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Investigations of the Formation of Cyclic Acetal and Ketal Derivatives of D-Ribono-1,4-lactone and 2-Deoxy-D-ribono-1,4-lactone

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Abstract: *The reactions of D-ribono-1,4-lactone, and 2-deoxy-D-ribono-1,4-lactone with benzaldehyde and acetone in acidic media were investigated. The products obtained were isolated and characterized. The ^1H NMR spectra of the 1,5-lactone product resulting from the thermodynamically controlled reaction of D-ribono-1,4-lactone with benzaldehyde were examined between 300 °K and 200 °K in a polar solvent. No conformational changes in the 1,5-lactone ring were observed within this temperature range. Detailed NMR studies showed that the acetalization of D-ribono-1,4-lactone proceeded with the initial formation of the endo-2,3-acetal derivative, which in the presence of aqueous acids underwent ring expansion and isomerization to the 3,4-acetal of the 1,5-lactone. The endo preference of benzylidene acetals was explained by the transition state conformation of the reactants and the thermodynamic stability of the products, as calculated with molecular mechanics.*

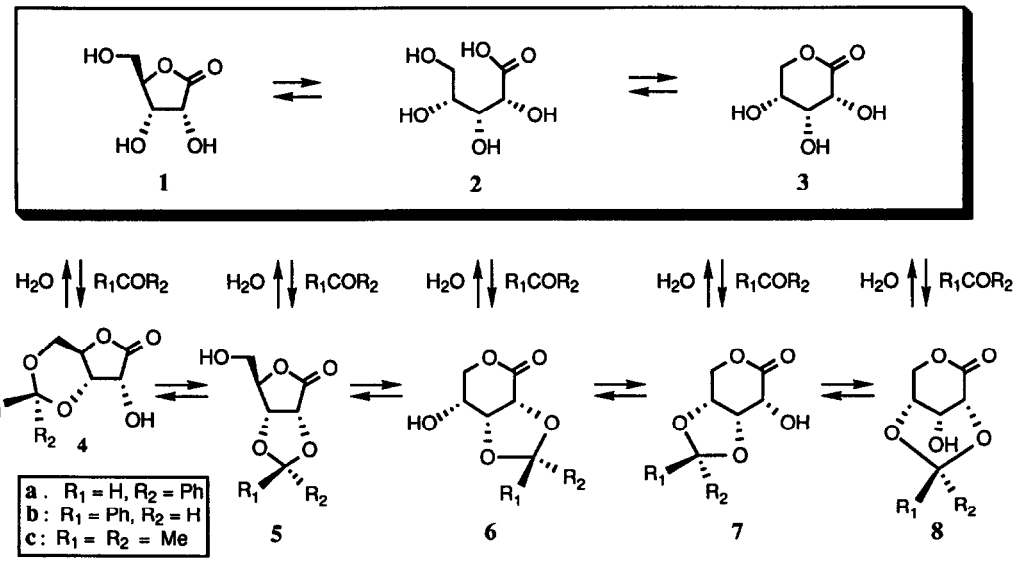
Introduction

The utilization of cyclic acetals or ketals as protecting groups[1] has been a convenient and widespread technique for over a century.[2] These derivatives are especially valuable in carbohydrate chemistry because the polyhydroxyl functions of sugars offer numerous possibilities for the simultaneous and selective protection of two neighboring hydroxyl groups. The resulting cyclic acetals have also been used extensively in asymmetric syntheses which utilize sugars as chiral templates, and where selective transformations of polyhydroxyl groups are required.[3] The synthetic, mechanistic and stereochemical aspects of cyclic acetals and ketals of carbohydrates have been thoroughly reviewed.[4,5]

The usual method of preparing cyclic acetals or ketals involves the reaction of a diol with an aldehyde or ketone, commonly benzaldehyde or acetone, in the presence of a protic or Lewis acid as a catalyst. Depending on the substrate and the carbonyl compound used, it is often possible to obtain one of several isomeric products. Although there have been many studies on this subject, it is not always possible to predict which isomer will be obtained under acetalization conditions. This uncertainty is due to the various equilibria that occur under different reaction conditions with kinetic or thermodynamic control. In addition to variations in the regioselectivity of the reaction, products with different acetal ring sizes (commonly 1,3-dioxanes or 1,3-dioxolanes) may also be obtained. Interconversions between the furanose and the pyranose forms of the carbohydrates are also observed.

In recent years, there has been an increasing interest in the use of aldonolactones as chiral templates in natural product synthesis. Among these, the commercially available D-ribono-1,4-lactone (**1**, γ-D-ribonolactone) has been explored in our laboratories[6,7,8] and elsewhere[9] as an effective alternative to simple sugars. These syntheses have often involved the formation of acetal or ketal intermediates, and in the course of these investigations, some unexpected results, including ring rearrangements, have been observed. Thus, benzylidenation of **1** can theoretically lead to five possible types of lactone products under equilibrium conditions: the 3,5- (**4**) and 2,3- (**5**) benzylidene-1,4-lactones, and the 2,3- (**6**), 3,4- (**7**) and 2,4- (**8**) benzylidene-1,5-lactones, each of which can exist as a pair of acetal epimers (Scheme 1). These products can be derived from prior isomerization of the 1,4-lactone (**1**) to the 1,5-lactone (**3**), via the aldonic acid (**2**), or via isomerization of the acetal derivatives after the benzylidenation.

Scheme 1

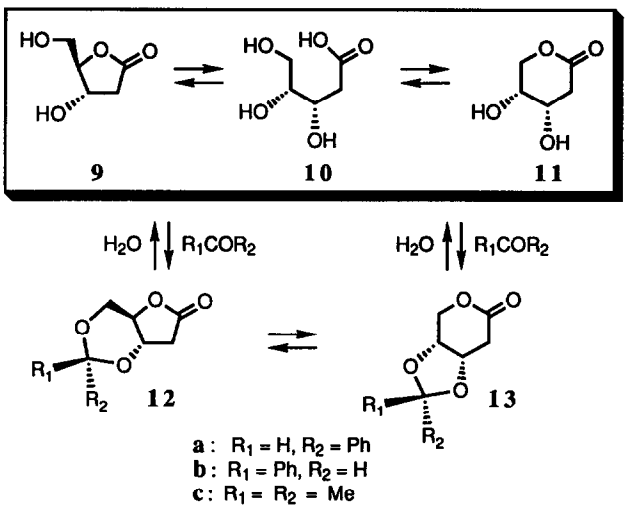


The structural similarity of compounds **4-8**, combined with their facile interconversion, has led to several wrong assignments. Structures **4a,b** were first reported by Zinner[10] as the products of the reaction of ribonic acid salt with benzaldehyde and HCl, while structures **8a,b** were assigned to the reaction of ribonic acid methyl ester with benzaldehyde and zinc chloride. Both of these assignments, however, were shown to be incorrect.

As no other 3,5-cyclic acetals of furanoid derivatives of ribose or arabinose had previously been observed under equilibrating conditions, Baggett et al.[11] investigated the structure of the benzylidene acetal obtained from **1** and benzaldehyde with HCl as the catalyst. X-Ray analysis of the product showed that it was the 3,4-O-benzylidene-1,5-lactone (**7a**). The products obtained by the $ZnCl_2$-catalyzed reaction were found by Chittenden and Regeling[12] to be the 2,3-O-benzylidene-1,4-lactones (**5a,b**).

In another study,[6a] the 2-deoxy derivatives **12a,b** were the presumed intermediates used in the synthesis of (-)-litsenolides C_1 and C_2, which involved a deoxygenation and acetal hydrolysis sequence. While the correct intermediates were **13a,b** in this case, the desired structure of the natural product was obtained since the acidic hydrolysis of **13a,b** (thought to be **12a,b**) occurred with a further rearrangement of the resulting 1,5-lactone (**11**) to the 1,4-lactone (**9**) via the aldonic acid (**10**) (Scheme 2).

Scheme 2



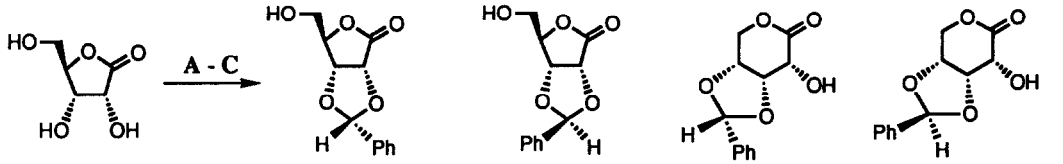
Although the detailed formation and behavior of acetals and ketals obtained from glycosides have been studied,[5] the formation of similar derivatives from aldonolactones has not been well examined. In order to understand and rationalize these findings, a detailed investigation of the reactions of D-ribono-1,4-lactone (**1**) and 2-deoxy-D-ribono-1,4-lactone (**9**) with benzaldehyde and acetone under different reaction conditions, was carried out.

Results and Discussion

Syntheses of benzylidene acetals

As shown in Scheme 3, D-ribono-1,4-lactone (**1**) was treated with benzaldehyde and a catalytic amount of concentrated hydrochloric acid at room temperature for 20 h to yield 63% of 3,4-(R)-benzylidene-D-ribono-1,5-lactone (**7a**). When *p*-toluenesulfonic acid (*p*-TsOH·H_2O) was used as a catalyst, four compounds were isolated (**5a**, **5b**, **7a**, **7b**, in 5%, 7%, 48%, and 2% yield, respectively). Compound **7a** was the major product. Treatment of **1** with α,α-dimethoxytoluene and a catalytic amount of anhydrous $SnCl_2$ in dimethoxyethane (DME) yielded compounds **5a** (60%) and **5b** (4%). The formation of **7a** was not observed under non-aqueous reaction conditions. The structure of compound **5a** was confirmed by X-ray analysis of its acetate.

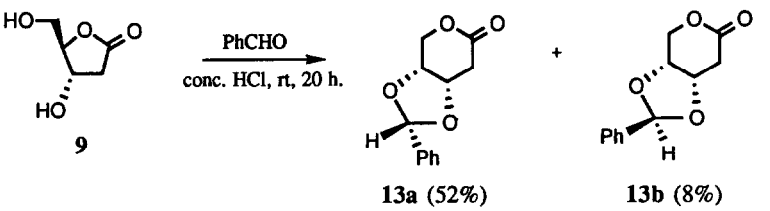
Scheme 3



	1	5a	5b	7a	7b
A: PhCHO, conc. HCl, rt, 20 h		-	-	63%	-
B: PhCHO, *p*-TSOH.H_2O, rt, 20 h		5%	7%	48%	2%
C: $PhCH(OMe)_2$, $SnCl_2$, DME, Δ, 45 min		60%	4%	-	-

When 2-deoxy-D-ribono-1,4-lactone (**9**) was treated with benzaldehyde and concentrated hydrochloric acid, 3,4-O-(R)-benzylidene-2-deoxy-1,5-ribonolactone (**13a**) and 3,4-O-(S)-benzylidene-2-deoxy-1,5-ribonolactone (**13b**) were obtained in 52% and 8% yield, respectively (Scheme 4). The structure of **13b** was confirmed by comparison of its spectroscopic data (^1H NMR, IR) with those of **13a**. Compound **5a** was derivatized to an acetate (**14**) to confirm its structure by X-ray analysis.

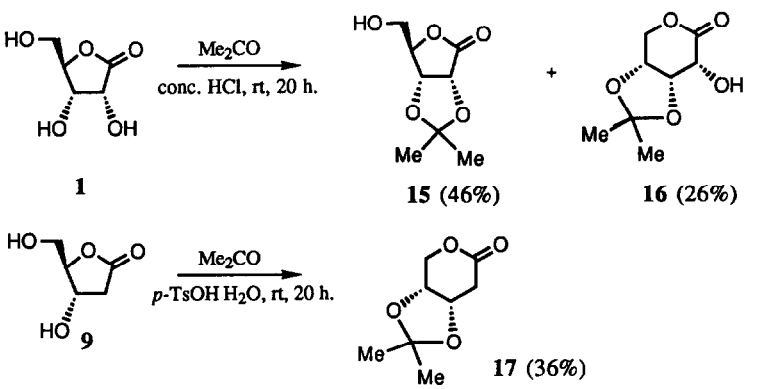
Scheme 4



Syntheses of isopropylidene ketals

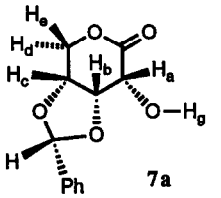
Mitchell[13] reported that reaction of D-ribono-1,4-lactone (**1**) with acetone and HCl as catalyst, for 18 h at room temperature, formed 2,3-O-isopropylidene-D-ribono-1,4-lactone (**15**) in 73% yield, as the only product. We found that compounds **15** and **16** were obtained in 46% and 26% yields, respectively. Also, reaction of 2-deoxy-D-ribono-1,4-lactone (**9**) with acetone and concentrated HCl, afforded **17** in 36% yield (Scheme 5).

Scheme 5



Low-temperature ^1H NMR (500 MHz) of 3,4-O-(R)-benzylidene-D-ribono-1,4-lactone (7a) in acetone-d_6

The ^1H NMR spectra of **7a** in a polar solvent (acetone-d_6), at 300 °K and lower temperatures, were examined to test the conformational stability of the molecule. Table I lists the chemical shifts and coupling constants for the protons of lactone **7a** at 300, 260, 240, 220, and 200 °K. Deuterated acetone was chosen as the solvent because of its low freezing point and high polarity. As seen in Table I, lowering the temperature did not affect the coupling constant $J_{a,b}$. This result indicated that the conformation of **7a** was not affected by changes of temperature between 300 °K and 200 °K. Furthermore, the coupling constant $J_{g,a}$ increased as the temperature was lowered, suggesting an environmental change related to the hydrogen bonding of -OH_g. The chemical shift of H_g had a large temperature-coefficient value (-0.0098 ppm/°K) suggesting the presence of solvent-exposed hydrogen bonding.[14] The small temperature-coefficient value (-0.0011 ppm/°K) of the H_a chemical shift could be related to the environmental change of the adjacent hydroxyl group hydrogen bonding to the solvent.



7a

Table I

Temperature	Chemical shift (ppm)	Coupling constants (J)	
300 °K	H_a 4.68	H_a-H_b	3.38
		H_a-H_g	7.10
	H_b 4.84	H_b-H_a	3.31
		H_b-H_c	8.12
	H_c 4.75	H_c-H_e	1.17
		H_c-H_d	1.71
		H_c-H_b	8.11
	H_d 4.52	H_d-H_e	13.24
		H_d-H_c	1.71
	H_e 4.43	H_e-H_d	13.22
	H_f 5.78		
	H_g 4.44	H_g-H_a	7.21
260 °K	H_a 4.72	H_a-H_b	3.34
	H_b 4.83	H_b-H_a	3.34
	H_g4.86	H_g-H_a	7.58
	H_f 5.77		
240 °K	H_a 4.74	Ha-H_b	3.27
	H_b 4.83	H_b-H_a	3.29
	H_g 5.06	H_g-H_a	7.87
	H_f 5.76		
220 °K	H_a 4.77	H_a-H_b	3.29
	H_b 4.82	H_b-H_a	3.14
	H_g 5.25	H_g-H_a	8.14
	H_f 5.75		
200 °K	H_a 4.79	H_a-H_b	3.09
	H_b 4.81	H_b-H_a	3.16
	H_g 5.42	H_g-H_a	8.17
	H_f 5.74		

Formation of acetals in acidic media. Equilibria studies of aldonolactones with benzaldehyde and acetone

The formation of the O-benzylidene acetals and O-isopropylidene ketals of D-ribono-1,4-lactone (**1**) and 2-deoxy-D-ribono-1,4-lactone (**9**) with benzaldehyde or acetone in NMR solvents (DMSO-d_6 and $CDCl_3$) containing concentrated hydrochloric acid were monitored by ^{13}C NMR spectroscopy to study the reaction pathways. *As seen from these studies, acetal formation occurs first, and then rearrangement follows.* The representative procedures used are illustrated below with D-ribono-1,4-lactone (See Schemes 3 and 4):

O-Benzylidene acetals: A solution of D-ribono-1,4-lactone (**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 spectrum of the reaction mixture after 32 min indicated the formation of 2,3-O-(R)-benzylidene-D-ribono-1,4-lactone (**5a**). Another ^{13}C NMR spectrum taken after 53 min indicated the presence of a trace amount of 2,3-O-(S)-benzylidene-D-ribono-1,4-lactone (**5b**). The 3,4-O-(R)-benzylidene-D-ribono-1,5-lactone (**7a**) started to appear on ^{13}C NMR spectra along with unidentified intermediates 2h and 8 min after the reaction was initiated. A ^{13}C NMR spectrum taken after 5 h revealed about a 2:1 ratio of D-ribono-1,4-lactone (**1**) and 2,3-O-(R)-benzylidene-D-ribono-1,4-lactone (**5a**). Since a white precipitate was produced in the NMR tube due to the formation of 3,4-O-(R)-benzylidene-D-ribono-1,5-lactone (**7a**), a sufficient amount of DMSO-d_6 was added to obtain a homogeneous solution. Another ^{13}C NMR spectrum taken after 88 h and 44 min showed the ratio of D-ribono-1,4-lactone (**1**):3,4-O-(R)-benzylidene-1,5-lactone (**7a**):2,3-O-(R)-benzylidene-1,4-lactone (**5a**) to be 2:2:1.

When ribonolactone **1** was treated with benzaldehyde and zinc chloride in DMSO-d_6, two products were formed. The major product was **5a** and the minor product was **5b**. Formation of **7a** was not detected even after a week at room temperature.

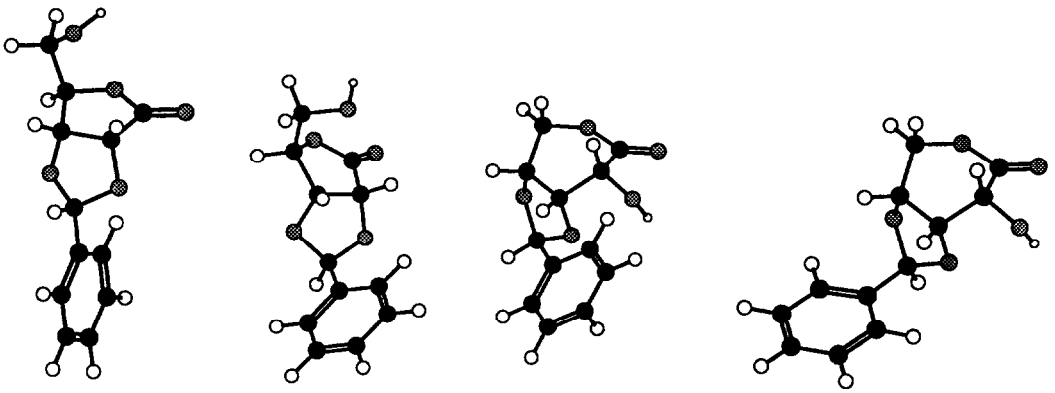
O-Isopropylidene ketals: A solution of D-ribono-1,4-lactone (**1**, 0.0741 g, 0.500 mmol) in acetone (0.396 g, 0.500 ml, 6.81 mmol) and $CDCl_3$ (0.750 g, 0.500 ml, 6.23 mmol) with 12 N HCl (0.034 g, 28.7 ml, 0.344 mmol) was allowed to stand at ambient temperature. A ^{13}C NMR spectrum of the reaction mixture after 15 min revealed formation of 2,3-O-isopropylidene-D-ribono-1,4-lactone (**15**) along with the trace amount of 3,4-O-isopropylidene-D-ribono-1,5-lactone (**16**) and a small amount of unreacted 1,4-lactone. Another ^{13}C NMR spectrum taken after 110 min indicated an increase in the amount of compound **16**. After 39 h 25 min, a ^{13}C NMR spectrum showed the ratio of the 2,3-O-isopropylidene derivative and 3,4-O-isopropylidene derivative to be 2:1 along with a small amount of unreacted D-ribono-1,4-lactone. This ratio remained constant at further ^{13}C NMR study. To examine the direct interconversion between the 1,4- and 1,5- lactones, both **15** and **16** were treated with an acetone-$CDCl_3$ mixture containing 3% (w/w) concentrated hydrochloric acid. A ^{13}C NMR spectrum of the reaction mixture after 25 min revealed interconversion between 2,3-O-isopropylidene-D-ribono-1,4-lactone (**15**) and 3,4-O-isopropylidene-D-ribono-1,5-lactone (**16**). At equilibrium, the ratio among **15** and **16** was 3:2. This result agrees with the previous equilibrium study of ribonolactone.

Molecular mechanics calculations of 5ab and 7ab

In order to obtain information on the relative thermodynamic stabilities of the *endo* (**5a**) and *exo* (**5b**) benzylidene 2,3-acetals of D-ribono-1,4-lactone and the corresponding 3,4-derivatives (**7a**) and (**7b**) of D-ribono-1,5-lactone, we carried out molecular mechanics calculations with PCMODEL (Version 4.41).[15] As shown in Scheme 6, the *exo*-isomer is slightly higher in energy (0.12 Kcal/mol) than the *endo*-isomer in the case of the

1,4-lactone, (**5b** vs **5a**) but much higher in energy (1.15 Kcal/mol) in the case of the 1,5-lactone (**7b** vs **7a**). The calculated ^{1}H-NMR coupling constants, J_{ab} and J_{bc}, for compounds **5ab** and **7ab** agreed well with the experimental values. For example, in the case of **7a**, the calculated values were J_{ab} = 7.90 Hz and J_{bc} = 3.90 Hz, while the experimental values were: J_{ab}=8.10 Hz and J_{bc}=3.38 Hz, respectively. Thus, while both isomers **5a** and **5b** were observed at equilibrium, with **5a** being the major product, in the case of **7** only the thermodynamically more stable *endo*-isomer **7a** could be isolated.

Scheme 6



5a (*endo*) 23.32 Kcal/mol

5b (*exo*) 23.44 Kcal/mol

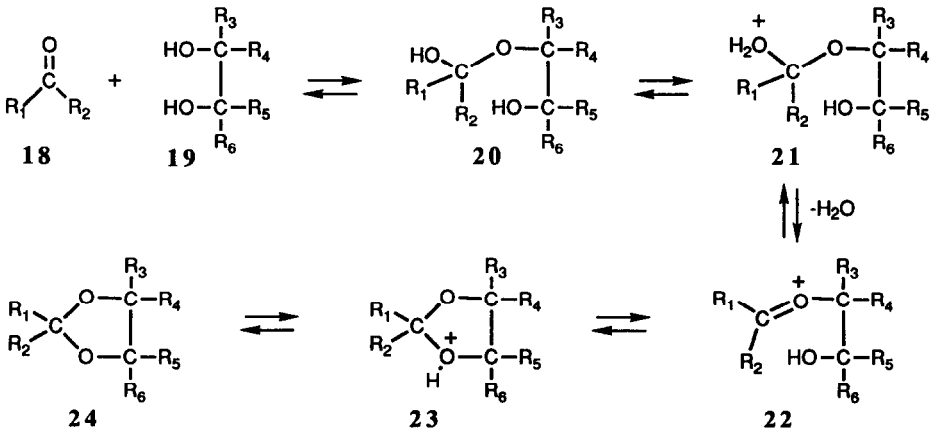
7a (*endo*) 24.42 Kcal/mol

7b (*exo*) 25.57 Kcal/mol

Mechanism of acetal or ketal formation

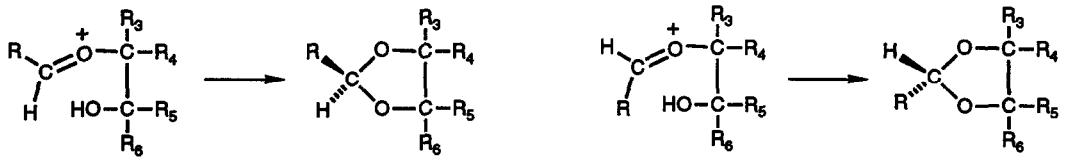
The mechanism of acetal formation is believed to proceed through hemiacetal intermediates,[5] shown in Scheme 7. The rate-limiting step in this sequence is considered to be the ring closure of intermediate **22** to the protonated acetal **23**. The oxocarbonium ion **22** will react with the nearest hydroxyl group to form the kinetic acetal product (**24**) which may subsequently rearrange to the thermodynamically most stable product.

Scheme 7



The two isomeric acetals (**26**, **28**) are formed via the two rotamers of oxonium ion **22**, namely the transoid **25** and the cisoid **27** (Scheme 8). Clode[5] assumed that the transoid arrangement (**25**) was more stable than the cisoid (**27**). For secondary oxocarbonium ions, rotamers with an *anti* arrangement are assumed to be preferable to those with a *syn* arrangement. Clode postulated that the *anti*-transoid oxocarbonium ion resembled the rate-determining transition state and should be the most stable ion for steric reasons. Such an intermediate should lead to the rapid formation of the acetal with an *endo*-phenyl group by a kinetic process.

Scheme 8

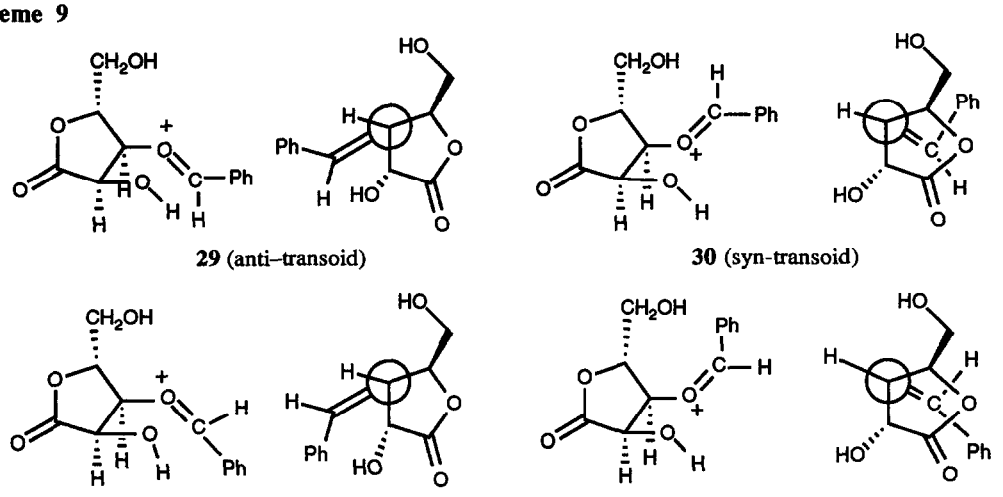


25 *transoid* **26** **27** *cisoid* **28**

In the reaction of ribonolactone with benzaldehyde, we first observed the formation of 2,3-O-(R)-benzylidene-D-ribono-1,4-lactone (**5a**). Four oxonium ions are possible (Scheme 9). The *anti*-transoid oxocarbonium ion **29** should be the most stable intermediate and resemble the rate-limiting transition state in the acetal formation. Intermediate **29** would then cyclize to give **5a** as the major product.

The comparable thermodynamic stability calculated for the *endo*- (**5a**) and *exo*-(**5b**) benzylidene derivatives was confirmed by monitoring the reaction with ^{13}C NMR spectroscopy. Thus, the *endo* benzylidene acetal (**5a**) was formed first (kinetic product) and then it partially rearranged to the lower energy product (**5b**) at equilibrium. Products **5a** and **5b** were then slowly equilibrated with 3,4-(R)-benzylidene-D-ribono-1,5-lactone (**7a**). The formation of **7b** was not observed in our study, confirming that it is higher in energy than **7a**.

Scheme 9

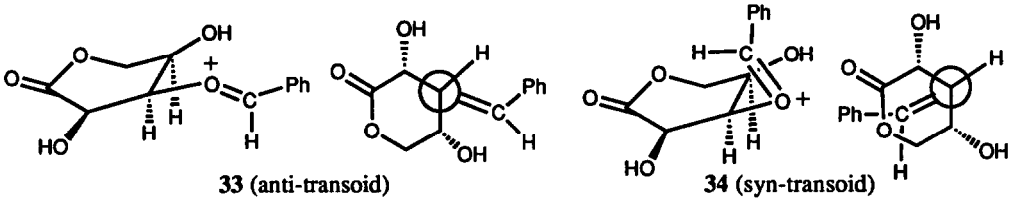


29 (anti–transoid) **30** (syn-transoid)

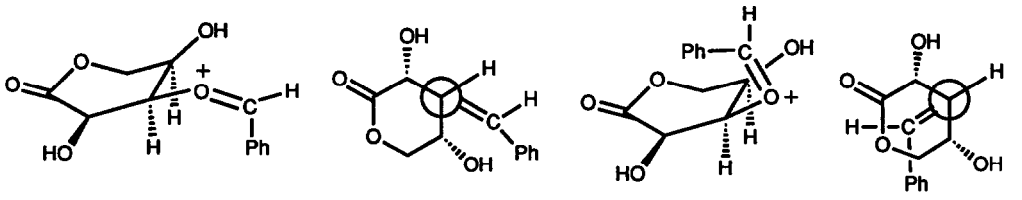
31 (anti–cisoid) **32** (syn-cisoid)

The mechanism of acetal migration from **5** to **7** is less clear. Since the *endo* product is formed as a single diastereomer, one might suggest that the rigid ring formation occurred prior to the acetal migration. The acetal migration reaction involves the same oxocarbonium ion intermediate, and thus the energetically favored transition state resembles the oxonium ion in the preferred *anti*-transoid conformation. The four possible oxocarbonium ion intermediates with a 1,5-lactone ring system are shown in Scheme 10. Protonation and subsequent acetal ring opening of **7** would lead to the oxocarbonium ion **33**, having an *anti*-transoid conformation, and rapid ring closure by the hydroxyl group on C-4 would afford the *endo*-benzylidene acetal **7a**.

Scheme 10



33 (anti-transoid) **34** (syn-transoid)



35 (anti-cisoid) **36** (syn-cisoid)

The boat conformation for the lactone ring of 3,4-benzylidene-D-ribono-1,5-lactone (**7a**) is supported by X-ray crystallography[11] and molecular mechanics calculations (Scheme 6). Either an *anti*-cisoid or a *syn*-transoid conformation (**35** and **34**, respectively) of the intermediate oxocarbonium ion is required for the formation of the *exo*-benzylidene isomer **7b**. These ions resemble energetically unfavored forms of the transition state, and thus reaction through these ions may be very slow or, as we observed, may not occur at all. It is assumed that the existence of a *syn*-cisoid conformation (**36**) is highly unlikely due to unfavorable steric effects.

The formation and mechanism of benzylidene acetals from other lactones are expected to follow similar pathways to afford the most stable *endo* products, followed by rearrangement if warranted by thermodynamic considerations. The mechanism of the ketalization of lactones with acetone, in aqueous acidic media, can be explained similarly.

Conclusions

The different reactivities of ribonolactones toward either benzaldehyde or acetone in acidic media are associated with relatively minor changes in structure. The acetalization of D-ribono-1,4-lactone proceeds with the initial formation of the 2,3-acetal, with a preference for the *endo*-isomer, determined by the transition state conformation. In the presence of aqueous acids the 2,3-acetal of the 1,4-lactone undergoes ring expansion and isomerization to the 3,4-acetal of the 1,5-lactone. This study showed that the structures and conformations of the products of aldehydes and ketones with polyhydroxylated lactones cannot be easily predicted and should be elucidated rather than assumed.

Experimental

Methods: 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 chromatography 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 magnetic resonance spectra (1D: ^{1}H-, ^{13}C-, INEPT, DEPT, and 2D: ^{1}H,^{1}H-COSY, ^{1}H,^{1}H-COSYDQF, ^{1}H,^{1}H-COSYPH, ^{1}H,^{13}C-COSY NMR) were recorded on an IBM NR/250 AF (250 MHz) or a Bruker AM-500 (500 MHz) 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}). 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). Elemental analyses were performed at the Instituto de Qùimica Bio-Orgànica, CSIC, Barcelona and at the microanalytical facilities of the University of Pennsylvania, Philadelphia, PA.

Materials: 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. D-Ribono-1,4-lactone was purchased from Aldrich Chemical Company, Milwaukee, WI.

2-Deoxy-D-ribono-1,4-lactone (9).[16] A solution of 2-deoxy-D-ribose (5.00 g, 37.28 mmol) in water (130 ml) was treated with bromine (4.80 ml, 14.9 g, 93.2 mmol), and the mixture was stirred for 4 days at ambient temperature in the dark. The excess bromine was removed under reduced pressure and the solution was neutralized with silver carbonate. The precipitate was removed by filtration and the filtrate was concentrated under reduced pressure in a bath kept at 35-40 °C. The residue was purified by silica gel flash-column chromatography using ethyl acetate as eluant to afford 2-deoxy-D-ribono-1,4-lactone (**9**) as a colorless oil (4.264 g, 86% yield).

9: TLC (methanol:ethyl acetate, 1:9) R_f 0.56; $[\alpha]_D^{22}$ +19.9° (c 0.71, H_2O) [lit.[17] $[\alpha]_D^{20}$ +18.5° (c 0.31, H_2O)]. IR (neat): 3700-3100, 2950, 2890, 1770, 1640, 1400, 1365, 1270, 1190, 1090, 1055, 1020, 990, 940, 905, 875, 835 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 2.24 (dd, 1H, J^1 2.3 Hz, J^2 17.7 Hz), 2.81 (dd, 1H, J^1 6.47 Hz, J^2 17.8 Hz), 3.51-3.60 (m, 2H), 4.25-4.29 (m, 2H), 5.02 (t, 1H, J 5.42 Hz), 5.45 (d, 1H, J 4.2 Hz); ^{13}C NMR (DMSO-d_6): δ 37.99, 60.79, 67.78, 88.26, 176.19. HRMS: Found: (M^+ + NH_4) at m/z 150.0753. $C_5H_{12}NO_4$ requires 150.0766.

2,3-O-(R)-Benzylidene-D-ribono-1,4-lactone (5a) and 2,3-O-(S)-benzylidene-D-ribono-1,4-lactone (5b). To a suspension of lactone **1** (1.00 g, 6.752 mmol) in dry 1,2-dimethoxyethane (4.5 ml) were added 2,2-dimethoxytoluene (1.12 ml, 1.23 g, 8.10 mmol) and a catalytic amount of anhydrous stannous chloride (0.0128 g, 0.0675 mmol).[12] The reaction mixture was heated to reflux and stirred for 45 min, under an argon atmosphere. After evaporation of the solvent under reduced pressure, the residue was purified by silica gel flash-column chromatography eluting with ethyl acetate:hexane (1:4, 1:2, 1:1, 2:1) to afford compounds **5a** (0.9512 g, 60% yield) and **5b** (0.0598 g, 4% yield) as white solids.

5a: TLC (ethyl acetate:petroleum ether, 1:1) R_f 0.27; mp 156-158 °C [lit.[10] mp 160-164 °C, lit.[18] mp 164-166 °C, lit.[11] mp 163-164 °C]; $[\alpha]_D^{22}$ -79.1° (c 0.56, $CHCl_3$) [lit.[10] $[\alpha]_D$ -70.2° (DMF), lit.[18] $[\alpha]_D$ -85° (DMF), lit.[11] $[\alpha]_D$ -70° (DMF)]. IR ($CHCl_3$): 3650-3300, 3020, 2940, 2880, 1785, 1460, 1400, 1355, 1310, 1290, 1250, 1175, 1090, 970, 915, 870, 850 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.26 (t, 1H, J 5.3 Hz), 3.86 (ddd, 1H, J^1 1.7 Hz, J^2 5.4 Hz, J^3 11.9 Hz), 4.03 (ddd, 1H, J^1 2.2 Hz, J^2 5.2 Hz, J^3 12.1 Hz), 4.77 (t, 1H, J 2.0 Hz), 4.92 (d, 1H, J 5.9 Hz), 4.98 (d, 1H, J 5.9 Hz), 5.98 (s, 1H), 7.38-7.48 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 60.38, 75.23, 79.87, 81.87, 105.08, 126.74, 128.43, 129.87, 135.85, 173.54. HRMS: Found: $(M^+ + NH_4)$ at m/z 254.1052 $C_{12}H_{16}NO_5$ requires 254.1029. Anal.: Found: C, 61.27; H, 5.03. $C_{12}H_{12}O_5$ requires C, 61.02; H, 5.12.

5b: TLC (ethyl acetate:petroleum ether, 1:1) R_f 0.44; mp 83-84 °C, (lit.[11] 87-88 °C); $[\alpha]_D^{22}$ -39.3° (c 1.16, $CHCl_3$), [lit.[11] $[\alpha]_D$ -40° ($CHCl_3$)]. IR ($CHCl_3$): 3640, 3540-3280, 1790, 1490, 1460, 1405, 1350, 1310, 1290, 1260, 1230, 1180, 1010, 995, 980, 915, 880 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.13 (t, 1H, J 5.1 Hz), 3.87 (ddd, 1H, J^1 1.8 Hz, J^2 5.4 Hz, J^3 12.1 Hz), 4.03 (ddd, 1H, J^1 2.3 Hz, J^2 5.1 Hz, J^3 12.1 Hz), 4.80 (t, 1H, J 2.0 Hz), 4.85 (d, 1H, J 5.9 Hz), 5.07 (d, 1H, J 5.8 Hz), 5.98 (s, 1H), 7.39-7.49 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 62.27, 76.17, 77.54, 84.13, 104.73, 126.42, 128.50, 129.86, 135.61, 173.50. HRMS: Found: $(M^+ + NH_4)$ at m/z 254.1022. $C_{12}H_{16}NO_5$ requires 254.1029.

3,4-O-(R)-Benzylidene-D-ribono-1,5-lactone (7a). *Method A.* To a solution of lactone **1** (1.00 g, 6.752 mmol) in concentrated hydrochloric acid (0.597 ml, 0.717 g, 7.17 mmol) was added benzaldehyde (6.86 ml, 7.17 g, 67.5 mmol). The mixture was stirred for 20 h at room temperature, under argon. Ether (80 ml) was added and the precipitate was filtered, washed thoroughly with ether, and dried *in vacuo*. Recrystallization twice from acetone/ petroleum ether afforded compound **7a** (0.997 g, 63% yield) as a white solid.

Method B. To a mixture of lactone **1** (1.000 g, 6.752 mmol) and benzaldehyde (6.863 ml, 7.165 g, 67.52 mmol) was added *p*-toluenesulfonic acid monohydrate (0.1284 g, 0.6751 mmol). The mixture was stirred for 20 h at room temperature, under argon, and the resulting crude material was purified using silica gel flash-column chromatography, eluting with ethyl acetate:petroleum ether (1:4, 1:2, 2:1, 1:0), to yield 48 % (0.7601 g of compound **7a**, 5% (0.0764 g) of compound **5a**, and 7% (0.1071 g) of compound **5b** as white solids.

7a: TLC (ethyl acetate:methanol, 18:1) R_f 0.73; mp 230-231 °C [lit.[6b] 230-231.5 °C]; $[\alpha]_D^{22}$ -180.5° (c 0.47, DMF) [lit.[6b] $[\alpha]_D$ -177.0° (c 2.37, DMF)]. IR (KBr): 3430, 3280, 3050, 3010, 3000, 2930, 2880, 2780, 1745, 1450, 1440, 1410, 1360, 1330, 1300, 1280, 1235, 1230, 1180, 1140, 1110, 1095, 1070, 1050, 1040, 1005, 945, 925, 865, 855, 760, 710, 645 cm^{-1}. ^1H NMR (DMSO-d_6): δ 4.32 (d, 1H, J 13.1 Hz), 4.42 (d, 1H, J 13.1 Hz), 4.61 (m, 1H), 4.64 (m, 1H), 4.69 (dd, 1H, J^1 3.2 Hz, J^2 8.1 Hz), 5.74 (s, 1H), 5.83 (d, 1H, J 6.2 Hz), 7.39-7.44 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 66.82, 67.74, 73.31, 76.73, 102.59, 127.12, 128.15, 129.73, 136.12, 171.68. HRMS: Found: (M^+) at m/z 236.0692. $C_{12}H_{12}O_5$ requires 236.0685.

3,4-O-(S)-Benzylidene-2-deoxy-D-ribono-1,5-lactone (13a) and 3,4-O-(R)-benzylidene-2-deoxy-D-ribono-1,5-lactone (13b). A mixture of lactone **9** (0.891 g, 6.751 mmol), benzaldehyde (6.86 ml, 7.16 g, 67.5 mmol) and concentrated hydrochloric acid (0.597 ml, 0.716 g, 7.16 mmol) was stirred for 20 h at room temperature, under an argon atmosphere. After evaporation of the solvent *in vacuo*, the crude material was purified by silica gel flash-column chromatography, eluting with ethyl acetate:petroleum ether (1:2, 1:1, 2:1), to afford compounds **13a** (0.777 g, 52 % yield) and **13b** (0.1160 g, 8% yield) as white solids.

13a: TLC (ethyl acetate:petroleum ether, 3:1) R_f 0.41; mp 138-139 [lit.[6b] 139-139.5 °C]; $[\alpha]_D^{22}$ -169.6° (c 0.5, $CHCl_3$) [lit.[6b] $[\alpha]_D$ -172.3° (c 1.71, $CHCl_3$)]. IR (KBr): 3040, 3000, 2960, 2940, 2780, 1740, 1450, 1400, 1340, 1305, 1260, 1220, 1150, 1090, 1050, 965, 920, 890, 860, 825. 750, 705, 695 cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.69 (dd, 1H, J^1 2.3 Hz, J^2 15.8 Hz), 2.98 (dd, 1H, J^1 3.6 Hz, J^2 15.9 Hz), 4.38 (m, 2H), 4.59 (dt, 1H, J^1 1.2 Hz, J^2 8.1 Hz), 4.76 (ddd, 1H, J^1 2.4 Hz, J^2 3.5 Hz, J^3 8.1 Hz), 5.71 (s, 1H), 7.41 (m, 5H). ^{13}C NMR (DMSO-d_6): δ 34.20, 67.89, 72.12, 72.23, 101.98, 126.95, 128.21, 129.71, 136.17, 170.20. HRMS: Found: ($M^+ + NH_4$) at m/z 238.1067. $C_{12}H_{16}NO_4$ requires 238.1080.

13b: TLC (ethyl acetate:petroleum ether, 3:1) R_f 0.61; mp 151-152 °C; $[\alpha]_D^{22}$ -104.0° (c 0.45, $CHCl_3$). IR (KBr): 3080, 3010, 2960, 2910, 1740, 1490, 1460, 1450, 1415, 1390, 1365, 1345, 1270, 1230, 1200, 1160, 1100, 1070, 1030, 1005, 970, 940, 920, 880, 825, 760, 735, 700, 680 cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.71 (br d, 1H, J 16.0 Hz), 2.94 (dd, 1H, J^1 3.4 Hz, J^2 16.0 Hz), 4.42 (dd, 1H, J^1 2.9 Hz, J^2 9.0 Hz), 4.63 (m, 1H), 6.13 (s, 1H), 4.72 (m, 1H), 7.40 (m, 5H). ^{13}C NMR (DMSO-d_6): δ 34.39, 68.62, 71.53, 71.96, 102.85, 125.91, 128.33, 128.93, 138.39, 170.32. HRMS: Found: (M^+) at m/z 220. 0754. $C_{12}H_{12}O_4$ requires 220.0736.

5-O-Acetyl-2,3-O-(R)-benzylidene-D-ribono-1,4-lactone (14). To a stirred slurry of 2,3-O-(R)-benzylidene-D-ribono-1,4-lactone (0.2000 g, 0.8474 mmol) in dry dichloromethane (8 ml) was added acetic anhydride (0.113 g, 0.104 ml, 1.10 mmol) followed by dimethylaminopyridine (0.1864 g, 1.525 mmol) at 0 °C, in an ice-water bath, under argon. 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 successively with water (15 ml), 10% sodium carbonate (15 ml), and saturated NaCl (15 ml) solution. The organic layer was dried (Na_2SO_4), concentrated under reduced pressure, and the crude product purified by silica gel flash-column chromatography using ethyl acetate:petroleum ether (1:2, 1:1) as eluants. The pure compound was obtained as white crystals (0.2014 g, 86% yield).

14: TLC (ethyl acetate:petroleum ether, 1:1) R_f 0.46; mp 143-144 °C (lit.[10] mp 143-145.5 °C, lit.[12] mp 143-145 °C); $[\alpha]_D^{22}$ -72.5° (c 1.48, $CHCl_3$), [lit.[10] $[\alpha]_D$ -71.2° ($CHCl_3$), lit.[12] $[\alpha]_D$ -72° (c 1.4, $CHCl_3$). IR ($CHCl_3$): 3030, 2960, 2880, 1800, 1760, 1460, 1400, 1385, 1365, 1350, 1310, 123, 1180, 1095, 1065, 1030, 970, 945, 910, 900 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.09 (s, 3H), 4.28 (dd, 1H, J^1 2.4 Hz, J^2 12.4 Hz), 4.40 (dd, 1H, J^1 2.8 Hz, J^2 12.4 Hz), 4.84 (d, 1H, J 5.9 Hz), 4.89 (t, 1H, J 2.6 Hz), 4.91 (d, 1H, J 5.9 Hz), 6.00 (s, 1H), 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: Found: ($M^+ + NH_4$) at m/z 296.1108. $C_{14}H_{18}NO_6$ requires 296.1134.

2,3-O-Isopropylidene-D-ribono-1,4-lactone (15) and 3,4-O-isopropylidene-D-ribono-1,5-lactone (16). A mixture of lactone **1** (0.2000 g, 1.350 mmol), acetone (0.992 ml, 0.784 g, 13.5 mmol), and concentrated hydrochloric acid (0.065 ml, 0.078 g, 0.78 mmol) was stirred at room temperature for 20 h. The solvent was concentrated under reduced pressure, and the residue purified by silica gel flash-column chromatography, eluting with ethyl acetate:petroleum ether (2:1), to afford compounds **15** (0.1168 g, 46% yield) and **16** (0.0647 g, 26% yield) as white crystals.

15: TLC (ethyl acetate:petroleum ether, 4:1) R_f 0.57; mp 139-140 °C (lit.[13] mp 138-139 °C, lit.[19] mp 137-138 °C); $[\alpha]_D^{26}$ -62.0° (c 0.2, acetone) [lit.[13] $[\alpha]_D$ -57.5° (c 2.3, H_2O)]. IR ($CHCl_3$): 3600-3200, 3040, 2990, 2940, 2880, 1790, 1600, 1450, 1380, 1350, 1260, 1230, 1180, 1150, 1090, 1005, 965, 915, 850 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.38 (s, 3H), 1.47 (s, 3H), 2.99 (br s, 1H), 3.81 (ddd, 1H, J^1 1.6 Hz, J^2 5.5 Hz, J^3 12.4 Hz), 3.99 (ddd, 1H, J^1 2.3 Hz, J^2 5.2 Hz, J^3 12.3 Hz), 4.64 (t, 1H, J 1.9 Hz), 4.79 (d, 1H, J 5.6 Hz), 4.84 (d, 1H, J 5.6 Hz). ^{13}C NMR ($CDCl_3$): δ 25.39, 26.67, 61.81, 75.64, 78.26, 82.91, 113.10, 175.21. HRMS: Found: ($M^+ + NH_4$) at m/z 206.1016. $C_8H_{16}NO_5$ requires 206.1029.

16: TLC (EtOAc:petroleum ether, 4:1) R_f 0.25; mp 140-142 °C; $[\alpha]_D^{22}$ -150.0° (c 1.92, $CHCl_3$). IR ($CHCl_3$): 3540, 3040, 3000, 2940, 1770, 1460, 1380, 1310, 1260, 1170, 1130, 1080, 1040, 990, 950, 900, 860, 830 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.37 (s, 3H), 1.47 (s, 3H),3.50 (br s, 1H), 4.22 (dd, 1H, J^1 1.7 Hz, J^2 13.2 Hz), 4.37 (d, 1H, J 3.5 Hz), 4.40 (br d, 1H, J 13.2 Hz), 4.59 (br d, 1H, J 7.7 Hz), 4.82 (dd, 1H, J^1 3.6 Hz, J^2 7.8 Hz). ^{13}C NMR ($CDCl_3$): δ 24.17, 25.78, 67.39, 68.59, 72.39, 74.66, 110.59, 171.86. Anal.: Found: C, 51.13; H, 6.64. $C_8H_{12}NO_5$ requires C, 51.04; H, 6.43. HRMS: Found: ($M^+ + NH_4$) at m/z 206.1032. $C_8H_{16}NO_5$ requires 206.1029.

3,4-O-Isopropylidene-2-deoxy-D-ribono-1,5-lactone (17). A mixture of lactone **9** (0.540 g, 4.09 mmol), acetone (3.00 ml, 2.38 g, 40.9 mmol), and concentrated hydrochloric acid (0.071 g, 0.059 ml, 0.71 mmol) was stirred for 20 h at room temperature. After evaporation of the solvent, the resulting product was purified by silica gel flash-column chromatography, eluting with ethyl acetate:petroleum ether (1:2), to afford compound **17** (0.2513 g, 36% yield) as white crystals.

17: TLC (ethyl acetate:petroleum ether, 1:1) R_f 0.34; mp 118-119 °C; $[\alpha]_D^{22}$ -146.83° (c 0.62, $CHCl_3$). IR ($CHCl_3$): 3030, 3000, 2960, 2930, 1760, 1460, 1415, 1385, 1380, 1350, 1320, 1285, 1255, 1170(s), 1145, 1105, 1060, 1000, 980, 930, 910, 890, 840 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.35 (s, 3H), 1.46 (s, 3H), 2.55 (dd, 1H, J^1 3.8 Hz, J^2 15.9 Hz), 2.86 (dd, 1H, J^1 2.4 Hz, J^2 15.9 Hz), 4.14 (dd, 1H, J^1 2.0 Hz, J^2 13.0 Hz), 4.41 (dd, 1H, J^1 1.4 Hz, J^2 12.9 Hz), 4.49 (dt, 1H, J^1 1.7 Hz, J^2 7.7 Hz), 4.74 (ddd, 1H, J^1 2.6 Hz, J^2 3.7 Hz, J^3 7.7 Hz). ^{13}C NMR ($CDCl_3$): δ 24.09, 25.97, 34.70, 68.35, 71.22, 71.51, 109.51, 169.38. HRMS: Found: ($M^+ + NH_4$) at m/z 190.1103. $C_8H_{16}NO_4$ requires 190.1080.

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