

Synthesis of 2-deoxy-4-octulose derivatives by highly diastereoselective alkylations of protected hexuloses †

Isidoro Izquierdo,* María T. Plaza, Rafael Robles and Antonio Mota
Department of Organic Chemistry, University of Granada, 18071 Granada, Spain

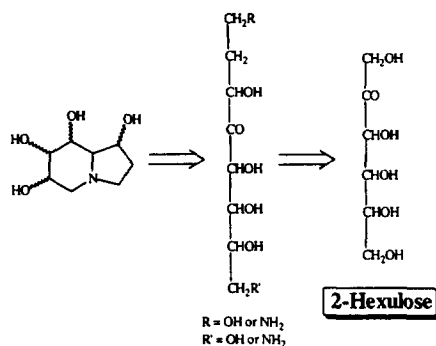
Abstract: Reformatsky reaction of 2,3:4,5-di-*O*-isopropylidene- β -D-*arabino*-hexos-2-ulo-pyranose **1** with methyl bromoacetate proceeded with high diastereoselectivity to give methyl 2-deoxy-4,5:6,7-di-*O*-isopropylidene- β -D-*manno*-oct-4-ulo-4,8-pyranosonate **2** and its -D-*gluco* isomer **3**, in an \approx 10:1 ratio. Configurations of the new stereogenic centres (C-3) in **2** and **3** were determined by reduction of their ester groups to the related 2-deoxy-4,5:6,7-di-*O*-isopropylidene- β -D-*manno*- **4** and -D-*gluco*-oct-4-ulo-4,8-pyranose **5**, respectively. When alkylation at C-1 of **1** was carried out with 2-lithio *tert*-butyl acetate, the corresponding *tert*-butyl ester of **2** (**6**) and **3** (**7**) were formed in an \approx 5.4:1 ratio. The stereochemistry of **6** and **7** was established by their respective reductions to **4** and **5**. On the other hand, reaction of **1** with methyl methoxycarbonylmethylenedimethylsulfurane gave only methyl 2,3-*anhydro*-4,5:6,7-di-*O*-isopropylidene- β -D-*glycero*-D-*galacto*-oct-4-ulo-4,8-pyranosonate **8**, whose stereochemistry was demonstrated by its transformation to **4**. On the other hand, Reformatsky reaction of 2,3:4,6-di-*O*-isopropylidene- α -L-*xylo*-hexos-2-ulofuranose **10** with methyl bromoacetate proceeded with moderate diastereoselectivity to give methyl 2-deoxy-4,5:6,8-di-*O*-isopropylidene- α -L-*gulo*-oct-4-ulo-4,7-furanosonate **11** and its -L-*ido* isomer **12**, in an \approx 3.5:1 ratio. Configuration of the new stereogenic centre (C-3) in **11**, and hence in **12**, was determined by degradation to the known dimethyl D-methoxymalate (+)-**13**. © 1997 Elsevier Science Ltd

Polyhydroxyindolizidines, such as castanospermine and their derivatives,² have received much attention in the recent years because of their potential as antitumor, anti-HIV, antidiabetic agents, etc., due to their potent glycosidase inhibitory character. Retrosynthesis of such molecules (see Scheme 1), clearly demonstrates that 2-deoxy-4-octuloses could be excellent chiral intermediates, since it would only be necessary to introduce, either at C-1 or C-8, an amino group that would form, by internal reductive-amination on the ketone at C-4, the required pyrrolidine or piperidine ring, and finally a new cyclization to the indolizidine ring, by internal nucleophilic displacement, of the appropriate derivative. On the other hand, the cheaper and readily available D-fructose and L-sorbose, can be considered excellent starting chiral templates for the stereoselective synthesis of such 2-deoxy-4-octuloses, and therefore of the above inhibitors, the choice depending on the required stereoisomers. An extension of the sugar chain would be necessary by two more carbon atoms at C-1, insertion in a stereocontrolled manner of one hydroxy group on such an extended chain to afford a 2-deoxy-4-octulose.

Although one such extension has been recently reported³ by our group, in order to shorten the synthetic route, it occurred to us that the use of alkylation reactions at C-1 of suitably protected hexos-2-uloses, could lead to 2-deoxy-4-octulose derivatives in a highly stereocontrolled manner due to the chiral information present in the sugar moiety. Thus, alkylation at C-1 could be achieved by using carbanions (Reformatsky or enolates) as shown in Scheme 2. Another possible synthesis for 2-deoxy-4-octuloses is that also outlined in such Scheme, where the suitably protected hexos-2-ulose

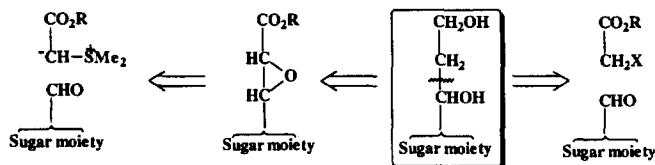
† Synthesis of 4-octuloses, Part IV. For Part III, see Ref.¹

* Corresponding author. Email: isidoro@platon.ugr.es



Scheme 1.

derivative reacts with a sulfur ylide⁴ to produce the corresponding α,β -epoxyester that could be easily transformed into the related 1,3-diol.

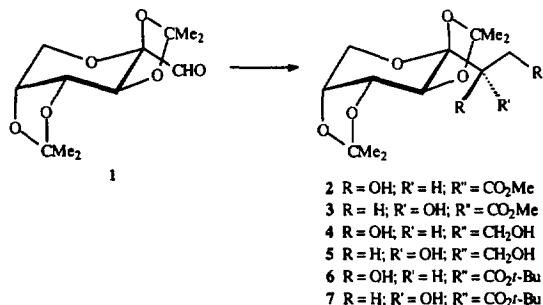


Scheme 2.

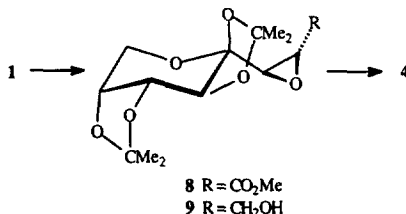
We report herein the results obtained from the application of the above methodologies on 2,3:4,5-di-*O*-isopropylidene- β -*D*-*arabino*-hexos-2-ulopyranose⁵ **1** and 2,3:4,6-di-*O*-isopropylidene- α -*L*-*xylo*-hexos-2-ulofuranose⁶ **10**.

Reformatsky reaction of **1** with methyl bromoacetate under Boudjouk conditions⁷ gave a mixture of methyl 2-deoxy-4,5:6,7-di-*O*-isopropylidene- β -*D*-*manno*-oct-4-ulo-4,8-pyranosonate **2** and its *D*-*gluco* isomer **3** in an $\approx 10:1$ ratio (GLC evidence), that could be partially resolved by chromatography, since compound **2** was obtained in a pure state, but **3** was slightly contaminated with **2**. The stereochemistry of the newly formed stereogenic centre (C-3) was demonstrated by reduction with LiAlH_4 of the ester group in **2** and **3** to the corresponding 2-deoxy-4,5:6,7-di-*O*-isopropylidene- β -*D*-*manno*- **4** and previously reported³ -*D*-*gluco*-oct-4-ulo-4,8-pyranose **5**, respectively.

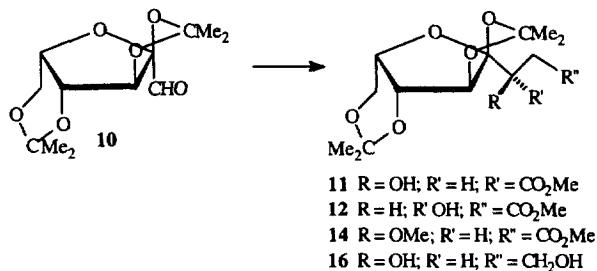
On the other hand, the 2-lithio *tert*-butyl acetate has been used⁸ as an excellent reagent to perform Reformatsky-type reactions on carbonyl compounds. Application of this protocol to **1**, resulted in the formation of the analogous ester **6** and **7**, with $\approx 5.4:1$ diastereoselectivity (GLC analysis), although in this case both isomers could not be totally separated, nevertheless the reduction of **6** slightly impurified with **7**, allowed the isolation of **4** and **5**.



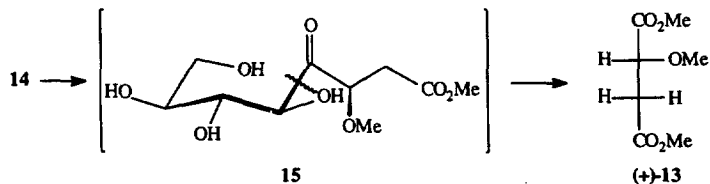
Reaction of **1** with methoxycarbonylmethylenedimethylsulfurane⁹ gave methyl 2,3-*anhydro*-4,5:6,7-di-*O*-isopropylidene- β -D-*glycero*-D-*galacto*-oct-4-ulo-4,8-pyranosonate **8**, in 57% yield. Treatment of **8** with NaBH₄ in methanol, did not open the α,β -oxirane ring but caused the reduction of the ester group to yield 2,3-*anhydro*-4,5:6,7-di-*O*-isopropylidene- β -D-*glycero*-D-*galacto*-oct-4-ulo-4,8-pyranose **9**. Regioselective opening of the oxirane ring in **9** with Red-Al,¹⁰ finally gave the 1,3-diol **4**, which established the D-*glycero*-D-*galacto* configurations in **8** and **9**.



On the basis of the above results it can be concluded that the Reformatsky methodology was the best alkylation procedure for the synthesis of 2-deoxy-4-octulose derivatives. As a consequence, this protocol was applied to 2,3:4,6-di-*O*-isopropylidene- α -L-*xylo*-hexos-2-ulofuranose **10**, giving methyl 4,5:6,8-di-*O*-isopropylidene- α -L-*gulo*-oct-4-ulo-4,7-furanosonate **11** and its -L-*ido* isomer **12**, in an $\approx 3.5:1$ ratio.



The absolute configurations of **11** and **12**, have been established by stereochemical correlation between the newly formed hydroxyl group with a compound of known absolute configuration, in our case dimethyl L-methoxymalate (-)-**13**, obtained from commercial dimethyl L-malate by Purdie's methylation procedure.¹¹ In this way, compound **11** was transformed into the corresponding 3-*O*-methyl derivative **14**, which was hydrolyzed to the uncharacterized methyl 3-*O*-methyl-L-*gulo*-oct-4-ulosonate **15** and subsequently oxidized with NaIO₄ to the unisolated methyl D-methoxymalate acid, that after treatment with diazomethane, gave the enantiomer¹² of the above mentioned dimethyl ester (-)-**13** showing 3*R* configuration for the newly formed stereogenic center in **11**.



The stereoselectivity found in all the alkylation reactions mentioned above, would result from a preferential attack of carbanion, on the more accessible face, in the less compressed conformations of **1** and **10**¹³⁻¹⁵ (see Figure 1).

Finally, reduction of compound **11** gave the corresponding 2-deoxy-4,5:6,8-di-*O*-isopropylidene- α -L-*gulo*-oct-4-ulo-4,7-furanose **16**.

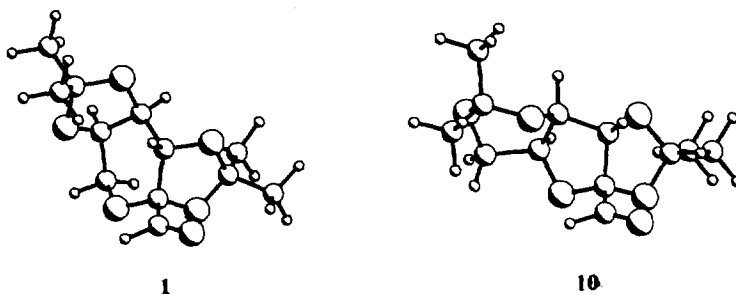


Figure 1. Less compressed conformations for **1** and **10**.

Experimental

General

Melting points were determined with a Gallenkamp apparatus and are uncorrected. Solutions were dried over MgSO_4 before concentration under reduced pressure. The ^1H and ^{13}C NMR spectra were recorded with Bruker AMX-300, AM-300 and ARX-400 spectrometers for solutions in CDCl_3 (internal Me_4Si). IR spectra were recorded with a Perkin-Elmer 782 instrument and mass spectra with a Fisons mod. Platform II and VG Autospec-Q mass spectrometers. Optical rotations were measured for solutions in CHCl_3 (1-dm tube) with a Jasco DIP-370 polarimeter. GLC was performed on a Perkin-Elmer 8410 gas chromatograph equipped with a flame-ionisation detector and a steel column (2 m \times 0.125 in. i.d.) packed with 5% OV-17 on Chromosorb W (100–120 mesh): (A) 3 min at 200°C, program 230°C, 15°C/min, (B) at 210°C, (C) 5 min at 190°C, program 230°C, 30°C/min, (D) at 160°C. The He flow rate was 30 mL/min, the injection port and the zone-detector temperatures were (A y C) at 250°C, (B) at 280°C, (D) at 200°C. TLC was performed on precoated silica gel 60 F₂₅₄ aluminium sheets and detection by charring with H_2SO_4 . Column chromatography was performed on silica gel (Merck, 7734). Some of the noncrystalline compounds, for which elemental analyses were not obtained were shown to be homogeneous by chromatography and characterised by NMR and HRMS.

Reformatsky reaction using 2,3:4,5-di-*O*-isopropylidene- β -D-arabino-hexos-2-ulopyranose (**1**) and methyl bromoacetate

An oven-dried, argon filled, 250 mL, single-necked, round-bottomed flask was charged with anhydrous dioxane (45 mL), compound **1**⁵ (5.49 g, 21.3 mmol), methyl bromoacetate (2.4 mL, 26 mmol), zinc dust (4.61 g, 40 mmol), and iodine (1.13 g, 4.5 mmol), and the mixture was sonicated for 1 h. GLC (A) then revealed the absence of **1** and the presence of two new compounds (T_R 6.17 and 6.88 min, $\approx 10:1$ ratio). The mixture was concentrated to a residue that was dissolved in ether (100 mL), washed with aqueous 10% hydrochloric acid, water, saturated aqueous sodium hydrogen carbonate, water, aqueous 10% sodium thiosulfate, water, then concentrated. Column chromatography (1:2 ether-hexane) of the residue afforded first methyl 2-deoxy-4,5:6,7-di-*O*-isopropylidene- β -D-manno-oct-4-ulo-4,8-pyranosonate (**2**, 6.11 g, 87%) as a syrup, $[\alpha]_D^{23}$: -4 (c 1.1); $\nu_{\text{max}}^{\text{film}}$ 3501 (OH), 1740 (C=O), 1383 and 1374 cm^{-1} (CMe_2). NMR data, see Tables 1 and 2. Mass spectrum (LSIMS): m/z 333.15429 (M^++1). For $\text{C}_{15}\text{H}_{25}\text{O}_8$ 333.15494 (deviation 2 ppm).

Eluted second was a small amount (250 mg) of syrupy methyl 2-deoxy-4,5:6,7-di-*O*-isopropylidene- β -D-gluc-oct-4-ulo-4,8-pyranosonate **3** slightly contaminated with **2**. NMR data, see Tables 1 and 2.

2-Deoxy-4,5:6,7-di-*O*-isopropylidene- β -D-manno-4 and D-gluc-oct-4-ulo-4,8-pyranose **5**

A stirred solution of compound **2** (220 mg, 0.66 mmol) in anhydrous ether (5 mL) was treated with LiAlH_4 (45 mg) at room temperature for 30 min. TLC (ether) then revealed the presence of a slower-running compound. Work-up of the reaction mixture as above afforded, after column chromatography

Table 1. ¹H NMR data for compounds 2-16

Compound	¹ H-Chemical shifts (δ), with multiplicities												
	H-1	H-1'	H-2	H-2'	H-3	H-5	H-6	H-7	H-8	H-8'	CMe ₃	OR	OH
2	--	--	2.89dd	2.60dd	4.07dd	4.56d	4.59dd	4.21bdd	3.87dd	3.72dd	1.50s 1.45s 1.40s 1.32s	3.68s	--
3	--	--	2.78dd	2.65dd	4.11dd	4.39d	4.57dd	4.22dd	3.86dd	3.77d	1.52s 1.47s 1.38s 1.35s	3.70s	--
4	--	3.94-3.74m	2.08d	1.78d	m	4.47d	4.58dd	4.21bdd	3.89dd	3.73d	1.52s 1.44s 1.40s 1.31s	--	3.00bs
6	--	--	2.79dd	2.49dd	4.00ddd	4.57d	4.58dd	4.20bd	3.87dd	3.71d	1.50s 1.46s 1.40s 1.32s	1.43s	3.29d
7	--	--	2.67dd	2.52dd	4.95ddd	4.37d	4.54dd	4.20bd	3.84dd	3.75bd	--	1.43s	3.09d
8	--	--	3.71d	--	3.40d	4.37d	4.61dd	4.23bdd	3.87dd	3.76d	1.50s 1.48s 1.35s 1.31s	3.77s	--
9	3.95ddd	3.63ddd	3.40dt	--	3.15d	4.36d	4.61dd	4.22dd	3.87dd	3.75d	1.48s 1.34s 1.33s	--	1.97dd
11	--	--	2.90dd	2.68dd	4.25dd	4.56s	4.10bs	4.30bs	4.05bd	3.99d	1.49s 1.41s 1.40s 1.36s	3.70s	--
12	--	--	2.86dd	2.67dd	4.30dd	4.54s	m	4.28bs	-4.11-4.03m	--	1.48s 1.43s 1.37s	3.70s	2.68bs
14	--	--	2.89dd	2.68dd	3.95dd	4.42s	4.29d	4.08m	4.03dd	3.96bd	1.48s 1.42s 1.39s 1.38s	3.69s 3.52s	--
16	--	3.88t	2.08ddt	1.83ddt	4.06dd	4.50s	4.30d	4.10dd	4.06dd	4.00bd	1.49s 1.41s 1.39s 1.34s	--	3.42bs

Compound Coupling constants (Hz)

Compound	$J_{1,1'}$	$J_{1,OH}$	$J_{1,OH}$	$J_{1,2}$	$J_{1,2}$	$J_{1,2}$	$J_{2,3}$	$J_{3,OH}$	$J_{3,5}$	$J_{4,7}$	$J_{7,8}$	$J_{7,8}$	$J_{8,9}$
2	--	--	--	--	16.4	3.1	9.1	--	2.6	7.7	1.9	0.6	13.0
3	--	--	--	--	16.1	3.3	9.5	--	2.6	7.9	2.0	0	13.1
4	--	--	--	--	14.6	--	--	7.1	2.6	7.9	1.9	0	13.0
6	--	--	--	--	16.2	3.1	9.0	6.7	2.6	7.9	1.8	0	13.0
7	--	--	--	--	16.1	3.2	9.6	4.6	2.4	7.9	2.0	0	13.0
8	--	--	--	--	--	1.7	--	--	2.5	7.9	1.9	0	13.0
9	12.8	5.1	7.2	2.4	4.5	2.1	--	--	2.6	7.9	1.9	0	13.0
11	--	--	--	--	16.2	3.3	8.9	--	0	0	0	0	13.5
12	--	--	--	--	16.0	3.2	9.8	--	0	0	0	0	--
14	--	--	--	--	16.4	3.3	9.1	--	0	2.3	2.3	0	13.5
16	0	--	--	5.5	5.5	3.4	9.5	--	0	2.3	1.7	0	13.2

(ether), syrupy **4** (157 mg, 79%), GLC (*B*) R_T 5.58 min, $[\alpha]_D^{29}$: -14 (c 0.63); ν_{\max}^{film} 3456 (OH), 1384 and 1374 cm^{-1} (CMe_2). NMR data, see Tables 1 and 2. Mass spectrum (LSIMS): m/z 327.14089 ($M^+ + \text{Na}$). For $\text{C}_{14}\text{H}_{24}\text{O}_7\text{Na}$ 327.14197 (deviation 3.3 ppm).

Reduction of the above **3** allowed the obtainment of **5**, which had the same physical and spectroscopical data that an authentic sample.³

Alkylation of 1 using lithium salt of t-butyl acetate

To a cooled (dry ice–acetone) and stirred solution of *t*-butyl acetate (1 mL, 7.5 mmol) in dry hexane (12 mL), was added a solution of 2 M lithium diisopropylamide in THF/heptane/ethylbenzene (3.8 mL, 7.6 mmol) under Ar. After 15 min, a solution of compound **1** (1.2 g, 5 mmol) in anhydrous ether (15 mL) was added dropwise at -78°C , then allowed to reach room temperature. GLC (A) then showed the presence of two compounds with a T_{R} 7.52 and 8.77 min, in an $\approx 5.4:1$ ratio. Ether saturated with aqueous 10% hydrochloric acid was added, the organic phase was separated and washed with water, then concentrated. Column chromatography (1:2 ether–hexane) of the residue afforded *t*-butyl 2-deoxy-4,5:6,7-di-*O*-isopropylidene- β -*D*-manno-oct-4-ulo-4,8-pyranosonate (**6**, 1.1 g, 59%) as a syrup slightly contaminated with its 3-epimer **7**, $[\alpha]_{\text{D}}^{23}$: -6 , $[\alpha]_{405}^{23}$: -10 (c 1.3); $\nu_{\text{max}}^{\text{film}}$ 3503 (OH), 1731 (C=O), 1383 and 1371 cm^{-1} (CMe₂). NMR data, see Tables 1 and 2. Mass spectrum (LSIMS): m/z 375.20120 ($\text{M}^{+}+1$). For C₁₈H₃₁O₈ 375.20189 (deviation 1.8 ppm).

Reduction of compound **6** (1.1 g) with LiAlH₄ (150 mg) in anhydrous ether as above, gave after work-up and column chromatography, first **4** (507 mg) and second **5** (55 mg).

Reaction of 1 with methoxycarbonylmethylenedimethylsulfurane

To a stirred solution of NaH (80% oil dispersion) (320 mg, 10.7 mmol) in dry Me₂SO (15 mL) and imidazole (100 mg) under Ar, methoxycarbonylmethyldimethylsulfonium bromide⁹ (1.87 g, 8.7 mmol) was added portionwise, and the mixture was sonicated at room temperature for 1 h. Then, a solution of **1** (1.2 g, 4.6 mmol) in dry THF (20 mL) was added dropwise and the mixture left at room temperature for 5 h and then at 60°C for 1 h. TLC (1:2 ether–hexane) then showed the presence of a faster-running product. The mixture was diluted with water and extracted with ether. The combined extracts were washed with brine and water, then concentrated. Column chromatography (1:3 ether–hexane) of the residue afforded methyl 2,3-*anhydro*-4,5:6,7-di-*O*-isopropylidene- β -*D*-glycero-*D*-galacto-oct-4-ulo-4,8-pyranosonate (**8**, 680 mg, 57%) as a colourless syrup, $[\alpha]_{\text{D}}^{25}$: -31.5 (c 1); $\nu_{\text{max}}^{\text{film}}$ 1757 (C=O), 1384 and 1374 cm^{-1} (CMe₂). NMR data, see Tables 1 and 2. Mass spectrum (LSIMS): m/z 331.13853 ($\text{M}^{+}+1$). For C₁₅H₂₃O₈ 331.13929 (deviation 2.3 ppm).

2,3-Anhydro-4,5:6,7-di-O-isopropylidene- β -D-glycero-D-galacto-oct-4-ulo-4,8-pyranose 9

To a cooled (ice–water) and stirred solution of **8** (180 mg, 0.54 mmol) in anhydrous methanol (3 mL) was added NaBH₄ (60 mg) portionwise. The mixture was left at room temperature overnight. TLC (1:2 ether–hexane) then revealed a slower-running compound. The mixture was neutralized with acetic acid, concentrated and the residue dissolved in Cl₂CH₂ and washed with brine, water and concentrated. Column chromatography (1:2 ether–hexane) gave crystalline **9** (120 mg, 73%), m.p.: $128\text{--}129^{\circ}\text{C}$ (from ether–hexane), $[\alpha]_{\text{D}}^{20}$: -27 (c 0.9); $\nu_{\text{max}}^{\text{KBr}}$ 3490 (OH), 1387 and 1373 cm^{-1} (CMe₂). NMR data, see Tables 1 and 2. Anal. Calcd. for C₁₄H₂₂O₇: C, 55.62; H, 7.33. Found: C, 55.35; H, 7.07.

Reduction of 9

To a stirred and cooled (ice–water) solution of **9** (110 mg, 0.36 mmol) in dry THF (3 mL), 3.5 M Red-Al in toluene (0.3 mL) was added dropwise under Ar. The mixture was allowed to reach room temperature and then left for 4 h. GLC (B) then revealed the presence of **4**. The excess of hydride was cautiously destroyed by addition of ether saturated with water, water and then aqueous 5% hydrochloric acid. The mixture was concentrated, extracted with ethyl acetate and the solvent was evaporated. Column chromatography (2:1 ether–hexane ether) of the residue afforded **4** (100 mg, 90%).

Reformatsky reaction using 2,3:4,6-di-O-isopropylidene- α -L-xylo-hexos-2-ulofuranose (10) and methyl bromoacetate

An oven-dried, argon filled, 50 mL, single-necked, round-bottomed flask was charged with anhydrous dioxane (25 mL), compound **10**⁶ (2.3 g, 8.9 mmol), methyl bromoacetate (1 mL, 10.8

Table 2. ¹³C NMR data for compounds 2–16

Compound	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	CM _{e1}	CM _{e2}	OR	CM _{e3}
2	173.73	35.65	70.85*	103.65	70.33*	69.84*	69.71*	61.33	109.05 108.75	26.68 25.88 25.63 24.02	51.84	--
3	172.82	36.60	72.51*	104.06	72.31*	71.00*	69.95*	61.06	109.22 108.64	26.05 25.41 25.27 24.00	51.77	--
4	61.44*	32.83	72.84*	104.29	70.86*	70.33*	70.15*	61.30*	109.05 108.61	26.73 25.73 25.81 24.00	--	--
6	172.80	36.72	70.89*	103.74	70.36*	69.84*	69.76*	61.23	108.99 108.62	26.72 25.89 25.65 24.00	80.97	28.12
7	172.00	37.87	70.89*	104.25	72.24*	70.50*	70.00*	60.92	109.00 108.50	26.40 25.60 25.20 23.81	80.50	28.17
8	168.81	58.06*	50.12*	100.42	72.09*	70.62*	69.97*	61.52	109.42 109.23	26.36 26.01 24.86	52.58	--
9	61.42*	55.72*	55.59*	101.06	71.94*	70.77*	70.07*	61.06*	109.15	26.39 26.01 24.99 24.11	--	--
11	173.41	35.88	68.82	115.28	84.55	73.17	72.69	60.37	112.62 97.42	28.94 27.75 26.72 18.64	51.86	--
12	172.57	37.40	70.26	114.90	85.70	73.37	72.15	60.18	112.04 97.78	28.78 27.33 26.49 18.62	51.69	--
14	172.69	35.48	78.99	115.56	84.50	73.15	72.46	60.32	112.32 97.39	28.88 27.63 26.57 18.80	59.93 51.69	--
16	61.31	33.56	71.48	116.04	84.59	73.21	72.42	60.46	112.65 97.56	28.94 27.90 27.04 18.66	--	--

*Interchangeable assignments

mmol), zinc dust (1.25 g, 18.3 mmol), and iodine (0.57 g, 2.2 mmol), and the mixture was sonicated for 4 h. GLC (C) then revealed the absence of **10** and the presence of two new compounds (T_R 8.3 and 9.3 min, ≈3.5:1 ratio). The mixture was concentrated to a residue that was dissolved in ether (100 mL), washed with aqueous 10% hydrochloric acid, water, saturated aqueous sodium hydrogen carbonate, water, aqueous 10% sodium thiosulfate, water, then concentrated. Column chromatography (1:4 ether–hexane) of the residue afforded first methyl 2-deoxy-4,5:6,8-di-*O*-isopropylidene- α -L-*gulo*-

oct-4-ulo-4,7-furanosonate (**11**, 2 g, 68%) as a syrup, $[\alpha]_{\text{D}}^{27}$: +14 (c 1.1); $\nu_{\text{max}}^{\text{film}}$ 3494 (OH), 1739 (C=O), 1383 and 1374 cm^{-1} (CMe₂). NMR data, see Tables 1 and 2. Mass spectrum (LSIMS): m/z 355.13625 (M⁺+Na). For C₁₅H₂₄O₈Na 355.13689 (deviation 1.8 ppm).

Eluted second was a small amount (240 mg, 8%) of syrupy methyl 2-deoxy-4,5:6,8-di-*O*-isopropylidene- α -L-ido-oct-4-ulo-4,7-furanosonate **12**, $[\alpha]_{\text{D}}^{27}$: -3, $[\alpha]_{405}^{27}$: -12 (c 0.7); $\nu_{\text{max}}^{\text{film}}$ 3512 (OH), 1740 (C=O), 1385 and 1375 cm^{-1} (CMe₂). NMR data, see Tables 1 and 2. Mass spectrum (LSIMS): m/z 355.13707 (M⁺+Na). For C₁₅H₂₄O₈Na 355.13689 (deviation -0.5 ppm).

Dimethyl L-methoxymalate (-)-**13**

To a solution of dimethyl L-malate (486 mg, 3 mmol) in iodomethane (6 mL) was added freshly prepared Ag₂O (1 g) and the mixture sonicated for 2 h. TLC (2:1 ether-hexane) then revealed (iodine) the presence of a faster-running compound. The mixture was diluted with ether, filtered and the filtrate concentrated. Column chromatography (1:4 ether-hexane) of the residue gave (-)-**13** (445 mg, 84%) as a colourless mobile oil, T_{R} 1.42 min (*D*), $[\alpha]_{\text{D}}^{25}$: -43.5, $[\alpha]_{405}^{25}$: -98.3 (c 1.34) [lit.¹² for (+)-**13** $[\alpha]_{\text{D}}$: +52.51 (neat)]; $\nu_{\text{max}}^{\text{film}}$ 1744 cm^{-1} (C=O). NMR data, ¹H δ 4.19 (dd, 1 H, J_{2,3} 4.8, J_{2,3'} 7.8 Hz, H-2), 3.76 and 3.70 (2 s, 6 H, 2 CO₂Me), 3.44 (s, 3 H, OMe), 2.79 (dd, 1 H, J_{3,3'} 16 Hz, H-3), and 2.72 (dd, 1 H, H-3'); ¹³C δ 171.76 and 170.54 (2 CO₂Me), 76.73 (C-2), 58.86 (OMe), 52.24 and 52.02 (2 CO₂Me), and 37.62 (C-3).

Methyl 2-deoxy-4,5:6,8-di-*O*-isopropylidene-3-*O*-methyl- α -L-gulo-oct-4-ulo-4,7-furanosonate **14**

Compound **11** (1.5 g, 4.5 mmol) was methylated with iodomethane (10 mL) and Ag₂O (5 g) according to the Purdie's procedure¹¹ for 24 h. TLC (2:1 ether-hexane) then revealed the presence of a faster-running compound. Work-up of the reaction mixture as above gave, after column chromatography (1:2 ether-hexane), syrupy **14** (800 mg, 51%), $[\alpha]_{\text{D}}^{26}$: +9, $[\alpha]_{405}^{27}$: +23 (c 0.5); $\nu_{\text{max}}^{\text{film}}$ 1744 (C=O), 1384 and 1374 cm^{-1} (CMe₂). NMR data, see Tables 1 and 2. Mass spectrum (LSIMS): m/z 369.15200 (M⁺+Na). For C₁₆H₂₆O₈Na 369.15253 (deviation 1.4 ppm).

Degradation of **14** to (+)-**13**

A solution of **14** (800 mg, 2.31 mmol) in aqueous 75% trifluoroacetic acid (8 mL) was left at room temperature for 2 days. TLC (ether) then revealed a non-mobile compound. The mixture was concentrated and repeatedly codistilled with water and the residue chromatographed (10:1 chloroform-methanol) to afford a colourless syrup (500 mg, 81%), presumably methyl 3-*O*-methyl-L-gulo-oct-4-ulosonate **15** that was not further characterized but oxidised in water (20 mL) with NaIO₄ (3.2 g, 15.2 mmol). The reaction was monitored by polarimetry to a constant rotation after 24 h at room temperature. The mixture was concentrated and the residue extracted with ethyl acetate. Concentration of the extracts gave a residue that was dissolved in dry methanol (15 mL) and saturated with a stream of CH₂N₂ until a slight yellow colour remained and the mixture left at room temperature for 30 min. GLC (*D*) then revealed a main product with a T_{R} 1.42 min. The reaction mixture was concentrated and the residue chromatographed (1:4 ether-hexane) to afford (+)-**13** (75 mg) which had $[\alpha]_{\text{D}}^{28}$: +27, $[\alpha]_{405}^{29}$: +64 (c 0.46), and their spectroscopic data were the same as those of (-)-**13**.

2-Deoxy-4,5:6,8-di-*O*-isopropylidene- α -L-gulo-oct-4-ulo-4,7-furanose **16**

Reduction of compound **11** (2.6 g, 7.8 mmol) in anhydrous ether (30 mL) with LiAlH₄ (660 mg) as above for 1.5 h, gave after work-up and column chromatography (1:1 ether-hexane ether) syrupy **16** (2 g, 84%), $[\alpha]_{\text{D}}^{27}$: +3, $[\alpha]_{405}^{27}$: +12 (c 1.7); $\nu_{\text{max}}^{\text{film}}$ 3462 (OH), 1385 and 1376 cm^{-1} (CMe₂). NMR data, see Tables 1 and 2. Mass spectrum (LSIMS): m/z 305.16114 (M⁺+1). For C₁₄H₂₅O₇ 305.16003 (deviation -3.6 ppm).

References

1. Izquierdo Cubero, I.; Plaza López-Espinosa, M.-T.; Rodríguez Alonso, M.; Asenjo Asenjo, R.; Ramírez Fernández, A., *J. Org. Chem.*, **1997**, in press.

2. Burgess, K.; Henderson, I., *Tetrahedron*, **1992**, 48, 4045–4066, and references therein.
3. Izquierdo Cubero, I.; Plaza López-Espinosa, M.-T.; Robles Díaz, R.; Rodríguez Melgarejo, C., *Tetrahedron: Asymmetry*, **1996**, 7, 3593–3604.
4. Payne, G. B., *J. Org. Chem.*, **1969**, 33, 3517–3523.
5. Izquierdo Cubero, I.; Plaza López-Espinosa, M.-T., *Carbohydr. Res.*, **1990**, 205, 393–304.
6. Izquierdo Cubero, I.; Plaza López-Espinosa, M.-T.; Kari, N., *Carbohydr. Res.*, **1994**, 261, 231–242.
7. Han, B.-H.; Boudjouk, P., *J. Org. Chem.*, **1982**, 47, 5030–5032.
8. Rathke, M. W.; Sullivan, D. F., *J. Am. Chem. Soc.*, **1973**, 95, 3050–3051.
9. Johnson, A. W.; Amel, R. T., *J. Org. Chem.*, **1969**, 34, 1240–1247.
10. Viti, S. M., *Tetrahedron Lett.* **1982**, 23, 4541–4544.
11. Hirst, E. L.; Percival, E., *Methods Carbohydr. Chem.*, **1963**, 2, 145–150.
12. Purdie, T.; Williamson, S., *J. Chem. Soc.* **1895**, 67, 957–982.
13. Computerized representation of the most stable conformations for **1** and **10**, calculated with the TRIPOS force field.
14. Clark, M.; Cramer III, R. D.; Van Opdenbosch, N., *J. Comput. Chem.* **1989**, 10, 982.
15. TRIPOS force field is implemented in the SYBYL 6.1 program, available from Tripos Inc. 1699 S. Hanley Road, St. Louis, Missouri 63144-2913, USA.

(Received in UK 10 June 1997)