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Note

Synthesis of 3-deoxy-2,4-di-*O*-methyl-D-*erythro*-pentono-1,5-lactone and of its L enantiomer by stereoselective hydrogenation of α,β-unsaturated aldono-1,5-lactones

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Carbohydrates are widely used as chiral templates in organic synthesis [1], and several pentonolactones have often been utilized as starting materials in natural product syntheses [2]. Also, the importance of aldonic and aldaric acids in metabolism is well known [3] and some aldono- and aldaro-lactones are highly specific, competitive inhibitors of certain glycosidases [4]. As a part of our current research on the synthesis of carbohydrate based biodegradable polymers [5,6], we describe herein the preparation of 3-deoxy-*erythro*-pentono-1,5-lactones and of some of its olefinic precursors and derivatives which will be used in the synthesis of new polymeric biomaterials and which can also be regarded as new chiral building blocks in the preparation of natural products.

The β-elimination reaction from *O*-benzoyl-1,5-aldonolactones [7,8] and *O*-benzyl-1,5-aldonolactams [9] is a well-established reaction that yields α,β-unsaturated lactones and lactams. Thus, when 2,3,4-tri-*O*-methyl-D-xylono-1,5-lactone [10] (**1**) was treated with base, elimination of the methoxyl group β to the carbonyl took place to give the α,β-unsaturated lactone **2**. The reaction can be carried out with different bases but the best yields were obtained by using 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) in THF. Under the same conditions, 2,3,4-tri-*O*-methyl-L-arabinono-1,5-lactone [11] (**8**) gave the α,β-unsaturated lactone **9**, enantiomeric to **2**. The IR spectra of these compounds show

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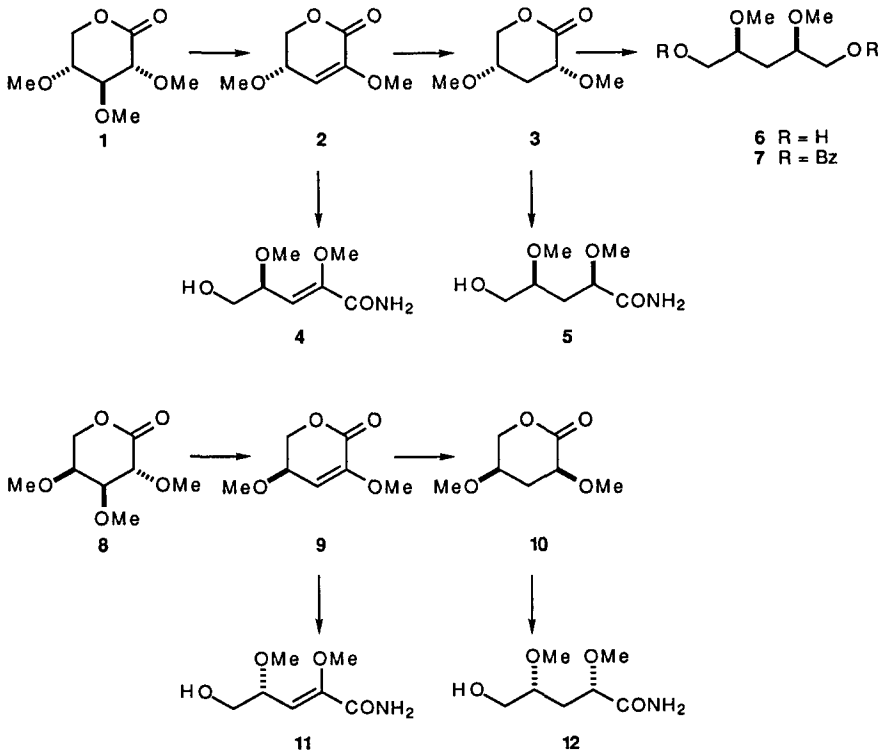
Table 1
^{1}H NMR data for **2–7**

Compound	H-2	H-3	H-3′	H-4	H-5	H-5′	Others
2 [a]	–	5.85 dd $J_{3,4}$ 5.8 $J_{3,5}$ 1.3	–	4.10 dq $J_{4,5}$ 2.5 $J_{4,5'}$ 3.1	4.55 dq $J_{5,5'}$ 12.4	4.40 dd	3.72 s (OMe) 3.40 s (OMe)
3 [a]	3.93 dd $J_{2,3}$ 8.1 $J_{2,3'}$ 10.6	2.74 dt $J_{3,4}$ 8.1 $J_{3,3'}$ 14.1	1.81 ddd $J_{3',4}$ 3.7 $J_{3',5}$ 1.1	3.81 m $J_{4,5}$ 2.7 $J_{4,5'}$ 2.6	4.43 ddd $J_{5,5'}$ 12.5	4.21 dd	3.54 s (OMe) 3.30 s (OMe)
4 [b]	–	4.70 m	–	4.70 m	← 3.35 m →		3.50 s (OMe) 3.16 s (OMe) 4.56 t (OH) J 5.9 7.43 and 7.35 bs (NH_2)
5 [c]	3.54 dd $J_{2,3}$ 5.9 $J_{2,3'}$ 7.1	1.73 dt $J_{3,4}$ 5.9 $J_{3,3'}$ 14.0	1.64 ddd $J_{3',4}$ 6.6	3.21 m	← 3.40 m →		3.24 s (OMe) 3.22 s (OMe) 4.54 t (OH) J 5.7 7.31 and 7.14 bs (NH_2)
5 [d]	3.52 dd $J_{2,3}$ 5.8 $J_{2,3'}$ 7.2	1.72 dt $J_{3,4}$ 5.8 $J_{3,3'}$ 14.0	1.64 ddd $J_{3',4}$ 6.6	3.20 m $J_{4,5}$ 4.4 $J_{4,5'}$ 5.4	3.39 dd $J_{5,5'}$ 11.3	3.33 dd	3.23 s (OMe) 3.21 s (OMe)
	H-1(5)	H-1′(5′)	H-2(4)	H-3	H-3′	Others	
6 [a]		← 3.55 m →		← 1.55 m →		3.35 s (2 OMe) 4.12 bs (2 OH)	
7 [a]	4.53 dd $J_{1,2}$ 3.9 $J_{1,1'}$ 11.8	4.35 dd $J_{1',2}$ 5.3	3.77 m $J_{2,3}$ 6.6	← 2.00 m → $J_{3,3'}$ 14.4		3.50 s (2 OMe) 8.08 and 7.42 m (Ph)	

[a] $CDCl_3$ at 200 MHz.
[b] $(CD_3)_2SO$ at 200 MHz.
[c] $(CD_3)_2SO$ at 500 MHz.
[d] $(CD_3)_2SO + D_2O$ at 500 MHz.
Primes are used for the labelling of the upfield proton of a methylene group. Signal multiplicities: b, broad; d, doublet; m, multiplet; q, quartet; s, singlet; and t, triplet.

an olefinic band at 1643 cm^{-1} and a carbonyl band at 1737 cm^{-1}, in agreement with an α,β-unsaturated lactone. The MS and the elemental analyses were also in agreement with these structures. Accordingly, the ^{1}H NMR spectra (see Table 1) show signals of only two methoxyl groups, but none for H-2, and a signal for H-3 which is shifted downfield, as compared to the parent lactones **1** or **8**. The ^{13}C NMR spectra (see Table 2) confirm the presence of two methoxyl groups, and show two signals at 146.5 and 106.5 ppm corresponding to the unsaturated carbons C-2 and C-3, respectively.



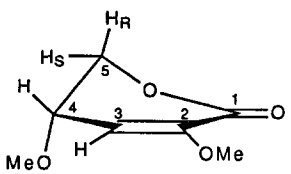
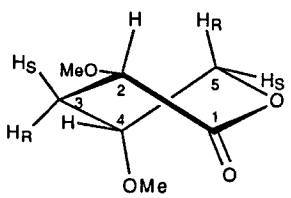
The hydrogenation of **2** and **9** took place with complete diastereoselection to give exclusively the enantiomeric 3-deoxy-*erythro*-pentono-1,5-lactones **3** and **10**, respectively. The elemental analyses, MS, IR, and NMR spectra of these compounds, were in agreement with these structures. The configuration of the new stereocenter was proved by reduction of the lactone **3** with sodium borohydride to give 3-deoxy-2,4-di-*O*-methyl-

Table 2
^{13}C NMR data for **2**–**7**

Compound	C-1	C-2	C-3	C-4	C-5	Others
2 [a]	159.9	146.5	106.5	69.4	69.0	55.9 and 55.3 (OMe)
3 [a]	171.4	72.8	32.5	71.7	67.5	58.2 and 55.6 (OMe)
4 [b]	164.8	150.6	106.1	77.1	64.4	55.6 and 54.9 (OMe)
5 [b]	174.0	79.1	34.3	78.4	62.5	57.1 and 56.5 (OMe)
	C-1(5)	C-2(4)	C-3	Others		
6 [a]	62.2	78.3	29.5	56.8 (OMe)		
7 [a]	65.6	75.9	33.5	57.6 (OMe), 166.4 (Ph–*C*OO), 133.0, 129.9, 129.6, 128.4 (Ph)		

[a] $CDCl_3$ at 50.3 MHz.
[b] $(CD_3)_2SO$ at 50.3 MHz.

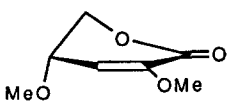
Table 3
Coupling constants ($J_{H,H}$) and torsion angles ($\phi_{H,H}$) for **2**-^5E and **3**-*S*

Compound	HH	$J_{H,H}$ [a]	$\phi_{H,H}$ [b]	$\phi_{H,H}$ [c]	$\phi_{H,H}$ [d]
 **2**-^5E	4,5S	2.5	−63	−66	−60
	4,5R	3.1	41	52	60
	3,5S	1.3			
 **3**-$^5S_1$	2,3	8.1	−33	−31	−33
	2,3R	10.6	−167	−147	−153
	3S,4	8.1	−17	−31	−33
	3R,4	3.7	124	84	87
	4,5S	2.7	−61	−55	−71
	3R,5S	1.1			

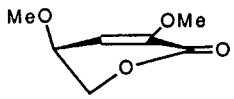
[a] From Table 1.
[b] Calculated from *J* [13].
[c] Calculated by MM2 [14].
[d] Taken from models of the ideal conformations [15].
The torsion angle ($\phi_{H,H}$) is defined $-180° < \phi \leq 180°$, being positive in the clockwise direction. H*R* and H*S* are used for the labelling of the pro-*R* and pro-*S* hydrogens of a prochiral methylene group.

D-*erythro*-pentitol (**6**). Compound **6** and its di-*O*-benzoyl derivative **7** were optically inactive, as expected for *meso* compounds. These lactones were easily converted into the corresponding amides by reaction with ammonia. In this reaction, the lactone ring is opened [12] and the acyclic amides (**4**, **5**, **11**, and **12**) were obtained as demonstrated by their ^{1}H NMR, which showed a triplet signal for the primary hydroxyl group at C-5. These acyclic amides can easily be converted into the corresponding 1-amino-1-deoxyalditols that will be used as monomers in the preparation of new stereoregular poly-esteramides [6].

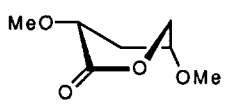
The $J_{4,5}$ and $J_{4,5'}$ values of **2** are correlated [13] with dihedral angles (Table 3) that can be in agreement with an envelope conformation [16] (**2**-^5E) with C-5 as the single exoplanar atom. This conformation is also in agreement with an approximately planar W arrangement for H-3 and H-5*S*, which explains the observed long-range coupling for these protons. In this conformation, the OMe group on C-4 is quasi-axial and it blocks the (*re*,*re*) face of the olefin, which could explain the high diastereoselectivity of the hydrogenation reaction.



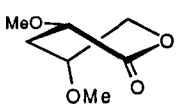
2-^5E



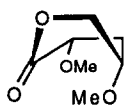
9-E_5



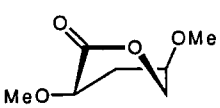
3-$^{2,5}B$



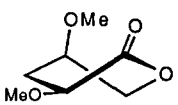
3-$^5S_1$



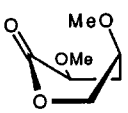
3-$B_{1,4}$



10-$B_{2,5}$



10-$^1S_5$



10-$^{1,4}B$

Table 3 also shows the dihedral angles calculated [13] from the observed coupling constant for the saturated lactone **3**. These indicate that **3** adopts a conformation close to a *skew* conformation **3**-$^5S_1$, intermediate between the two *boat* conformations **3**-$^{2,5}B$ and **3**-$B_{1,4}$, which is the conformation of minimal energy as calculated by MM2 [14]. The dihedral angles of **3**-$^5S_1$ are well correlated with those taken from models for an ideal *S* conformation [15]. A similar $^5S_1$ conformation was proposed [17] for 2,3,4-tri-*O*-acetyl-D-xylono-1,5-lactone on the basis of its ^{1}H NMR data, which Horton et al. [18] interpreted as being in accordance with a $^{2,5}B$ conformation. The lactones **9** and **10** may possess the enantiomeric conformations **9**-^5E and **10**-$^1S_5$.

1. Experimental

General methods.—Chemicals were all used as purchased from Aldrich Chemical Co. Solvents were dried and purified, when necessary, by appropriate standard procedures. Melting points were determined with a Gallenkamp apparatus and are uncorrected. Optical rotations were measured at 20 ± 5 °C with a Bellingham and Standley Inc., P20 polarimeter (5-cm cell). TLC was performed on Silica Gel 60 F_{254} (E. Merck) with detection by UV light or charring with sulfuric acid and flash column chromatogra-

phy with E. Merck Silica Gel 60 (230–400 mesh). FT IR spectra (films or KBr discs) were recorded with a Michelson 100 spectrometer. NMR spectra were recorded with Bruker 200 AC-P and AMX 500 spectrometers. Chemical shifts are reported as parts per million downfield from tetramethylsilane. MS were recorded on a Kratos MS-80-RFA mass spectrometer equipped with a combined EI–CI source. High-resolution mass measurements (EI, 70 eV) were taken with resolution 10,000. Elemental analyses were determined in the Microanalysis Laboratories at the Universidad de Sevilla and the Universidad Complutense de Madrid.

*3-Deoxy-2,4-di-*O*-methyl-*D-glycero-*pent-2-enono-1,5-lactone* (**2**).—A solution of 2,3,4-tri-*O*-methyl-D-xylono-1,5-lactone [10] (**1**, 4.0 g, 21.03 mmol) and 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU, 6.0 mL, 42.00 mmol) in THF (100 mL) was heated at 60 °C for 6 h, then concentrated. Column chromatography (1:1 EtOAc–hexane) of the residue gave pure **2** (2.1 g, 64%) as a syrup; $[\alpha]_D$ +70.5° (*c* 1.0, $CHCl_3$); ν 1737 and 1643 cm^{-1}. Mass spectrum: *m/z* 158.0583 ($M^{+\cdot}$; calcd for $C_7H_{10}O_4$ 158.0579). Anal. Calcd for $C_7H_{10}O_4$: C, 53.16; H, 6.37. Found: C, 52.77; H, 6.44.

*3-Deoxy-2,4-di-*O*-methyl-*D-erythro-*pentono-1,5-lactone* (**3**).—A solution of **2** (0.8 g, 5.05 mmol) in dry THF (20 mL) was hydrogenated at atmospheric pressure and room temperature in the presence of 10% Pd–C. After 3 h, the mixture was filtered, the solids were washed with THF, and the combined filtrate and washings were concentrated. Column chromatography (2:1 hexane–EtOAc) of the residue gave pure **3** (0.75 g, 87%) as a syrup; $[\alpha]_D$ +2.5° (*c* 1.0, $CHCl_3$); IR (film): ν 1758 cm^{-1}. Mass spectrum: *m/z* 160.0727 ($M^{+\cdot}$; calcd for $C_7H_{12}O_4$ 160.0735). Anal. Calcd for $C_7H_{12}O_4$: C, 52.49; H, 7.55. Found: C, 52.09; H, 7.57.

*3-Deoxy-2,4-di-*O*-methyl-*D-glycero-*pent-2-enonamide* (**4**).—Ammonia was bubbled through a cooled solution of **2** (0.25 g, 1.58 mmol) in MeOH (5 mL) for 15 min. The solution was kept at 0 °C for 24 h and then concentrated. The residue was crystallized from MeOH to give pure **4** (0.21 g, 78%), mp 120–122 °C; $[\alpha]_D$ +69.5° (*c* 1.0, $CHCl_3$); IR (KBr): ν 3459, 3327, and 1687 cm^{-1}. Anal. Calcd for $C_7H_{13}NO_4$: C, 47.99; H, 7.48; N, 7.99. Found: C, 48.16; H, 7.60; N, 8.14.

*3-Deoxy-2,4-di-*O*-methyl-*D-erythro-*pentonamide* (**5**).—A methanolic solution of **3** (0.5 g, 3.12 mmol) was treated as described for the preparation of **4**, followed by concentration under diminished pressure. Column chromatography (10:1 CH_2Cl_2–MeOH) of the residue gave pure **5** (0.54 g, quant.) as a syrup; $[\alpha]_D$ +45° (*c* 1.0, $CHCl_3$); ν 3420–3200, 1675 cm^{-1}. Mass spectrum: *m/z* 146.0807 ($[M - CH_3O]^+$; calcd for $C_6H_{12}NO_3$ 146.08172); 178.1074 ($[M + H]^+$; calcd for $C_7H_{16}NO_4$ 178.10793). Anal. Calcd for $C_7H_{15}NO_4 \cdot 0.5\ H_2O$: C, 45.15; H, 8.66; N, 7.52. Found: C, 44.97; H, 8.29; N, 7.77.

*3-Deoxy-2,4-di-*O*-methyl-*D-erythro-*pentitol* (**6**).—3-Deoxy-2,4-di-O-methyl-D-*erythro*-pentono-1,5-lactone (**3**; 0.6 g, 3.75 mmol) and Amberlite IR-120 (H^+) resin (7.5 mL) were added to a 0.05 M aq soln of boric acid (37.5 mL) and the mixture was cooled in an ice bath. With efficient stirring, a freshly prepared 0.3 M aq soln of $NaBH_4$ (37.5 mL) was added dropwise over 2–3 min. Stirring was continued for 30 min and a second portion (37.5 mL) of the $NaBH_4$ soln was added. After 30 min, the pH was adjusted to ~ 9 with a solution of NaOH, and the reaction mixture was kept at 5 °C overnight and then passed through a column of Amberlite IR-120 (H^+) resin (40 mL). The effluent

and washings were evaporated under diminished pressure and the boric acid was removed by repeated coevaporation with MeOH under diminished pressure. Column chromatography (20:1 CH_2Cl_2–MeOH) of the residue gave **6** (0.37 g, 60%) as a syrup; $[\alpha]_D$ 0° (*c* 1.0, $CHCl_3$); ν 3520–3320 cm^{-1}. Mass spectrum: *m/z* 133.0862 ($[M - CH_3O]^+$; calcd for $C_6H_{13}O_3$ 133.08647).

*1,5-Di-*O*-benzoyl-3-deoxy-2,4-di-*O*-methyl-*D*-erythro-pentitol* (**7**).—To a solution of **6** (0.20 g, 1.21 mmol) in dry pyridine (10 mL), cooled in an ice–salt bath, benzoyl chloride (1 mL) was added dropwise while stirring. The mixture was kept for 48 h in the refrigerator and then treated with water (0.5 mL), allowed to stand for 24 h at room temp and poured into ice–water containing $NaHCO_3$ (7 g). The aq soln was extracted with CH_2Cl_2, and the combined extracts were washed with water, dried ($MgSO_4$), and evaporated. Column chromatography (6:1 hexane–EtOAc) of the residue gave **7** (0.1 g, 23%) as a syrup; $[\alpha]_D$ 0° (*c* 1.0, $CHCl_3$); ν 1720 cm^{-1}. Mass spectrum: *m/z* 237.1134 ($[M - CH_2OBz]^+$; calcd for $C_{13}H_{17}O_4$ 237.11268). Anal. Calcd for $C_{21}H_{24}O_6$: C, 67.72; H, 6.49. Found: C, 67.35; H, 6.44.

*3-Deoxy-2,4-di-*O*-methyl-*L*-glycero-pent-2-enono-1,5-lactone* (**9**).—A solution of 2,3,4-tri-*O*-methyl-L-arabinono-1,5-lactone [11] (**8**, 3.0 g, 15.77 mmol) and DBU (4.0 mL, 30.00 mmol) in THF (60 mL) was heated at 60 °C for 6 h, then concentrated. Column chromatography (1:1 EtOAc–hexane) of the residue gave pure **9** (1.6 g, 77%) as a syrup; $[\alpha]_D$ −70° (*c* 1.0, $CHCl_3$); ν and NMR data were identical to that of its enantiomer **2**. Mass spectrum: *m/z* 158.0580 ($M^{+\cdot}$; calcd for $C_7H_{10}O_4$ 158.0579). Anal. Calcd for $C_7H_{10}O_4 \cdot 0.3\ H_2O$: C, 51.41; H, 6.53. Found: C, 51.39; H, 6.64.

*3-Deoxy-2,4-di-*O*-methyl-*L*-erythro-pentono-1,5-lactone* (**10**).—It was prepared from **9** as described in the preparation of **3**; $[\alpha]_D$ −2.5° (*c* 1.0, $CHCl_3$); ν and NMR data were identical to that of its enantiomer **3**. Mass spectrum: *m/z* 160.0731 ($M^{+\cdot}$; calcd for $C_7H_{12}O_4$ 160.0735). Anal. Calcd for $C_7H_{12}O_4 \cdot 0.5\ H_2O$: C, 49.70; H, 7.75. Found: C, 49.86; H, 7.56.

*3-Deoxy-2,4-di-*O*-methyl-*L*-glycero-pent-2-enonamide* (**11**).—It was prepared from **9** as described in the preparation of **4**; mp 120–122 °C; $[\alpha]_D$ −70° (*c* 1.0, $CHCl_3$); ν and NMR data were identical to that of its enantiomer **4**. Anal. Calcd for $C_7H_{13}NO_4$: C, 47.99; H, 7.48; N, 7.99. Found: C, 47.98; H, 7.68; N, 8.01.

*3-Deoxy-2,4-di-*O*-methyl-*L*-erythro-pentonamide* (**12**).—It was prepared from **10** as described in the preparation of **5**; $[\alpha]_D$ −44° (*c* 1.0, $CHCl_3$); ν and NMR data were identical to that of its enantiomer **5**. Mass spectrum: *m/z* 146.0819 ($[M - CH_3O]^+$; calcd for $C_6H_{12}NO_3$ 146.08172); 178.1073 ($[M + H]^+$; calcd for $C_7H_{16}NO_4$ 178.10793). Anal. Calcd for $C_7H_{15}NO_4 \cdot 0.75\ H_2O$: C, 44.09; H, 8.72; N, 7.34. Found: C, 43.99; H, 8.26; N, 7.18.

Acknowledgements

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