

Synthesis of L-Ribono- and L-Lyxono-lactone

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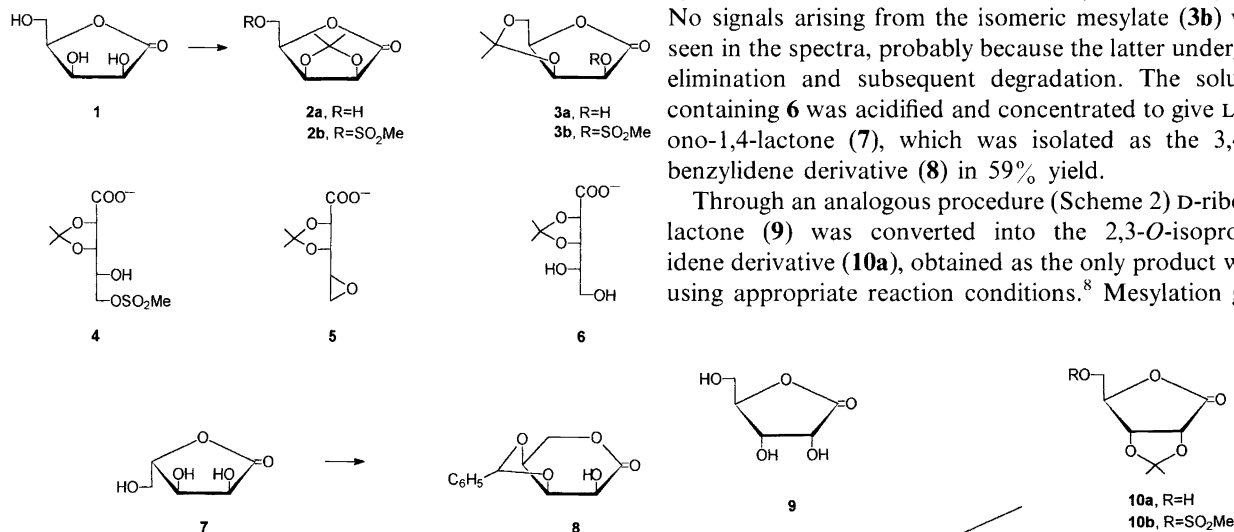
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L-Ribonolactone has been prepared in good yield by treatment of 2,3-*O*-isopropylidene-5-*O*-methanesulfonyl-D-lyxono-1,4-lactone with aqueous base. It was isolated as 3,4-*O*-benzylidene-L-ribono-1,5-lactone. A similar treatment of 2,3-*O*-isopropylidene-5-*O*-methanesulfonyl-D-ribo-1,4-lactone gave L-lyxonolactone, isolated as the 3,5-*O*-benzylidene derivative. The mechanisms of the reactions, as well as those of the reaction of 5-bromo-5-deoxy-D-ribo- and -D-lyxono-1,4-lactone, with aqueous base have been studied.

L-Ribono-1,4-lactone or derivatives thereof have been prepared from L-arabinose,^{1,2} from D-ribonolactone by oxidation of C-5 and reduction of C-1,³ or via microbial oxidation of chlorobenzene.⁴ L-Lyxonolactone has not been described previously. In the present paper a new synthesis of L-ribonolactone, isolated as the 3,4-*O*-benzylidene derivative, is described using the readily available D-lyxono-1,4-lactone as starting material.⁵ L-Lyxonolactone is prepared similarly from D-ribo-1,4-lactone.

(Scheme 1).⁶ Methanesulfonylation (mesylation) of the crude mixture yielded **2b** and **3b** which were not separated. Treatment of this mixture with aqueous potassium hydroxide gave the L-ribonic acid derivative **6** as the only product evident from a ¹³C NMR spectrum. When the reaction was monitored by ¹³C NMR spectroscopy the 4,5-epoxide (**5**) was observed (Table 1). The 5-*O*-mesylate (**4**), which must be the first product formed, was not observed. The conversion of **5** into **6** probably takes place by intramolecular substitution at C-4 by the carboxylate.⁷ No signals arising from the isomeric mesylate (**3b**) were seen in the spectra, probably because the latter undergoes elimination and subsequent degradation. The solution containing **6** was acidified and concentrated to give L-ribo-1,4-lactone (**7**), which was isolated as the 3,4-*O*-benzylidene derivative (**8**) in 59% yield.

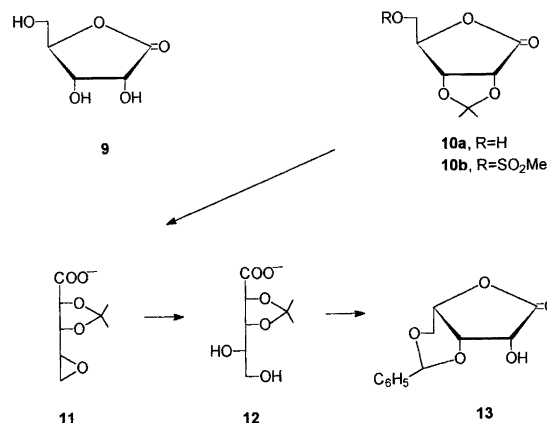
Through an analogous procedure (Scheme 2) D-ribonolactone (**9**) was converted into the 2,3-*O*-isopropylidene derivative (**10a**), obtained as the only product when using appropriate reaction conditions.⁸ Mesylation gave



Scheme 1.

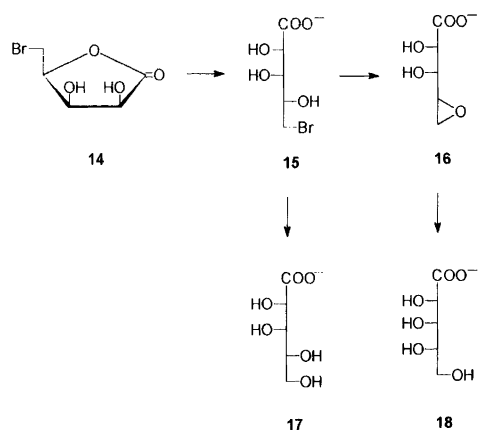
Results and discussion

Treatment of D-lyxonolactone (**1**) with acetone and acid gave a 3:1 mixture of 2,3-*O*-isopropylidene-D-lyxono-1,4-lactone (**2a**) and the 3,5-isopropylidene derivative **3a**



Scheme 2.

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Scheme 3.

10b and subsequent treatment with aqueous potassium hydroxide yielded the L-lyxonic acid derivative (**12**) via the 4,5-epoxide (**11**) as observed from ^{13}C NMR spectra (Table 1). Hydrolysis of **12** with acid and treatment with benzaldehyde gave 3,5-*O*-benzylidene-L-lyxono-1,4-lactone (**13**).

The reactions of the unprotected 5-*O*-mesyl-D-lyxono- and -D-ribonolactone, as well as of the corresponding 5-chloro- and 5-bromo derivatives, with aqueous base were also studied. They all behaved similarly to the isopropylidene derivatives **2b** and **10b** giving L-ribo- or L-lyxono-lactone as the main products, respectively. However, by-products were also formed. The reactions of 5-bromo-5-deoxy-D-lyxono-1,4-lactone (**14**) and 5-bromo-5-deoxy-D-ribo-1,4-lactone (**19**) with aqueous base (Scheme 3) were monitored by ^{13}C NMR spectroscopy. The reaction of **14** with potassium hydroxide was complete within ca. 7 min (Table 2) and gave 85% L-ribonate (**18**) together with 15% of the D-lyxonate (**17**). The only intermediate observed was the 4,5-epoxide (**16**), which would give **18** by intramolecular substitution. With potassium carbonate 31% of **17** was obtained and, besides **16**, the 5-bromo carboxylate (**15**) was observed as an intermediate (Table 2). This indicates that the lyxonate (**17**) is formed either by substitution of the bromine of **15** with

Table 1. Products observed during the reaction of 2,3-di-*O*-isopropylidene-5-*O*-methanesulfonyl-D-lyxono- (**2b**) and -D-ribo-1,4-lactone (**10b**) with KOH (3 mol equiv.) in D_2O at 20°C .

Time	Products ^a		Time	Products ^a	
	5	6		11	12
2b			10b		
5 min	88	12	5 min	91	9
15 min	68	32	15 min	73	27
30 min	55	45	30 min	50	50
2 1/2 h	7	93	1 h	18	82
3 1/2 h	3	97	2 h	0	100

^aRelative percentages estimated from peak heights of secondary carbon atoms in the ^{13}C NMR spectra.

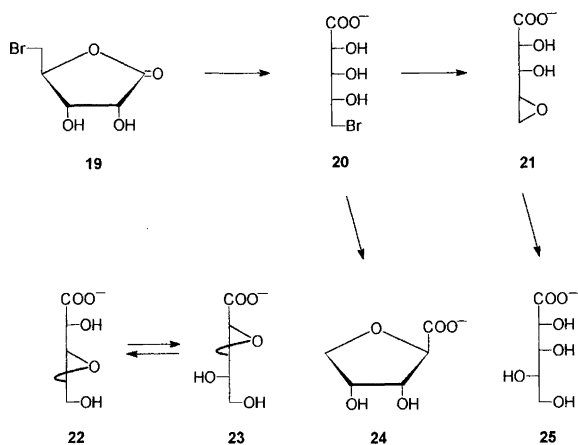
hydroxide or, more likely, by internal attack of the carboxylate of **15** via a six-membered transition state giving a 1,5-lactone as an intermediate.

The reaction of 5-bromo-D-ribonolactone (**19**) with base (Scheme 4) was much slower than that of **14**. With potassium hydroxide both the 4,5-epoxide (**21**), the 3,4-epoxide (**22**) and the 2,3-epoxide (**23**) were observed (Table 3) and they are probably in equilibrium in the strongly alkaline solution.^{7,9} The final products are the 2,5-anhydro-D-ribonate (**24**) and the L-lyxonate (**25**). The former was formed during the first few minutes (Table 3) indicating that it may arise from **20** by substitution of the 2-OH group at C-5 in competition with the formation of the 4,5-epoxide **21**. Similar internal substitution in **21** is less likely since it would require an *endo*-opening of the epoxide instead of the *exo*-opening which leads to **25**.¹⁰ When **19** was treated with potassium carbonate the bromo carboxylate (**20**) was observed in rather large amounts as the sole intermediate during the first hour and in agreement herewith **24** became the main product. The rather slow conversion of **19** into **25** with potassium hydroxide may be due to the formation of the two

Table 2. Products observed during the reaction of 5-bromo-5-deoxy-D-lyxono-1,4-lactone (**14**) with aqueous base.^a

	Percent ^b				
	14	15	16	17	18
KOH					
3 min			25		75
7 min				15	85
K ₂ CO ₃					
5 min	26	46	28		
30 min		22	25	11	42
2 h				23	77

^aTo the 5-bromolactone (400 mg) in a 7:3 mixture of H_2O and D_2O were added solutions of KOH (0.35 g, 3 mol equiv.) or K_2CO_3 (0.57 g, 3 mol equiv.) in a 7:3 mixture of H_2O and D_2O . ^bThe percentages were estimated from peak heights of the signals of secondary carbon atoms in the ^{13}C NMR spectra.



Scheme 4.

Table 3. Products observed during the reaction of 5-bromo-5-deoxy-D-ribo-1,4-lactone (**19**) with aqueous base.^a

	Percent ^b					
	20	21	22	23	24	25
KOH						
5 min		43	18		14	24
15 min		23	28		12	37
2 h			12	25	13	50
24 h			7	20	12	61
48 h					15	85
K ₂ CO ₃						
5 min	72				17	11
30 min	34				34	32
1 h	26				37	37
3 h	16				42	42
72 h					57	43

^{a, b} See Table 2.

dissecondary epoxides (**22** and **23**). These are rather stable because they are *trans*-epoxides and are therefore converted only slowly into **25** via the less stable epoxide (**21**). No epoxide migration was observed when **14** was reacted with potassium hydroxide, probably because this would lead to *cis*-substituted epoxides which, for steric reasons, would be less stable. ¹³C Chemical shifts of the products observed in reaction of **14** and **19** with base are presented in Table 4.

Experimental

Melting points are uncorrected. Optical rotations were measured on a Perkin Elmer 241 polarimeter. NMR spectra were obtained on Bruker AC-250 and AM-500 instruments using dioxane (67.4 ppm) as an internal reference for ¹³C NMR spectra in D₂O.

2,3- and 3,5-O-isopropylidene-D-lyxono-1,4-lactones (**2a** and **3a**). A mixture of D-lyxono-1,4-lactone (**1**, 10 g), acetone

Table 4. ¹³C NMR data of intermediates and products observed in the reactions of 5-bromo-5-deoxy-D-lyxono- (**14**) and -D-ribo-1,4-lactone (**19**) with aqueous base. The signals of C-1 are found between 175 and 180 ppm; they have in most cases not been assigned and are therefore not shown.

Compound	Chemical shift, δ-values			
	C-2	C-3	C-4	C-5
15	71.6	73.8 ^a	74.4 ^a	36.2
16	75.7 ^a	75.4 ^a	54.3	46.3
20	71.0	74.4 ^a	75.0 ^a	39.0
21	73.3	75.4	52.3	46.3
22	70.9	56.8	57.9	61.8
23	53.6	58.6	71.0	64.1
24	79.9	71.7 ^a	74.1 ^a	75.6 ^a
25	72.1 ^a	72.7 ^a	74.8 ^a	63.8

^a May be interchanged.

(200 ml) and conc. H₂SO₄ (0.5 ml) was placed in a flask equipped with a Soxhlet condenser, which contained 5 g of 4 Å molecular sieves. The solution was boiled for 4.5 h, then cooled in ice and neutralized with NaHCO₃. The mixture was filtered through activated carbon and the filtrate was concentrated to leave a mixture (6.35 g, 100%) of **2a** and **3a** in a 3:1 ratio.⁶ ¹³C NMR (acetone-*d*₆): **2a**, δ 173.1 (C-1), 112.1 (acetal C), 78.8, 75.4, 75.4 (C-2, 3, 4), 59.0 (C-5), 25.2, 24.1 (CH₃); **3a**, δ 174.4 (C-1), 96.3 (acetal C), 70.6, 68.3, 67.1 (C-2, 3, 4), 58.7 (C-5), 27.3, 17.5 (CH₃).

2,3-O-Isopropylidene-5-O-methanesulfonyl- and 3,5-O-isopropylidene-2-O-methanesulfonyl-D-lyxono-1,4-lactone (**2b** and **3b**). Methanesulfonyl chloride (3.94 ml, 50.7 mmol) was added dropwise to a stirred solution of the mixture of **2a** and **3a** (6.35 g, 33.8 mmol) in pyridine (10 ml) at 0°C. The mixture was kept at 0°C for 30 min and at 20°C for 30 min. Water (30 ml) was then added and the mixture was extracted with CH₂Cl₂ (4 × 15 ml). The extract was washed with dilute hydrochloric acid and with aqueous NaHCO₃, dried (Na₂SO₄), filtered through activated carbon and concentrated to leave 7.4 g (83%) of a mixture of **2b** and **3b** as yellow crystals in a ratio of 3:1. ¹³C NMR (acetone-*d*₆): **2b**, δ 173.1 (C-1), 113.7 (acetal C), 76.5, 76.1, 76.0 (C-2, 3, 4), 68.0 (C-5), 36.5 (mesyl), 26.0, 25.0 (CH₃); **3b**, δ 170.2 (C-1), 97.7 (acetal C), 76.0, 70.1, 67.4 (C-2, 3, 4), 59.3 (C-5), 38.4 (mesyl), 28.3, 18.2 (CH₃).

2,3-O-Isopropylidene-D-ribo-1,4-lactone (**10a**) was prepared as described above from D-ribo-1,4-lactone (**9**, 10 g), acetone (200 ml) and conc. H₂SO₄ (0.5 ml). The mixture was boiled for 1.5 h and processed as described above to give 12.6 g (99%) of crude **10a**, m.p. 118–123°C, [α]_D²⁰ – 63.0° (c 2.1, pyridine). Lit.¹¹ m.p. 138–139°C, [α]_D – 65.7°. ¹³C NMR data were identical with those reported.¹² When the reaction mixture was boiled for 3 h or longer considerable amounts of an isomeric product were found.⁸ The isomer was probably either 2,3- or 3,4-O-isopropylidene-D-ribo-1,5-lactone. Its ring size was indicated by the ¹³C chemical shifts of the carbonyl and acetal carbons¹³ both of which appeared upfield from those of **10a**.¹² ¹³C NMR (acetone-*d*₆): δ 165.8 (C-1), 109.3 (acetal C), 75.6, 73.0, 68.6, 67.1 (C-2, 3, 4, 5), 25.5, 23.6 (CH₃).

2,3-O-Isopropylidene-5-O-methanesulfonyl-D-ribo-1,4-lactone (**10b**) was prepared as described above from **10a** (5 g, 26.6 mmol), pyridine (10 ml) and mesyl chloride (3.1 ml, 39.9 mmol). The crude **10b**, 6.44 g (91%), m.p. 64–66°C, was sufficiently pure for further use. A sample was recrystallized from EtOAc–pentane to give a product with m.p. 66–67°C, [α]_D²⁰ – 49.9°C (c 1.0, CHCl₃). Anal. C₉H₁₄SO₇: C, H. ¹H NMR (500 MHz, CDCl₃): δ 4.82 (1 H, d, *J*_{2,3} 6 Hz, H-2), 4.79 (1 H, dd, *J*_{3,4} 1 Hz H-3), 4.77 (1 H, t, *J*_{4,5} 2, *J*_{4,5'} 2.5 Hz, H-4), 4.47 (1 H, dd, *J*_{5,5'} 11.5 Hz, H-5'), 4.44 (1 H, dd, H-5), 3.05

(1 H, s, CH₃SO₂), 1.49 (3 H, q, $J_{\text{Me,Me}}$ ca. 0.2 Hz, acetal Me), 1.40 (3 H, q, acetal Me). ¹³C NMR (CDCl₃): δ 173.1 (C-1), 113.8 (acetal C), 79.1 (C-4), 77.2 (C-3), 74.8 (C-2), 68.1 (C-5), 37.4 (mesyl), 26.5, 25.3 (CH₃).

Reaction of 2,3-O-isopropylidene-5-O-methanesulfonyl-D-lyxono-1,4-lactone (2b) with aqueous potassium hydroxide. To a solution of KOH (63 mg, 3 mol equiv.) in D₂O (1 ml) was added the 3:1 mixture of **2b** and **3b** (0.1 g) and the mixture was shaken. A ¹³C NMR spectrum obtained after 5 min showed that the epoxide **5** was the main product. ¹³C NMR: δ 175.3 (C-1), 111.5 (acetal C), 79.1, 77.4 (C-2, 3), 53.1 (C-4), 46.3 (C-5), 27.0, 25.1 (CH₃). After 2.5 h, the carboxylate **6** was the main product and after 24 h it was the only product. ¹³C NMR: δ 176.4 (C-1), 110.7 (acetal C), 78.0, 77.9 (C-2, 3), 71.8 (C-4), 63.5 (C-5), 26.8, 25.1 (CH₃). No product arising from the reaction of **3b** was observed. For further details see Table 1.

3,4-O-Benzylidene-L-ribo-1,5-lactone (8). The mixture of **2b** and **3b** (5 g, 18.8 mmol) was dissolved in H₂O (20 ml) containing KOH (3.16 g, 53.3 mmol) and stirred at room temperature for 24 h. The solution was then acidified with hydrochloric acid to pH ca. 1 and concentrated. The residue was stirred with benzaldehyde (25 ml) and conc. hydrochloric acid (5 ml) for 18 h during which time crystals of **8** were formed. Diethyl ether (25 ml) was then added and, after 1 h, the product was filtered off and washed successively with Et₂O, aqueous NaHCO₃, H₂O and Et₂O and dried over KOH. Colourless needles, 2.6 g (59%), m.p. 215–218°C, $[\alpha]_{\text{D}}^{20} + 172^\circ$ (c 2.3, DMF). Lit.¹⁴ m.p. 233–235.5°C, $[\alpha]_{\text{D}} - 171^\circ$ for the enantiomer. ¹³C and ¹H NMR spectra were in accordance with those reported for the enantiomer.¹⁵ A sample was recrystallized from acetone, m.p. 230–232°C, $[\alpha]_{\text{D}}^{20} + 173^\circ$ (c 2, DMF). Anal. C₁₂H₁₂O₅: C, H.

Reaction of 2,3-O-isopropylidene-5-O-methanesulfonyl-D-ribo-1,4-lactone (10b) with potassium hydroxide. The reaction was performed as described above for **2b**. A ¹³C NMR spectrum measured after 5 min showed that the 4,5-epoxide (**11**) was the main product. ¹³C NMR data: δ 175.2 (C-1), 111.2 (acetal C), 77.9, 76.5 (C-2,3), 51.4 (C4), 45.5 (C5), 26.7, 24.9 (CH₃). After 2 h, the 2,3-O-isopropylidene-L-lyxonate (**12**) was the only product. ¹³C NMR: δ 176.7 (C-1), 110.3 (acetal C), 77.5, 77.3 (C-2,3), 71.3 (C-4), 64.1 (C-5), 26.3, 24.7 (CH₃). Further details are shown in Table 1.

3,5-O-Benzylidene-L-lyxono-1,4-lactone (13) was prepared as described above for **8** from 5.0 g of **10b**, but using only a 4 h reaction time with KOH. The crude product (3.4 g, 77%) had m.p. 181–184°C, $[\alpha]_{\text{D}}^{20} - 31.1^\circ$ (c 2.3, DMF). A sample was recrystallized from acetone, m.p. 201.5–204°C, $[\alpha]_{\text{D}}^{20} - 30.9^\circ$ (c, DMF). Lit. for the D-enantiomer¹⁴ m.p. 203.5–206°C, $[\alpha]_{\text{D}}^{20} + 31.6^\circ$. Anal. C₁₂H₁₂O₅: C, H. ¹H and ¹³C NMR spectra were identical with those of the D-enantiomer.¹⁶

5-Bromo-5-deoxy-D-lyxono-1,4-lactone (14). A solution of D-lyxono-1,4-lactone (**1**, 1.0 g) in pyridine (31 ml) was cooled in ice and triphenylphosphine (4.6 g) was added. Tetrabromomethane (2.91 g) was then added in portions over 30 min, with stirring. The mixture was heated to 60°C for 3.5 h and then concentrated. The residue was stirred with 25 ml aqueous HBr (0.15 M). The mixture was then extracted with CH₂Cl₂ and the aqueous phase was concentrated to ca. 10 ml and extracted with EtOAc (2 × 10 ml). The extract was dried (MgSO₄) and concentrated to leave 90 mg (24%) of **14** which was recrystallized from EtOAc–pentane, m.p. 135–136°C, $[\alpha]_{\text{D}}^{20} - 6.9^\circ$ (c 1.1, EtOAc). Anal. C₅H₇BrO₄: C, H, Br. ¹³C NMR (D₂O): δ 178.4 (C-1), 81.2 (C-4), 71.5, 70.4 (C-2,3), 27.5 (C-5).

5-Bromo-5-deoxy-D-ribo-1,4-lactone (19) was prepared as described above from D-ribo-1,4-lactone (**9**, 3.5 g). After addition of the tetrabromomethane (10.2 g) the mixture was kept at room temperature for 2 h and then worked up as described above. The crude product, 2.7 g (55%), m.p. 98–101°C, was recrystallized from EtOAc–pentane to give **19**, m.p. 106–107°C, $[\alpha]_{\text{D}}^{20} + 24.6^\circ$ (c 1.1, EtOAc). Anal. C₅H₇BrO₄: C, H, Br. ¹³C NMR (D₂O): δ 178.4 (C-1), 85.6 (C-4), 70.6, 69.2 (C-2,3), 30.7 (C-5).

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