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CARBOHYDRATE RESEARCH

Note

Synthesis of uronic acid derivatives from 1,2;3,4-di-*O*-isopropylidene-α-D-*galacto*-hexodialdopyranose and aldulosonic acid derivatives from 2,3;4,5-di-*O*-isopropylidene-β-D-*arabino*-hexos-2-ulopyranose☆

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Abstract

A facile method for the formation of uronic and aldulosonic acids derivatives is described involving reaction of lithium dianions of carboxylic acids with *aldehydo*-sugar derivatives. Acetic, propanoic, phenylacetic, 3,3-dimethylacrylic, crotonic, and sorbic acids were the acids used for the preparation of the lithium dianions, and galactose and fructose were used for preparation of the aldehydo derivatives.

Keywords: Uronic acids; Ketoaldonic acids

1. Introduction

In recent years, uronic and aldulosonic acids [1] have received much attention because of their biological activities and their presence in nature, where they play an important role. The predominant ketoaldonic acids that occur in nature are sialic acids [2], a family of acylated aminodeoxynonulosonic acids, of which neuramic acid is the parent. Some uronic acids appear, as constituents of lipopolysaccharides, as important components of the outer membrane of Gram-negative bacteria, and others as constituents of glycosaminoglycans, for example hyaluronic acid, synthesized from D-glucose in the fibroblasts (used to lubricate body tissues and block the spread of invading microorganisms).

In this work a new access to uronic acids and aldulosonic acids has been developed, based on the reaction of lithium dianions of carboxylic acids with *aldehydo*-sugar derivatives. The reaction of such dianions with simple aldehydes and ketones has been studied previously [3], but applications to *aldehydo*- and *keto*-sugar derivatives have not been explored.

☆ Part 1 of a series: 'Reaction of lithium dianions of carboxylic acids with *aldehydo*- and *keto*-sugar derivatives'.

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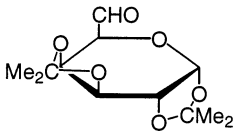
2. Results and discussion

The starting materials used, bearing a free aldehyde group, were 1,2;3,4-di-*O*-isopropylidene-α-D-*galacto*-hexodialdopyranose (**1**) and 2,3;4,5 - di - *O* - isopropylidene - β - D - *arabino*-hexos-2-ulopyranose (**2**) in reaction with the organolithium dianions (Table 1) derived from acetic, propanoic, phenylacetic, 3,3-dimethylacrylic, crotonic, and sorbic acids, to give products **3**–**13** (from **1**) and **14**–**21** (from **2**).



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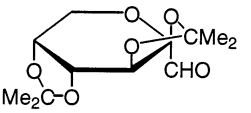

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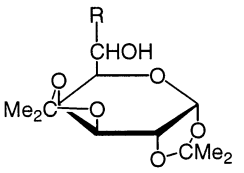
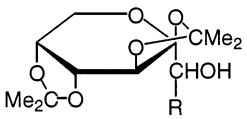
The assignment of configuration at the new stereogenic center formed in the reaction was made according to earlier studies on the stereochemistry of the addition of Grignard reagents to *aldehydo*-sugars and by molecular dynamic studies, and further by NMR studies (Tables 2 and 3). The first was accomplished by Wolfrom and Hanessian [4] and by Hoppe and Schöllkopf [5], and corroborated by Gentile [6], who studied the conformations of these aldehydes. The second provided information about thermodynamic stability and charge distributions [7] of the compounds described in this work. Supporting NMR data were based on proton shifts (referring to the starting sugars) for the galactose derivatives at position 1, and in fructose derivatives at position 3. In the case of the S enantiomers this proton appears at higher shifts, due to a slightly greater positive charge than that in R enantiomers.



	R	
3	(6*R*)	$-CH_2CO_2H$
4	(6*S*)	$-CH_2CO_2H$
5		$-CH(CH_3)CO_2H$
6	(6*R*, 7*R*)	$-CH(Ph)CO_2H$
7	(6*S*, 7*R*)	$-CH(Ph)CO_2H$
8	(6*R*, 7*S*)	$-CH(Ph)CO_2H$
9	(6*S*)	$-CH(CH{=}CH_2)CO_2H$
10	(6*R*, 7*S*)	$-CH(C(CH_3){=}CH_2)CO_2H$
11	(6*R*, 7*R*	$-CH(C(CH_3){=}CH_2)CO_2H$
12	(6*S*, 7*R*)	$-CH(C(CH_3){=}CH_2)CO_2H$
13	(6*S*)	$-CH(CH{=}CHCH{=}CH_2)CO_2H$



	R	
14	(3*S*)	$-CH_2CO_2H$
15	(3*R*)	$-CH_2CO_2H$
16		$-CH(CH_3)CO_2H$
17	(3*S*)	$-CH(Ph)CO_2H$
18	(3*R*)	$-CH(Ph)CO_2H$
19		$-CH_2CH{=}CHCO_2H$
20		$-CH_2C(CH_3){=}CHCO_2H$
21		$-CH_2CH{=}CHCH{=}CHCO_2H$

Table 1
Conditions for formation of dianions of acids

Carboxylic acid	Initial temperature (°C)	Time (min)	Final temperature (°C)	Time (min)
Acetic	−70	15	room temperature	120
Propanoic	−70	15	0	60
Phenylacetic	−70	30	0	5
3,3-Dimethylacrylic	−70	60	0	5
Crotonic	−70	60	0	5
Sorbic	−70	60	0	5

Table 2
NMR spectroscopy data of products obtained from 1,2;3,4-di-*O*-isopropylidene-α-D-*galacto*-hexodialdopyranose (**1**)

Compound	2 $(CH_3)_2C$-	H-1	H-2	H-3	H-4	H-5	H-6	H-7	Others
Chemical shifts of protons in ^1H NMR									
3	1.51, 1.46, 1.37, 1.33	5.52	4.33	4.64	4.49	3.68	4.23	(a) 2.93, (b) 2.56	
4	1.49, 1.48, 1.34, 1.33	5.61	4.35	4.63	4.36	3.78	4.32	(a) 2.78, (b) 2.67	
5	1.45, 1.43, 1.34, 1.29	5.59	4.32–4.22	4.62	4.45	3.64	4.32–4.22	2.93	1.34 Me, 3.87 OH
6	1.48, 1.31, 1.19, 0.73	5.59	4.22	4.51	4.28	3.36	4.64	3.98	7.38 H-*o*-phenyl, 7.30–7.22 H-*p*,*m*-phenyl
7	1.43, 1.30, 1.21, 1.00	5.40	4.15	4.46	4.28	3.26	4.07	3.95	7.41–7.05 H-phenyl, 6.90 OH
8	1.43, 1.32, 1.24, 1.19	5.52	4.31	4.53	4.25	3.70	4.51	3.93	7.38–7.11 H-phenyl
9	1.48, 1.45, 1.34, 1.31	5.62	4.32	4.62	4.38	3.74	4.22	3.50	5.79 H-7^1, 5.40 H-7^{2a}, 5.29 H-7^{2b}
10	1.46, 1.44, 1.35, 1.29	5.33	4.20	4.60	4.46	3.60	4.20	3.33	1.83 Me-7^1, 5.03 H-7^{2a}, 4.95 H-7^{2b}
11	1.45, 1.41, 1.31, 1.29	5.32	4.08	4.59	4.36	3.64	4.42	3.64	1.80 Me-7^1, 5.03 H-7^{2a}, 4.97 H-7^{2b}
12	1.45, 1.40, 1.32, 1.29	5.47	4.20	4.58	4.43		4.43		1.82 Me-7^1, 5.02 H-7^{2a}, 5.00 H-7^{2b}
13	1.48, 1.40, 1.34, 1.30	5.63	4.33	4.62	4.38	3.73	4.23	3.53	5.68 H-7^1, 6.31 H-7^2, 6.30 H-7^3 5.10 H-7^{4a}, 5.22 H-7^{4b}

Compound	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{6,7a}$	$J_{6,7b}$	$J_{7a,7b}$	Others
Coupling data of protons in ^1H NMR (Hz)									
3	5.1	2.4	8.0	1.9	8.6	3.0	8.6	17.0	
4	5.1	2.5	8.0	1.9	4.8	5.5	6.9	16.2	
5	4.7	2.2	8.0	1.8	9.3				$J_{7,Me}$ 5.0
6	5.1	1.8	8.0	1.4	1.0	10.3			$J_{o,p}$ 4.6
7	5.0	2.5	8.0	1.5	9.0	3.0			
8	5.0	2.0	8.0	2.0	1.0	8.0			
9	5.3	2.3	7.8	2.0	2.0	8.3			$J_{7,71a}$ 8.3, $J_{71,72a}$ 16.8, $J_{71,72b}$ 10.3
10	5.0	2.4	8.0	1.8	8.8	4.0			$J_{72a,72b}$ 1.9
11	5.1	2.4	8.0	1.8		10.4			
12	5.2	2.2	8.0	1.6					
13	5.1	2.4	8.0	2.1	2.6	9.0			$J_{7,71a}$ 9.3, $J_{71,72a}$ 14.6, $J_{72,73}$ 10.2, $J_{73,74a}$ 10.4, $J_{73,74b}$ 16.8, $J_{74a,74b}$ 1.7, $J_{o,p}$ 1.7

Table 3
NMR spectroscopy data of products obtained from 2,3;4,5-di-*O*-isopropylidene-β-D-*arabino*-hexos-2-ulopyranose (**2**)

Compound	2 $(CH_3)_2C$-	H-2	H-3	H-4	H-5	H-6	H-7	H-8	H-9	H-10	H-11	H-12	OH	Me	Ph
Chemical shift of protons in ^1H NMR															
14	1.54, 1.48, 1.43, 1.35	(a) 2.98, (b) 2.65	4.11		4.56	4.62	4.24	(a) 3.90, (b) 3.75							
15	1.50, 1.34	(a) 2.89, (b) 2.75	4.04		4.36	4.58	4.22	(a) 3.85, (b) 3.76					3.53		
16	1.47, 1.46, 1.35, 1.32	3.15	3.58		4.62	4.60	4.20	(a) 3.87, (b) 3.71					3.59	1.37	
17	1.51, 1.41, 1.37, 1.31	3.86	4.38		4.65	4.62	4.25	(a) 3.92, (b) 3.78					4.79		7.50–7.30
18	1.57, 1.52, 1.35, 1.33	3.98	4.50		4.52	4.62	4.22	(a) 3.86, (b) 3.78					2.71		7.45–7.29
19	1.53, 1.44, 1.40, 1.32	5.91	7.13	(a) 2.84, (b) 2.42	3.68		4.46	4.59	4.22	(a) 3.90, (b) 3.74			3.79		
20	1.56, 1.48, 1.43, 1.36	5.81		(a) 2.88, (b) 2.26	3.88		4.52	4.63	4.25	(a) 3.93, (b) 3.78			3.79	2.21	
21	1.50, 1.44, 1.39, 1.32	5.77	7.35	7.27	6.27	(a) 2.79, (b) 2.39	3.74		4.50	4.59	4.21	(a) 3.99, (b) 3.90			

Compound	$J_{2a,3}$	$J_{2b,3}$	$J_{2a,2b}$	$J_{2,Me}$	$J_{3,4a}$	$J_{3,4b}$	$J_{4a,4b}$	$J_{4a,5}$	$J_{4b,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$	$J_{6a,7}$	$J_{6b,7}$	$J_{7,8a}$	$J_{7,8b}$	$J_{8a,8b}$	$J_{8,9}$	$J_{9,10}$	$J_{10a,10b}$	$J_{10,11}$	$J_{11,12b}$	$J_{12a,12b}$
Coupling data of protons in ^1H NMR																							
14	3.0	9.2	16.6							2.6			7.9		1.8	0.6	13.0						
15	4.2	9.8	8.6							2.6			7.8		1.8		13.0						
16	2.0			7.4						2.7			9.3		1.8	0.7	13.0						
17	1.4									2.7			7.6		1.8	0.7	12.4						
18	8.1									2.6			7.8		1.8	0.7	12.8						
19	15.7				7.2	7.5	15.3	2.6	9.5						2.6		8.0	8.0	1.8	13.0			
20							14.1	2.0	10.8						2.6		7.9	7.9	1.8	12.8			
21	15.2				1.6			7.4		5.8	5.6	14.4	2.4	9.2					2.4		7.8	1.8	8.8

3. Experimental

General procedures.—^{1}H NMR chemical shift values are given in ppm relative to internal Me_4Si as the standard and were recorded on a Varian Gemini 200 instrument (200 MHz) using $CDCl_3$ as solvent. Microanalyses were performed with a Carlo Erba EA1108 instrument. Optical rotations were recorded on a DIP-370 instrument. Melting points were recorded on Mettler FP 80 instrument. Thin-layer chromatography (TLC) was performed on Merck Kiesegel 60 F_{254} precoated plates (0.25 mm thickness), with detection by EtOH–H_2SO_4. Preparative TLC used Scharlau silica gel with gypsum and F_{254} indictation (1.5 mm thickness on 20×20 cm plates) (25:35:1 hexane–EtOAc–AcOH for elution). All reactions involving air- or moisture-sensitive reagents and/or compounds were carried out under dry nitrogen.

Synthesis.—To a solution of LDA (lithium diisopropylamide), prepared following the general method of Pfeffer et al. [8], and cooled to -78 °C, the carboxylic acid (10 mmol) dissolved in 15 mL of THF (oxolane) was added dropwise by syringe over a period of 30 min. This solution was stirred as indicated in Table 1. Thereupon the solution was cooled to -78 °C in a dry ice–acetone bath and the sugar derivative (10 mmol dissolved in THF) was added dropwise by syringe over a period of 15 min. When the reaction was finished (as observed by TLC) it was quenched with aq H_3PO_4 (10%). Neutral material was first extracted from the mixture with CH_2Cl_2 (3×30 mL) and the acidic products were then extracted with satd aq $NaHCO_3$ (3×30 mL), The combined organic layers were washed successively with H_2O (2×30 mL) and brine (30 mL), and dried (anhydrous Na_2SO_4). Evaporation of the solvent yielded the product (see the following reaction schemes). When a mixture of isomers was obtained, they were separated by preparative TLC.

*Products from 1,2;3,4-di-*O*-isopropylidene-α-*D*-galacto-hexodialdopyranose* (**1**)

*7-Deoxy-1,2;3,4-di-*O*-isopropylidene-*D*-glycero-α-*D*-galacto-octopyranuronic acid* (**3**). Crude yield 61%, mp 137 °C (benzene); $[\alpha]_D^{21}$ $-118.4°$ ($CHCl_3$, *c* 1.00); TLC R_f: 0.40. Anal. Calcd for $C_{14}H_{22}O_8$: C, 52.83; H, 6.97. Found: C, 53.00; H, 7.01.

*7-Deoxy-1,2;3,4-di-*O*-isopropylidene-*L*-glycero-α-*D*-galacto-octopyranuronic acid* (**4**). Crude yield 61%, syrup; TLC R_f: 0.30. Anal. Calcd for $C_{14}H_{22}O_8$: C, 52.83; H, 6.97. Found: C, 53.00; H, 7.01.

*7-Deoxy-1,2;3,4-di-*O*-isopropylidene-7-*C*-methyl-*D*-glycero-α-*D*-galacto-octopyranuronic acid* (**5**). Crude yield 84%, syrup; $[\alpha]_D^{26}$ $-59.5°$ ($CHCl_3$, *c* 2.00). Anal. Calcd for $C_{15}H_{24}O_8$: C, 54.20; H, 7.28. Found: C, 54.16; H, 7.30.

*(7*R*)-7-Deoxy-1,2;3,4-di-*O*-isopropylidene-7-*C*-phenyl-*D*-glycero-α-*D*-galacto-octopyranuronic acid* (**6**). Crude yield 78%, mp 195–196 °C (toluene); $[\alpha]_D^{22}$ $-65.3°$ ($CHCl_3$, *c* 1.01); TLC R_f: 0.40. Anal. Calcd for $C_{20}H_{26}O_8$: C, 60.90; H, 6.64. Found: C, 60.85; H, 6.70.

*(7*R*)-7-Deoxy-1,2;3,4-di-*O*-isopropylidene-7-*C*-phenyl-*L*-glycero-α-*D*-galacto-octopyranuronic acid* (**7**). Crude yield 78%. TLC R_f: 0.43. Anal. Calcd for $C_{20}H_{26}O_8$: C, 60.90; H, 6.64. Found: C, 60.85; H, 6.70.

*(7*S*)-7-Deoxy-1,2;3,4-di-*O*-isopropylidene-7-*C*-phenyl-*D*-glycero-α-*D*-galacto-octopyranuronic acid* (**8**). Crude yield 78%, syrup; $[\alpha]_D^{24}$ $-82.9°$ ($CHCl_3$, *c* 0.7); TLC R_f: 0.48. Anal. Calcd for $C_{20}H_{26}O_8$: C, 60.90; H, 6.64. Found: C, 60.85; H, 6.70.

*7-Deoxy-1,2;3,4-di-*O*-isopropylidene-7-*C*-vinyl-*L*-glycero-α-*D*-galacto-octopyranuronic acid* (**9**). Crude yield 62%, mp 145.6–146.0 °C (hexane); $[\alpha]_D^{23}$ $-62.0°$ ($CHCl_3$, *c* 1.15). Anal. Calcd for $C_{16}H_{24}O_8$: C, 55.81; H, 7.03. Found: C, 55.29; H, 7.36.

*(7*S*)-7-Deoxy-1,2;3,4-di-*O*-isopropylidene-7-*C*-(1-methylvinyl)-*D*-glycero-α-*D*-galacto-octopyranuronic acid* (**10**). Crude yield 68%, syrup; TLC R_f: 0.49. Anal. Calcd for $C_{17}H_{26}O_8$: C, 56.97; H, 7.31. Found: C, 57.10; H, 7.42.

*(7*R*)-7-Deoxy-1,2;3,4-di-*O*-isopropylidene-7-*C*-(1-methylvinyl)-*D*-glycero-α-*D*-galacto-octopyranuronic acid* (**11**). Crude yield 68%, syrup; TLC R_f: 0.44. Anal. Calcd for $C_{17}H_{26}O_8$: C, 56.97; H, 7.31. Found: C, 57.10; H, 7.42.

*(7*R*)-7-Deoxy-1,2;3,4-di-*O*-isopropylidene-7-*C*-(1-methylvinyl)-*L*-glycero-α-*D*-galacto-octopyranuronic acid* (**12**). Crude yield 68%, syrup; TLC R_f: 0.40. Anal. Calcd for

$C_{17}H_{26}O_8$: C, 56.97; H, 7.31. Found: C, 57.10; H, 7.42.

(7R)-7-Deoxy-1,2;3,4-di-O-isopropylidene-7-C-(1-methylvinyl)-L-glycero-α-D-galacto-octopyranuronic acid (**12**). Crude yield 68%, syrup; TLC R_f: 0.40. Anal. Calcd for $C_{17}H_{26}O_8$: C, 56.97; H, 7.31. Found: C, 57.10; H, 7.42.

7-C-[(E)-1,3-Butadienyl]-7-deoxy-1,2;3,4-di-O-isopropylidene-L-glycero-α-D-galacto-octopyranuronic acid (**13**). Crude yield 68%, syrup. Anal. Calcd for $C_{18}H_{26}O_8$: C, 58.37; H, 7.08. Found: C, 58.33; H, 7.00.

Products from 2,3;4,5-di-O-isopropylidene-β-D-arabino-hexos-2-ulopyranose (**2**)

2-Deoxy-4,5;6,7-di-O-isopropylidene-β-D-gluco-oct-4-ulopyranosonic acid (**14**). Crude yield 63%, mp 120.0–120.2 °C (CH_2Cl_2); $[\alpha]_D^{24}$ −18.8° ($CHCl_3$, *c* 1.00). Anal. Calcd for $C_{14}H_{22}O_8$: C, 52.83; H, 6.97. Found: C, 52.87; H, 6.75.

2-Deoxy-4,5;6,7-di-O-isopropylidene-β-D-manno-oct-4-ulopyranosonic acid (**15**). Crude yield 63%, syrup; $[\alpha]_D^{23}$ −33.1° ($CHCl_3$, *c* 2.55). Anal. Calcd for $C_{14}H_{22}O_8$: C, 52.83; H, 6.97. Found: C, 52.46; H, 7.33.

2-Deoxy-4,5;6,7-di-O-isopropylidene-2-C-methyl-β-D-gluco-oct-4-ulopyranosonic acid (**16**). Crude yield 75%, syrup; $[\alpha]_D^{24}$ −18.9° ($CHCl_3$, *c* 1.00). Anal. Calcd for $C_{15}H_{24}O_8$: C, 54.20; H, 7.28. Found: C, 54.27; H, 7.32.

(2R)-2-Deoxy-4,5;6,7-di-O-isopropylidene-2-C-phenyl-β-D-gluco-oct-4-ulopyranosonic acid (**17**). Crude yield 75%, mp 143.4 °C (ether–hexane); $[\alpha]_D^{22}$ −228.0° ($CHCl_3$, *c* 0.10); TLC R_f: 0.46. Anal. Calcd for $C_{20}H_{26}O_8$: C, 60.90; H, 6.64. Found: C, 60.54; H, 6.81.

2-Deoxy-4,5;6,7-di-O-isopropylidene-2-C-phenyl-β-D-manno-oct-4-ulopyranosonic acid (**18**). Crude yield 75%, syrup; $[\alpha]_D^{22}$ +37.3° ($CHCl_3$, *c* 0.85); TLC R_f: 0.50. Anal. Calcd for $C_{20}H_{26}O_8$: C, 60.90; H, 6.64. Found: C, 60.54; H, 6.81.

(E)-2,3,4-Trideoxy-6,7;8,9-di-O-isopropylidene-β-D-gluco-dec-2-eno-6-ulopyranosonic acid (**19**). Crude yield 76.6%, syrup; $[\alpha]_D^{22}$ −4.53° ($CHCl_3$, *c* 1.04). Anal. Calcd for $C_{16}H_{24}O_8$: C, 55.81; H, 7.03. Found: C, 56.33; H, 7.27.

(E)-2,3,4-Trideoxy-6,7;8,9-di-O-isopropylidene-3-C-methyl-β-D-gluco-dec-2-eno-6-ulopyranosonic acid (**20**). Crude yield 59%, syrup; $[\alpha]_D^{24}$ 25.9° ($CHCl_3$, *c* 0.95). Anal. Calcd for $C_{17}H_{26}O_8$: C, 56.97; H, 7.31. Found: C, 56.82; H, 7.78.

(E,E)-2,3,4,5,6-Pentadeoxy-8,9;10,11-di-O-isopropylidene-β-D-gluco-dodec-2,4-dieno-8-ulopyranosonic acid (**21**). Crude yield 67%, syrup; $[\alpha]_D^{21}$ +3.45° ($CHCl_3$, *c* 0.68). Anal. Calcd for $C_{18}H_{26}O_8$: C, 58.37; H, 7.08. Found: C, 58.04; H, 7.22.

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