First Synthesis of Aldopentono-1,4-thiolactones

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A convenient synthesis of enantiomerically pure aldopentono-1,4-thiolactones is described. Thus, 4-thio-D-ribono-1,4-lactone (12) has been prepared from D-gulono-1,4-lactone (1), *via* its 2,3-*O*-isopropylidene derivative 3. The 5,6-glycol system of 3 was oxidized with $NaIO_4$. Chemoselective reduction of the resulting aldehyde function with $NaBH_3CN$ led to 2,3-*O*-isopropylidene-L-lyxono-1,4-lactone (7). Tosylation of 7 and subsequent treatment of the tosylate 8 with sodium methoxide afforded methyl 4,5-epoxy-2,3-*O*-isopropylidene-L-lyxonate (9) as a key intermediate. Treatment of 9 with thiourea gave the 4,5-thiirane derivative having the D-*ribo* configuration (10). Regioselective opening of the thiirane ring and simultaneous thiolactonization took place by heating 10 with KOAc–HOAc–DMF. The resulting 5-*O*-acetyl-2,3-*O*-isopropylidene-4-thio-D-ribono-1,4-lactone (11) was readily converted, by acid removal (2% HCl) of the protecting groups, into the crystalline thiolactone 12. A similar approach was employed for the synthesis of 4-thio-L-lyxono-1,4-lactone (19), starting from D-ribono-1,4-lactone (13).

Introduction

D-Ribono-1,4-lactone has been considered[1] a "chiral cornerstone" because of its use as a chiral template in the synthesis of natural products and molecules of biological interest.[2-4] In spite of the numerous derivatives described for D-ribonolactone, its 4-thio analogue, the 4-thio-D-ribono-1,4-lactone, had not been previously synthesized. In fact, only a few attempts to prepare sugar thiolactones from aldonic acids have been reported.[5] Thus, 2,3-*O*-isopropylidene-4-thio-D-erythrono-1,4-lactone was obtained by nucleophilic attack of potassium thioacetate on C-4 of the 2,3-acetal derivative of D-erythronolactone. However, this procedure proved to be unsuccessful for higher-carbon sugar lactones having C-4 substitution. Recently, per-*O*-alkylated derivatives of 5-thio-D-glucono-1,5-lactone were obtained by HO-1 oxidation of the corresponding 2,3,4,6-tetra-*O*-alkyl-5-thio-D-glucopyanoses.[6] As far as we know, the above-mentioned are the only examples of the preparation of sugar thiolactones. In the search for a general synthetic procedure for the preparation of 4-thioaldopentono-1,4-lactones, and in connection with our project on the synthesis and properties of 4-thiosugars,[7-11] we report here the first syntheses of 4-thio-D-ribono-1,4-lactone (12) and 4-thio-L-lyxono-1,4-lactone (19). Compounds 12 and 19, enantiomerically pure and with the opposite configuration at C-4, may be employed as convenient chiral precursors for the synthesis of naturally occurring thiolactones.[12,13]

Results and Discussion

The retrosynthetic analysis for the construction of the thiolactone ring is depicted in Scheme I. Disconnection of the C-1–S bond produces a synthon i (D-*ribo* configuration), which would derive from an open-chain precursor ii, with opposite configuration at C-4 (L-*lyxo*) since the thiol group is commonly introduced by nucleophilic displacement of conveniently substituted HO-4.[7-9] Since the synthetic equivalent of ii, the L-lyxono-1,4-lactone, is not commercially available, we employed D-gulono-1,4-lactone (1) as a suitable starting material.

Isopropylidenation of 1 with acetone–H_2SO_4 afforded the 2,3:5,6-di-*O*-isopropylidene derivative 2, which was selectively hydrolyzed to 2,3-*O*-isopropylidene-D-gulono-1,4-lactone[14] (3) in 82% overall yield (Scheme II). The 5,6-diol functionality of 3 was oxidized with 1 mol equiv of sodium periodate in water to give the L-arabinuronic acid 2,5-lactone derivative 4 in almost quantitative yield. The ^{13}C NMR spectrum of 4 showed that the aldehyde carbonyl group was partially hydrated, since besides the aldehyde carbon signal (195.0 ppm), a characteristic resonance[15] for the hydrated carbonyl (88.7 ppm) was observed.

Attempted selective reduction of the aldehyde function of 4 with 1 mol of $NaBH_4$ in ethanol resulted also in the reduction of the lactone carbonyl group, affording 2,3-*O*-isopropylidene-α-L-lyxofuranose (5) in 62% yield. This procedure itself constitutes a short and convenient synthesis of an L-lyxose derivative. Conventional acetylation of 5 with acetic anhydride–pyridine gave the diacetate 6. Compound 6 gave the same mp and optical rotation value (but opposite in sign) as its enantiomer, obtained on acetonation of D-lyxose under kinetic control, followed by

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(1) *Aldrichim. Acta* **1989**, *22*, 49.
(2) Lederkremer, R. M.; Varela, O. *Adv. Carbohydr. Chem. Biochem.*, in press.
(3) Bhat, K. L.; Chen, S. Y.; Joullié, M. M. *Heterocycles* **1985**, *23*, 691.
(4) Drew, M. G. B.; Mann, J.; Thomas, A. *J. Chem. Soc. Perkin Trans. 1* **1986**, 2279.
(5) Dominguez, J. N.; Owen, L. N. *Carbohydr. Res.* **1979**, *75*, 101.
(6) Yuasa, H.; Tamura, J.; Hashimoto, H. *J. Chem. Soc. Perkin Trans. 1* **1990**, 2763.
(7) Varela, O.; Cicero, D.; Lederkremer, R. M. *J. Org. Chem.* **1989**, *54*, 1884.
(8) Cicero, D.; Varela, O.; Lederkremer, R. M. *Tetrahedron* **1990**, *46*, 1131.
(9) Cicero, D.; Varela, O.; Lederkremer, R. M. *Carbohydr. Res.* **1991**, *211*, 295.
(10) Cicero, D.; Varela, O. *Tetrahedron* **1990**, *46*, 8019.
(11) Zunszain, P. A.; Varela, O. *Carbohydr. Res.* **1991**, *222*, 131.
(12) Chambers, M. S.; Thomas, E. J. *J. Chem. Soc. Chem. Commun.* **1989**, 23.
(13) Dolak, L. A.; Castle, T. M.; Truesdell, S. E.; Sebek, O. K. *J. Antibiot.* **1986**, *39*, 26.
(14) Hulyalkar, R. K.; Jones, J. K. N. *Can. J. Chem.* **1963**, *41*, 1898.
(15) Wu, J.; Serianni, A. S. *Carbohydr. Res.* **1991**, *210*, 51.

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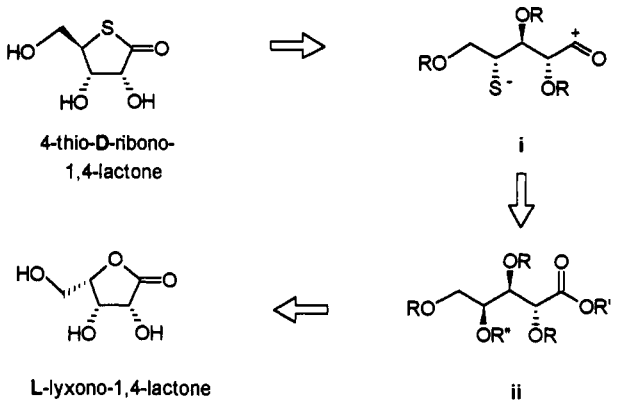
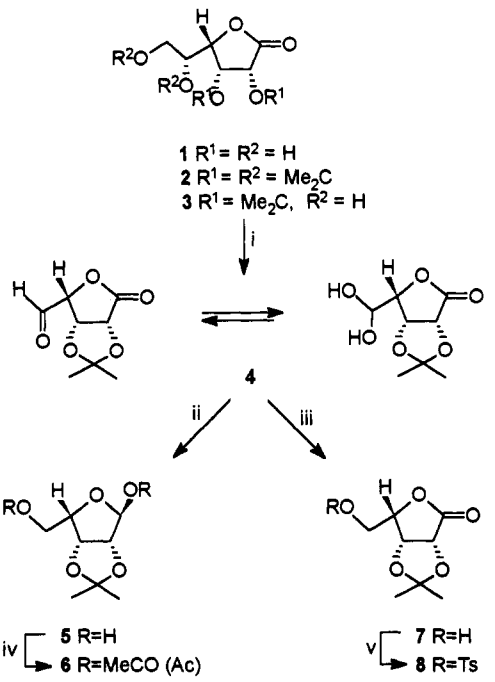
Scheme I



Scheme II[a]



[a] (i) $NaIO_4$; (ii) $NaBH_4$, EtOH; (iii) $NaBH_3CN$, pH 4; (iv) Ac_2O, pyridine; (v) TsCl, pyridine, $CHCl_3$.

acetylation.[16] The ^1H and ^{13}C NMR spectra for **5** and **6** are shown in Tables I and II. On the other hand, when **4** was treated with 0.25 mol of $NaBH_4$ in order to avoid the reduction of the lactone group, a mixture of at least three products and some unreacted **4** were detected by TLC. The mixture was not further analyzed.

Chemoselective reduction of the aldehyde function of **4** was achieved by using $NaBH_3CN$ in acid medium (pH 4). Under these conditions the 2,3-*O*-isopropylidene-L-lyxono-1,4-lactone (**7**) was obtained with a yield (74% from **3**) much higher than those reported[17,18] for the preparation of the enantiomer of **7**. Furthermore, the synthesis of **7** by these published procedures would require the very expensive L-lyxose[17] or L-galactose[18] as the starting sugar.

Sulfonylation of the free hydroxyl group of **7** with *p*-toluenesulfonyl chloride (tosyl chloride) in pyridine gave the tosylate **8** in 60% yield. A better yield (78%) was obtained by conducting the reaction in chloroform and with pyridine–tosyl chloride in a 1.3:1 molar ratio.[19] Treatment of compound **8** with sodium methoxide caused opening of the lactone ring by methanolysis, followed by nucleophilic attack of the resulting C-4 alkoxide on C-5 and displacement of the tosylate, to give the 4,5-epoxide **9** (Scheme III). The formation of the oxirane ring was readily determined by the ^1H and ^{13}C NMR spectra of **9**. Thus, H-4, 5, and 5′ showed the same chemical shift pattern (δ 3.01, 2.80, and 2.69, respectively) and coupling constant values ($J_{4,5}$ 4.0, $J_{4,5'}$ 2.6, and $J_{5,5'}$ 5.1 Hz) as those described for similar epoxide derivatives of sugars.[20] As C-4 and C-5 are now incorporated within the three-membered oxirane ring, their resonances are shifted considerably upfield (25 and 23 ppm, respectively) relative to the same signals of **8**. Reaction of epoxide **9** with thiourea gave the thiirane derivative **10**, with inversion of the C-4 configuration. The replacement of the ring oxygen atom of the epoxide by sulfur produces a further upfield displacement for the C-4 and C-5 signals (20 ppm) in the ^{13}C NMR spectrum of **10**.

Attempts to open the thiirane ring under acid or alkaline conditions proved unsuccessful, as decomposition took place. However, regioselective ring opening and simultaneous thiolactonization could be accomplished on treatment of **10** with KOAc in HOAc–DMF, at reflux temperature. The formation of the thiolactone ring was evident from the ^{13}C NMR spectrum of **11**, which showed a downfield shift of the thiolactone carbon resonance (δ 203.6) and a strong upfield shift of the C-4 signal (δ 47.5) relative to the same signals of D-ribono-1,4-lactone[21,22] (180.0 and 88.3 ppm, respectively). Removal of the 5-*O*-acetyl and the 2,3-*O*-isopropylidene groups of **11** by hydrolysis with HCl in H_2O–THF afforded the free 4-thio-D-ribono-1,4-lactone (**12**) in crystalline form. The ^{13}C NMR spectrum in ^2H_2O of **12** showed a signal characteristic of a thiolactone carbonyl at 210.1 ppm. The mass spectrum of the 2,3,5-tris-*O*-trimethylsilyl (TMS) derivative of **12** showed a fragmentation pattern similar to that of the TMS derivative of D-ribonolactone.[23]

A similar sequence of reactions was employed for the synthesis of 4-thio-L-lyxono-1,4-lactone (**19**) from D-ribono-1,4-lactone (**13**) (Scheme IV). Isopropylidenation of the *cis*-diol system of **13**, followed by tosylation of HO-5 led to 2,3-*O*-isopropylidene-5-*O*-tosyl-D-ribono-1,4-lactone (**15**) in 80% overall yield from **13**. Treatment of **15** with sodium methoxide afforded the 4,5-epoxide derivative **16**, whose ^1H NMR spectrum was like that of **9**. The $J_{3,4}$ values (5.8 Hz for **9** and 6.4 Hz for **16**) would indicate some degree of conformational unstability around the C-3–C-4 bond, the rotamer having H-3–H-4 in an antiperiplanar relationship being preferential. The epoxide function of **16** reacted with thiourea in methanol to give the thiirane derivative **17**. Its ^1H and ^{13}C NMR spectra were also similar to those of **10**. The large value for $J_{3,4}$ for **10** (8.7 Hz) and for **17** (8.5 Hz) would indicate that the most populated conformation is the one having an antiperplanar disposition of H-3 and H-4. These rotamers are free of unstabilizing effects such as 1,3-parallel interactions and

(16) Barbat, J.; Gelas, J.; Horton, D. *Carbohydr. Res.* **1991**, *219*, 115.
(17) Schaffer, R. *J. Res. Natl. Bur. Stand. Sect. D* **1961**, *65A*, 507.
(18) Morgenlie, S. *Acta Chem. Scand.* **1975**, *B29*, 367.
(19) Kabalka, G. W.; Varma, M.; Varma, R. S.; Srivastava, P. C.; Knapp, F. F., Jr. *J. Org. Chem.* **1986**, *51*, 2386.
(20) Hashimoto, H.; Fujimori, T.; Yuasa, H. *J. Carbohydr. Chem.* **1990**, *9*, 683.
(21) Angelotti, T.; Krisko, M.; O'Connor, T.; Serianni, A. S. *J. Am. Chem. Soc.* **1987**, *109*, 4464.
(22) Horton, D.; Walaszek, Z. *Carbohydr. Res.* **1982**, *105*, 111.
(23) Petersson, G.; Samuelson, O.; Anjou, K.; von Sydow, E. *Acta Chem. Scand.* **1967**, *21*, 1251.

Table I. ^{1}H NMR Chemical Shift and Coupling Constant Data

	δ (ppm)							J (Hz)				
compd	H-2	H-3	H-4	H-5	H-5′	$C(CH_3)_2$	OCH_3	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{4,5'}$	$J_{5,5'}$
2[a]	4.72	4.62	4.31			1.25, 1.29, 1.35 (×2)		5.6	3.2			
3[a]	4.75		4.46	4.02		1.28, 1.36				7.2		
5[b]	4.60	4.79	4.27	3.89		1.30, 1.44		5.9	3.7			
6[b]	4.66	4.80	4.10–4.46			1.32, 1.46		5.8	3.2			
7	4.87		4.59	3.97		1.38, 1.46						
8[c]	4.82		4.70	4.40	4.27	1.36, 1.38			1.9	4.5	7.1	11.2
9	4.73	4.12	3.01	2.80	2.69	1.39, 1.63	3.80	7.2	5.8	4.0	2.6	5.1
10	4.72	3.80	2.83	2.52	2.29	1.37, 1.64	3.80	6.8	8.7	6.1	5.0	1.5
11[d]	4.67	4.64	4.12	4.35		1.40, 1.50		4.9	0.6	4.5		
12[e]	4.66	4.45	3.84–3.90					4.4	1.2			
16	4.78	4.07	3.00	2.81	2.72	1.40, 1.62	3.80	6.9	6.4	3.9	2.5	5.1
17	4.73	3.88	2.86	2.42	2.23	1.38, 1.64	3.80	7.1	8.5	6.4	5.3	1.5
18[d]	4.69	4.77	4.24	4.63	4.39	1.39, 1.46		4.6	4.2	6.0	8.3	11.3
19[e]	4.62	4.57	4.15	4.07	3.89			4.0	3.1	6.3	8.0	11.4

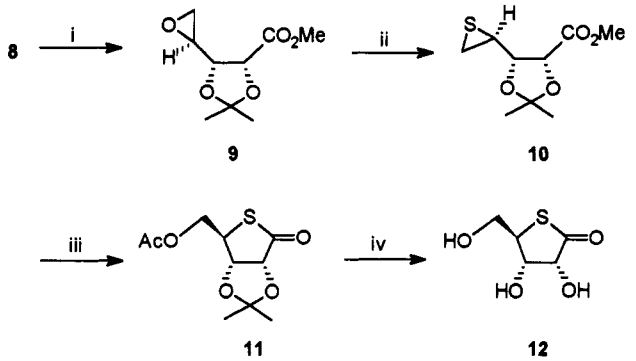
[a] Resonances for H-6, H-6′ appeared at 3.71 and 4.11 ppm (for 2), and 3.69 and 3.78 ppm (for 3). [b] Resonances for H-1 appeared at 5.42 ppm, $J_{1,2} < 0.5$ Hz (for 5), and 6.14, $J_{1,2} < 0.5$ Hz (for 6). [c] It showed a singlet (3 H) at 2.47 ppm due to the $CH_3C_6H_4$. [d] It showed a singlet (3H) at 2.10 ppm due to CH_3CO. [e] Recorded in ^2H_2O.

Table II. ^{13}C NMR Chemical Shift Data (δ, ppm)

compd	C-1	C-2	C-3	C-4	C-5	$C(CH_3)_2$	$C(CH_3)_2$
2[b]	173.5	76.1[a]	75.8[a]	80.9	75.3[a]	114.7, 110.5	26.8, 26.7, 25.9, 25.3
3[c]	173.2	76.5[a]	76.1[a]	79.4	70.9	114.7	26.8, 25.9
5	100.5	85.4	79.9	79.9	60.8	112.4	25.7, 24.4
6	100.7	85.0	79.9[a]	79.4[a]	62.4	113.4	26.2, 25.0
7	174.2	76.0	76.0	79.7	60.4	113.9	26.5, 25.5
8	172.4	75.8[a]	75.6[a]	75.2[a]	66.7	114.4	26.5, 25.6
9	169.5	75.3	78.2	50.0	43.7	111.5	26.6, 25.3
10	169.4	76.9	82.7	30.5	22.7	111.4	27.0, 25.5
11	203.6	83.4	78.6	47.5	65.1	112.6	27.5, 25.9
12[d]	210.1	78.7	71.7	54.6	63.3		
16	169.4	76.2	77.7	49.5	45.0	111.6	26.9, 25.4
17	169.2	76.8	82.3	32.8	21.3	110.0	26.5, 25.3
18	203.3	85.0	75.4	44.5	63.7	113.0	27.2, 25.9
19[d]	209.5	81.3	70.9	50.3	61.8		

[a] Signals may be interchanged. [b] C-6 appeared at 65.3 ppm. [c] C-6 appeared at 62.5 ppm. [d] Recorded in ^2H_2O. Data for compound 4, see Experimental Section.

Scheme III[a]

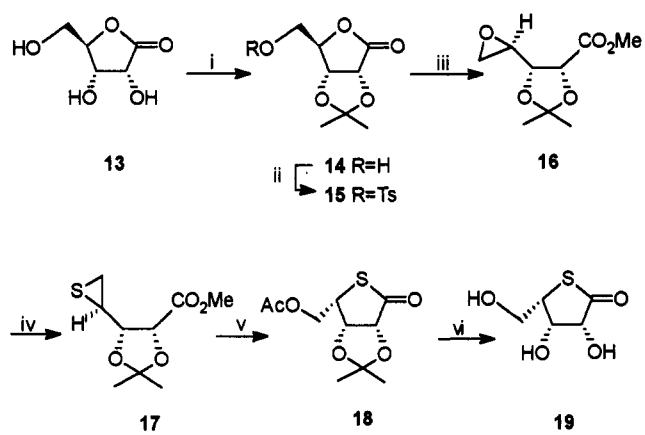


[a] (i) NaOMe, MeOH; (ii) $(NH_2)_2CS$, MeOH; (iii) KOAc, HOAc, DMF; (iv) 2% HCl in 2:1 THF–H_2O.

the sulfur atom hockey sticks effect,[24] which will operate in the other possible conformations.

Thiirane ring opening and thiolactonization took place by heating 17 at reflux with KOAc in HOAc–DMF. The 5-*O*-acetyl-2,3-*O*-isopropylidene-4-thio-L-lyxono-1,4-lactone (18) was obtained in crystalline form after chromatographic purification. The ^{13}C NMR spectrum of 18 showed the characteristic signal for the thiolactone carbon at 203.3 ppm. Acid removal of the acetyl and isopropylidene protecting groups of 18 afforded crystalline 4-thio-L-lyxono-1,4-lactone (19). The presence of a sulfur atom within the ring was again evidenced in the ^{13}C NMR spectrum of 19, by the large shift of the signals corresponding to the carbons bonded to sulfur (δ_{C-1} 209.5 and δ_{C-4} 50.3).

Scheme IV[a]



[a] (i) Me_2CO, H_2SO_4; (ii) TsCl, pyridine, $CHCl_3$; (iii) NaOMe, MeOH; (iv) $(NH_2)_2CS$, MeOH; (v) KOAc, HOAc, DMF; (vi) 2% HCl in 2:1 THF–H_2O.

The synthetic routes described herein constitute efficient procedures for the preparation of aldono-1,4-thiolactones having D-*ribo* (12) and L-*lyxo* (19) configurations [the overall yield for 12 was 20% from 1 (37% from 7), and for 19, 32% from 13]. This methodology can also be applied to the synthesis of other aldopentonothiolactones having different configurations.

Experimental Section

General Procedures. Melting points were determined in a Thomas-Hoover apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 141 polarimeter. ^{1}H NMR spectra were determined with a Varian XL-100 or a Bruker 500 spectrometer at 100 or 500 MHz, respectively. ^{13}C NMR spectra were recorded with a Varian XL-100 at 25.2 MHz. Unless otherwise indicated the spectra were determined in $CDCl_3$ solutions and with tetramethylsilane (0.00 ppm) as an internal reference. Signal assignments for the ^{13}C NMR spectra were made on the basis of selective heteronuclear decoupling experiments. Data are shown in Tables I and II. Analytical thin-layer chromatography (TLC) was performed on 0.25-mm silica gel 60 F_{254} (Merck) aluminum-supported plates with A, EtOAc; B, 1:1

(24) Zefirov, N. S.; Blagoveshchensky, V. S.; Kazimirchik, I. V.; Surova, N. S. *Tetrahedron* **1971**, *27*, 3111.

hexane–EtOAc; C, 3:1 toluene–EtOAc; and D, 6:1 hexane–EtOAc. Detection was affected by exposure to UV light or charring with 10% H_2SO_4 (v/v) in EtOH. Column chromatography was performed on silica gel 60 (230–400 Mesh, Merck). The following solvents were distilled before use: MeOH (from I_2/Mg), THF (from Na/benzophenone), acetone (from $KMnO_4$ and K_2CO_3), and acetic acid[25] (from Ac_2O and CrO_3). DMF was purified by sequential drying[26] with 3-Å molecular sieves and distillation. The GC-MS of the TMS derivatives of **12** and **19** were performed with a Varian Aerograph 1400 chromatograph coupled to a mass spectrometer Varian MAT CH7 A (70 eV), employing a SP-2330 column.

2,3-*O*-Isopropylidene-D-gulono-1,4-lactone (3). Compound **3** was prepared from D-gulono-1,4-lactone (**1**) *via* the 2,3:5,6-di-*O*-isopropylidene-D-gulono-1,4-lactone (**2**) as previously described.[14]

2,3-*O*-Isopropylidene-α-L-lyxose (5). To a solution of compound **3** (2.28 g, 10.4 mmol) in water (28 mL) was added a 1 M solution of aqueous $NaIO_4$ (10.5 mmol). After 20 min of stirring in the dark at room temperature, the starting material **3** (R_f 0.32, solvent A) was not detected by TLC. The solution was freeze-dried and the residue extracted with CH_2Cl_2 and concentrated. The homogeneous (R_f 0.57, solvent A) syrupy product obtained, characterized as **3,4-*O*-isopropylidene-L-arabinuronic acid 2,5-lactone** (**4**, 1.94 g, 99% yield) showed to be a mixture of the aldehyde and its hydrated form: ^{13}C NMR ($CDCl_3$) aldehyde δ 195.0 (C-5, *C*HO), 174.8 (C-1), 114.1 (*C*Me_2), 81.2 (C-4), 76.4, 76.2 (C-2,3), 26.7, 25.7 (C(*C*H_3)$_2$); hydrated form δ (*inter alia*) 173.4 (C-1), 114.9 (*C*Me_2), 88.7 (*C*H(OH)$_2$).

To a solution of crude **4** (124 mg, 0.57 mmol) in ethanol (5 mL) was added $NaBH_4$ (22 mg, 0.58 mmol). After 40 min of stirring at 0 °C, monitoring by TLC showed the formation of a single spot (R_f 0.55, solvent A) slower moving than **4**. The solution was made neutral by addition of 10% aqueous HOAc and then concentrated. The residue was filtered through a short column of silica gel with 1:1 hexane–EtOAc as solvent, affording **5** (66 mg, 62%): mp 78–80 °C (lit.[16] mp 80–82 °C for the enantiomer).

1,5-Di-*O*-acetyl-2,3-*O*-isopropylidene-α-L-lyxofuranose (6). Acetylation of **5** (35 mg, 0.18 mmol) with acetic anhydride (0.5 mL) and pyridine (0.5 mL) for 2 h afforded, after evaporation, compound **6** (42 mg, 84% yield) which had mp 47–49 °C; $[\alpha]_D$ −53.4° (*c* 1.1, $CHCl_3$) (lit.[16] mp 48–50 °C; $[\alpha]_D$ +59.5° for the enantiomer).

2,3-*O*-Isopropylidene-L-lyxono-1,4-lactone (7). The crude aldehyde derivative **4** (1.94 g) was dissolved in methanol (16 mL) containing a trace of bromocresol green. To this solution was added $NaBH_3CN$ (1.7 g, 26 mmol), and the yellow color (pH 4) was maintained by dropwise addition of 0.4 N methanolic HCl. After 6 h of stirring at room temperature, the solution was concentrated. The residue was extracted with CH_2Cl_2, and the extract was washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated. The resulting syrupy product (R_f 0.51, solvent A) was purified by flash chromatography (3:1 hexane–EtOAc). Compound **7** crystallized from hexane–EtOAc (1.46 g, 74%); recrystallized from the same solvent it gave mp 96–98 °C, $[\alpha]_D$ −85° (*c* 1.1, acetone). The analogous derivative in the D series had[17] mp 99–100 °C, $[\alpha]_D$ +106°, and[18] mp 88–93 °C, $[\alpha]_D$ +108°. Anal. Calcd for $C_8H_{12}O_5$: C, 51.06; H, 6.43. Found: C, 50.90; H, 6.27.

2,3-*O*-Isopropylidene-5-*O*-(*p*-tolylsulfonyl)-L-lyxono-1,4-lactone (8). (A) To a solution of **7** (0.70 g, 3.70 mmol) in dry pyridine was added tosyl chloride (1.50 g, 7.90 mmol). The mixture was kept at 0 °C for 24 h and then poured into ice–water to yield compound **8** as a chromatographically homogeneous solid (R_f 0.56, solvent B), which was recrystallized from EtOH (0.76 g, 60%). After recrystallization from the same solvent, **8** had mp 121–123 °C; $[\alpha]_D$ −66.8° (*c* 0.4, $CHCl_3$). Anal. Calcd for $C_{15}H_{18}O_7S$: C, 52.62; H, 5.29. Found: C, 52.47; H, 5.24.

(B) To a stirring solution of **7** (0.96 g, 5.1 mmol) in dry $CHCl_3$ (5 mL), cooled at 0 °C, were added pyridine (0.82 mL, 10.1 mmol) and tosyl chloride (1.44 g, 7.6 mmol). After 4 h of stirring at 0 °C was added water (5 mL) dropwise, and the stirring was maintained for 0.5 h. The mixture was diluted with CH_2Cl_2 (60 mL) and it was successively washed with 2 N aqueous HCl, saturated aqueous $NaHCO_3$, and water. The organic extract was dried ($MgSO_4$) and concentrated. Compound **8** crystallized upon addition of EtOH (1.36 g, 78%); it showed the same physical constants as those described in A.

Methyl 4,5-epoxy-2,3-*O*-isopropylidene-L-lyxonate (9). Compound **8** was added to a stirring solution prepared by dissolving sodium (40 mg) in anhydrous methanol (6.5 mL). After 20 min of stirring at room temperature, a single spot, migrating faster than **8** (R_f 0.60, solvent B) was detected by TLC. Evaporation of the solvent afforded a residue which was extracted with ether. The extract was concentrated and the resulting syrup dissolved in hexane and filtered. Upon evaporation of the solvent, compound **9** was obtained as a chromatographically homogeneous oil (0.30 g, 85%): $[\alpha]_D$ −13.1° (*c* 1.1, $CHCl_3$). Anal. Calcd for $C_9H_{14}O_5$: C, 53.45; H, 6.98. Found: C, 53.22; H, 6.98.

Methyl 4,5-Dideoxy-4,5-epithio-2,3-*O*-isopropylidene-D-ribonate (10). To a stirring solution of **9** (0.13 g, 0.64 mmol) in anhydrous methanol (7.7 mL) was added thiourea (83 mg, 1.1 mmol). After 48 h of stirring at room temperature, TLC showed a single spot (R_f 0.74, solvent C). The solution was concentrated, and the resulting residue was treated as described for **9**, to afford compound **10** as a clear oil (0.13 g, 93%): $[\alpha]_D$ −84.4° (*c* 1.2, $CHCl_3$). Anal. Calcd for $C_9H_{14}O_4S$: C, 49.52; H, 6.46; S, 14.60. Found: C, 49.64; H, 6.36; S, 14.82.

5-*O*-Acetyl-2,3-*O*-isopropylidene-4-thio-D-ribono-1,4-lactone (11). Compound **10** (0.16 g, 0.73 mmol) was dissolved in a mixture of anhydrous DMF (6 mL), glacial HOAc (6 mL), and KOAc (0.75 g, 7.6 mmol). The solution was heated at the reflux temperature for 16 h, under nitrogen, when a main spot (R_f 0.50, solvent C) was detected by TLC. The reaction mixture was diluted with CH_2Cl_2 (60 mL) and washed with aqueous KOAc and water. The organic extract was dried ($MgSO_4$) and concentrated to a syrup, which was chromatographed using 5:1 hexane–EtOAc. From the column, unreacted starting **10** (24 mg) was recovered, and the fractions containing the product of R_f 0.50 were pooled and evaporated affording the thiolactone **11** (0.11 g, 70% yield, based on reacted **10**); $[\alpha]_D$ +23.5° (*c* 1.1, $CHCl_3$). Anal. Calcd for $C_{10}H_{14}O_5S$: C, 48.77; H, 5.73. Found: C, 48.50; H, 5.56.

4-Thio-D-ribono-1,4-lactone (12). Compound **11** (165 mg, 0.67 mmol) dissolved in a mixture of THF (5 mL) and 6% aqueous HCl (2.5 mL) was stirred for 16 h at room temperature. Evaporation afforded a clear oil, which was filtered through a silica gel column with EtOAc as eluent. Fractions containing the product of R_f 0.22 (solvent A) were evaporated, and compound **12** slowly crystallized upon standing (95 mg, 86%). It had mp 112–114 °C; $[\alpha]_D$ +60.3° (*c* 0.9, methanol). Anal. Calcd for $C_5H_8O_4S$: C, 36.58; H, 4.91; S, 19.53. Found: C, 37.03; H, 5.19; S, 19.51.

Compound **12** was conventionally silylated with Sylon HTP. The GC-MS of the silylated derivative was performed: MS *m/z* (rel inten) 380 (0.6), 365 (11), 290 (6), 262 (13), 260 (11), 219 (10), 218 (40), 217 (41), 204 (8), 191 (9), 147 (41), 146 (14), 133 (13), 103 (16), 75 (13), 74 (11), 73 (100).

2,3-*O*-Isopropylidene-5-*O*-(*p*-tolylsulfonyl)-D-ribono-1,4-lactone (15). To a solution of 2,3-*O*-isopropylidene-D-ribono-1,4-lactone[27] (**14**, 3.0 g, 15.9 mmol) in pyridine (2.6 mL, 32 mmol) and $CHCl_3$ (16 mL) was added tosyl chloride (4.57 g, 24 mmol) at 0 °C. The mixture was stirred for 6 h at 0 °C, when water was added dropwise, and the stirring was maintained for 0.5 h. TLC examination showed a single spot of R_f 0.71 (solvent A). The product was isolated as described for **8**, method B, affording a syrup, which crystallized upon addition of methanol (4.8 g, 88%); mp 116–118 °C; $[\alpha]_D$ −15.5° (*c* 2.4, acetone) (lit.[28] mp 117.5–118 °C, $[\alpha]_D$ −15.8°).

Methyl 4,5-epoxy-2,3-*O*-isopropylidene-D-ribonate (16). It was prepared as described for **9**, starting from **15** (0.67 g, 1.9 mmol). Compound **16** was obtained as a syrup (0.36 g, 93%), $[\alpha]_D$ −10.7° (*c* 4.7, $CHCl_3$) (lit.[29] $[\alpha]_D$ −11.7°).

Methyl 4,5-Dideoxy-4,5-epithio-2,3-*O*-isopropylidene-L-lyxonate (17). To a solution of **16** (0.12 g, 0.6 mmol) in dry

(25) Orton, K. J. P.; Bradfield, A. E. *J. Chem. Soc.* **1927**, 983.
(26) Burfield, D. R.; Smithers, R. H. *J. Org. Chem.* **1978**, *43*, 3966.
(27) Kandil, A. A.; Slessor, K. N. *J. Org. Chem.* **1985**, *50*, 5649.
(28) Hough, L.; Jones, J. K. N.; Mitchell, D. L. *Can. J. Chem.* **1958**, *36*, 1720.
(29) Hoffmann, R. W.; Ladner, W. *Chem. Ber.* **1983**, *116*, 1631.

methanol (8 mL) was added thiourea (92 mg, 1.2 mmol). The solution was stirred for 48 h at room temperature, when TLC showed a single spot (R_f 0.65, solvent C). The residue was treated as described for **9**, to afford compound **10** as a clear oil (0.12 g, 88%); $[\alpha]_D$ −84.4° (*c* 1.2, $CHCl_3$). Anal. Calcd for $C_5H_{14}O_4S$: C, 49.52; H, 6.46. Found: C, 49.45; H, 6.19.

5-*O*-Acetyl-2,3-*O*-isopropylidene-4-thio-L-lyxono-1,4-lactone (18). Compound **17** (0.20 g, 0.9 mmol) was dissolved in a mixture of DMF (7 mL), HOAc (7 mL), and KOAc (0.9 g, 9.1 mmol) and refluxed, under nitrogen, for 18 h. TLC showed a main spot (R_f 0.52, solvent C) which was isolated and purified (column chromatography with 5:1 hexane–EtOAc) as described for **11**. The thiolactone **18** (0.14 g, 57%) gave mp 56–58 °C, $[\alpha]_D$ −114° (*c* 1, $CHCl_3$). Anal. Calcd for $C_{10}H_{14}O_5S$: C, 48.77; H, 5.73; S, 13.02. Found: C, 48.96; H, 5.63; S, 13.36.

4-Thio-L-lyxono-1,4-lactone (19). Compound **18** (0.30 g, 1.2 mmol) was dissolved in a mixture of THF (9 mL) and 6% HCl (4.5 mL), and the resulting solution was stirred for 18 h at room temperature. The reaction mixture, which showed by TLC a main spot of R_f 0.26 (solvent A), was concentrated. The resulting syrup was purified through a short column of silica gel with EtOAc as eluent. Upon evaporation of the solvent, crystalline **19** (0.17 g, 86%) was obtained. After recrystallization from acetone, **19** gave mp 146–148 °C; $[\alpha]_D$ −136° (*c* 1, methanol). Anal. Calcd for $C_5H_8O_4S$: C, 36.58; H, 4.91; S, 19.53. Found: C, 36.71; H, 4.71; S, 19.49.

Compound **19** was conventionally silylated with Sylon HTP. The GC-MS of the silylated derivative was performed: MS *m/z* (rel inten) 380 (3), 365 (33), 290 (11), 262 (26), 219 (18), 218 (68), 217 (100), 204 (16), 191 (11), 147 (41), 146 (14), 133 (11), 103 (7), 75 (4), 73 (47).

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