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Spectroscopic, Crystallographic and Computational Studies of the Formation and Isomerization of Cyclic Acetals and Ketals of Pentonolactones[1]

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Abstract: The different reactivities of D-ribonolactone, L-arabinonolactone, D-xylonolactone, D-lyxonolactone and 2-deoxy-D-ribonolactone toward benzaldehyde and acetone in acidic media, were examined. The reactions involved complex equilibria and were investigated with extensive ^{13}C NMR studies as well as X-ray crystallographic analysis of selected products. Molecular mechanics (MM2) and semiempirical (PM3 and AM1) calculations of some derivatives were carried out in order to facilitate structural and conformational assignments. The differences in reactivity observed for the reactions of D-pentono-1,4-lactones with benzaldehyde and acetone are rationalized in terms of their structural and conformational features.

Introduction

The concept of using carbohydrates as chiral templates is widely used in organic synthesis.[2] Manipulations involving pyranose or furanose sugars, however, suffer from the tedious protection and deprotection[3, 4] of the anomeric center and the difficulty in performing regio- and stereoselective transformations among the various hydroxyl groups.[5, 6] To overcome these problems several pentono-1,4-lactones, particularly D-ribono-1,4-lactone,[7, 8] have often been utilized as starting materials in natural product syntheses. Although there have been many studies on the formation of cyclic acetal and ketal derivatives of these aldonolactones,[9-14] it is not always possible to predict which structure will prevail due to the various equilibria that occur under different reaction conditions with kinetic or thermodynamic control.[7] In addition to variations in the regioselectivity of the reaction, interconversion between the 1,4- and 1,5-lactones is also observed.

In order to understand the role of conformationally stable lactones in the formation of cyclic acetals and ketals, we recently examined these reactions for D-ribono-1,4-lactone and 2-deoxy-D-ribono-1,4-lactone.[7] As a continuation of this work, we report herein a detailed and systematic investigation of the reactions and interconversions of several aldonolactones with benzaldehyde and acetone under several reaction conditions.

Results and Discussion

Preparation of Pentonolactones. The acetalization and ketalization of the following five pentonolactones (Figure 1) were investigated: D-ribono-1,4-lactone (**1**), L-arabinono-1,4-lactone (**2**), D-xylono-1,4-lactone (**3**), D-lyxono-1,4-lactone (**4**), and 2-deoxy-D-ribono-1,4-lactone (2-deoxy-D-*erythro*-pentono-1,4-lactone) (**5**). Compounds **1** and **3** were obtained commercially **2**, **4** and **5** were prepared by aqueous bromine oxidation of L-arabinose, D-lyxose, and 2-deoxy-D-ribose, respectively.[15]

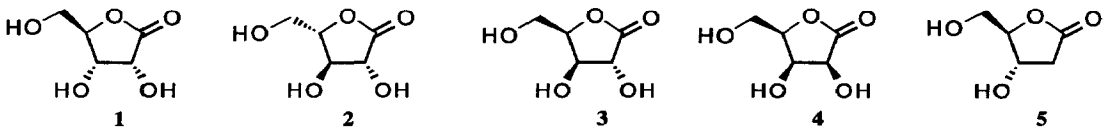


Figure 1

Conformations of Pentonolactones. The conformations and dynamics of furanose rings have been studied extensively due to their importance to the structure and function of nucleic acids in biological systems. When the furanose anomeric sp^3 carbon is replaced by an sp^2 carbon, as in the case of aldono-1,4-lactones, the ring conformations and dynamics are changed considerably due to the near-planarity of the carbonyl group.[16] The conformations of aldono-1,4-lactones have been investigated by their chiroptical properties,[17-22] as well as by systematic NMR studies[23-26] in solution and by X-ray diffraction studies in the crystalline state.[27-32] The 1,4-lactone ring exists in one planar (P) and four envelope (E_3, ^3E, E_4, ^4E) forms because of the structural constraints of the planar OC(O) group.[16] Forms E_3 and ^3E are generally more stable than E_4 and ^4E, while the E_3-^3E interconversion properly describes the lactone ring dynamics (Figure 2).[24, 25]

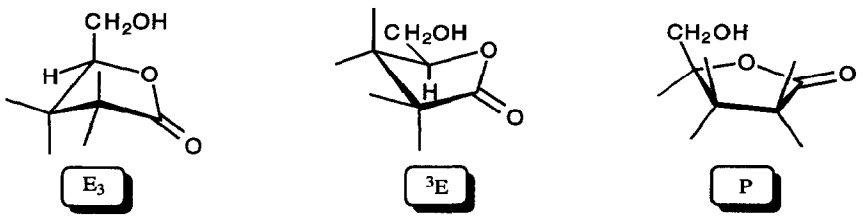


Figure 2

Another widely studied feature of carbohydrate conformation is the rotation of the primary hydroxymethyl group.[33] Although all three possible *gauche* configurations are known, the preferred conformation is often the *gauche-gauche* (GG) rather than the *gauche-trans* (GT) or the *trans-gauche* (TG) conformations (Figure 3).[24, 25] The preferred C_4-C_5 rotamer has been attributed to several factors, including the *gauche* effect, 1,3-diaxial interactions, hydrogen bonding and solvation.[33]

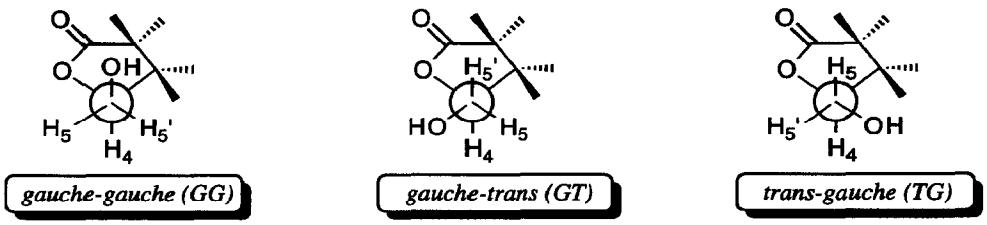
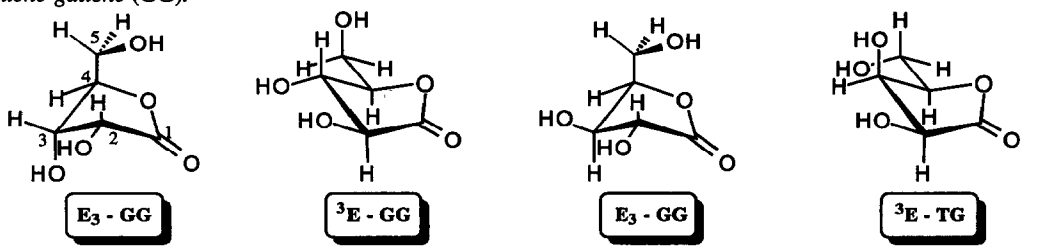


Figure 3

Significant conformational differences are observed among the various isomeric aldono-1,4-lactones, resulting from substituent effects. The preferred conformations in solution of four common D-aldono-1,4-lactones, as suggested by an early NMR study[24] are shown in Figure 4. A recent conformational analysis of substituted aldono-1,4-lactones using coupling constants and MM2 calculations[34] have also indicated that a C-2 hydroxyl group shows a general preference for the equatorial position while C-3 or C-4 groups generally preferred the axial positions. Although the X-ray structure of D-ribono-1,4-lactone[32] showed a *gauche-trans* (GT) disposition of the exocyclic CH_2OH group, it was concluded that in solution[24] the predominant form is the *gauche-gauche* (GG).



D-Ribono-1,4-lactone D-Arabino-1,4-lactone D-Xylono-1,4-lactone D-Lyxono-1,4-lactone

Figure 4

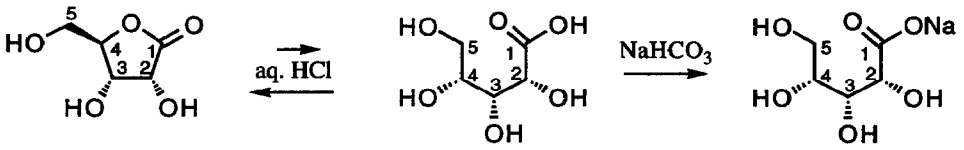
From the above analysis is apparent that even a single stereochemical change in these molecules results in a dramatic change in conformational preferences, which complicates structural assignments by the usual NMR methods. An even greater structural change occurs when these aldonolactones are hydrolyzed to the aldonic acids or are isomerized to the aldono-1,5-lactones. Since both of these transformations can take place during the conversion of these compounds to their acetals or ketals, these reactions often give products whose structures are difficult to assign unequivocally.

Hydrolysis of Pentonolactones. Before attempting to understand and rationalize the formation and behavior of acetals derived from D-pentono-1,4-lactones, we examined the equilibrium compositions of D-pentonolactones and D-pentonic acids in aqueous acidic media. Horton and Walaszek in their elegant and definitive investigations of the conformations of D-pentono-1,4-lactones in solution had already examined the equilibrium compositions of D-pentonolactones and D-pentonic acids in D_2O.[24] However, as their data was obtained for specific concentrations and temperatures in D_2O, and equilibrium compositions could vary with changes in these parameters and the acidity of the solution, it was necessary to reexamine these equilibria under conditions that would simulate those of acetal formation.

The equilibria studies were carried out by dissolving the lactones in deuterium oxide and adding 12 N hydrochloric acid to the solutions. The solutions were allowed to stand at 22 °C for a period of time (19 h for D-ribono, 20 h for D-arabinono, 39 h for 2-deoxy-D-ribono, 44 h for D-lyxono and D-xylono). After this time, their ^{13}C NMR spectra and the ratios of lactone to acid were examined. Another ^{13}C NMR study was carried out later to verify that the ratio of lactone to acid had remained unchanged. The equilibria compositions were also calculated from peak integrations of the protons in the ^1H NMR spectra. The formation of the acids was confirmed by converting them to their corresponding salts with sodium bicarbonate and monitoring the salt formation by ^{13}C NMR. The results obtained were comparable to those reported previously, notwithstanding the differences in conditions. As found by the previous authors,[24] only one example of a 1,5-lactone, D-xylono-1,5-lactone, was observed. It is also the only case in which the equilibrium favors the acid.

Hydrolysis of D–Ribono–1,4–lactone (1). The equilibrium study of D-ribono-1,4-lactone in aqueous acidic media was conducted at 22 °C, and is shown in Scheme I. A quantitative equilibrium composition ratio of the lactone and its corresponding acid in aqueous acidic medium was obtained from the ^1H NMR spectrum of D–ribono–1,4–lactone in deuterium oxide with concentrated HCl. The equilibrium composition of the two components was calculated from the peak integrations of their protons. The percentage obtained was 76% of lactone and 24% of acid, respectively. The ^{13}C NMR chemical shifts are shown in Table I.

Scheme I



1 **6** **7**

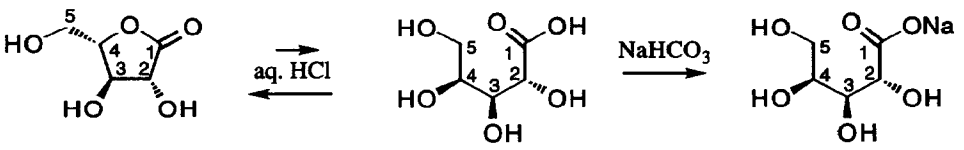
Table I. The ^{13}C NMR Chemical Shifts of **1**, **6** and **7** in D_2O.

	1, δ (ppm)	**6**, δ (ppm)	**7**, δ (ppm)
C_1	178.37	175.04	178.21
C_2	69.56	72.65[a]	73.55[a]
C_3	69.80	71.75[a]	73.31[a]
C_4	86.60	70.44[a]	71.58[a]
C_5	60.52	62.92	62.93

[a] Carbon assignments are tentative.

Hydrolysis of L–Arabinono–1,4–lactone (2). The equilibrium study of L–arabinono–1,4–lactone in aqueous acidic media was conducted at 22 °C, and is shown in Scheme II. A ^1H NMR spectrum of L–arabinono–1,4–lactone in deuterium oxide with concentrated HCl at equilibrium showed a ratio of 72% of the 1,4–lactone and 28% of its acid. The ^{13}C NMR chemical shifts are shown in Table II.

Scheme II



2 **8** **9**

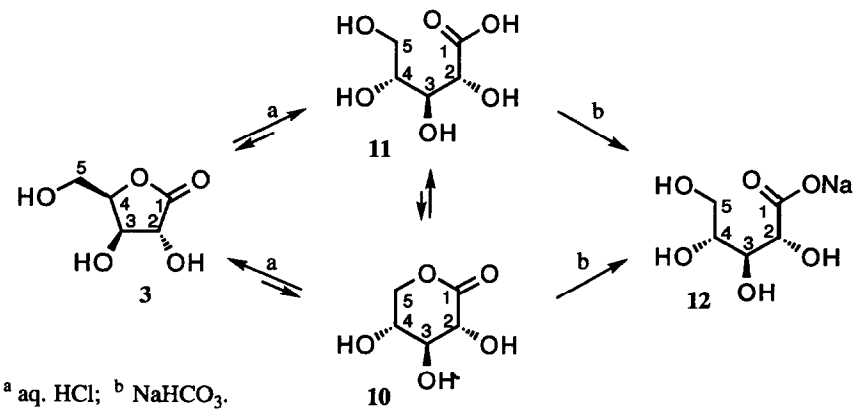
Table II. The ^{13}C NMR Chemical Shifts of **2**, **8** and **9** in D_2O.

	2, δ (ppm)	**8**, δ (ppm)	**9**, δ (ppm)
C_1	175.95	176.30	179.24
C_2	73.76	71.72[a]	72.19[a]
C_3	72.39	70.41[a]	71.56[a]
C_4	81.14	70.21[a]	71.24[a]
C_5	59.23	62.85	63.12

[a] Carbon assignments are tentative.

Hydrolysis of D–Xylono–1,4–lactone (3). The equilibrium study of D–xylono–1,4–lactone in aqueous acidic media was conducted at 22 °C, and is shown in Scheme III. For a quantitative equilibrium composition ratio in aqueous acidic medium, a ^1H NMR spectrum of D–xylono–1,4–lactone in deuterium oxide with concentrated HCl was obtained. The equilibrium composition of the 1,4-lactone, acid and 1,5–lactone was calculated from peak integration of the protons in ^1H NMR spectrum. The ratio was 36%, 60%, and 4.4%, respectively. The ^{13}C NMR chemical shifts are shown in Table III.

Scheme III



[a] aq. HCl; [b] $NaHCO_3$.

Table III. The ^{13}C NMR Chemical Shifts of **3**, **10**, **11** and **12** in D_2O.

	3, δ (ppm)	**10**, δ (ppm)	**11**, δ (ppm)	**12**, δ (ppm)
C_1	177.10	174.78	175.60	178.57
C_2	73.04	71.08[a]	71.98[a]	72.78[a]
C_3	72.08	70.15[a]	71.77[a]	72.75[a]
C_4	80.29	69.34[a]	71.18[a]	72.40[a]
C_5	58.81	75.79	62.22	62.50

[a] Carbon assignments are tentative.

Hydrolysis of D–Lyxono–1,4–lactone (4). The equilibrium study of D–lyxono–1,4–lactone in aqueous acidic media was conducted at 22 °C (Scheme IV). A ^1H NMR spectrum of D–lyxono–1,4–lactone in deuterium oxide with concentrated HCl afforded a quantitative equilibrium composition. The calculated values were 83% for D–lyxono–1,4–lactone and 17% for its acid. The ^{13}C NMR chemical shifts are shown in Table IV.

Scheme IV

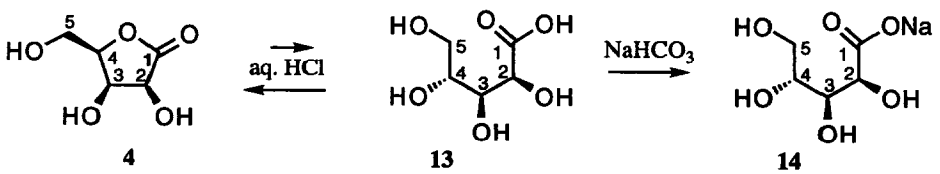


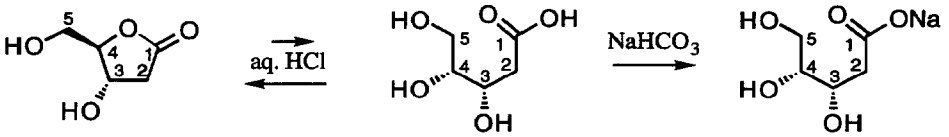
Table IV. The ^{13}C NMR Chemical Shifts of **4**, **13** and **14** in D_2O.

	4, δ (ppm)	**13**, δ (ppm)	**14**, δ (ppm)
C_1	177.90	175.65	178.63
C_2	70.44	71.62[a]	73.67[a]
C_3	69.38	71.29[a]	71.83[a]
C_4	81.42	70.50[a]	71.18[a]
C_5	59.66	62.50	62.96

[a] Carbon assignments are tentative.

Hydrolysis of 2–Deoxy–D–ribono–1,4–lactone (5). The equilibrium study of 2–deoxy–D–ribono–1,4–lactone in aqueous acidic media was conducted at 22 °C, and is shown in Scheme V. A ^1H NMR spectrum of 2–deoxy–D–ribono–1,4–lactone in deuterium oxide with concentrated HCl at equilibrium showed a ratio of 90% of the 1,4-lactone and 10% of its acid. The ^{13}C NMR chemical shifts are shown in Table V.

Scheme V



5 **15** **16**

Table V. The ^{13}C NMR Chemical Shifts of **5**, **15** and **16** in D_2O.

	5, δ (ppm)	**15**, δ (ppm)	**16**, δ (ppm)
C_1	179.27	175.86	180.20
C_2	37.54	37.88	40.49
C_3	68.06	68.45	69.73
C_4	88.74	73.98	74.39
C_5	60.78	62.36	62.45

A summary of the equilibrium compositions after mutarotation of D-pentonolactones and D-pentonic acids in D_2O for our specific concentrations and temperatures is shown in Table VI. The calculated values are from the total peak integrations of all the protons in the ^1H NMR spectra.

Table VI. Equilibrium composition of aldonolactones and their acids in aqueous acidic media.

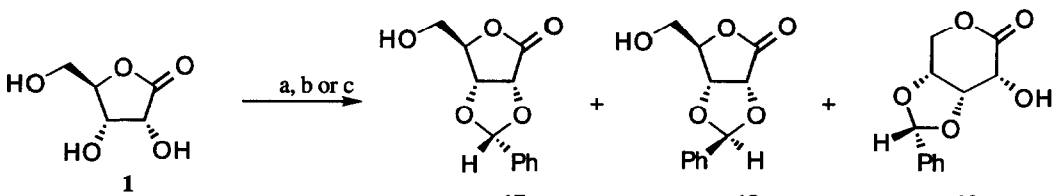
	Percent (%) of equilibrium composition[a]		
Aldonolactone	1,4-Lactone	Acid	1,5-Lactone
D-ribono-1,4-lactone	75.7	24.3	-
L-arabinono-1,4-lactone	71.6	28.4	-
D-xylono-1,4-lactone	35.9	59.7	4.4
D-lyxono-1,4-lactone	82.6	17.4	-
2-deoxy-D-ribono-1,4-lactone	90.1	9.9	-

[a] Calculated from peak integrations of protons in ^1H NMR spectra.

Syntheses of Benzylidene Acetals. The interest in the benzylidene acetal derivatives of D-ribono-1,4-lactone (**1**) was generated by a report[35] which questioned whether the product of the reaction between D-ribono-1,4-lactone (**1**) and benzaldehyde, using HCl as a catalyst, was the 3,5-γ-lactone previously reported by Zinner.[36] The skepticism of Baggett et al.[35] was based on the fact that no other genuine 3,5-cyclic acetals of furanoid derivatives of ribose, or arabinose, had been known to form under equilibrating conditions. The product was found to be the 3,4-δ-lactone based on an X-ray analysis of its 2-acetate.

Several reaction conditions were tried for the formation of cyclic acetals of D-ribono-1,4-lactone (**1**). They are shown in Scheme VI. Where D-ribono-1,4-lactone (**1**) was treated with benzaldehyde and catalytic amount of concentrated hydrochloric acid at room temperature for 20 h, a yield of 63% of 3,4-O-(R)-benzylidene-D-ribono-1,5-lactone (**19**) was obtained. When *p*-toluenesulfonic acid was used as a catalyst, three compounds were isolated (**17**, **18**, **19**, in 5%, 7%, and 48% yield, respectively). Compound **19** was the major product. Treatment of **1** with α,α-dimethoxytoluene and anhydrous stannous chloride in dimethoxyethane yielded compounds **17** (60%) and **18** (4%). The formation of **19** was not observed under non-aqueous reaction conditions. Compound **17** was derivatized to an acetate (**20**) to confirm its structure by X-ray analysis. Thus, compound **17** was treated with acetic anhydride and N,N-dimethylaminopyridine in methylene chloride to afford the acetate (**20**) in 86% yield.

Scheme VI

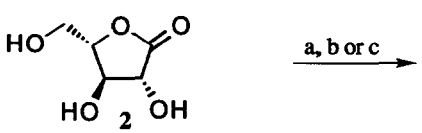


1 **17** **18** **19**

[a] PHCHO, conc. HCl, rt, 20 h	–	–	63%
[b] PhCHO, *p*-TsOH•H_2O, rt, 20 h	5%	7%	48%
[c] $PhCH(OMe)_2$, $SnCl_2$, DME, Δ, 45 min	60%	4%	–

When L-arabinono-1,4-lactone (**2**) was treated with benzaldehyde under similar conditions, no reaction was observed (Scheme VII). Although modifications of the standard conditions (solvent, temperature, time, catalyst) were tried, all failed to afford the corresponding benzylidene derivative.

Scheme VII

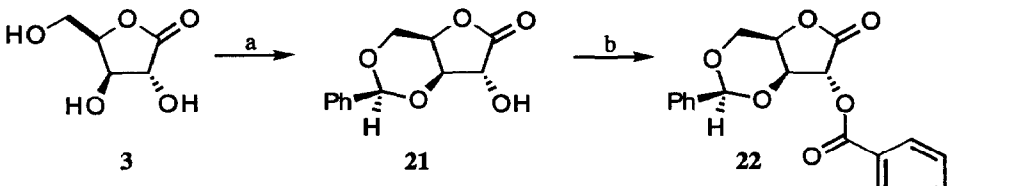


2

[a] PhCHO, conc. HCl, THF, rt, 20 h
[b] PhCHO, *p*-TsOH•H_2O, THF, rt, 20 h
[c] PhCHO, conc. HCl, DMSO, rt, 20 h.

When D-xylono-1,4-lactone (**3**) was treated with benzaldehyde and concentrated hydrochloric acid at room temperature, the corresponding 3,5-O-(S)-benzylidene-D-xylono-1,4-lactone (**21**) was obtained in 49% yield (Scheme VIII). The structure of **21** was confirmed by a single crystal X-ray analysis of its *p*-nitrobenzoate derivative **22** obtained from the reaction of **21** with *p*-nitrobenzoylchloride, in the presence of DMAP.

Scheme VIII



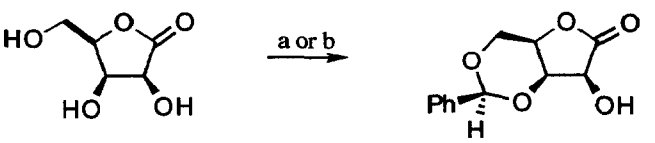
3 **21** **22**

[a] PhCHO, conc. HCl, DMSO, rt, 5 d, 49%

[b] *p*-nitrobenzoylchloride, DMAP, CH_2Cl_2, O °C, 10 min, 100%.

When D-lyxono-1,4-lactone (**4**) was treated with benzaldehyde and concentrated hydrochloric acid at room temperature, compound **23** was obtained as the only isolable product (84% yield, Scheme IX). The same product was isolated by treatment of compound **4** with α,α-dimethoxytoluene and catalytic amount of stannous chloride (48% yield). The structure of **23** was confirmed by a single crystal X-ray analysis. The preferred epimer in both xylono- and lyxono- benzylidene acetals was the one with an *endo*-phenyl group. It is clear that **21** and **23** are both kinetically and thermodynamically favored products.

Scheme IX



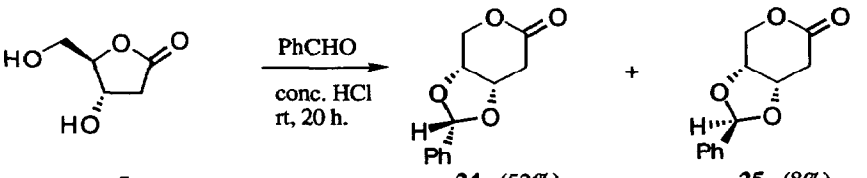
4 **23**

[a] PhCHO, conc. HCl, rt, 20 h, 84%

[b] $PhCH(OMe)_2$, $SnCl_2$, THF, Δ, 2 h, 48%.

When 2-deoxy-D-ribono-1,4-lactone (**5**) was treated with benzaldehyde and concentrated HCl, 3,4-O-(S)-benzylidene-2-deoxy-D-ribono-1,5-lactone (**24**) and 3,4-O-(R)-benzylidene-2-deoxy-D-ribono-1,5-lactone (**25**) were obtained, in 52% and 8% yields, respectively (Scheme X)[7]. The structure of **25** was confirmed by comparison of its spectroscopic data (NMR, IR) with those of **24**.

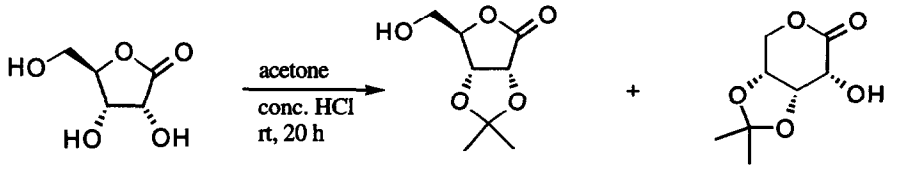
Scheme X



5 **24** (52%) **25** (8%)

Synthesis of Isopropylidene Ketals. The five pentono-1,4-lactones were subjected to the ketal formation conditions shown in Scheme XI. The reaction of D-ribono-1,4-lactone (**1**) with acetone and concentrated hydrochloric acid, for 20 h at room temperature, afforded 2,3-O-isopropylidene-D-ribono-1,4-lactone (**26**) and 3,4-O-isopropylidene-D-ribono-1,5-lactone (**27**) in 46% and 26% yields, respectively. The structures of **26** and **27** were confirmed by X-ray diffraction.

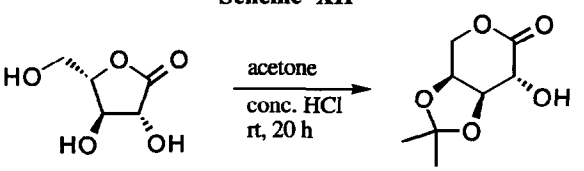
Scheme XI



1 **26** (46%) **27** (26%)

When L-arabinono-1,4-lactone (**2**) was subjected to the same reaction conditions, the ring-expanded ketal **28** was formed in 16% yield (Scheme XII). The structure of **28** was confirmed by comparison of its spectroscopic data with those of **26** and **27**, since a crystal suitable for X-ray analysis could not be obtained.

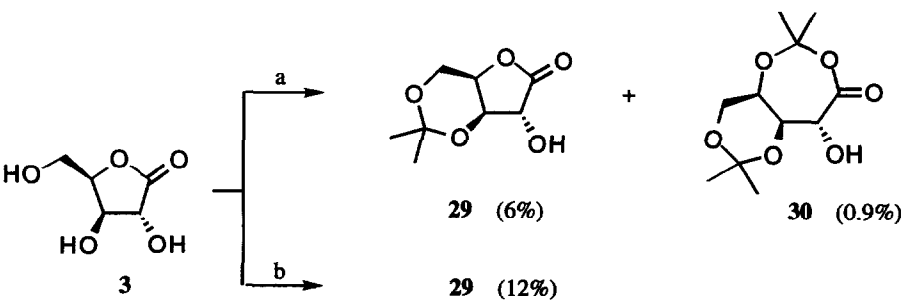
Scheme XII



2 **28** (16%)

When D-xylono-1,4-lactone (**3**) was treated with acetone in concentrated HCl, compound **29** was obtained in 6% yield along with 0.9% of compound **30** (Scheme XIII). The structure of compound **29** was confirmed by a single crystal X-ray analysis. The formation of compound **30** is probably due to the equilibrium of the lactone in acidic media. When compound **3** was treated with acetone and *p*-TsOH·H_2O, compound **29** was obtained in 12% yield and the formation of compound **30** was not observed.

Scheme XIII



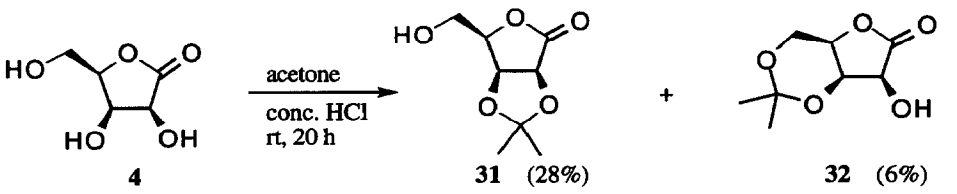
3 **29** (6%) **30** (0.9%)

29 (12%)

[a] acetone, conc. HCl, rt, 20 h; [b] acetone, *p*-TsOH·H_2O, rt, 20 h.

When D-lyxono-1,4-lactone (**4**) was treated with acetone and concentrated HCl, compounds **31** and **32** were formed in 28% and 6% yields, respectively (Scheme XIV). Both structures were confirmed by single crystal X-ray analyses.

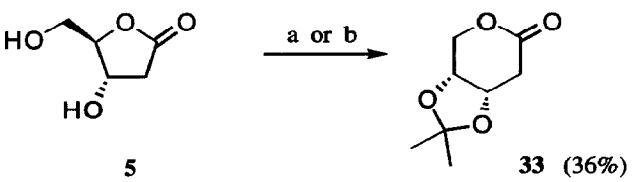
Scheme XIV



4 **31** (28%) **32** (6%)

When 2-deoxy-D-ribono-1,4-lactone (**5**) was treated with acetone and concentrated HCl, product **33** was obtained in 36% yield (Scheme XV)[7] . The structure of compound **33** was confirmed by a single crystal X-ray analysis. Neither **1** nor **5** form the 3,5-O-isopropylidene isomers due to unfavorable cyclic transition states.

Scheme XV



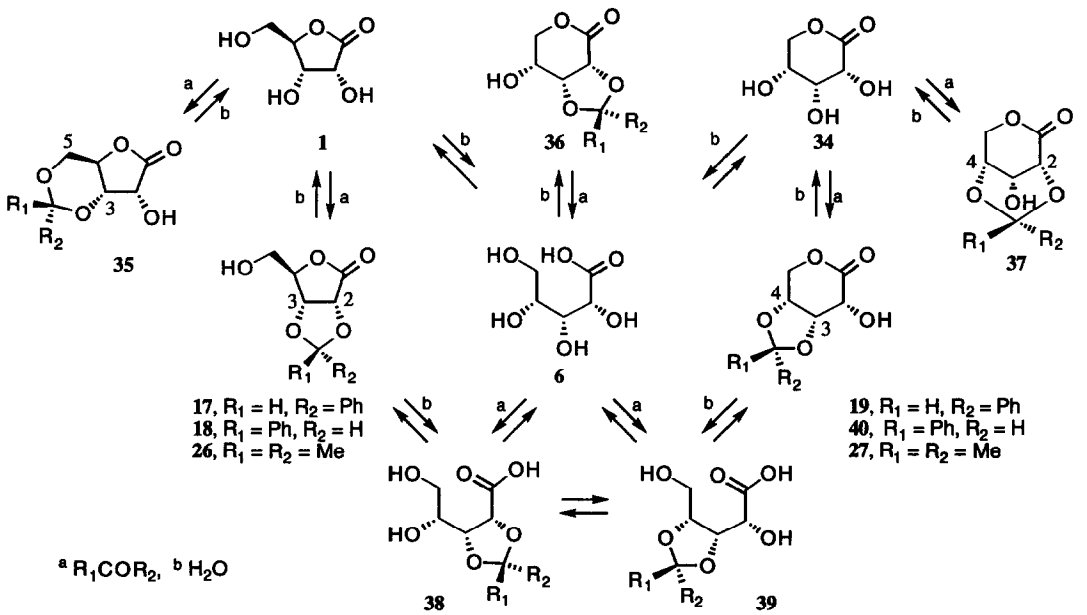
5 **33** (36%)

[a] acetone, conc. HCl, rt, 20 h; [b] acetone, *p*-TsOH•H_2O, rt, 20 h.

Formation and Isomerization of Acetals and Ketals in Acidic Media. The acid-promoted acetalization or ketalization of aldonolactones is potentially a very complex process resulting from the participation of several different oxygen atoms. Scheme XVI shows the possible reaction pathways and equilibria that may operate during the acetalization or ketalization of D-ribono-1,4-lactone (**1**).[7] Under anhydrous conditions and under kinetic control the major products are the 2,3-acetals or ketals of the 1,4- (or γ-) lactone (**17**, **18**, **26**), while under aqueous conditions and thermodynamic control, significant amounts of the 3,4-derivatives of the 1,5- (or δ-) lactone (**19**, **27**) are formed. While, in principle, other isomeric ketals such as the initially implicated 3,5-γ-lactone derivative (**35**), the 2,3-δ-lactone derivative (**36**), and the 2,4-δ-lactone derivative (**37**), are also possible, these were not detected. Presumably, as confirmed by our computational studies described below, these derivatives have significantly higher energy and are disfavored.

Although compounds **19** and **27** can be formed directly from the 1,5-lactone **34**, the absence of this lactone in our equilibrium hydrolysis studies suggests that it is more likely that these products are formed from the acid **6** via ketalization to **39** followed by lactonization, or from the initially formed ketals of the 1,4-lactone (**17**, **18**, **26**) via hydrolysis to **38**, isomerization to **39** and lactonization. In order to clarify this point, we used ^{13}C NMR spectroscopy to monitor the formation of the O-benzylidene acetals and O-isopropylidene ketals of ribono-1,4-lactones during the reaction with benzaldehyde or acetone in NMR solvents (DMSO-d_6 and $CDCl_3$) containing concentrated hydrochloric acid.

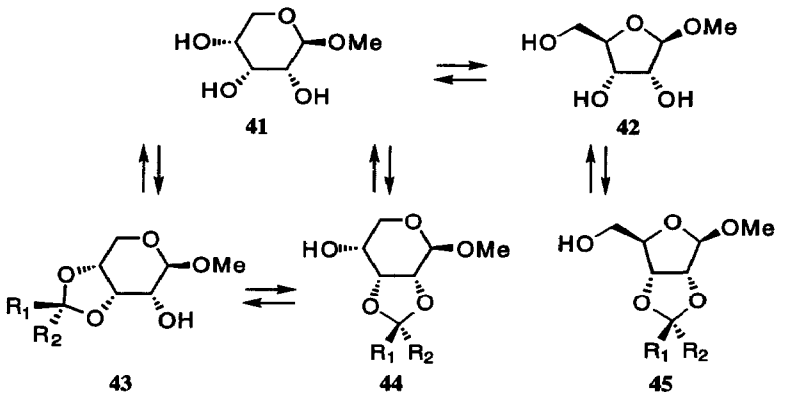
Scheme XVI



O–Benzylidene Acetals of D–Ribono–1,4–lactone (1). A solution of **1** (0.629 g, 4.25 mmol) in benzaldehyde (1.57 g, 1.50 mL, 14.8 mmol) and DMSO–d_6 (0.733g, 0.616 mL, 8.71 mmol) with 12 N HCl (0.064 g, 0.053 mL, 0.64 mmol) was allowed to stand at ambient temperature. A ^{13}C NMR of the reaction mixture after 32 min indicated the formation of (R)-2,3–acetal (**17**). Another ^{13}C NMR spectrum taken after 53 min indicated the presence of a trace amount of (S)-2,3–acetal (**18**). The presence of the (R)-3,4–benzylidene–D–ribono–1,5–lactone (**19**) was detected along with unidentified intermediates, 2 h after the reaction was initiated. A ^{13}C NMR spectrum taken after 5 h revealed about a 2:1 ratio of **1** and **17**. Since an appreciable amount of white precipitate was produced in the NMR tube due to the formation of **19**, a sufficient amount of DMSO–d_6 was added to obtain a homogeneous solution. Another ^{13}C NMR spectrum was taken after 89 h from the beginning of the reaction. This spectrum showed the ratio of **1** : **19** : **17** to be 2:2:1. When **1** was treated with benzaldehyde and $ZnCl_2$ in DMSO-d_6, formation of **17** as the major product and **18** as the minor one was observed. Formation of **19** was not detected even after a week at room temperature. These NMR studies clearly indicate that acetal formation occurs first at the 1,4-lactone and is then followed by isomerization.

Similar processes on glycosides were reported by Barker et al,[37] who showed that the reaction of methyl β-D-ribopyranoside (**41**) with benzaldehyde and $ZnCl_2$ as the catalyst, gave methyl 2,3-O-benzylidene-β-D-ribofuranosides (**45a,b**) as the main products (Scheme XVII). In another study, Clode[38] showed that the 3,4-O-benzylidene-β-D-ribopyranosides (**43a,b**) can be equilibrated with the corresponding 2,3-derivatives (**44a,b**) by treatment with 0.2% HCl-$CHCl_3$. Further adjustment of the reaction conditions to a higher acid concentration causes ring contraction of all four pyranosides (**43a,b** or **44a,b**) to afford a 1:1 mixture of furanosides **45a** and **45b**. These results show that ring contraction can indeed take place after the condensation of **41** with benzaldehyde, and that prior isomerization of **41** to **42** before the acetalization is not necessary.

Scheme XVII



a: R_1 = H, R_2 = Ph, **b:** R_1 = Ph, R_2 = H.

O–Isopropylidene Ketals of Ribono–1,4–lactone (1): The formation and behavior of the O–isopropylidene ketals of D– (**1**) were also monitored by ^{13}C NMR experiments. A solution of **1** (0.0741 g, 0.50 mmol) in acetone (0.396 g, 0.500 mL, 6.81 mmol) and $CDCl_3$ (0.750 g, 0.500 mL, 6.23 mmol) with 12 N HCl (0.034 g, 28.7 mL, 0.34 mmol) was allowed to stand at ambient temperature. A ^{13}C NMR of the reaction mixture after 15 min revealed instant formation of **26** along with a trace amount of **27** and a small amount of starting 1,4–lactone. Another ^{13}C NMR spectrum taken after 110 min indicated the increase in the percentage of compound **27**. After 39 h 25 min, a ^{13}C NMR spectrum showed the ratio of **26** and **27** to be 2:1 along with a small amount of unreacted **1**. This ratio remained constant on further ^{13}C NMR examinations. To support the direct interconversion between the 1,4- and 1,5- lactones, both **26** and **27** were treated with acetone-$CDCl_3$ mixtures containing 3% (w/w) of concentrated hydrochloric acid. A ^{13}C NMR of the reaction mixture after 25 min revealed instant interconversion between **26** and **27**. At equilibrium, the ratio between **26** and **27** was 3:2, and remained constant. This result agrees with the previous equilibrium study of D-ribonolactone.

Spectroscopic Assignments: In order to confidently assign chemical shifts and coupling constants in the ^1H and ^{13}C NMR spectra of aldonolactone derivatives to a given structure, it is critical to understand the various isomeric and conformational possibilities. A valuable method for the stereochemical assignment of diols relies on the ^{13}C NMR chemical shifts of the corresponding acetonides. This method, first used by Rogers[39] and later applied to carbohydrate derivatives by Buchanan,[40] was more recently employed for alternating polyols by Rychnovsky[41, 42] and propionate-derived polyols by Evans.[43] The range of values found for ^{13}C NMR resonances of *syn* (chair) and *anti* (twist boat) acetonides are shown in Figure 5.

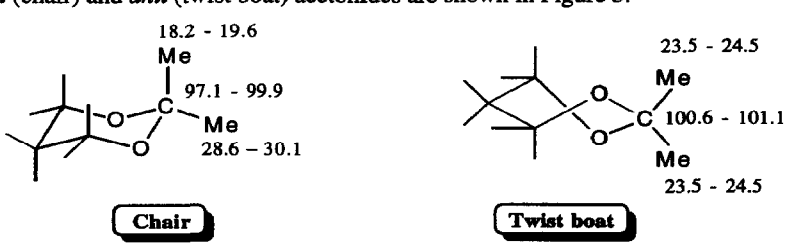
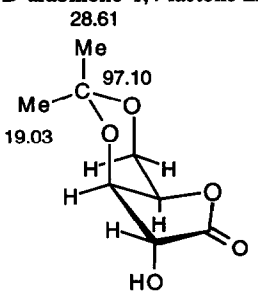
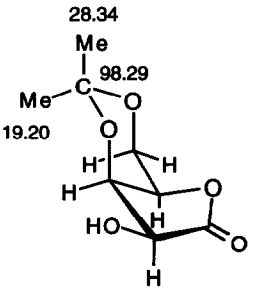


Figure 5

We found that these observations can also be applied to the 3,5-acetonides of D-xylono- and D-lyxono-1,4-lactones. The X-ray analyses show both 1,3-dioxolanes (**29** and **32**) to be in their chair forms. The ^{13}C resonance of one methyl group appears at 9 ppm lower field than the other, indicating that the two methyl groups in the chair conformation are in different environments (Figure 6). In addition, the ^{13}C chemical shifts of the acetal carbons appear below 100 ppm, in agreement with a chair conformation. In contrast, the reported data for the 3,5-acetonide of D-arabinono-1,4-lactone indicate a twist-boat conformation.[61]



29



32

Figure 6

As observed in the present study, the large differences in reactivity exhibited by the pentonolactones in the formation of acetals and ketals, under aqueous acidic media, are associated with relatively minor changes in structure or configuration.

X-Ray Crystallography: Due to the ambiguities in the structural and conformational assignments of the aldonolactone acetals and ketals, we carried out several structure determinations by X-ray crystallography. The structures determined are shown in Figure 7. In both compounds **20** and **26**, the D-ribonolactone ring has the E_3 conformation with the hydroxymethyl appendage in the *gauche-gauche* (GG) configuration. Structures **22** and **29** show the ^3E ring conformation of D-xylonolactone with a chair conformation for the 1,3-dioxane ring system consistant with the ^{13}C NMR assignments. Similar ^3E-chair conformations are indicated for derivatives **23** and **32** of D-lyxonolactone. As expected, the six-membered lactones **27** and **33** exist in the boat conformation, while the 2,3-acetonide of D-lyxonolactone (**31**) exists in the ^3E conformation with the hydroxymethyl group in the GG configuration.

Conformational Analysis: The availability of the cartesian coordinates of these X-ray structures allows us to evaluate the use of spectroscopic and computational methods for the conformational analysis of these systems. In addition to verifying the ring conformations and the configuration of the hydroxymethyl appendages, these structures also reveal the configurations of the C-OH bonds, which is more difficult to determine. The usual notations[44, 45] for the possible configurations of the hydroxyl groups in the ^3E form of D-ribonolactone are shown in Figure 8. The notation **t** is used for the *trans* configuration, while the notations $\mathbf{g}^+$ and $\mathbf{g}^-$ are used for the *gauche* configurations, which have the hydroxyl H positioned clockwise or counterclockwise relatively to the **t** configuration. A number indicating the position of the OH group precede these notations. Despite the numerous combinations that are possible for polyhydroxy compounds, some of these often predominate. As indicated in the X-ray structures **23**, **26**, **27**, **29**, **31** and **32** the OH group usually prefers the **t** configurations.

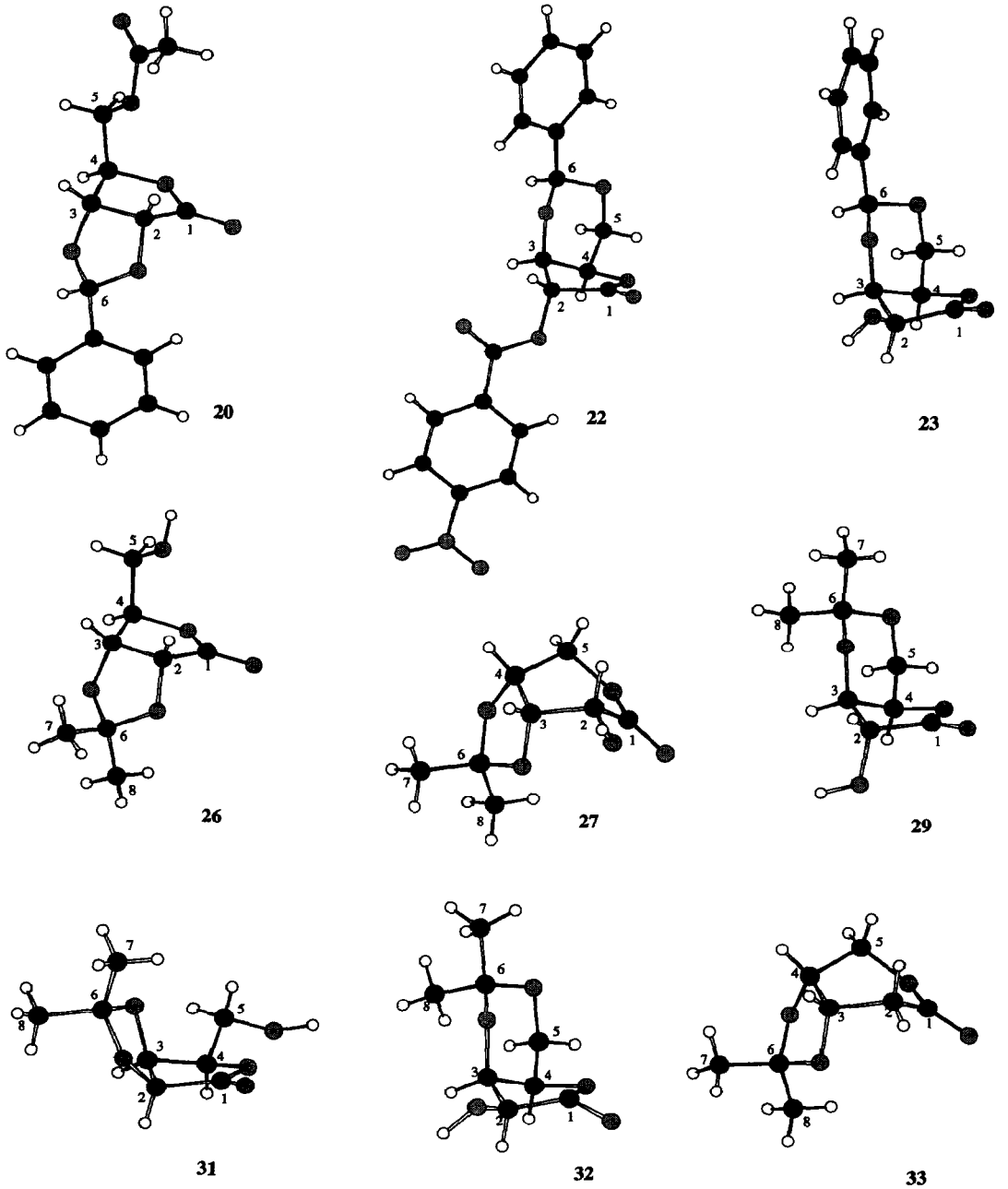


Figure 7. Structures of acetals and ketals of pentonolactones determined by X-ray crystallography.

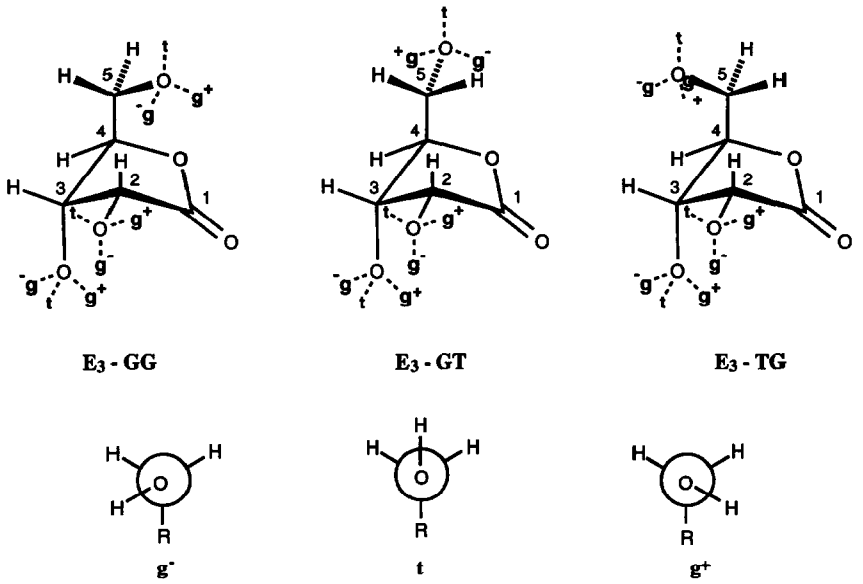
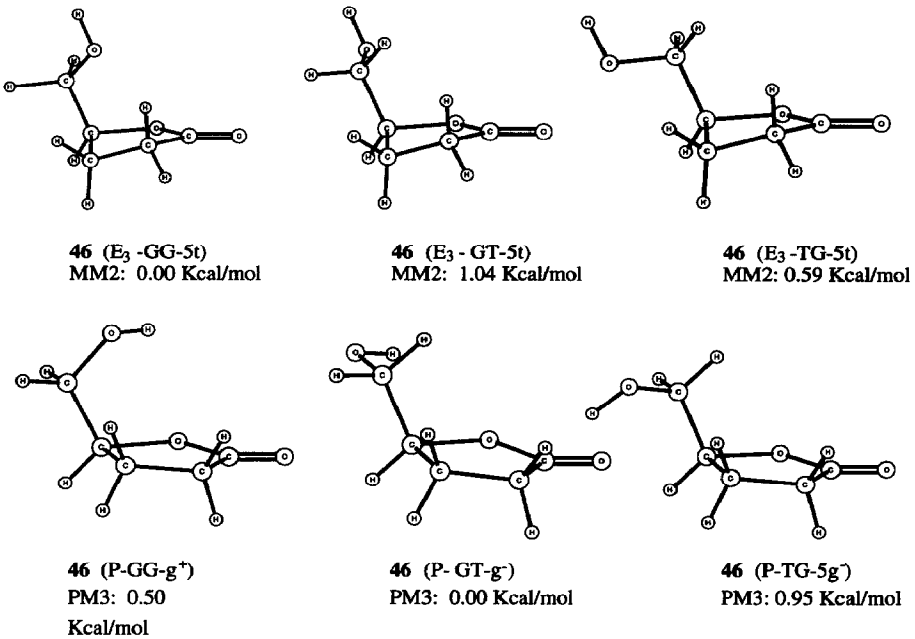


Figure 8

Computational Studies: While a variety of computational methods are becoming increasingly available for routine structural and conformational analysis of carbohydrates,[16, 33, 34, 44, 46-48] several drawbacks still complicate their widespread utilization. While molecular mechanics calculations (MM2, MM3) are the easiest to carry out and even though they often accurately reproduce the structural geometries of molecules,[34] these methods often do not give reliable energy data, particularly for different structural isomers. Semiempirical methods (AM1,[49] PM3[50, 51]) tend to give slightly less accurate geometries but more meaningful energetic data for systems with anomeric effects[47, 48] and hydrogen bonding.[44] However, both AM1 and PM3 sometimes exaggerate certain hydrogen - oxygen interactions and can give distorted geometries in some ring systems.[45] Finally, *ab initio* approaches[16, 48, 52] give the most accurate structural and energetic results, but are still difficult to do for fairly large molecules, such as the ones discussed herein.

In the present study we compared several computational approaches as tools for structural and conformational assignments, as well as for providing a theoretical basis for the observed structures and equilibria. For this purpose we used the MM2, PM3 and AM1 methods for optimizing several of the structures under consideration and subsequently calculated the heats of formation and the predicted ^1H NMR coupling constants, arising from the resulting structural geometries.

Figure 9 shows the calculated geometries and energy differences for 4-hydroxymethyl butyrolactone conformers (**46**) using the MM2 and PM3 methods. These calculations of the parent pentonolactone 5-ring system illustrate the major differences among these methods. While MM2 predicts the common E_3 ring conformation and a 5t hydroxyl group rotamer, PM3 optimizes the structure to the planar ring conformation and a gauche (g^+ or g^-) configuration for the C_5-OH bond. This tendency of the semiempirical methods is precedented.[45] In addition to these geometry differences, PM3 differs from MM2 in predicting that the GT configuration is more stable than the GG and TG forms, as in the X-ray structure of D-ribono-1,4-lactone.[32]



46 (E_3 -GG-5t)
MM2: 0.00 Kcal/mol

46 (E_3 - GT-5t)
MM2: 1.04 Kcal/mol

46 (E_3 -TG-5t)
MM2: 0.59 Kcal/mol

46 (P-GG-g^+)
PM3: 0.50
Kcal/mol

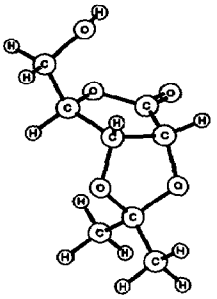
46 (P- GT-g^-)
PM3: 0.00 Kcal/mol

46 (P-TG-$5g^-$)
PM3: 0.95 Kcal/mol

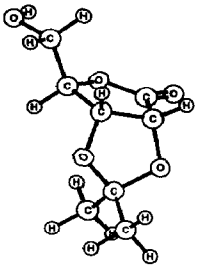
Figure 9

In an effort to understand and quantify the origin of the preferred ketalization of D-ribonolactone at the 2,3-position of the 1,4-lactone and the 3,4-position of the 1,5-lactone, we calculated all of the possible acetonides suggested in Scheme XVI. The geometries and PM3 heat of formation differences of the various isomers are shown in Figure 10. The calculated conformations of the 1,4-lactone rings of **26** have the planar (P) arrangement with the GT form being slightly lower in energy than the GG, with the TG form being somewhat less stable. Among the 1,5-lactone isomers the boat conformations have the lowest energies in all substitution patterns (**27**, **36**, **37**). The 2,3-acetonide of the 1,4-lactone (**26**) has the lowest energy amongst the various isomers, while the 2,4-acetonide **35** a much higher heat of formation despite a chair conformation of the 1,3-dioxane ring system. These relative energy trends are concistent with the experimental results. Thus, while compound **27** is close enough in energy with the kinetically formed isomer (**26**), making it possible to convert **26** to **27** under thermodynamic control, the other isomers (**35** - **37**) are much higher in energy and cannot be formed. The lower energy of the boat form of **27** is concistent with the observed geometry in the crystal structure of this compound. In constrast with the X-ray structures of **26** and **27**, which have the hydroxyl groups in the *trans* (t) configuration, the PM3 optimized structures universally have the hydroxyl groups in one of the *gauche* configurations.

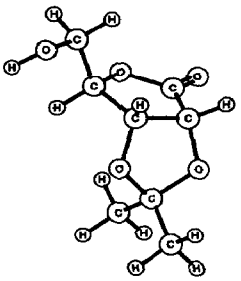
Additional data obtained by the calculations of these D-ribonolactone acetonides with MM2, PM3 and AM1 are listed in Table VIII, together with ^1H - ^1H coupling constants calculated from these geometries. The experimental values for these coupling constants as well as those calculated by the X-ray geometries are also listed for comparison.



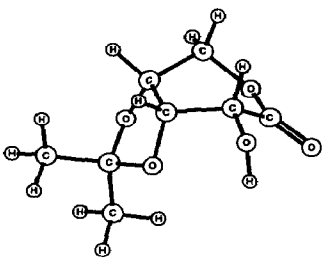
26 (P-GG-5g$^+$)
0.09 Kcal/mol



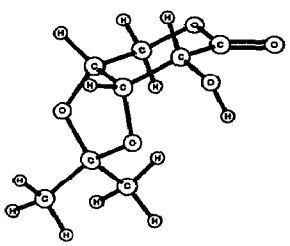
26 (P-GT-5g$^-$)
0.00 Kcal/mol



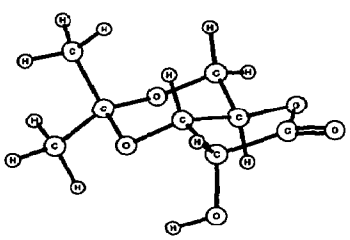
26 (P-TG-5g$^-$)
0.83 Kcal/mol



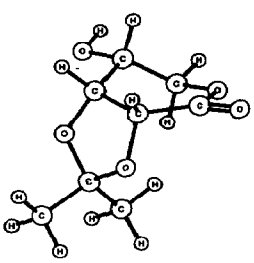
27 (Boat-2g$^-$)
1.61 Kcal/mol



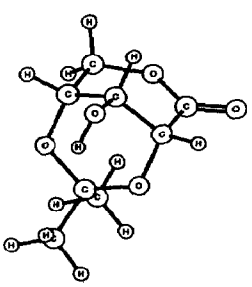
27 (Chair-2g$^-$)
5.97 Kcal/mol



35 (^{3}E-Chair-2t)
17.65 Kcal/mol



36 (Boat-4g$^+$)
4.97 Kcal/mol



37 (Boat-3g$^-$)
9.61 Kcal/mol

Figure 10. Structures and relative heats of formation calculated with PM3 for D-ribonolactone acetonides.

Table VIII. Data for D-ribonolactone acetonides.

Compound	Conformation	Energy (Kcal/mol)			Coupling Constants (Hz)			
		MM2	PM3	AM1	$J_{2,3}$	$J_{3,4}$	$J_{4,5a}$	$J_{4,5b}$
26 (NMR)					**5.6**		**2.3**	**1.5**
26 (X-ray)	E_3-GG-5t				7.8	0.8	2.5	1.4
26 (calcd)	E_3-GG-5t	**15.77**			7.3	1.1	2.5	1.5
	E_3-GG-5g$^+$	18.41			8.2	1.5	3.1	0.9
	P-GG-5g$^+$		-213.12		8.4	2.5	3.1	1.0
	P-GG-5g$^+$			-215.81	8.4	2.4	3.5	0.7
	E_3-GT-5t	18.15			7.6	0.8	2.5	10.3
	E_3-GT-5g$^-$	19.49			8.3	1.9	2.5	10.4
	P-GT-5g$^-$		**-213.21**		8.4	2.4	1.7	9.3
	P-GT-5g$^-$			-215.94	8.4	2.2	2.5	10.4
	E_3-TG-5t	17.35			7.1	2.7	10.7	5.6
	E_3-TG-5g$^-$	19.96			8.2	2.7	10.7	5.4
	P-TG-5g$^-$		-212.38		8.4	2.2	10.6	4.2
	P-TG-5g$^-$			-214.70	8.4	2.0	10.5	6.0
27 (NMR)					**3.5**	**7.8**	**1.7**	**1.7**
27 (X-ray)	Boat-2t				4.9	7.9	1.7	2.7
27 (calcd)	Boat-2t	20.71			3.6	7.9	2.0	1.9
	Boat-2g$^-$	17.93			3.5	7.9	1.8	2.1
	Boat-2g$^-$		-211.60		4.3	7.8	1.7	2.7
	Boat-2g$^-$			**-216.72**	4.2	7.9	1.9	2.4
	Chair-2g$^-$		-207.24		5.8	5.8	8.8	8.3
	Chair-2g$^-$			-211.60	6.3	6.7	8.1	8.3
35 (calcd)	^{3}E-Chair-2g$^+$	23.60			4.8	9.7	10.7	5.6
	^{3}E-Chair-2t	23.71			5.2	9.1	10.5	6.2
	^{3}E-Chair-2t		-195.56		5.7	9.1	10.4	6.6
	^{3}E-Chair-2t			-190.09	5.8	9.1	10.5	6.3
36 (calcd)	Boat-4g$^-$	18.40			8.4	4.3	10.7	5.0
	Boat-4g$^+$	18.94			8.4	4.5	10.7	5.0
	Boat-4g$^+$		-208.24		8.3	4.2	10.7	5.0
	Boat-4g$^+$			-210.06	8.1	3.9	10.7	4.7
37 (calcd)	Boat-3g$^-$	25.81			2.8	2.2	1.5	3.1
	Boat-3g$^-$		-203.60		2.3	2.1	1.6	3.0
	Boat-3g$^-$			-198.14	2.5	2.6	1.3	4.7

These data show that none of the studied computational methods gives universally correct results. It is again apparent that MM2 accurately predicts that the 1,4-lactone ring system has the observed envelop (E_3) conformation, while both PM3 and AM1 incorrectly optimize it to a planar (P) structure. In this case, MM2 gives the correct prediction for the most stable rotamer of the hydroxymethyl group but it exaggerates the energy difference among the GG and GT rotamers. Both semiempirical methods seem to offer more reasonable energy results, showing that the GT and GG configurations are fairly close in energy. However, AM1 suggests that the boat conformation of **27** is even lower in energy than any conformation of **26**, which is in disagreement with the equilibrium results. Regarding the calculated relative stabilities of **35** - **37**, all three methods indicate a higher energy, but with variable amounts.

It appears that the calculated coupling constants from these structures can be used to select the most likely match with the experimental values. Despite some differences depending on the method used to optimize these structures, the values for the different possible isomers are significant enough to make such an assignment possible. While the experimental values are averages among the populated conformations, a comparison with the computed values can still be meaningful. Thus, all methods correctly predict a larger $J_{2,3}$ value for isomer **26** than for isomer **27** and a larger $J_{3,4}$ value for **27** than for **26**.

Table IX. Data for compounds **29**, **31**, **32** and **33**.

Compound	Conformation	Energy (Kcal/mol)			Coupling Constants (Hz)			
		MM2	PM3	AM1	$J_{2,3}$	$J_{3,4}$	$J_{4,5a}$	$J_{4,5b}$
29 (NMR)					**2.8**		**2.3**	
29 (X-ray)	^{3}E-Chair-2g$^+$				2.0	2.8	2.5	1.7
29 (calcd)	^{3}E-Chair-2t	15.58			0.9	2.9	2.4	1.7
	P-Chair-2t		-208.11		0.4	5.4	5.8	1.5
	P-Chair-2t			-212.80	0.6	6.2	6.7	1.8
31 (NMR)								
31 (X-ray)	^{3}E-GG-5t				7.1	4.0	9.7	2.3
31 (calcd)	^{3}E-GG-5t	17.6			7.1	4.0	9.7	2.3
	P-GG-5g$^+$		-212.46		8.4	6.8	9.2	2.3
	P-GG-5g$^+$			-214.71	8.3	6.4	9.9	2.2
32 (NMR)					**4.4**	**2.9**	**4.2**	
32 (X-ray)	^{3}E-Chair-2t				4.8	3.3	2.6	1.8
32 (calcd)	^{3}E-Chair-2t	18.22			5.0	2.7	2.2	1.8
	P-Chair-2g$^+$		-206.64		7.8	4.3	5.0	1.4
	P-Chair-2g$^+$			-211.49	8.0	5.4	6.0	1.6
33 (NMR)					**3.7, 2.6**	**7.7**	**2.0**	**1.4**
33 (X-ray)	Boat				3.2, 3.0	7.4	2.6	1.4
33 (calcd)	Boat	21.67			3.4, 2.9	7.5	1.7	2.7
	Boat		-172.77		5.2, 1.7	7.5	1.7	2.7
	Boat			-174.24	4.8, 1.9	7.5	1.8	2.6

A rather surprising result from these calculations is the significant differences among the energies and the corresponding coupling constant differences that are predicted for various rotamers around C-OH bonds. While such differences are often neglected, they can have a dramatic effect in the solvation of a given derivative and its ability to form inter- or intramolecular hydrogen bonds.

Some additional calculation results for the remaining structures for which we have obtained X-ray crystal structures are listed in Table IX. Again, PM3 and AM1 favor planar conformations for the 5-membered ring lactones, which can lead to noticable errors in the predicted coupling constant values (e.g. **29**). The overall trends, however are again reasonable.

Differences in Reactivity Among 1,4-Lactones and 1,5-Lactones: The relative reactivities of 1,4-lactones and 1,5-lactones have been studied both experimentally[53] and computationally.[53-56] In general, the 1,5-lactones have a higher ring strain and a higher basicity. Consequently, they undergo a more facile acid-mediated hydrolysis than the corresponding 1,4-lactones. This difference among the two isomeric ring systems of pentonolactones is probably responsible for the observed product formation during acetalization and ketalizations. The equilibria in Scheme XVI that involve 1,5-lactones are probably driven by the more facile ring opening of these systems relatively to the 1,4-lactones.

Conclusions

The different reactivities of D-ribono-1,4-lactone (**1**), L-arabinono-1,4-lactone (**2**), D-xylono-1,4-lactone (**3**), D-lyxono-1,4-lactone (**4**), and 2-deoxy-D-ribono-1,4-lactone (**5**), toward either benzaldehyde or acetone, in acidic media are associated with relatively minor changes at C-2 and C-3: the presence or absence of an OH group and changes in relative configuration. The observed ring expansion in the reactions of **1**, **2**, and **5** with benzaldehyde or acetone may be explained by invoking prior acetal formation followed by ring expansion. The observed formation and isomerization of acetals and ketals of the 1,4- and 1,5-lactones are presumably the result of complex equilibria which involve lactone ring opening, isomerization and re-lactonization processes.

The calculated relative energies for the possible ketalization products are in general agreement with the experimental results and can explain why some of these isomers are not formed. While the semiempirical methods, particularly PM3, gave reasonable energy predictions, in some cases the optimized geometries varied from those observed in the X-ray crystal structures in that the 1,4-lactone ring is predicted to be planar, rather than having the observed envelop conformation. In certain derivatives, significant differences were calculated for the hydroxymethyl group rotamers, as well as for the rotamers of the C-OH groups. Despite small differences among different methods, the calculated NMR coupling constants are helpful in determining the most likely structural assignment for a given isomer. Overall, these studies have demonstrated the subtle nature of the structures and reactivities of pentonolactones and have provided some means for guiding structural and conformational assignments.

Experimental Section

General Methods. All solvents were reagent grade. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride (CaH_2). Dimethoxyethane (DME) was distilled from a mixture of sodium and potassium with benzophenone. Benzaldehyde was distilled before use. Benzaldehyde dimethyl acetal was distilled over lithium aluminum hydride (LAH). Analytical thin-layer chromatography (TLC) was performed on Merck silica gel (60 F 254) plates (0.25 mm), precoated with a fluorescent indicator. Visualization was effected with ultraviolet light (UV) anisaldehyde (5% v/v) in 95% ethanol containing 5% sulfuric acid and 1% acetic acid, phosphomolybdic acid (7% w/v) in 95% ethanol, or potassium permanganate (1% w/v) in water containing 7% potassium carbonate and 0.09% aqueous sodium hydroxide. Flash column was carried out on Merck silica gel 60 (240–400 mesh). Melting points (mp) were determined with a Thomas–Hoover capillary melting point apparatus. They are expressed in °C, and are uncorrected. Proton and carbon NMR spectra were recorded on an IBM NR/250 AF (250 MHz) or a Bruker AM–500 (500 MHz) Fourier transform (FT) spectrometer, using $CDCl_3$, DMSO–d_6, D_2O, or acetone–d_6 as solvents. Chemical shifts (δ) are given in parts per million (ppm) relative to tetramethylsilane (TMS), acetone, DMSO–d_6, $CDCl_3$, or 1,4–dioxane as both internal and external standards. Coupling constants (J values) are in Hertz (Hz). Multiplicities are designated as singlet (s), doublet (d). triplet (t), or multiplet (m). Infrared (IR) spectra were recorded on Perkin–Elmer Model 281–B spectrometers. Solid samples were analyzed as potassium bromide (KBr) disks or as chloroform solutions in sodium chloride cells. Liquids or oils were analyzed as neat films between sodium chloride plates or as chloroform solutions in sodium chloride cells. Absorptions are reported in wave number (cm^{-1}). The spectra are calibrated against the 1601 cm^{-1} band of a polystyrene film, and only the most prominent or characteristic absorptions are noted. Optical rotations (in degrees, °) were obtained on a Perkin–Elmer model 241 polarimeter at the sodium D line. High resolution mass spectra (HRMS) were obtained on a VG 70–70 HS high resolution double focusing mass spectrometer using ammonia chemical ionization (CI). The mass spectrometer was interfaced to a VG/DEC 11–73 data system. Elemental analyses were performed at the microanalytical facilities of the University of Pennsylvania, Philadelphia, PA. D-Ribono-1,4-lactone was purchased from Aldrich Chemical Company, Inc., Milwaukee, WI. D-Xylono-1,4-lactone was purchased from Pfanstiehl Laboratories, Inc., Waukegan, Illinois. Compounds which do not appear on the experimental section are described in our previous report.[7]

Preparation of L-arabinono-1,4-lactone (3). A solution of L-arabinose (5.000 g, 33.30 mmol) in water (117 mL) was treated with bromine[15] (4.29 mL, 13.3 g, 83.3 mmol), and the mixture was stirred in the dark and at ambient temperature for 4 days. Excess bromine was removed under reduced pressure. The resulting solution was neutralized by treatment with silver carbonate. The precipitate was removed by filtration, and the filtrate was concentrated under reduced pressure (35-40 °C bath). The residue was purified by silica gel flash-column chromatography using methanol:ethyl acetate (1:9) as eluants to afford L-arabinono-1,4-lactone as white crystals (3.129 g, 63% yield): R_f (MeOH:EtOAc, 1:9) 0.46; mp 99-101 °C; $[\alpha]_D^{22}$ -74.0 (*c* 0.54, H_2O) [lit.[57] $[\alpha]_D$ -33 (*c* 1, H_2O)]; IR (KBr) 3700-3100, 2930, 2890, 1770, 1410, 1320, 1230, 1170, 1140, 1110, 1060, 1020 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.50 (m, 1H, H_2), 3.71 (ddd, 1H, H_{5a}, J = 1.9, 5.1, 12.8 Hz), 3.97 (m, 1H, H_{5b}), 4.00 (m, 1H, H_4), 4.23 (dd, 1H, H_2, J = 6.7, 7.9 Hz), 5.02 (t, 1H, 5-OH, J = 5.6 Hz), 5.79 (d, 1H, 3-OH, J = 5.4 Hz), 6.04 (d, 1H, 2-OH, J = 6.7 Hz); ^{13}C NMR (DMSO-d_6) δ 59.24, 72.41, 73.89, 81.30, 174.74; HRMS calcd for $C_5H_{12}NO_5$ ($M^+ + NH_4$): 166.0715, found: 166.0702.

Preparation of D-lyxono-1,4-lactone (4). A solution of D-lyxose (5.000 g, 33.30 mmol) in water (117 mL) was treated with bromine (4.29 mL, 13.3 g, 83.3 mmol), and the mixture was stirred for 4 days at ambient temperature in the dark. Excess bromine was removed under reduced pressure. The resulting solution was neutralized by treatment with silver carbonate. The precipitate was removed by filtration, and the filtrate was concentrated *in vacuo* (35-40 °C bath). The residue was purified by silica gel flash-column chromatography using methanol:ethyl acetate (1:9) as eluants to afford D-lyxono-1,4-lactone as white crystals (3.555 g, 72% yield): R_f (MeOH:EtOAc, 1:9) 0.20; mp 94-96 °C (lit.[58] 110-112 °C); $[\alpha]_D^{22}$ +79.1 (*c* 0.54, H_2O) [lit.[58] $[\alpha]_D^{24}$ +82.5 (*c* 4.0, H_2O)]; IR (KBr) 3650-3120, 2980, 1770, 1460, 1370, 1285, 1195, 1170, 1100, 1045 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.59-3.69 (m, 2H, H_5), 4.20 (m, 1H, H_3), 4.32 (ddd, 1H, H_4, J = 2.9, 4.5, 7.3 Hz), 4.44 (dd, 1H, H_2, J = 4.6, 7.5 Hz), 4.86 (t, 1H, 5-OH, J = 5.6 Hz), 5.25 (d, 1H, 3-OH, J = 4.0 Hz), 5.75 (d, 1H, 2-OH, J = 7.6 Hz); ^{13}C NMR (DMSO-d_6) δ 59.50, 69.12, 70.56, 80.62, 176.26; HRMS calcd for $C_5H_{12}NO_5$ ($M^+ + NH_4$): 166.0715, found: 166.0704.

Equilibrium study of D-ribono-1,4-lactone (1) in aqueous acidic media. To a solution of D-ribono-1,4-lactone (0.604 g, 4.08 mmol) in deuterium oxide (1.68 g, 1.52 mL, 84.0 mmol) was added 12 N HCl (0.046 g, 0.038 mL, 0.46 mmol). After standing at 22 °C for 19 h, a ^{13}C NMR spectrum of the mixture revealed a 4 to 1 mixture of D-ribono-1,4-lactone and the presumed D-ribonic acid. Another ^{13}C NMR study, after 62 h, showed that this ratio had remained constant and that equilibration favored the D-ribono-1,4-lactone. The formation of D-ribonic acid, at equilibrium, in acidic medium, was confirmed by treatment of the reaction mixture with saturated $NaHCO_3$ to pH 7. After 30 min, a ^{13}C NMR spectrum indicated the complete conversion of D-ribonic acid to the corresponding sodium salt while the amount of D-ribono-1,4-lactone remained almost unaltered. After the mixture was allowed to stand at 22 °C for 24 h, the ratio between D-ribonic acid and its sodium salt was close to 1:1. An excess of saturated $NaHCO_3$ was then added to the reaction mixture. After 24 h, complete conversion of the mixture to the sodium salt of D-ribonic acid was observed by ^{13}C NMR.

Equilibrium study of L-arabinono-1,4-lactone (2) in aqueous acidic media. To a solution of L-arabinono-1,4-lactone (0.040 g, 0.27 mmol) in deuterium oxide (1.1 g, 1.0 mL, 55 mmol) was added 12 N HCl (0.033 g, 0.028 mL, 0.33 mmol). After standing at 22 °C for 20 h, a ^{13}C NMR spectrum of the mixture revealed a 2.8 to 1 mixture of L-arabinono-1,4-lactone and the presumed L-arabinoic acid. Another ^{13}C NMR study, after 39 h, showed that this ratio had remained constant and that equilibration favored the L-arabinono-1,4-lactone. The formation of L-arabinonic acid, at equilibrium, in acidic medium, was confirmed following the procedure described for D-ribonic acid by treatment of the reaction mixture with saturated $NaHCO_3$ to pH 7. After 10 min, a ^{13}C NMR spectrum indicated the complete conversion of L-arabinoic acid to the corresponding sodium salt while the amount of L-arabinono-1,4-lactone remained constant. After the mixture was allowed to stand at 22 °C for 24 h, the ratio between L-arabinonic acid and its sodium salt was close to 1:1. An excess of saturated $NaHCO_3$ was then added to the reaction mixture. After 24 h, complete conversion of the mixture to the sodium salt of L-arabinonic acid was observed by ^{13}C NMR.

Equilibrium study of D-xylono-1,4-lactone (3) in aqueous acidic media. To a solution of D-xylono-1,4-lactone (0.0500 g, 0.338 mmol) in deuterium oxide (0.70 mL, 0.78 g, 0.039 mol) was added 12 N HCl (0.030 g, 0.025 mL, 0.82 mmol). After standing at 22 °C for 44 h, a ^{13}C NMR spectrum of the mixture revealed a 9:5:1 mixture of the D-xylonic acid, D-xylono-1,4-lactone, and D-xylono-1,5-lactone. This 1,4-lactone is the only example of an equilibration in which the acid is favored, and where the

formation of a 1,5-lactone is also observed. The formation of D–xylonic acid, at equilibrium, in acidic medium, was confirmed by the treatment of the reaction mixture with saturated $NaHCO_3$ to pH 8. After 25 min, a ^{13}C NMR spectrum indicated the complete conversion of D–xylonic acid and D–xylono–1,5–lactone to the corresponding sodium salt while the amounts of D–xylono–1,4–lactone remained almost unaltered. An excess of saturated $NaHCO_3$ was then added to the reaction mixture. After 24 h, complete conversion of the mixture to the sodium salt of D–xylonic acid was observed by ^{13}C NMR.

Equilibrium study of D–lyxono–1,4–lactone (4) in aqueous acidic media. To a solution of D–lyxono–1,4–lactone (0.0700 g, 0.473 mmol) in deuterium oxide (1.11 g, 1.00 mL, 55.3 mmol) was added 12 N HCl (0.034 g, 0.028 mL, 0.34 mmol). After standing at 22 °C for 44 h, a ^{13}C NMR spectrum of the mixture revealed a 6:1 mixture of D–lyxono–1,4–lactone and the presumed D–lyxonic acid. The formation of D–lyxonic acid, at equilibrium, in acidic medium, was confirmed by treatment of the reaction mixture with saturated $NaHCO_3$ to pH 7. After 15 min, a ^{13}C spectrum indicated the complete conversion of D–lyxonic acid to the corresponding salt while the amount of D–lyxono–1,4–lactone remained unaltered. An excess of saturated $NaHCO_3$ was then added to the reaction mixture. After 22 h, complete conversion of the mixture to the sodium salt of D–lyxonic acid was observed by ^{13}C NMR.

Equilibrium study of 2–deoxy–D–ribono–1,4–lactone (5) in aqueous acidic media. To a solution of 2–deoxy–D–ribono–1,4–lactone (0.0493 g, 0.373 mmol) in deuterium oxide (1.12 g, 1.00 mL, 55.3 mmol) was added 12 N HCl (0.034 g, 0.028 mL, 0.34 mmol). After standing at 22 °C for 34 h, a ^{13}C NMR spectrum of the mixture revealed a 9 to 1 mixture of 2–deoxy–D–ribono–1,4–lactone and the presumed 2–deoxy–D–ribonic acid. The formation of 2–deoxy–D–ribonic acid, at equilibrium, in acidic medium, was confirmed by treatment of the reaction mixture with saturated $NaHCO_3$ to pH 7. After 30 min, a ^{13}C NMR spectrum indicated the complete conversion of 2–deoxy–D–ribonic acid to the corresponding sodium salt while the amount of 2–deoxy–D–ribono–1,4–lactone remained almost constant. An excess of saturated $NaHCO_3$ was then added to the reaction mixture. After 23 h, only partial conversion of the mixture to sodium salt of D–ribonic acid was observed. Complete conversion required 92 h 25 min, as observed by ^{13}C NMR.

5-O-Acetyl-2,3-O-(R)-benzylidene-D-ribono-1,4-lactone (20). To a stirred slurry of 2,3–O–(R)–benzylidene–D–ribono–1,4–lactone (**17**, 0.200 g, 0.847 mmol)[7] in dry CH_2Cl_2 (8 mL) was added acetic anhydride (0.113 g, 0.104 mL, 1.10 mmol) followed by dimethylaminopyridine (0.186 g, 1.525 mmol) at 0 °C, in an ice–water bath, under an argon atmosphere. The reaction mixture was stirred first at 0 °C for 5 min, and then at ambient temperature for 40 min. Diethyl ether (40mL) was added, and the organic layer was washed with water (15 mL), 10% $NaHCO_3$ (15 mL), and saturated NaCl (15 mL) solution. The organic layer was dried (Na_2SO_4), concentrated *in vacuo*, and the crude product purified by silica gel flash-column chromatography with ethyl acetate:petroleum ether (1:2, 1:1) as eluants. The pure compound was obtained as white crystals (0.201 g, 86% yield): R_f (EtOAc:petroleum ether, 1:1) 0.46; mp 143-144 °C (lit.[36] mp 143-145.5 °C, lit.[59] mp 143-145 °C; $[\alpha]_D^{22}$ -72.5 (*c* 1.48, $CHCl_3$), [lit.[36] $[\alpha]_D$ -71.2 ($CHCl_3$), lit.[59] $[\alpha]_D$ -72 (*c* 1.4, $CHCl_3$); IR ($CHCl_3$) 3030, 2880, 1760, 1400, 1385, 1350, 1230, 1180, 1095 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.09 (s, 3H, $COCH_3$), 4.28 (dd, 1H, H_{5a}, J = 2.4, 12.4 Hz), 4.40 (dd, 1H, H_{5b}, J = 2.8, 12.4 Hz), 4.84 (d, 1H, H_3, J = 5.9 Hz), 4.89 (t, 1H, H_4, J = 2.6 Hz), 4.91 (d, 1H, H_2, J = 5.9 Hz), 6.00 (s,1H, OCHO), 7.39-7.46 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 20.57, 63.44, 75.23, 78.79, 79.31, 107.12, 126.73, 128.54, 130.17, 134.86, 169.63, 172.17; HRMS calcd for $C_{14}H_{18}NO_6$ (M^++NH_4): 296.1134, found: 296.1108.

3,5-O-(S)-Benzylidene-D-xylono-1,4-lactone (21). Method A: To a solution of lactone **3** (1.000 g, 6.752 mmol) in DMSO (3.43 mL) were added benzaldehyde (3.43 mL, 3.58 g, 33.8 mmol) and concentrated HCl (0.17 mL, 0.21 g, 2.1 mmol). The mixture was stirred for 5 days, at room temperature, under argon, and then concentrated *in vacuo*. The residue was purified by silica gel column-chromatography, eluting with ethyl acetate: petroleum ether (1:2, 1:1), to afford **21** (0.7469 g, 49% yield) as a white solid. Method B: To a mixture of lactone **3** (1.000 g, 6.752 mmol) in DME (4.5 mL) were added α,α–dimethoxytoluene (1.12 mL, 1.23 g, 8.10 mmol) and anhydrous stannous chloride (0.0128 g, 0.0625 mmol). The reaction mixture was heated to reflux for 4 h, under argon. The solvent was evaporated *in vacuo*, and the residue purified by silica gel flash-column chromatography, eluting with ethyl acetate:petroleum ether (1:2, 1:1), to afford 0.214 g (14% yield) of compound **21**: R_f (EtOAc:petroleum ether, 1:1) 0.28; mp 118-119 °C; $[\alpha]_D^{22}$ +81.10 (c 0.46, $CHCl_3$); IR ($CHCl_3$) 3600-3200, 3020, 2940, 1790, 1380, 1180, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.42 (br s, 1H, 2-OH), 4.20 (dd, 1H, H_{5a}, J = 2.0, 13.8 Hz), 4.31 (br s, 1H, H_3), 4.58-4.62 (m, 3H), 5.53 (s, 1H), 7.36-7.44 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 66.16, 73.63, 73.67, 76.78, 99.36, 126.09, 128.36, 129.46, 136.78, 175.43; HRMS calcd for $C_{12}H_{12}O_5$ (M^+): 236.0685, found: 236.0658.

3,5-O-(S)-Benzylidene-2-O-(*p*-nitro)benzoyl-D-xylono-1,4-lactone (22). To a solution of compound **21** (0.1000 g, 0.4237 mmol) in CH_2Cl_2 (4 mL) were added 4-nitrobenzoylchloride (0.0943 g, 0.508 mmol) and 4-dimethylaminopyridine (0.0673 g, 0.551 mmol) at 0 °C in an ice-water bath, under argon . After 10 min, the mixture was concentrated *in vacuo*. The residue was purified by silica gel flash-column chromatography, eluting with ethyl acetate:petroleum ether: dichloromethane (1:4:2), to afford compound **22** (0.168 g, 100% yield) as white crystals: R_f (EtOAc:petroleum ether, 1:1) 0.68; mp 191-192 °C; $[\alpha]_D^{22}$ +120.47 (c 0.22, $CHCl_3$); IR ($CHCl_3$) 3040, 2960, 1750, 1610, 1530, 1400, 1380, 1255, 1185, 1100, 1060, 950 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.43 (s, 1H, H_2), 4.80 (d, 1H, H_3, J = 2.7 Hz), 4.69 (m, 1H, H_4), 4.26 (dd, 1H, H_{5a}, J = 2.3, 14.0 Hz), 4.67 (m, 1H, H_{5b}), 5.60 (s, 1H), 7.40-7.50 (m, 5H), 8.22, 8.33 (d, 4H, J = 8.9 Hz); ^{13}C NMR ($CDCl_3$) δ 65.96, 73.43, 74.57, 74.81, 99.60, 123.82, 126.11, 128.43, 129.64, 131.24, 133.34, 136.44, 151.15, 163.05, 170.40; HRMS calcd for $C_{19}H_{15}NO_8$ (M^+): 385.0798, found: 385.0784.

3,5-O-(S)-Benzylidene-D-lyxono-1,4-lactone (23). Method A: To a solution of lactone **4** (2.000 g, 13.50 mmol) in concentrated HCl (0.358 mL, 0.430 g, 4.30 mmol) was added benzaldehyde (23.73 mL, 24.77 g, 233.5 mmol). The reaction mixture was stirred for 20 h at room temperature, under argon. The precipitate was collected by filtration, and chromatographed on silica gel, eluting with ethyl acetate:petroleum ether (2:1, 1:0), to afford compound **23** (2.690 g, 84% yield) as a white solid. Method B: A mixture of lactone **4** (1.000 g, 6.752 mmol), α,α-dimethoxytoluene (1.12 mL, 1.23 g, 8.10 mmol), and anhydrous stannous chloride (0.0128 g, 0.0625 mmol) in THF (4.5 mL) was heated to reflux and stirred for 2h, under argon. After evaporation of the solvent *in vacuo*, the residue was purified by silica gel flash-column chromatography, eluting with ethyl acetate:petroleum ether (1:2, 1:1, 4:1) to afford 0.7661 g (48% yield) of compound **23** as a white solid: R_f (EtOAc:petroleum ether, 1:1) 0.14, mp 202-203 °C, $[\alpha]_D^{22}$ +31.1 (c 0.23, acetone); IR (KBr) 3460, 3080, 2870, 1770, 1455, 1190, 1100, 1010, 865 cm^{-1}; ^1H NMR (DMSO-d_6) δ4.20 (dd, 1H, H_{5a}, J = 1.7, 13.6 Hz), 4.31 (d, 1H, H_{5b}, J = 13.6 Hz), 4.39 (m, 1H, H_3), 4.68-4.71 (m, 2H, H_2, H_3), 5.65 (s, 1H), 5.99 (d,1H, J = 7.1 Hz), 7.36-7.45 (m, 5H); ^{13}C NMR (DMSO-d_6) δ 65.87, 69.58, 70.94, 74.21, 97.65, 126.24, 127.95, 128.81, 137.75, 175.97; HRMS calcd for $C_{12}H_{13}O_5$ (M^+ + H): 237.0763, found: 237.0748. Anal. calcd for $C_{12}H_{12}O_5$: C, 61.02; H, 5.12. Found: C, 60.95; H, 5.42.

3,4-O-Isopropylidene-L-arabinono-1,5-lactone (28). A mixture of lactone **2** (1.000 g, 6.752 mmol), acetone (4.96 mL, 3.92 g, 67.5 mmol), and concentrated HCl (0.12 g, 0.098 mL, 1.2 mmol) was stirred at room temperature for 20 h. Solid $NaHCO_3$ (0.1087 g, 1.294 mmol) was added, and the mixture stirred for 20 min. The solid was collected, washed thoroughly with acetone, and the filtrate concentrated *in vacuo*. The resulting product was purified by silica gel flash-column chromatography, eluting with petroleum ether:ethyl acetate (2:1,1:1), to afford compound **28** (0.201 g, 16% yield) as a white foam: R_f (EtOAc:petroleum ether, 2:1) 0.6; $[\alpha]_D^{22}$ -9.80° (c 1.8, MeOH); IR ($CHCl_3$) 3600-3400, 2960, 1760, 1385, 1375, 1260, 1160, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (s, 3H), 1.52 (s, 3H), 3.53 (d, 1H, 2-OH, J = 3.5 Hz), 4.14 (dd, 1H, H_{5a}, J = 8.0, 11.4 Hz), 4.37 (dd, 1H, H_3, J = 5.9, 7.7 Hz), 4.43 (dd, 1H, H_2, J = 3.4, 5.9 Hz),4.51 (dt, 1H, H_4, J = 4.9, 7.8 Hz), 4.59 (dd, 1H, H_{5b}, J = 4.9, 11.4 Hz); ^{13}C NMR ($CDCl_3$) δ 24.36, 26.56, 66.86, 70.13, 70.22, 77.26, 112.02, 172.12; HRMS calcd for $C_8H_{13}O_5$ (M^+ + H): 189.0763, found: 189.0746.

3,5-O-Isopropylidene-D-xylono-1,4-lactone (29) and 1,4:,3,5-Di-O-isopropylidene-D-xylono-1,4-lactone (30). Method A: A mixture of lactone **3** (2.000 g, 13.50 mmol), acetone (9.92 mL, 7.84 g, 135 mmol), and concentrated HCl (0.196 mL, 0.235 g, 2,35 mmol) was stirred for 20 h at room temperature. Solid $NaHCO_3$ (0.2174 g, 2.585 mmol) was added, and the mixture stirred for 20 min. The solid was collected, washed thoroughly with acetone, and the filtrate concentrated under reduced pressure. The residue was purified by silica gel flash-column chromatography, eluting with ethyl acetate:petroleum ether (1:3, 1:2), to afford compound **29** (0.1624 g, 6% yield) as white crystals and compound **30** (0.0282 g, 0.9% yield) as a colorless oil. Method B: A mixture of lactone **3** (1.000 g, 6.752 mmol), acetone (4.96 mL, 3.92 g, 67.5 mmol), and *p*-toluenesulfonic acid (0.124 g, 0.652 mmol) was stirred at room temperature for 20 h. After concentration, the residue was purified by silica gel flash-column chromatography, eluting with ethyl acetate:petroleum ether (1:3, 1:2), to afford compound **29** (0.153 g, 12% yield) as the only product. The formation of compound **30**, as seen in Method A, was not observed.

Physical data for **29**: R_f (EtOAc:petroleum ether, 1:1) 0.42; mp 90-92 °C; $[\alpha]_D^{22}$ +77.03 (c 0.37, acetone); IR ($CHCl_3$) 3600-3100, 3000, 2950, 1785, 1385, 1380, 1180, 1160, 1120, 1065 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (s, 3H), 1.48 (s, 3H), 3.48 (br s, 1H, 2-OH), 4.14 (ddd, 2H, H_{5ab}, J = 2.3, 13.8, 23.0 Hz), 4.21 (br s, 1H, H_4), 4.42 (d, 1H, H_3, J = 2.9 Hz), 4.57 (dd, 1H, H_2, J = 2.8, 5.5 Hz); ^{13}C NMR ($CDCl_3$) δ 19.48, 28.08, 59.43, 71.36, 73.65, 73.93, 98.16, 175.61; HRMS calcd for $C_8H_{13}O_5$ (M^+ + H): 189.0763, found: 189.0774.

Physical data for **30**: R_f (EtOAc:petroleum ether, 1:2) 0.26; $[\alpha]_D^{22}$ +29.1 (c 0.39, $CHCl_3$); IR ($CHCl_3$): 3600-3400, 2990, 2850, 1795, 1380, 1270, 1235, 1170, 1150, 1120, 1095, 1060, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.43 (s, 3H), 1.44 (s, 3H), 1.59 (s, 3H), 1.66 (s, 3H), 3.75 (dd, 1H, H_{5a}, J = 3.9, 12.0 Hz), 3.88 (dd, 1H, H_{5b}, J = 3.6, 12.0 Hz), 4.21 (m, 1H, H_4), 4.28 (dd, 1H, H_3, J = 2.5, 8.5 Hz),4.46 (d, 1H, H_2, J = 2.4 Hz); ^{13}C NMR ($CDCl_3$) δ 26.62, 26.84, 26.93, 27.10, 61.46, 73.49, 75.99, 76.68, 110.12, 111.78, 170.29; HRMS calcd for $C_{11}H_{19}O_6$ (M^+ + H): 247.1181, found: 247.1155.

2,3-O-Isopropylidene-D-lyxono-1,4-lactone (31) and 3,5-O-isopropylidene-D-lyxono-1,4-lactone (32). A mixture of lactone **4** (1.000 g, 6.752 mmol), acetone (4.96 mL, 3.92 g, 67.5 mmol), and concentrated HCl (0.12 g, 0.098 mL, 1.2 mmol) was stirred at room temperature for 20 h. Solid $NaHCO_3$ (0.1087 g, 1.294 mmol) was added, and the mixture stirred for 20 min. The solid was collected, washed thoroughly with acetone, and the filtrate concentrated under reduced pressure. The residue was purified by silica

gel flash-column chromatography, eluting with ethyl acetate:petroleum ether (1:2, 1:1), to afford compounds **31** (0.3504 g, 28% yield) and **32** (0.0775 g, 6% yield) as white crystals.

Physical data for **31**: R_f(EtOAc:petroleum ether, 1:1) 0.19; mp 97-98 °C (lit.[60] 88-93 °C); $[\alpha]_D^{22}$ +92.3 (c 0.37, acetone) [lit.[60]+108 (c 1, acetone)]; IR ($CHCl_3$) 3600-3300, 2940, 1790, 1390, 1375, 1260, 1230, 1180, 1159, 1110, 1090, 1050, 1020, 970, 910 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (s, 3H), 1.48 (s, 3H), 2.30 (br s, 1H, OH), 3.97 (m, 2H, H_{5ab}), 4.63 (m, 1H, H_4), 4.89 (m, 2H, H_2, H_3); ^{13}C NMR ($CDCl_3$) δ 25.66, 26.60, 60.77, 76.06, 76.15, 79.27, 114.41, 173.70; HRMS calcd for $C_8H_{16}NO_5$ ($M^+ + NH_4$): 206.1028, found: 206.1048.

Physical data for **32**: R_f(EtOAc:petroleum ether, 3:1) 0.24; mp 109-110 °C (lit.[60] 137-138 °C); $[\alpha]_D^{22}$ +30.4 (c 0.27, acetone) [lit.[60] $[\alpha]_D^{22}$ +22 (c 2, acetone)]; IR (KBr) 3600-3100, 3000, 2960, 1770, 1380, 1320, 1270, 1180, 1140, 1035, 1010, 970 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.43 (s, 3H), 1.52 (s, 3H), 2.99 (d, 1H, OH, J = 9.9 Hz), 4.14 (m, 2H, H_{5ab}), 4.23 (dd, 1H, H_4, J = 2.9, 4.2 Hz), 4.52 (dd, 1H, H_2, J = 4.4, 9.9 Hz), 4.62 (dd, 1H, H_3, J = 2.3, 4.3 Hz); ^{13}C NMR ($CDCl_3$) δ 19.20, 28.34, 59.71, 67.12, 69.63, 71.56, 98.29, 174.89; HRMS calcd for $C_8H_{16}NO_5$ ($M^+ + NH_4$) 206.1028, found 206.1019.

X-Ray Crystal Structure Determinations: The determination of all of the X-ray crystal structures were performed at the X-ray crystallography facility of the University of Pennsylvania. X-ray intensity data were collected on an Enraf-Nonius CAD4 diffractometer employing graphite-monochromated Cu-Kα radiation (λ=1.54184Å) and using the ω-2θ scan technique. The intensity data were corrected for Lorentz and polarization effects but not for absorption. Of the reflections measured a number of unique reflections with $F2>3\sigma(F2)$ were used during subsequent structure refinement. The structures were solved by direct methods (MULTAN 11/82). Refinement was by full-matrix least squares techniques based on F to minimize the quantity $\Sigma w(|Fo|-|Fc|)^2$ with $w=1/\sigma^2(F)$. Non-hydrogen atoms were refined anisotropically and hydrogen atoms were included as constant contributions to the structure factors and were not refined. Refinements converged to $R_1<0.08$ and $R_2<0.12$.

Calculations: Molecular mechanics calculations with the MM2 force field and calculations of the NMR coupling constants were performed with the PC Model 4.41 program for the Macintosh, obtained from Serena Software. The NMR coupling constants of the X-ray geometries were also calculated with the PC Model 4.41 program. Semiempirical calculations at the PM3 level were performed with MOPAC 6.1 at the San Diego Supercomputer Center (SDSC) on the Cray-90 platform. Complete geometry and energy otimizations were performed using the PRECISE criteria of the program.

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