 1162.
[16] N. Menashe, Y. Shvo, *Organometallics* **1991**, *10*, 3885.
[17] Y. Blum, Y. Shvo, *Isr. J. Chem.* **1984**, *24*, 144.
[18] G.-Z. Wang, U. Andereasson, J. E. Bäckvall, *J. Chem. Soc., Chem. Commun.* **1994**, 1037.
[19] M. L. S. Almeida, M. Beller, G.-Z. Wang, J.-E. Bäckvall, *Chem. Eur. J.* **1996**, *2*, 1533.
[20] O. Pàmies, J.-E. Bäckvall, *Chem. Eur. J.* **2001**, *7*, 5052.
[21] C. P. Casey, S. W. Singer, D. R. Powell, R. K. Hayashi, M. Kavana, *J. Am. Chem. Soc.* **2001**, *123*, 1090.
[22] See Supporting Information.
[23] Z. Walaszek, D. Horton, I. Ekiel, *Carbohydr. Res.* **1982**, *106*, 193.
[24] See Supporting Information for images of spectra for all lactones.
[25] K. Marat, Winnipeg, University of Manitoba, **2003**.
[26] Z. Walaszek, D. Horton, *Carbohydr. Res.* **1982**, *105*, 131.
[27] M. Karplus, *J. Chem. Phys.* **1959**, *30*, 11.
[28] M. Karplus, *J. Am. Chem. Soc.* **1963**, *85*, 2870.
[29] C. Altona, R. Francke, R. d. Haan, J. H. Ippel, G. J. Daalsmans, A. J. A. W. Hoekzema, J. v. Wijk, *Magn. Reson. Chem.* **1994**, *32*, 670.
[30] The values of λ_i derived by Altona et al. were: OH = 1.34, C(=O)R = 0.51, OC(=O)R = 1.17, and CH(OH) ≈ CH_3. See ref.[29].
[31] C. Adamo, V. Barone, *J. Chem. Phys.* **1997**, *108*, 664.
[32] J. G. Kirkwood, *J. Chem. Phys.* **1934**, *2*, 351.
[33] L. Onsager, *J. Am. Chem. Soc.* **1936**, *58*, 1486.
[34] M. W. Wong, M. J. Frisch, K. B. Wiberg, *J. Am. Chem. Soc.* **1991**, *113*, 4776.
[35] J. C. Christofides, D. B. Davies, *J. Chem. Soc., Perkin Trans. 2* **1987**, 97.
[36] S. J. Angyal, J. C. Christofides, *J. Chem. Soc., Perkin Trans. 2* **1996**, 1485.
[37] B. Bernet, A. Vasella, *Helv. Chim. Acta* **2000**, *83*, 995.
[38] J. M. Brown, A. D. Conn, G. Pilcher, M. L. Leitao, Y. Meng-Yan, *J. Chem. Soc., Chem. Commun.* **1989**, 1817.
[39] K. B. Wiberg, R. F. Waldon, *J. Am. Chem. Soc.* **1991**, *113*, 7697.
[40] R. J. Abraham, A. Ghersi, G. Petrillo, F. Sancassan, *J. Chem. Soc., Perkin Trans. 2* **1997**, 1279.
[41] M. A. Jermyn, *Biochim. Biophys. Acta* **1960**, *37*, 78.
[42] Y. Pocker, E. Green, *J. Am. Chem. Soc.* **1973**, *96*, 113.
[43] Isbell and Frush have noted that "the δ-(mannono)-lactone is difficult to purify as it is easily converted into γ-lactone". See ref.[5] or ref.[9]

Received December 4, 2003

