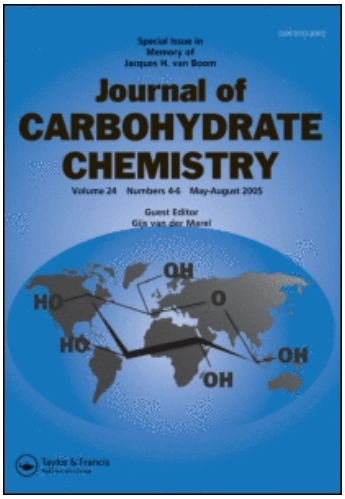

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SYNTHESIS OF BRANCHED CHAIN 2-DEOXYOCT-3-ULOSONIC ACID DERIVATIVES AS PRECURSORS FOR C-NUCLEOSIDE ANALOGUES

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ABSTRACT

Reaction of 2,3,4,5,6-penta-*O*-acetyl-D-galactonic **1** and D-gluconic acid chloride **2**, respectively, with derivatives of malonic acid furnished substituted 2-deoxyoct-3-ulosonic acid esters, amides, and nitriles. Further modification was carried out by O-acylation and halogenation.

INTRODUCTION

Naturally occurring C-nucleosides such as pyrazofurin, showdomycin, oxazinomycin, and formycin B are important due to their antibacterial, antiviral, and antitumor properties.[1] Acyclovir and gancyclovir are biologically active C-nucleoside analogues with an open chain sugar fragment.[2] The development of strategies for the formation of acyclic C-nucleoside analogues is a topic of current interest in organic synthesis.[3]

Only some building blocks for syntheses of C-nucleoside analogues with a polyhydroxyalkyl chain have been reported. Thus, 1,3-dicarbonyl sugar derivatives were

prepared by vinylogous Nef reaction of *O*-benzyl sugar nitroalkenes.[3d, 4] Sugar β-ketoesters were obtained by reaction of *aldehydo*-sugars with alkyl diazotates.[3a, 5] These 1,3-dicarbonyl sugars could be used to prepare pyrazole and pyrimidine acyclo-C-nucleosides.[3d, 3a, 6]

A C-chain elongation of 2,3,4,5-tetra-*O*-acetyl-D-ribonic acid chloride with dibenzyl malonate was carried out to prepare 1-deoxypsicose. However, the authors described only one crude acylation product without purification and identification.[7]

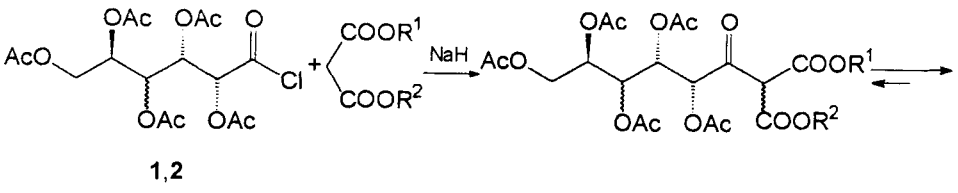
We therefore wish to describe a convenient synthesis of substituted 2-deoxyoct-3-ulosonic acid esters, amides, and nitriles by C-chain elongation in which 2,3,4,5,6-penta-*O*-acetyl-D-galactonic **1** and D-gluconic acid chloride **2**, respectively, was reacted with derivatives of malonic acid. Decarboalkoxylations of these branched chain 2-deoxy-oct-3-ulosonic acid derivatives provided the unbranched 2-deoxyoct-3-ulosonic acid esters and nitriles.[8] These sugar β-ketoesters reacted with hydrazine derivatives and thiosemicarbazide to give pyrazole, thiazole and thiadiazole derivatives, respectively, which possess a polyhydroxyalkyl chain.[9]

RESULTS AND DISCUSSION

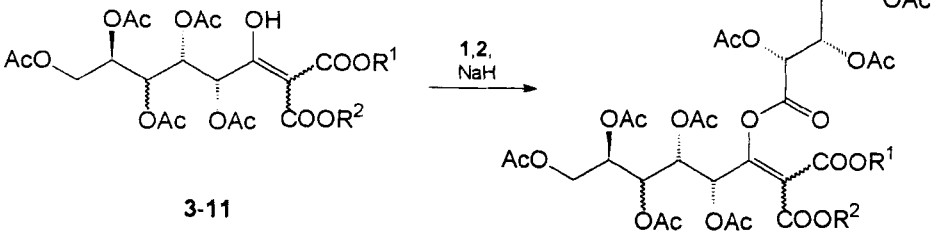
The reaction of 2,3,4,5,6-penta-*O*-acetyl-D-galactonic **1** and D-gluconic acid chloride **2** with malonic acid esters in the presence of sodium hydride affords alkyl 4,5,6,7,8-penta-*O*-acetyl-2-deoxy-2-alkoxycarbonyl-D-*galacto* (or D-*gluco*)-oct-3-ulos-onates (**3-11**) and the corresponding O-acylated products **12-14**.

An equilibrium exists between the two structures in the solution of **3** in $CDCl_3$. Signals for the enol and keto form were found in the ^1H NMR spectrum of **3** in $CDCl_3$. Similarly, in the ^{13}C NMR spectrum, signals at 99.8 and 62.5 suggest the presence of sp^2 and sp^3 C-2 carbon, respectively. The proportions of the keto and enol tautomers are 60:40.

When three equivalents of malonic acid ester as well as the base and one equivalent of acid chloride were allowed to react, the formation of O-acylated products was reduced. On the other hand, using half the equivalent of malonic acid ester and one equivalent of base and acid chloride provided the alkyl 3-*O*-acyloctenoates **12-14** in moderate yields (Scheme 1).



1,2



3-11

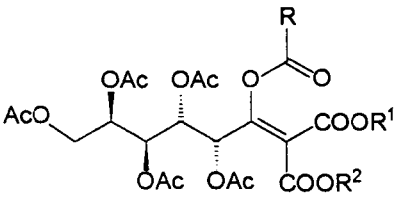
12-14

	config.	R^1	R^2
1	D-*galacto*		
2	D-*gluco*		
3	D-*galacto*	Me	Me
4	D-*gluco*	Me	Me
5	D-*galacto*	Et	Et
6	D-*gluco*	Et	Et
7	D-*galacto*	Bn	Bn
8	D-*galacto*	Bn	Me
9	D-*gluco*	Bn	Me
10	D-*galacto*	Bn	Et
11	D-*galacto*	Oct	Oct

	config.	R^1	R^2
12	D-*galacto*	Me	Me
13	D-*gluco*	Me	Me
14	D-*galacto*	Et	Et

Scheme 1

If the reactants were used in the molar ratio 1:3:3 (acid chloride **1**, malonic acid ester, base) and two molar equivalents of another acid chloride (acetic acid chloride and chloroacetic acid chloride, respectively) were subsequently added, the crystalline enol esters **15-17** could be isolated (Scheme 2).



15-17

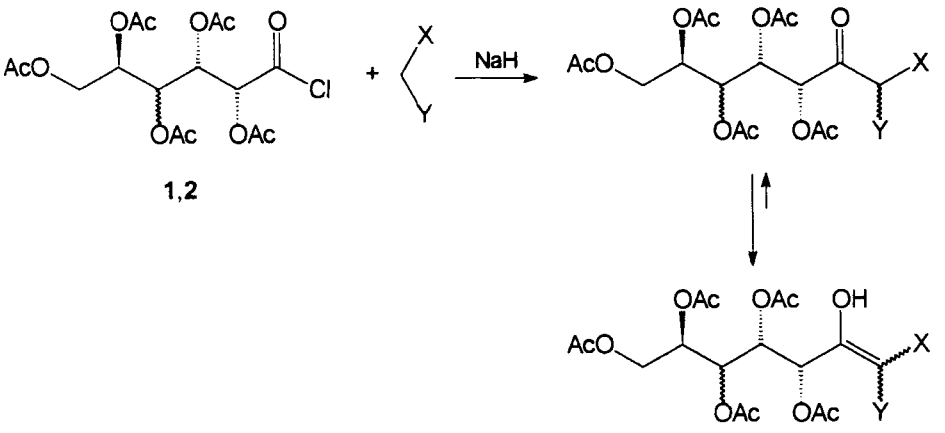
	R	R^1, R^2
15	Me	Me
16	Me	Bn
17	$ClCH_2$	Me

Scheme 2

The reactions of malonanilide, ethyl cyanoacetate and malononitrile with 2,3,4,5,6-penta-*O*-acetyl-D-galactonic **1** and D-gluconic acid chloride **2** were successfully carried out in THF. The derivatives of the D-*galacto*(or D-*gluco*-)-oct-3-ulosonic acids **18-21** were isolated. The NMR spectra of compounds **18-21** showed that they exist in $CDCl_3$ predominantly in the enol form. A solution of **18** in DMSO contains only the keto tautomer (Scheme 3).

Compound **19** was subjected to X-ray analysis at 293 K. The relevant crystallographic data for **19** are provided in Table 1. The structure was solved by direct methods with the assistance of the Siemens program XS,[10] and refined with SHELXL-93.[11] All non-hydrogen atoms were refined anisitropically, hydrogens introduced at theoretical positions and refined according to the riding model. An ORTEP drawing of this enol tautomer **19** with 50 % probability of the thermal ellipsoids is shown in Figure 1, which gives the numbering scheme of the atoms.

The derivatives of D-*galacto* (or D-*gluco*-)-oct-3-ulosononic acids **3-5**, and **21** reacted with diazomethane furnishing the enol methyl ethers **22-25** (Scheme 4).[12]

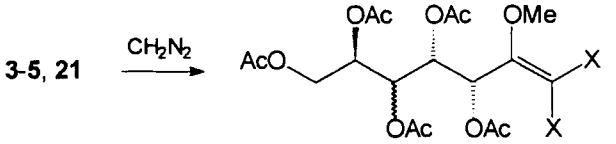


1,2

18-21

	config.	X	Y
18	D-*galacto*	CONHPh	CONHPh
19	D-*galacto*	CO_2Et	CN
20	D-*gluco*	CO_2Et	CN
21	D-*galacto*	CN	CN

Scheme 3



22-25

	config.	X
22	D-*galacto*	COOMe
23	D-*gluco*	COOMe
24	D-*galacto*	COOEt
25	D-*galacto*	CN

Scheme 4

The crystallographic data for **23** are given in Table 1. An ORTEP drawing of **23** is shown in Figure 1.

The bromination of acylated malonic acid esters **3-5,** 7, and **11** at 0 °C in chloroform led to crystalline α-monobromo derivatives **26-30** in good and moderate yields. In the case of 4,5,6,7,8-penta-*O*-acetyl-2-benzoxycarbonyl-2-deoxy-D-*galacto*-oct-3-ulosonic acid alkyl ester, **7**, **8** and **10** were brominated with 2 molar equivalents of bromine at room temperature and the corresponding 4,5,6,7,8-penta-*O*-acetyl-2,2-dibromo-2-deoxy-D-*galacto*-oct-3-ulosonic acid alkyl esters **31-33** were isolated. The formation of these products is due to the instability of the benzyl position facing radical attack (Scheme 5).

Ethyl 4,5,6,7,8-penta-*O*-acetyl-2-deoxy-2-ethoxycarbonyl-D-*galacto*-oct-3-ulosonate (**5**) was easily transformed into ethyl 4,5,6,7,8-penta-*O*-acetyl-2-chloro-2-deoxy-2-ethoxycarbonyl-D-*galacto*-oct-3-ulosonic acid ethyl ester (**34**) in good yields using sulfuryl chloride as reagent and solvent.[13]

The crystallographic data for **27** are given in the Table. An ORTEP drawing of **27** is shown in Figure 2.

EXPERIMENTAL

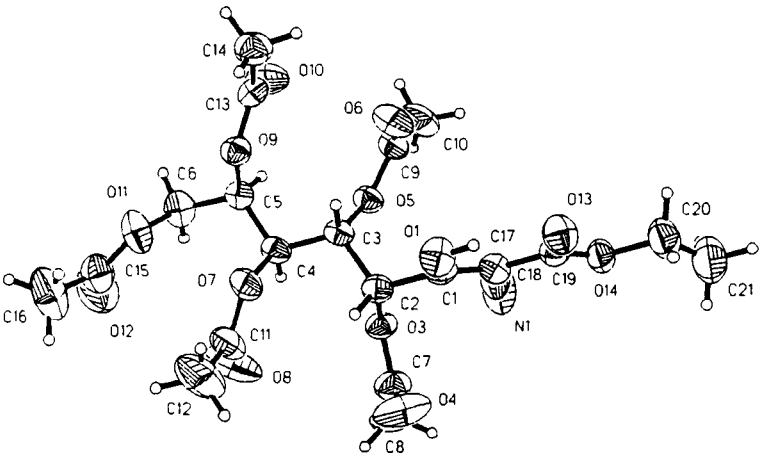
General Procedures. Melting points were determined with a BOETIUS melting point apparatus and have been corrected. Specific rotations were determined with a Polar LμP (IBZ Messtechnik). IR spectra were recorded with a Nicolet 205 FT-IR spectrometer. ^{1}H NMR (300.133 MHz and 250.133 MHz, respectively) and ^{13}C NMR (75.466 MHz and 62.896 MHz, respectively) were obtained on Bruker instruments WM 300 and AC 250, respectively. The ^{13}C NMR spectra were determined by DEPT and/or ^{1}H, ^{13}C, COSY experiments. ^{1}H and ^{13}C chemical shifts (δ) are given in ppm relative to the solvent signal. The mass spectra were recorded on an AMD 402/3 spectrometer. For column chromatography Merck Silica gel 60 (63 - 200 mesh) was used. toluene/ethyl acetate = 2:1 was used as eluent. TLC was performed on silica gel 60 GF_{254} (Merck) with detection by UV light (λ = 254 nm) and/or staining by heating. If not otherwise described, a mixture of toluene/ethyl acetate = 1:2 was used as eluent. Elemental analyses was carried out on a Leco CHNS-932.

Table Crystallographic data for ethyl 4,5,6,7,8-penta-*O*-acetyl-2-cyano-2-deoxy-D-*galacto*-oct-3-ulosonate (**19**), methyl 4,5,6,7,8-penta-*O*-acetyl-2-deoxy-2-methoxycarbonyl-3-*O*-methyl-D-*gluco*-oct-2-enoate (**23**), methyl 4,5,6,7,8-penta-*O*-acetyl-2-bromo-2-deoxy-2-methoxycarbonyl-D-*gluco*-oct-3-ulosonate (**27**).

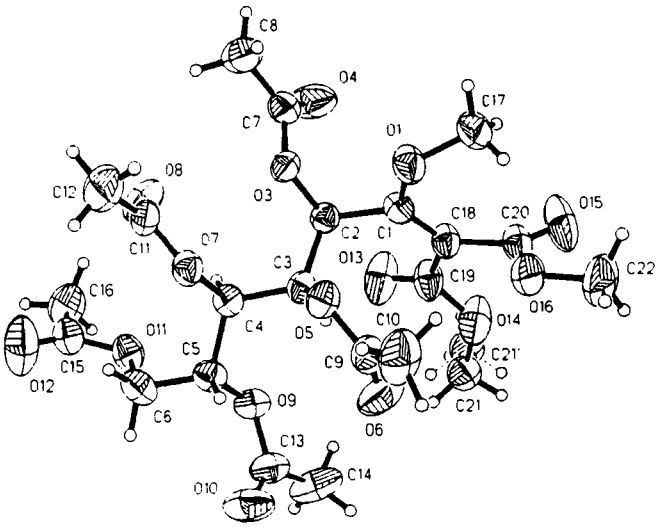
Compound	**19**	**23**	**27**
Crystal size (mm)	0.64 x 0.58 x 0.32	0.84 x 0.58 x 0.56	0.6 x 0.36 x 0.15
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_1$
Cell parameters (Å, degrees)[a]			
a	8.730 (1)	8.005 (2)	7.679 (1)
b	16.735 (2)	16.250 (3)	19.866 (1)
c	17.041 (1)	20.336 (4)	8.848 (1)
β			98.66 (1)
Volume (Å^3)[a]	2489.6 (4)	2645.3 (10)	1334.4 (2)
Z	4	4	2
F(000)	1056	1128	616
Density D_x (Mg m^{-3})	1.338	1.342	1.492
λ (Mo Kα) (Å)	0.71073	0.71073	0.71073
μ (cm^{-1})	1.13	1.15	16.11
2 Θ range (degrees)	4.5 - 45	4 - 45	4 - 45
Symmetry independent reflections	3255	3458	3482
Observed reflections with $I>2\sigma(I)$	2928	3284	2831
Number of refined parameters	327	350	347
Ratio of parameters to valued reflections	9.95	9.88	10.03
$R1_{(obs)}$	0.0499	0.0385	0.0465

a. Standard deviations given in parentheses.

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-101343. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: Int. code +(1223) 336-033; e-mail: deposit@ccdc.cam.ac.uk).

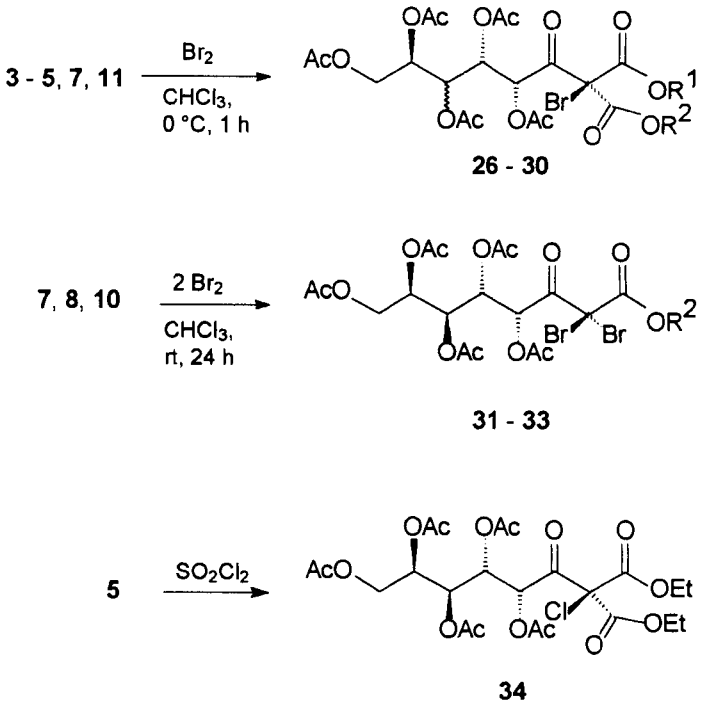


Compound **19**



Compound **23**

Fig. 1. ORTEP drawings of **19** and **23**



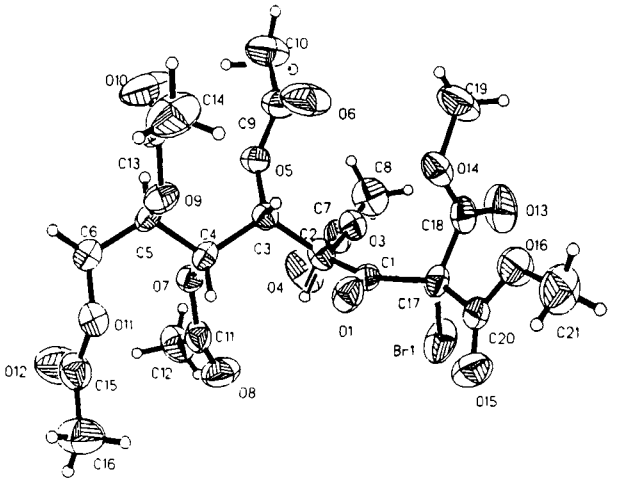
	config.	R^1	R^2
26	D-*galacto*	Me	Me
27	D-*gluco*	Me	Me
28	D-*galacto*	Et	Et
29	D-*galacto*	Bn	Bn

	config.	R^1	R^2
30	D-*galacto*	Oct	Oct
31	D-*galacto*	-	Me
32	D-*galacto*	-	Et
33	D-*galacto*	-	Bn

Scheme 5

2,3,4,5,6-Penta-*O*-acetyl-D-galactonic acid chloride (1) was prepared according to a literature procedure.[14]

2,3,4,5,6-Penta-*O*-acetyl-D-gluconic acid chloride (2) was prepared by refluxing a solution of 2,3,4,5,6-penta-*O*-acetyl-D-gluconic acid (60 g, 0.14 mol) in oxalyl chloride (30 mL, 0.35 mol) until the solid was dissolved. The solution was concentrated under reduced pressure, the residue was crystallized over several days, washed with dry ether and stored under exclusion of moisture. **2** was obtained as pale yellow crystals (54.6 g, 87%): mp 72-75 °C (Lit.:[15] 68-70 °C)



Compound **27**

Fig. 2. ORTEP drawing of **27**

General C-acylation procedure. The reagent (30 mmol; malonic acid ester, malonanilide, cyanoacetic acid ester and malononitrile, respectively) dissolved in dry solvent (30 mL; toluene or THF, in case of dimethyl malonate 3 mL of DMF were added) was carefully dropped into a suspension of sodium hydride (0.72 g, 30 mmol; activated) in dry solvent (80 mL), while the solution was rapidly stirred. After foaming had subsided, stirring was continued for 10 min and 2,3,4,5,6-penta-*O*-acetyl-D-galactonic (gluconic) acid chloride (**1** and **2**, respectively, 4.24 g, 10 mmol) dissolved in dry solvent (30 mL) was added. The solution was stirred for 30 min and washed with water (150 mL) containing $NaHSO_4$ (10 g). In the case that THF was used as solvent, chloroform (200 mL) was added while washing. The phases were separated and the organic phase was washed 2x with water. The solution was dried over $MgSO_4$ and the solvent was evaporated.

Methyl 4,5,6,7,8-Penta-*O*-acetyl-2-deoxy-2-methoxycarbonyl-D-*galacto*-oct-3-ulosonate (3). The reaction of dimethyl malonate and **1** was carried out in toluene as described above. After drying and evaporating of the solvent the compound was crystallized from ether and recrystallized from methanol to yield **3** as a white solid

(4.025 g, 77%): mp 118-123 °C; R_f = 0.53; $[\alpha]_D^{20}$ +26.2° (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 2.00-2.14 (9s, 15H, OAc), 3.75-3.82 (4s, 6H, OMe), 3.84 (dd, $J_{8,8'}$ = 11.7 Hz, $J_{7,8'}$ = 7.3 Hz, keto-H-8'), 3.90 (dd, $J_{8,8'}$ = 11.6 Hz, $J_{7,8'}$ = 7.5 Hz, enol-H-8'), 4.27 (dd, $J_{7,8}$ = 5.1 Hz, keto-H-8), 4.28 (dd, $J_{7,8}$ = 5.1 Hz, enol-H-8), 4.72 (s, keto-H-2), 5.19 (m, $J_{6,7}$ = 1.9 Hz, keto-H-7), 5.31 (dd, $J_{5,6}$ = 9.9 Hz, keto-H-6), 5.39 (m, $J_{6,7}$ = 2.0 Hz, enol-H-7), 5.48 (dd, $J_{5,6}$ = 9.8 Hz, enol-H-6), 5.63 (d, keto-H-4), 5.64 (dd, $J_{4,5}$ = 1.7 Hz, enol-H-5), 5.67 (d, enol-H-4), 5.76 (dd, $J_{4,5}$ = 2.2 Hz, keto-H-5), 13.75 (s, enol-OH); ^{13}C NMR ($CDCl_3$) δ 20.2-20.7 (CH_3CO), 52.2-53.2 (OMe), 61.9 (keto-C-8, enol-C-8), 62.5 (keto-C-2), 67.2 (keto-C-7), 67.4 (enol-C-7), 67.5 (keto-C-6), 67.7 (enol-C-6), 68.0 (keto-C-5), 68.3 (enol-C-5), 68.8 (keto-C-4), 74.2 (enol-C-4), 99.8 (enol-C-2), 163.3, 163.9 (keto-C-1, C-1'), 165.0, 168.8 (enol-C-1, C-1'), 168.8-171.5 (CH_3CO), 176.3 (enol-C-3), 194.5 (keto-C-3). Mass spectrum (DCI/isobutane): *m/z*(%) = 521 (9, $[M+H]^+$), 461 (100).

Anal. Calcd for $C_{21}H_{28}O_{15}$: C, 48.46; H, 5.42. Found C, 48.41; H, 5.30.

Methyl 4,5,6,7,8-Penta-*O*-acetyl-2-deoxy-2-methoxycarbonyl-D-*gluco*-oct-3-ulosonate (4). Dimethyl malonate and **2** were allowed to react in toluene as described above and yielded after chromatography **4** as a colorless syrup (3.4 g, 65.4%). The pure syrup solidified after several months: mp 74-80 °C; R_f = 0.53; $[\alpha]_D^{20}$ +8.6° (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 2.01-2.15 (9s, 15H, OAc), 3.74-3.81 (4s, 6H, OMe), 4.08 (dd, $J_{8,8'}$ = 12.2 Hz, $J_{7,8'}$ = 5.5 Hz, keto-H-8'), 4.08 (dd, $J_{8,8'}$ = 12.5 Hz, $J_{7,8'}$ = 6.1 Hz, enol-H-8'), 4.26 (dd, $J_{7,8}$ = 3.0 Hz, enol-H-8), 4.28 (dd, $J_{7,8}$ = 4.3 Hz, keto-H-8), 4.73 (s, keto-H-2), 5.04 (m, $J_{6,7}$ = 6.1 Hz, keto-H-7), 5.10 (m, $J_{6,7}$ = 7.3 Hz, enol-H-7), 5.37 (dd, $J_{5,6}$ = 0.9 Hz, enol-H-6), 5.45 (dd, $J_{5,6}$ = 5.2 Hz, keto-H-6), 5.58 (t, $J_{4,5}$ = 4.3 Hz, keto-H-5), 5.65 (d, keto-H-4), 5.79 (t, $J_{4,5}$ = 1.1 Hz, enol-H-5), 5.79 (d, enol-H-4), 13.56 (s, enol-OH); ^{13}C NMR ($CDCl_3$) δ 20.2-20.7 (CH_3CO), 52.4-53.2 (OMe), 61.4 (keto-C-8), 61.8 (enol-C-8), 62.5 (keto-C-2), 68.1 (keto-C-7), 68.6 (enol-C-7), 68.7 (enol-C-6), 69.1 (keto-C-6), 69.2 (keto-C-5, enol-C-5), 70.7 (keto-C-4), 74.0 (enol-C-4), 101.6 (enol-C-2), 164.1, 164.9 (keto-C-1, C-1'), 163.7, 164.9 (enol-C-1, C-1'), 169.2-171.4 (CH_3CO), 174.0 (enol-C-3), 194.1 (keto-C-3). Mass spectrum (DCI/isobutane): *m/z*(%) = 521 (2, $[M+H]^+$), 347 (100).

Anal. Calcd for $C_{21}H_{28}O_{15}$: C, 48.46; H, 5.42; Found: C, 48.74; H, 5.51.

Ethyl 4,5,6,7,8-Penta-*O*-acetyl-2-deoxy-2-ethoxycarbonyl-D-*galacto*-oct-3-ulosonate (5). The reaction of diethyl malonate and **1** was carried out in toluene as described above. After drying and evaporating of the solvent the compound was crystallized in ether and recrystallized from ethanol furnishing **5** as a white solid (3.16 g, 57.6%): mp 87-89 °C; R_f = 0.73; $[\alpha]_D^{20}$ +11.3° (*c* 1.0, chloroform); IR (KBr) 1651 (C=C-OH), 1607 (C=C). Mass spectrum (DCI/isobutane): *m/z*(%) = 549 (70, $[M+H]^+$), 461 (100).

Anal. Calcd for $C_{23}H_{32}O_{15}$: C, 50.37; H, 5.88; Found: C, 50.35; H, 5.90.

Ethyl 4,5,6,7,8-Penta-*O*-acetyl-2-deoxy-2-ethoxycarbonyl-D-*gluco*-oct-3-ulosonate (6). The reaction of diethyl malonate and **2** was carried out in toluene as described above. After drying and evaporating of the solvent the residue was dissolved in ether (400 mL) and extracted 2x with saturated aqueous $NaHCO_3$. The combined $NaHCO_3$ phases were acidified with 5% HCl until pH < 2 and extracted 2x with ether (200 mL). The combined ether phases were dried over Na_2SO_4 and the solvent was evaporated furnishing **6** as a colorless syrup (4.49 g, 82%): R_f = 0.73; $[\alpha]_D^{20}$ +22.1° (*c* 1.0, chloroform). Mass spectrum (DCI/isobutane): *m/z* = 549 (39, $[M+H]^+$), 461 (100).

Anal. Calcd for $C_{23}H_{32}O_{15}$: C, 50.37; H, 5.88; Found: C, 50.20; H, 5.86.

Benzyl 4,5,6,7,8-Penta-*O*-acetyl-2-benzoxycarbonyl-2-deoxy-D-*galacto*-oct-3-ulosonate (7). The reaction of dibenzyl malonate and **1** was carried out in toluene as described above. After drying and evaporating of the solvent the compound was crystallized in ether and recrystallized from ethanol furnishing **7** as a white solid (3.73 g, 55.2%): mp 99-101.5 °C; R_f = 0.76; $[\alpha]_D^{20}$ +13.3° (*c* 1.0, chloroform). Mass spectrum (DCI/isobutane): *m/z*(%) = 673 (18, $[M+H]^+$), 91 (100).

Anal. Calcd for $C_{33}H_{36}O_{15}$: C, 58.93; H, 5.39; Found: C, 58.99; H, 5.28.

Benzyl 4,5,6,7,8-Penta-*O*-acetyl-2-methoxycarbonyl-2-deoxy-D-*galacto*-oct-3-ulosonate (8). The reaction of benzyl methyl malonate and **1** was carried out in toluene as described above. After drying and evaporating of the solvent the compound was crystallized in ether and recrystallized from methanol furnishing **8** as a white solid (5.06 g, 51.3%): mp 74-78 °C; R_f = 0.69; $[\alpha]_D^{20}$ +12.5° (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.84, 1.97-2.10 (12s, 15H, OAc), 3.69-3.75 (4s, 3H, OMe), 3.78 (dd, $J_{8,8'}$ = 11.6 Hz, $J_{7,8'}$ = 7.3 Hz, keto-H-8'), 3.88 (dd, $J_{8,8'}$ = 11.6 Hz, $J_{7,8'}$ = 7.3 Hz, enol-H-8'),

4.23 (dd, $J_{7,8}$ = 5.2 Hz, keto-H-8), 4.25 (dd, $J_{7,8}$ = 4.9 Hz, enol-H-8), 4.72, 4.74 (2s, keto-H-2), 5.14 (m, $J_{6,7}$ = 1.9 Hz, keto-H-7), 5.18 (AB, keto-C*H*$_2$Ph), 5.25 (AB, enol-C*H*$_2$Ph), 5.25 (dd, $J_{5,6}$ = 9.9 Hz, keto-H-6), 5.35 (m, $J_{6,7}$ = 2.1 Hz, enol-H-7), 5.46 (dd, $J_{5,6}$ = 9.8 Hz, enol-H-6), 5.59, 5.61 (d, keto-H-4), 5.62, 5.63 (dd, $J_{4,5}$ = 1.8 Hz, enol-H-5), 5.68, 569 (d, enol-H-4), 5.71, 5.73 (dd, $J_{4,5}$ = 2.2 Hz, keto-H-5), 7.33-7.37 (m, 5H, Ph), 13.72, 13.74 (s, enol-OH); ^{13}C NMR ($CDCl_3$) δ 20.2-20.7 (*C*H$_3$CO), 52.1-53.1 (OMe), 62.0 (keto-C-8, enol-C-8), 62.5, 62.7 (keto-C-2), 66.9, 67.3 (enol-*C*H$_2$Ph), 67.3, 67.4 (keto-C-7), 67.5, 67.6 (enol-C-7), 67.6 (keto-C-6), 67.8 (enol-C-6), 68.0, 68.1 (keto-C-5), 68.2 (keto-*C*H$_2$Ph), 68.4, 68.5 (enol-C-5), 68.8, 68.9 (keto-C-4), 74.3, 74.4 (enol-C-4), 100.0, 100.1 (enol-C-2), 127.5-135.7 (Ph), 163.0, 163.3, 163.4 (keto-C-1, C-1'), 163.8, 164.6, 164.9 (enol-C-1, C-1'), 169.2 - 171.4 (CH$_3$*C*O), 176.5 (enol-C-3), 194.2, 194.5 (keto-C-3). Mass spectrum (DCI/isobutane): *m/z*(%) = 597 (16, $[M+H]^+$), 447 (100).

Anal. Calcd for $C_{27}H_{32}O_{15}$: C, 54.36; H, 5.41; Found: C, 54.24; H, 5.34.

Benzyl 4,5,6,7,8-Penta-*O*-acetyl-2-methoxycarbonyl-2-deoxy-D-*gluco*-oct-3-ulosonate (9). The reaction of benzyl methyl malonate and **2** was carried out in toluene as described above and yielded after chromatography **9** as a colorless syrup (1.96 g, 33%): R_f = 0.69; $[\alpha]_D^{20}$ +19.7° (*c* 1.0, chloroform). Mass spectrum (DCI/isobutane): *m/z*(%) = 597 (14, $[M+H]^+$), 447 (100).

Anal. Calcd for $C_{27}H_{32}O_{15}$: C, 54.36; H, 5.41; Found: C, 54.17; H, 5.45.

Benzyl 4,5,6,7,8-Penta-*O*-acetyl-2-ethoxycarbonyl-2-deoxy-D-*galacto*-oct-3-ulosonate (10). The reaction of benzyl ethyl malonate and 2,3,4,5,6-penta-*O*-acetyl-D-galactonic acid chloride (**1**) was carried out in toluene as described above. After drying and evaporating of the solvent the compound was crystallized in ether and recrystallized from methanol furnishing **10** as a white solid (1.88 g, 31%): mp 68-72 °C; R_f = 0.77. - $[\alpha]_D^{20}$ +17.4° (*c* 1.0, chloroform). Mass spectrum (DCI/isobutane): *m/z*(%) = 611 (26, $[M+H]^+$), 461 (100).

Anal. Calcd for $C_{28}H_{34}O_{15}$: C, 55.08; H, 5.61; Found: C, 55.08; H, 5.79.

Octyl 4,5,6,7,8-Penta-*O*-acetyl-2-deoxy-2-octoxycarbonyl-D-*galacto*-oct-3-ulosonate (11). The reaction of dioctyl malonate and **1** was carried out in toluene as described above and yielded after chromatography **11** as a colorless syrup (3.63 g,

50.6%). The syrup solidified to a waxy solid, that melts at 80 °C: R_f = 0.86; $[\alpha]_D^{20}$ +5.2° (*c* 1.0, chloroform). Mass spectrum (DCI/isobutane): *m/z*(%) = 717 (40, $[M+H]^+$), 545 (100).

Anal. Calcd for $C_{35}H_{56}O_{15}$: C, 58.65; H, 7.87; Found: C, 58.78; H, 8.00.

4,5,6,7,8-Penta-*O*-acetyl-2-anilinocarbonyl-2-deoxy-D-*galacto*-oct-3-uloson-anilide (18). The reaction of malonanilide and **1** was carried out in THF as described above. After adding 100 mL of chloroform and washing with water (150 mL) containing $NaHSO_4$ (5 g) the malonanilide precipitated, was filtered off and the two phases were separated. The organic phase was dried, concentrated to 1/3 of the volume and than toluene (30 mL) was added. Column chromatography, crystallization in ether and recrystallization from ethanol yielded **18** as white needles (0.68 g, 21.2%): mp 88-89 °C; R_f = 0.67; $[\alpha]_D^{20}$ +20.8° (*c* 1.0, chloroform); IR (KBr) 1669 (CONH), 1601 (C=C), 1542 (CONH); ^{1}H NMR ($CDCl_3$) δ 1.45, 1.98, 2.04, 2.04, 2.28 (5s, 15H, OAc), 3.84 (dd, $J_{8,8'}$ = 11.3 Hz, $J_{7,8'}$ = 7.3 Hz, 1H, H-8'), 4.19 (dd, $J_{7,8}$ = 5.5 Hz, 1H, H-8), 5.35 (dd, $J_{5,6}$ = 9.8 Hz, 1H, H-6), 5.36 (m, $J_{6,7}$ = 2.1 Hz, 1H, H-7), 5.46 (dd, $J_{4,5}$ = 2.1 Hz, 1H, H-5), 5.48 (d,1H, H-4), 7.10-7.70 (m, 10H, Ph), 9.62, 10.11 (s, 2H, NH), 15.42 (s, enol-OH); ^{13}C NMR ($CDCl_3$) δ 19.4-20.6 (CH_3CO), 61.7 (C-8), 67.3 (C-7), 68.2 (C-6), 68.7 (C-5), 69.4 (C-4), 102.5 (C-2), 119.5-137.8 (Ph), 165.2 (C-1'), 168.5 (C-1), 169.8 - 173.0 (CH_3CO), 173.7 (C-3). Mass spectrum (DCI/isobutane): *m/z*(%) = 643 (0.5, $[M+H]^+$), 136 (100).

Anal. Calcd for $C_{31}H_{34}N_2O_{13}$: C, 57.94; H, 5.33; N 4.36; Found: C, 57.97; H, 5.33; N, 4.60.

Ethyl 4,5,6,7,8-Penta-*O*-acetyl-2-cyano-2-deoxy-D-*galacto*-oct-3-ulosonate (19). The reaction of ethyl cyanoacetate and **1** was carried out in THF as described above. After adding chloroform (200 mL) and washing with water (150 mL) containing $NaHSO_4$ (10 g), the two phases were separated and the organic phase was washed two additional times with water, the chloroform phase was dried and the solvent evaporated. The residue was dissolved in ether (20 mL) and crystallized. Recrystallization by dissolving in a low volume of acetone and adding ether gave **19** as colorless crystals (4.1 g, 80.4%): mp 118 - 120 °C; R_f (toluene / ethyl acetate / acetic acid, 1:2:1) = 0.59; $[\alpha]_D^{20}$ +3.6° (*c* 1.0, chloroform); IR (KBr) 2226 (CN), 1676 (C=C-OH), 1606 (C=C); ^{1}H NMR

($CDCl_3$) δ 1.33 (t, J = 7,3 Hz, 3H, CH_3CH_2), 1.99 - 2.19 (5s, 15H, OAc), 3.86 (dd, $J_{8,8'}$ = 11.5 Hz, $J_{7,8'}$ = 7.3 Hz, 1H, H-8'), 4.24 (dd, $J_{7,8}$ = 5.5 Hz, 1H, H-8), 4.31 (q, 2H, CH_3CH_2), 5.32 (d,1H, H-4), 5.34 (m, $J_{6,7}$ = 1.9 Hz, 1H, H-7), 5.44 (dd, $J_{4,5}$ = 1.3 Hz, 1H, H-5), 5.47 (dd, $J_{5,6}$ = 10.0 Hz, 1H, H-6), 13.82 (s, enol-OH); ^{13}C NMR ($CDCl_3$) δ 13.8 (CH_3CH_2), 20.0 - 20.5 (CH_3CO), 62.7 (C-8), 63.2 (CH_3CH_2), 67.4 (C-7), 67.5 (C-6), 68.2 (C-5), 69.2 (C-4), 81.5 (C-2), 112.5 (CN), 169.4 - 170.2 (CH_3CO), 169.8 (C-1), 183.1 (C-3). Mass spectrum (DCI/isobutane): *m/z*(%) = 502 (14, $[M+H]^+$), 442 (100).

Anal. Calcd for $C_{21}H_{27}NO_{13}$: C, 50.30; H, 5.43; N, 2.79; Found: C, 50.35; H, 5.49; N, 2.90.

Ethyl 4,5,6,7,8-Penta-*O*-acetyl-2-cyano-2-deoxy-D-*gluco*-oct-3-ulosonate (20). The reaction of ethyl cyanoacetate and **2** was carried out in THF as described above. After adding chloroform (200 mL) and washing with water (150 mL) containing $NaHSO_4$ (10 g) the two phases were separated and the organic phase was washed two additional times with water, the chloroform phase was dried and the solvent evaporated. The residue was dissolved in ether (20 mL) and crystallized. Recrystallization by dissolving in a low volume of acetone and adding ether gave **20** as colorless crystals (3.4 g, 66.7%): mp 124 - 127 °C; R_f (toluene / ethyl acetate / acetic acid, 1:2:1) = 0.59; $[\alpha]_D^{20}$ +17.3° (*c* 1.0, chloroform); Mass spectrum (DCI/isobutane): *m/z*(%) = 502 (14, $[M+H]^+$), 442 (100).

Anal. Calcd for $C_{21}H_{27}NO_{13}$: C, 50.30; H, 5.43; N, 2.79; Found: C, 50.26; H, 5.41; N, 2.82.

4,5,6,7,8-Penta-*O*-acetyl-2-cyano-2-deoxy-D-*galacto*-oct-3-ulosononitrile (21). The reaction of malononitrile and **1** was carried out in THF as described above. After adding ether (100 mL) and washing with water (150 mL) containing $NaHSO_4$ (5 g) two phases were separated and the organic phase was washed with water (50 mL), the aqueous phases were combined, acidified with concentrated HCl (100 mL) and extracted with two portions of chloroform (50 mL). The combined chloroform phases were dried and the solvent carefully evaporated furnishing **21** as a solid foam (1.5 g, 33%): R_f (toluene / ethyl acetate / acetic acid, 1:2:1) = 0.24; $[\alpha]_D^{20}$ -2.7° (*c* 1.0, chloroform); IR (KBr) 2235, 2223 (CN), 1650, 1658 (C=C-OH),1605 (C=C); ^1H NMR ($CDCl_3$) δ 1.92 -

2.04 (5s, 15H, OAc), 3.90 (dd, $J_{8,8'}$ = 11.6 Hz, $J_{7,8'}$ = 7.0 Hz, 1H, H-8'), 4.14 (dd, $J_{7,8}$ = 4.9 Hz, 1H, H-8), 5.05 (d,1H, H-4), 5.16 (m, $J_{6,7}$ = 2.1 Hz, 1H, H-7), 5.28 (dd, $J_{5,6}$ = 9.5 Hz, 1H, H-6), 5.40 (dd, $J_{4,5}$ = 2.1 Hz, 1H, H-5), 9.56 (s, enol-OH); ^{13}C NMR ($CDCl_3$) δ 20.5 - 20.7 (CH_3CO), 46.7 (C-2), 62.0 (C-8), 67.6 (C-7), 68.0 (C-5), 68.04 (C-6), 72.0 (C-4), 120.1, 120.7 (CN), 168.8 - 170.2 (CH_3CO), 184.5 (C-3). Mass spectrum (DCI/isobutane): *m/z*(%) = 455 (7, $[M+H]^+$), 395 (100).

Anal. Calcd for $C_{19}H_{22}N_2O_{11}$: C, 50.22; H, 4.88; N, 6.17; Found: C, 50.22; H, 4.95; N, 6.02.

General C/O-bisacylation procedure (method A, only one acid chloride was used). Malonic acid ester (5 mmol) dissolved in dry toluene (30 mL) was dropped into a suspension of sodium hydride (0.24 g, 10 mmol, activated) in dry toluene (50 mL) containing **1** and **2**, respectively (4.24 g, 10 mmol) while the solution was rapidly stirred. The solution was stirred for 30 min and washed three times with water (100 mL). The phases were separated, the organic phase was dried over $MgSO_4$ and the solvent was evaporated. The residue was dissolved in warm ether, the product crystallized overnight at 4 °C and was recrystallized from methanol or ethanol.

Methyl 4,5,6,7,8-Penta-*O*-acetyl-3-*O*-(2,3,4,5,6-penta-*O*-acetyl-D-galactonoyl)-2-deoxy-2-methoxycarbonyl-D-*galacto*-oct-2-enoate (12). The reaction of dimethyl malonate and **1** was carried out in toluene as described above and yielded **12** as a white solid (1.13 g, 24.9%): mp 147-149 °C; R_f = 0.63; $[\alpha]_D^{20}$ +3.7° (*c* 1.0, chloroform); IR (KBr) 1653 (C=C-C=O); ^{1}H NMR ($CDCl_3$) δ 1.96-2.17 (s, 30H, OAc), 3.69, 3.81 (s, 6H, OMe), 3.83 (dd, $J_{6a,6a'}$ = 11.6 Hz, $J_{5a,6a'}$ = 7.1 Hz, 1H, H-6a'), 3.83 (dd, $J_{8,8'}$ = 11.6 Hz, $J_{7,8'}$ = 7.0 Hz, 1H, H-8'), 4.23 (dd, $J_{5a,6a}$ = 4.6 Hz, 1H, H-6a), 4.24 (dd, $J_{7,8}$ = 5.5 Hz, 1H, H-8), 5.12 (m, $J_{6,7}$ = 1.8 Hz, 1H, H-7), 5.30 (dd, $J_{5,6}$ = 10.1 Hz, 1H, H-6), 5.31 (dd, $J_{3a,4a}$ = 9.8 Hz, 1H, H-4a), 5.32 (m, $J_{4a,5a}$ = 1.9 Hz, 1H, H-5a), 5.48 (dd, $J_{4,5}$ = 2.0 Hz, 1H, H-5), 5.58 (d, 1H, H-4), 5.82 (dd, $J_{4,5}$ = 1.9 Hz, 1H, H-3a), 6.07 (d, 1H, H-2a); ^{13}C NMR ($CDCl_3$) δ 20.1-20.8 (CH_3CO), 52.9, 53.0 (OMe), 61.8 (C-6a), 62.2 (C-8), 66.4 (C-2a), 67.2 (C-3a), 67.4 (C-5a), 67.5 (C-4a, C-7, C-6), 68.5 (C-5), 68.9 (C-4), 121.9 (C-2), 155.3 (C-3), 161.3, 162.8 (C-1, C-1'), 163.7 (C-1a), 168.8-170.3 (CH_3CO). Mass spectrum (DCI/isobutane): *m/z*(%) = 909 (1, $[M+H]^+$), 461 (100).

Anal. Calcd for $C_{37}H_{48}O_{26}$: C, 48.90; H, 5.32; Found: C, 48.63; H, 5.28.

Methyl 4,5,6,7,8-Penta-*O*-acetyl-3-*O*-(2,3,4,5,6-penta-*O*-acetyl-D-gluconoyl)-2-deoxy-2-methoxycarbonyl-D-*gluco*-oct-2-enoate (13). The reaction of dimethyl malonate and **2** was carried out in toluene as described above and yielded **13** as a white solid (1.44 g, 31.7%): mp 118-120.5 °C; R_f = 0.63; $[\alpha]_D^{20}$ +24.0° (*c* 1.0, chloroform); IR (KBr) 1665 (C=C-C=O); ^{1}H NMR ($CDCl_3$) δ 1.98-2.23 (10s, 30H, OAc), 3.77, 3.81 (s, 6H, OMe), 4.15 (dd, $J_{6a,6a'}$ = 12.5 Hz, $J_{5a,6a'}$ = 5.8 Hz, 1H, H-6a'), 4.16 (dd, $J_{8,8'}$ = 12.5 Hz, $J_{7,8'}$ = 5.2 Hz, 1H, H-8'), 4.24 (dd, $J_{5a,6a}$ = 3.2 Hz, 1H, H-6a), 4.34 (dd, $J_{7,8}$ = 4.9 Hz, 1H, H-8), 5.02 (m, $J_{4a,5a}$ = 3.7 Hz, 1H, H-5a), 5.04 (m, $J_{6,7}$ = 5.5 Hz, 1H, H-7), 5.34 (dd, $J_{3a,4a}$ = 6.1 Hz, 1H, H-4a), 5.48 (dd, $J_{5,6}$ = 6.1 Hz, 1H, H-6), 5.60 (dd, $J_{4,5}$ = 5.8 Hz, 1H, H-3a), 5.74 (d, 1H, H-4), 5.78 (dd, $J_{4,5}$ = 3.8 Hz, 1H, H-5), 6.21 (d, 1H, H-2a); ^{13}C NMR ($CDCl_3$) δ 20.2-20.8 (CH_3CO), 53.1, 53.2 (OMe), 61.3 (C-6a), 61.6 (C-8), 68.3 (C-2a), 68.7 (C-5a, C-7), 68.8 (C-4a), 68.9 (C-6), 69.0 (C-3a), 69.5 (C-5), 69.7 (C-4), 123.6 (C-2), 153.5 (C-3), 161.5, 162.7 (C-1, C-1'), 163.7 (C-1a), 169.2-170.5 (CH_3CO). Mass spectrum (DCI/isobutane): *m/z*(%) = 909 (1, $[M+H]^+$), 461 (100).

Anal. Calcd for $C_{37}H_{48}O_{26}$: C, 48.90; H, 5.32; Found: C, 48.97; H, 5.39.

Ethyl 4,5,6,7,8-Penta-*O*-acetyl-3-*O*-(2,3,4,5,6-penta-*O*-acetyl-D-galactonoyl)-2-deoxy-2-ethoxycarbonyl-D-*galacto*-oct-2-enoate (14). The reaction of diethyl malonate and **1** was carried out in toluene as described above and yielded **14** as a white solid (1.65 g, 34.9%): mp 146.5-148 °C; R_f = 0.73; $[\alpha]_D^{20}$ +6.3° (*c* 1.0, chloroform); IR (KBr) 1655 (C=C-C=O). Mass spectrum (DCI/isobutane): *m/z*(%) = 937 (1, $[M+H]^+$), 489 (100).

Anal. Calcd for $C_{39}H_{52}O_{26}$: C, 50.00; H, 5.59; Found: C, 50.01; H, 5.20.

General C/O-bisacylation procedure (method B, two different acid chlorides were used). Malonic acid ester (30 mmol) dissolved in dry toluene (30 mL) was carefully dropped into a suspension of sodium hydride (0.72 g, 30 mmol, activated) in dry toluene (80 mL), while the solution was rapidly stirred. After foaming had subsided, stirring was continued for 10 min and **1** or **2**, respectively (4.24 g, 10 mmol) dissolved in dry toluene (30 mL) was added. The solution was stirred for 30 min and another acid chloride (20 mmol, acetic acid chloride and chloracetic acid chloride, respectively) was added. After 15 min the precipitated product was filtered off and the solution was

washed three times with water (100 mL). The phases were separated, the organic phase was dried with $MgSO_4$ and the solvent evaporated. The residue was dissolved in warm ether, the product crystallized within a few min and was recrystallized by dissolving the solid in a low volume of acetone and adding ethanol or ether to this solution.

Methyl 3,4,5,6,7,8-Hexa-*O*-acetyl-2-deoxy-2-methoxycarbonyl-D-*galacto*-oct-2-enoate (15). The reaction of dimethyl malonate, **1** and acetic acid chloride was carried out in toluene as described above and yielded **15** as colorless crystals (2.25 g, 40%): mp 184-186 °C; R_f = 0.72; $[\alpha]_D^{20}$ +17.5° (*c* 1.0, chloroform); IR (KBr) 1656 (C=C-C=O); ^{1}H NMR ($CDCl_3$) δ 1.99-2.17 (6s, 18H, OAc), 3.74, 3.85 (s, 6H, OMe), 3.85 (dd, $J_{8,8'}$ = 11.4 Hz, $J_{7,8'}$ = 7.3 Hz, 1H, H-8'), 4.27 (dd, $J_{7,8}$ = 4.9 Hz, 1H, H-8), 5.33 (m, $J_{6,7}$ = 2.2 Hz, 1H, H-7), 5.38 (dd, $J_{5,6}$ = 9.6 Hz, 1H, H-6), 5.63 (dd, $J_{4,5}$ = 2.5 Hz, 1H, H-5), 6.16 (d, 1H, H-4); ^{13}C NMR ($CDCl_3$) δ 20.1-20.5 (CH_3CO), 52.4, 52.7 (OMe), 61.9 (C-8), 66.7 (C-7), 67.4 (C-6), 67.5 (C-5), 68.5 (C-4), 120.7 (C-2), 156.7 (C-3), 161.9, 163.0 (C-1, C-1'), 166.5-170.1 (CH_3CO). Mass spectrum (DCI/isobutane): *m/z*(%) = 563 (1, $[M+H]^+$), 461 (100).

Anal. Calcd for $C_{23}H_{30}O_{16}$: C, 49.11; H, 5.38; Found: C, 49.20; H, 5.20.

Benzyl 3,4,5,6,7,8-Hexa-*O*-acetyl-2-deoxy-2-benzoxycarbonyl-D-*galacto*-oct-2-enoate (16). The reaction of dibenzyl malonate, **1** and acetic acid chloride was carried out in toluene as described above and yielded **16** as colorless crystals (3.63 g, 50.8%): mp 143-145 °C; R_f = 0.79; $[\alpha]_D^{20}$ +37.1° (*c* 1.0, chloroform); IR (KBr) 1636 (C=C-C=O). Mass spectrum (DCI/isobutane): *m/z*(%) = 715 (2, $[M+H]^+$), 523 (100).

Anal. Calcd for $C_{35}H_{38}O_{16}$: C, 58.82; H, 5.36; Found: C, 58.60; H, 5.30.

Methyl 4,5,6,7,8-Penta-*O*-acetyl-3-*O*-chloracetyl-2-deoxy-2-methoxycarbonyl-D-*galacto*-oct-2-enoate (17). The reaction of dimethyl malonate, **1** and chloracetic acid chloride was carried out in toluene as described above and yielded **17** as white needles (1.15 g, 19.3%): mp 163-167 °C; R_f = 0.80, R_f (toluene / ethyl acetate 2:1) = 0,45; $[\alpha]_D^{20}$ +12.1° (*c* 1.0, chloroform). Mass spectrum (DCI/isobutane): *m/z*(%) = 597, 599 (1, 3, $[M+H]^+$), 461 (100).

Anal. Calcd for $C_{23}H_{29}ClO_{16}$: C, 46.28; H, 4.90; Cl, 5.94; Found: C, 46.29; H, 4.91; Cl, 6.01.

General O-methylation procedure of alkyl 2-alkoxycarbonyl-2-deoxy-oct-3-ulosonates and 2-cyano-2-deoxy-oct-3-ulosononitriles, respectively. Ethereal diazomethane solution is added to **3**, **5**, **21** (10 mmol) dissolved in acetone until the color of the diazomethane persists. The excess of diazomethane is decomposed by addition of acetic acid. The solvent is evaporated and the product is crystallized from ether and recrystallized by dissolving the solid in a low volume of acetone and adding ether to this solution.

Methyl 4,5,6,7,8-Penta-*O*-acetyl-2-deoxy-2-methoxycarbonyl-3-*O*-methyl-D-*galacto*-oct-2-enoate (22). **3** (10.4 g, 20 mmol) was used to react with diazomethane as described above and yielded **22** as a white solid (8.65 g, 80.9%): mp 118.5-120 °C; R_f = 0.70; $[\alpha]_D^{20}$ +11.0° (*c* 1.0, chloroform); IR (KBr) 1613 (C=C-OMe); ^{1}H NMR ($CDCl_3$) δ 1.90 - 2.12 (s, 15H, OAc), 3.74, 3.74, 3.75 (s, 9H, OMe), 3.86 (dd, $J_{8,8'}$ = 11.6 Hz, $J_{7,8'}$ = 7.5 Hz, 1H, H-8'), 4.25 (dd, $J_{7,8}$ = 5.0 Hz, 1H, H-8), 5.35 (m, $J_{6,7}$ = 2.1 Hz, 1H, H-7), 5.43 (dd, $J_{5,6}$ = 9.8 Hz, 1H, H-6), 5.54 (dd, $J_{4,5}$ = 2.1 Hz, 1H, H-5), 6.15 (d, 1H, H-4); ^{13}C NMR ($CDCl_3$) δ 20.4 - 20.6 (CH_3CO), 52.3, 52.5, 60.5 (OMe), 62.1 (C-8), 67.7 (C-7), 67.9 (C-6), 68.5 (C-5), 69.0 (C-4), 108.3 (C-2), 164.8, 165.2 (C-1, C-1'), 166.4 (C-3), 169.4 - 170.4 (CH_3CO). Mass spectrum (DCI/isobutane): *m/z*(%) = 535 (54, $[M+H]^+$), 461 (100).

Anal. Calcd for $C_{22}H_{30}O_{15}$: C, 49.44; H, 5.66; Found: C, 49.60; H, 5.61.

Ethyl 4,5,6,7,8-Penta-*O*-acetyl-2-deoxy-2-ethoxycarbonyl-3-*O*-methyl-D-*galacto*-oct-2-enoate (24). Ethyl 4,5,6,7,8-penta-*O*-acetyl-2-deoxy-2-ethoxycarbonyl-D-*galacto*-oct-3-ulosonate (**5**, 1.1 g, 2 mmol) was used to react with diazomethane as described above and yielded **24** as a white solid (0.6 g, 50%): mp 102-103 °C; R_f = 0.73; $[\alpha]_D^{20}$ +12.9° (*c* 1.0, chloroform). Mass spectrum (DCI/isobutane): *m/z*(%) = 563 (49, $[M+H]^+$), 475 (100).

Anal. Calcd for $C_{24}H_{34}O_{15}$: C, 51.24; H, 6.09; Found: C, 51.26; H, 6.12.

4,5,6,7,8-Penta-*O*-acetyl-2-cyano-2-deoxy-3-*O*-methyl-D-*galacto*-oct-2-enononitrile (25). 4,5,6,7,8-Penta-*O*-acetyl-2-cyano-2-deoxy-D-*galacto*-oct-3-ulosononitrile (**21**, 0.91 g, 2 mmol) was used to react with diazomethane as described above and yielded **25** as a white solid (0.57 g, 61%): mp 117-121 °C; R_f = 0.75; $[\alpha]_D^{20}$ -22.7° (*c* 1.0, chloroform); IR (KBr) 2229 (CN), 1590 (C=C-OMe); ^{1}H NMR ($CDCl_3$) δ 2.00 - 2.19

(5s, 15H, OAc), 3.87 (dd, $J_{8,8'}$ = 11.6 Hz, $J_{7,8'}$ = 7.3 Hz, 1H, H-8'), 4.24 (dd, $J_{7,8}$ = 5.2 Hz, 1H, H-8), 4.27 (s, 3H, OMe), 5.23 (dd, $J_{4,5}$ = 1.5 Hz, 1H, H-5), 5.25 (d, 1H, H-4), 5.37 (m, $J_{6,7}$ = 2.1 Hz, 1H, H-7), 5.46 (dd, $J_{5,6}$ = 9.8 Hz, 1H, H-6); ^{13}C NMR ($CDCl_3$) δ 20.0 - 20.5 (CH_3CO), 61.7 (C-8), 61.8 (OMe), 65.2 (C-2), 67.40 (C-6), 67.44 (C-7), 68.4 (C-5), 70.3 (C-4), 111.1, 111.3 (CN), 169.5 - 170.2 (CH_3CO), 180.5 (C-3). Mass spectrum (DCI/isobutane): *m/z*(%) = 469 (22, $[M+H]^+$), 409 (100).

Anal. Calcd for $C_{20}H_{24}N_2O_{11}$: C, 51.28; H, 5.16; N, 5.98; Found: C, 51.33; H, 5.15; N, 5.98.

Methyl 4,5,6,7,8-Penta-*O*-acetyl-2-deoxy-2-methoxycarbonyl-3-*O*-methyl-D-*gluco*-oct-2-enoate (23). Dimethyl malonate (12.54 mL, 0.15 mol) dissolved in dry toluene (150 mL) was carefully added dropwise to a suspension of sodium hydride (3.6 g, 0.15 mol, activated) in dry toluene (400 mL), while the solution was rapidly stirred. After foaming had subsided, stirring was continued for 10 min and **2** (21.2 g, 50 mmol) dissolved in dry toluene (150 mL) was added. The solution was stirred an additional 30 min and the solution was then washed three times with water (500 mL). The phases were separated, the organic phase was dried over $MgSO_4$ and the solvent evaporated. The residue was dissolved in ether and an appropriate volume of ethereal diazomethane solution was added. The product crystallized within a few min and was recrystallized by dissolving the solid in a low volume of acetone and adding ether to this solution to yield **23** as colorless crystals (14.02 g, 52.5%): mp 124-127 °C; R_f = 0.70; $[\alpha]_D^{20}$ +51.4° (*c* 1.0, chloroform); IR (KBr) 1599 (C=C-OMe); ^{1}H NMR ($CDCl_3$) δ 2.02 - 2.10 (5s, 15H, OAc), 3.73, 3.76, 3.82 (s, 9H, OMe), 4.10 (dd, $J_{8,8'}$ = 12.2 Hz, $J_{7,8'}$ = 6.4 Hz, 1H, H-8'), 4.26 (dd, $J_{7,8}$ = 3.0 Hz, 1H, H-8), 5.08 (m, $J_{6,7}$ = 7.0 Hz, 1H, H-7), 5.34 (dd, $J_{5,6}$ = 3.7 Hz, 1H, H-6), 5.68 (dd, $J_{4,5}$ = 6.4 Hz, 1H, H-5), 6.36 (d, 1H, H-4); ^{13}C NMR ($CDCl_3$) δ 20.4 - 20.7 (CH_3CO), 52.6, 60.7, 62.5 (OMe), 61.8 (C-8), 68.4 (C-6), 68.9 (C-7), 69.5 (C-5), 70.3 (C-4), 110.7 (C-2), 164.6, 164.8 (C-1, C-1'), 165.1 (C-3), 169.2 - 170.4 (CH_3CO). Mass spectrum (DCI/isobutane): *m/z*(%) = 535 (35, $[M+H]^+$), 461 (100).

Anal. Calcd for $C_{22}H_{30}O_{15}$: C, 49.44; H, 5.66; Found: C, 49.50; H, 5.80.

General bromination procedure of alkyl 2-alkoxycarbonyl-2-deoxy-oct-3-ulosonates. Bromine (0.28 mL, 5.5 mmol) was added dropwise to an ice-cooled, stirred solution of alkyl 2-alkoxycarbonyl-2-deoxyoct-3-ulosonates (5 mmol) dissolved in

chloroform (50 mL) containing ether (5 mL). After 1h at 0 °C, the solution was washed with 10% $NaHCO_3$ solution (100 mL), the phases were separated and the aqueous phase was washed with another portion of chloroform (30 mL). The combined organic phases were washed an additional two times with water, dried and the solvent evaporated. The product crystallized from ether and then was recrystallized from methanol and ethanol.

Methyl 4,5,6,7,8-Penta-*O*-acetyl-2-bromo-2-deoxy-2-methoxycarbonyl-D-*galacto*-oct-3-ulosonate (26). **3** (2.6 g, 5 mmol) was brominated as described above and yielded **26** as a white solid (2.13 g, 71%): mp 108-111 °C; R_f = 0.76; $[\alpha]_D^{20}$ +26.6° (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.98 - 2.12 (5s, 15H, OAc), 3.75 (dd, $J_{8,8'}$ = 11.8 Hz, $J_{7,8'}$ = 7.2 Hz, 1H, H-8'), 3.82, 3.85 (s, 6H, OMe), 4.30 (dd, $J_{7,8}$ = 4.6 Hz, 1H, H-8), 5.12 (dd, $J_{5,6}$ = 9.7 Hz, 1H, H-6), 5.20 (m, $J_{6,7}$ = 2.0 Hz, 1H, H-7), 5.86 (dd, $J_{4,5}$ = 2.3 Hz, 1H, H-5), 6.04 (d, 1H, H-4); ^{13}C NMR ($CDCl_3$) δ 20.4 - 20.8 (CH_3CO), 54.6 (OMe), 62.4 (C-8), 62.5 (C-2), 67.6 (C-7, C-6), 67.7 (C-5), 72.8 (C-4), 162.6, 163.4 (C-1, C-1'), 168.7 - 170.5 (CH_3CO), 190.5 (C-3). Mass spectrum (DCI/isobutane): *m/z*(%) = 601, 599 (4, 4, $[M+H]^+$), 461 (100).

Anal. Calcd for $C_{21}H_{27}BrO_{15}$: C, 42.08; H, 4.54; Found: C, 42.10; H, 4.60.

Methyl 4,5,6,7,8-Penta-*O*-acetyl-2-bromo-2-deoxy-2-methoxycarbonyl-D-*gluco*-oct-3-ulosonate (27). **4** (3.9 g, 7.5 mmol) was brominated as described above and yielded **27** as a white solid (1.75 g, 38.9%): mp 154-158 °C; R_f = 0.76; $[\alpha]_D^{20}$ +35.0° (*c* 1.0, chloroform). Mass spectrum (DCI/isobutane): *m/z*(%) = 601, 599 (11, 9, $[M+H]^+$), 541, 539 (100, 99).

Anal. Calcd for $C_{21}H_{27}BrO_{15}$: C, 42.08; H, 4.54; Found: C, 42.23; H, 4.51.

Ethyl 4,5,6,7,8-Penta-*O*-acetyl-2-bromo-2-deoxy-2-ethoxycarbonyl-D-*galacto*-oct-3-ulosonate (28). **5** (2.7 g, 5 mmol) was brominated as described above and yielded **28** as a white solid (2.31 g, 73.6%): mp 106-109 °C; R_f = 0.78; $[\alpha]_D^{20}$ +28.2° (*c* 1.0, chloroform). Mass spectrum (DCI/isobutane): *m/z*(%) = 629, 627 (9, 8, $[M+H]^+$), 461 (100).

Anal. Calcd for $C_{23}H_{31}BrO_{15}$: C, 44.03; H, 4.98; Found: C, 44.07; H, 5.00.

Benzyl 4,5,6,7,8-Penta-*O*-acetyl-2-bromo-2-deoxy-2-benzoxycarbonyl-D-*galacto*-oct-3-ulosonate (29). **7** (0.336 g, 0.5 mmol) was brominated as described above and yielded **29** as a white solid (0.195 g, 51.9%): mp 80-84 °C; R_f = 0.86, R_f (toluene /

ethyl acetate 2:1) = 0.65; $[\alpha]_D^{20}$ +30.7° (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.85 - 2.10 (5s, 15H, OAc), 3.78 (dd, $J_{8,8'}$ = 11.8 Hz, $J_{7,8'}$ = 7.4 Hz, 1H, H-8'), 4.30 (dd, $J_{7,8}$ = 4.7 Hz, 1H, H-8), 5.11 (dd, $J_{5,6}$ = 9.7 Hz, 1H, H-6), 5.20 (m, $J_{6,7}$ = 2.1 Hz, 1H, H-7), 5.20, 5.22 (AB, J = 12.2 Hz, 4H, C*H*$_2$Ph), 5.88 (dd, $J_{4,5}$ = 2.4 Hz, 1H, H-5), 6.06 (d, 1H, H-4), 7.25 - 7.34 (m, 10H, Ph); ^{13}C NMR ($CDCl_3$) δ 20.2 - 20.8 (*C*H$_3$CO), 62.5 (C-8), 63.2 (C-2), 67.6 (C-7), 67.7 (C-6, C-5), 69.5, 69.6 (*C*H$_2$Ph), 72.8 (C-4), 128.4 - 134.0 (Ph), 162.1, 162.7 (C-1, C-1'), 168.8 - 170.5 (CH$_3$*C*O), 190.6 (C-3). Mass spectrum (DCI/isobutane): *m/z*(%) = 753, 751 (16, 13 $[M+H]^+$), 522 (100).

Anal. Calcd for $C_{33}H_{35}BrO_{15}$: C, 52.74; H, 4.69; Found: C, 53.30; H, 4.86.

Octyl 4,5,6,7,8-Penta-*O*-acetyl-2-bromo-2-deoxy-2-octoxycarbonyl-D-*galacto*-oct-3-ulosonate (30). **11** (1.434 g, 2 mmol) was brominated as described above and yielded **30** as a white solid (0.74 g, 46.5%): mp 52-53 °C; R_f = 0.94, R_f (toluene / ethyl acetate 2:1) = 0,77; $[\alpha]_D^{20}$ +19.7° (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.3 Hz, 6H, OCH$_2$CH$_2$(CH$_2$)$_5$C*H*$_3$), 1.25 (m, 10H, OCH$_2$CH$_2$(C*H*$_2$)$_5$CH$_3$), 1.65 (m, 4H, OCH$_2$C*H*$_2$(CH$_2$)$_5$CH$_3$), 1.99 - 2.10 (5s, 15H, OAc), 3.82 (dd, $J_{8,8'}$ = 11.6 Hz, $J_{7,8'}$ = 7.0 Hz, 1H, H-8'), 4.20, 4.21 (q, 4H, OC*H*$_2$CH$_2$(CH$_2$)$_5$CH$_3$), 4.30 (dd, $J_{7,8}$ = 4.6 Hz, 1H, H-8), 5.17 (dd, $J_{5,6}$ = 9.2 Hz, 1H, H-6), 5.22 (m, $J_{6,7}$ = 2.1 Hz, 1H, H-7), 5.86 (dd, $J_{4,5}$ = 2.4 Hz, 1H, H-5), 6.04 (d, 1H, H-4); ^{13}C NMR ($CDCl_3$) δ 14.0 (OCH$_2$CH$_2$(CH$_2$)$_5$*C*H$_3$), 20.4 - 20.7 (*C*H$_3$CO), 22.6 - 29.0 (OCH$_2$CH$_2$(*C*H$_2$)$_5$CH$_3$), 31.7 (OCH$_2$*C*H$_2$(CH$_2$)$_5$CH$_3$), 62.4 (C-8), 63.0 (C-2), 67.8 (C-7), 67.9 (C-6), 68.0 (C-5), 68.1, 68.2 (O*C*H$_2$CH$_2$(CH$_2$)$_5$CH$_3$), 72.8 (C-4), 162.4, 163.0 (C-1, C-1'), 168.7 - 170.4 (CH$_3$*C*O), 190.6 (C-3). Mass spectrum (DCI/isobutane): *m/z*(%) = 797, 795 (4, 4, $[M+H]^+$), 545 (100).

Anal. Calcd for $C_{35}H_{55}BrO_{15}$: C, 52.83; H, 6.97; Found: C, 53.3; H, 6.88.

General dibromination procedure of alkyl 2-benzoxycarbonyl-2-deoxyoct-3-ulosonates. Bromine (0.11 mL, 2.2 mmol) was added dropwise to a stirred solution of alkyl 2-deoxy-2-benzoxycarbonyl-D-*galacto*-oct-3-ulosonates **7**, **8**, **10** (1 mmol) dissolved in chloroform (9 mL) containing ether (1 mL). After 24 h at room temperature chloroform (20 mL) was added, the solution was then washed with 10% $NaHCO_3$ solution (50 mL) and the phases separated. The organic phase was washed an additional two times with water, dried and the solvent evaporated. The product crystallized from

ethanol and was recrystallized in methanol and ethanol. The crystalline substances must be carefully dried.

Methyl 4,5,6,7,8-Penta-*O*-acetyl-2,2-dibromo-2-deoxy-D-*galacto*-oct-3-ulosonate (31). **8** (0.6 g, 1 mmol) was brominated as described above and yielded **31** as a white solid (0.39 g, 62.3%): mp 144-150 °C; R_f = 0.82, R_f (toluene / ethyl acetate 2:1) = 0.52; $[\alpha]_D^{20}$ +28.4° (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.99 - 2.10 (5s, 15H, OAc), 3.79 (dd, $J_{8,8'}$ = 11.9 Hz, $J_{7,8'}$ = 7.3 Hz, 1H, H-8'), 3.87 (s, 3H, OMe), 4.30 (dd, $J_{7,8}$ = 4.7 Hz, 1H, H-8), 5.13 (dd, $J_{5,6}$ = 9.8 Hz, 1H, H-6), 5.20 (m, $J_{6,7}$ = 2.1 Hz, 1H, H-7), 5.92 (dd, $J_{4,5}$ = 2.4 Hz, 1H, H-5), 6.12 (d, 1H, H-4); ^{13}C NMR ($CDCl_3$) δ 20.4 - 20.7 (CH_3CO), 55.0 (OMe), 57.8 (C-2), 62.4 (C-8), 67.7 (C-7, C-6), 68.4 (C-5), 71.9 (C-4), 163.0 (C-1), 168.5 - 170.4 (CH_3CO), 187.0 (C-3). Mass spectrum (DCI/isobutane): *m/z*(%) = 623, 621, 619 (0.6, 0.6, 0.2, $[M+H]^+$), 403 (100).

Anal. Calcd for $C_{19}H_{24}Br_2O_{13}$: C, 36.80; H, 3.90; Found: C, 36.65; H, 3.81.

Ethyl 4,5,6,7,8-Penta-*O*-acetyl-2,2-dibromo-2-deoxy-D-*galacto*-oct-3-ulosonate (32). **10** (0.61 g, 1 mmol) was brominated as described above and yielded **32** as a white solid (0.355 g, 56%): mp 86-92 °C; R_f = 0.80, R_f (toluene / ethyl acetate 2:1) = 0.57; $[\alpha]_D^{20}$ +26.8° (*c* 1.0, chloroform). Mass spectrum (DCI/isobutane): *m/z*(%) = 637, 635, 633 (0.3, 0.3, 0.2, $[M+H]^+$), 61 (100).

Anal. Calcd for $C_{20}H_{26}BrO_{13}$: C, 37.88; H, 4.13; Found: C, 37.76; H, 3.96.

Benzyl 4,5,6,7,8-Penta-*O*-acetyl-2,2-dibromo-2-deoxy-D-*galacto*-oct-3-ulosonate (33). 7 (0.67 g, 1 mol) was brominated as described above and yielded **33** as a white solid (0.34 g, 48.8%): mp 134-139 °C; R_f = 0.86, R_f (toluene / ethyl acetate 2:1) = 0.65; $[\alpha]_D^{20}$ +34.3° (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.91 - 2.08 (5s, 15H, OAc), 3.80 (dd, $J_{8,8'}$ = 11.6 Hz, $J_{7,8'}$ = 7.3 Hz, 1H, H-8'), 4.30 (dd, $J_{7,8}$ = 4.9 Hz, 1H, H-8), 5.13 (dd, $J_{5,6}$ = 9.5 Hz, 1H, H-6), 5.20 (m, $J_{6,7}$ = 2.1 Hz, 1H, H-7), 5.26 (AB, 2H, CH_2Ph), 5.93 (dd, $J_{4,5}$ = 2.1 Hz, 1H, H-5), 6.13 (d, 1H, H-4), 7.33 - 7.37 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ 20.3 - 20.7 (CH_3CO), 58.2 (C-2), 62.4 (C-8), 67.7 (CH_2Ph), 67.7 (C-7), 68.4 (C-6), 70.3 (C-5), 71.8 (C-4), 128.6 - 133.7 (Ph), 162.4 (C-1), 168.6 - 170.4 (CH_3CO), 187.1 (C-3). Mass spectrum (DCI/isobutane): *m/z*(%) = 699, 697, 695 (2, 3, 2, $[M+H]^+$) 559, 557 (100, 99).

Anal. Calcd for $C_{25}H_{28}Br_2O_{13}$: C, 43.12; H, 4.05; Found: C, 43.28; H, 4.02.

Ethyl 4,5,6,7,8-Penta-*O*-acetyl-2-chloro-2-deoxy-2-ethoxycarbonyl-D-*galacto*-oct-3-ulosonate (34). **5** (0.548 g, 1 mmol) was dissolved in sulfuryl chloride (1 mL) and stirred for 1 h. After heating the solution to reflux for 2 min, ether was added to crystallize the product. The solution was stored 2 h at 4 °C for complete crystallization. Recrystallization of the substance from ethanol gave **34** as a white solid (0.41 g, 70.3%): mp 97-98 °C; R_f = 0.79; $[\alpha]_D^{20}$ +24.0° (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.27, 1.30 (t, J = 7.3 Hz, 6H, CH_3CH_2), 1.98 - 2.10 (5s, 15H, OAc), 3.78 (dd, $J_{8,8'}$ = 11.8 Hz, $J_{7,8'}$ = 7.2 Hz, 1H, H-8'), 4.27, 4.29 (q, 4H, CH_3CH_2), 4.30 (dd, $J_{7,8}$ = 5.0 Hz, 1H, H-8), 5.14 (dd, $J_{5,6}$ = 9.6 Hz, 1H, H-6), 5.19 (m, $J_{6,7}$ = 2.0 Hz, 1H, H-7), 5.83 (dd, $J_{4,5}$ = 2.3 Hz, 1H, H-5), 6.00 (d, 1H, H-4); ^{13}C NMR ($CDCl_3$) δ 13.6, 13.8 (CH_3CH_2), 20.3 - 20.7 (CH_3CO), 62.3 (C-8), 64.0, 64.1 (CH_3CH_2), 67.7 (C-7, C-6, C-5), 72.1 (C-2), 72.4 (C-4), 162.1, 162.5 (C-1, C-1'), 168.7 - 170.4 (CH_3CO), 191.0 (C-3). Mass spectrum (DCI/isobutane): *m/z*(%) = 585, 583 (4, 11, $[M+H]^+$), 525, 523 (39, 100).

Anal. Calcd for $C_{23}H_{31}ClO_{15}$: C, 47.39; H, 5.40; Cl, 6.08; Found: C, 47.40; H, 5.32; Cl, 6.12.

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REFERENCES

1. L. I. Haynes, *Adv. Carbohydr. Chem.*, **18**, 227 (1963), **20**, 357 (1965).
2. a) H. J. Schaeffer, L. Beauchamp, P. de Miranda, G. B. Elion, D. J. Bauer and P. Collins, *Nature (London)*, **272**, 583 (1978); b) C. K. Chu and S. J. Cutler, *J. Heterocycl. Chem.*, **23**, 289 (1986); c) R. J. Remy and J. A. Secrist, *Nucleosides & Nucleotides*, **4**, 411 (1985); d) M. Hocek, M. Masojídková and A. Holý, *Tetrahedron*, **53**, 2291 (1996).
3. a) M. Valpuesta Fernández, F. J. López Herrera and C. Gómez Pérez, *Carbohydr. Res.*, **124**, 333 (1983); b) M. Mancera, E. Rodriguez, I. Roffé and J. A. Galbis, C. F. Conde and A. Conde, *Carbohydr. Res.*, **210**, 327 (1991); c) M. Mancera, E. Rodriguez, I. Roffé and J. A. Galbis, *Carbohydr. Res.*, **253**, 307 (1994); d) J. C.

Bernal Montes, P. Borrachero Moya, F. Cabrera Escribano, M. Gómez Guillén, F. Madrid Díaz and J. M. Moreno Martínez, *Carbohydr. Res.*, **285**, 49 (1996).
4. M. P. Derri Alcántara, F. Cabrera Escribano, A. Gómez Sánchez, M. Jesús Diánez, Dolores Estrada, A. López Castro and S. Pérez Garrido, *Synthesis*, 64 (1996).
5. F. J. Lopez Aparicio, F. J. Lopez Herrera and M. Valpuesta Fernandez, *An. Quim.* **74**, 1561 (1978).
6. C. Gomez Perez, M. Valpuesta Fernandez and F. J. Lopez Herrera, *An. Quim.* **80**, 45 (1984).
7. E. J. Reist, P.A. Hart, B. R. Baker and L. Goodman, *J. Org. Chem.*, **27**, 1722 (1962).
8. R. Meisel, K. Peseke and H. Reinke, *J. Carbohydr. Chem.*, in preparation.
9. R. Meisel and K. Peseke, *J. Carbohydr. Chem.*, in preparation.
10. XS-Crystal Structure Solution Version 4.2 for MSDOS, Siemens Analytical Xray Inst. Inc., Copyright 1990.
11. G. M. Sheldrick, SHELXL-93, Crystal structure refinement, University of Göttingen, Germany 1993.
12. F. Arndt and C. Martius, *Liebigs Ann. Chem.*, **499**, 228 (1932).
13. S. Rosenfeld and A. Williams, *J. Chem. Educ.*, **68**, 66 (1991).
14. M. L. Wolfrom and R. L. Brown, *J. Am. Chem. Soc.*, **65**, 1021 (1943).
15. R. T. Major and E. W. Cook, *J. Am. Chem. Soc.*, **58**, 2477 (1936).