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CARBOHYDRATE RESEARCH

Note

Synthesis of branched-chain sugar derivatives from 1,2;5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose and 1,2;4,5-di-*O*-isopropylidene-β-D-*erythro*-2-hexulopyranos-3-ulose☆

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Abstract

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

Keywords: Sialic acid analogues; Branched-chain sugars

1. Introduction

The biological interest in branched and higher sugars has led to the development of suitable synthetic methods. Additionally, the use of sugars as precursors for compounds having multiple chiral centers has increased in recent years. These sugars are also a source of chirally substituted short carbon chains [1].

Synthetic organic chemistry involving asymmetric induction requires a suitable stereogenic site for effective transfer of chirality. 1,2;5,6-Di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose (**1**) and 1,2;4,5-di-*O*-isopropylidene-β-D-*erythro*-2-hexulopyranos-3-ulose (**2**) have significant intrinsic merits as stereogenic sources, because of their ready accessibility and their cyclic structure. The preference for addition from the *exo* face in furanoses and pyranoses in *keto*-sugars has been effectively applied in the selective synthesis of branched-chain sugars [2].

This work describes a new access to branched-chain sugars, based on the reaction of lithium dianions of carboxylic acids with *keto*-sugar derivatives. The reaction of such dianions with *aldehydo* sugars has been studied previously [3].

☆ Part 2 of a series: Reaction of lithium dianions of carboxylic acids with *aldehydo*- and *keto*-sugar derivatives.

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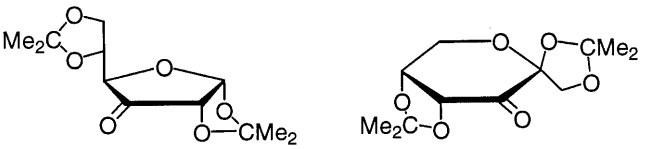
2. Results and discussion

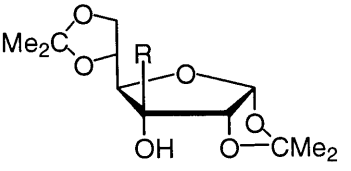
The starting materials used, bearing a carbonyl group, were 1,2;5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose (**1**) and 1,2;4,5-di-*O*-isopropylidene-β-D-*erythro*-2-hexulopyranos-3-ulose (**2**) in reaction with the organolithium dianions derived from acetic, propanoic, phenylacetic, 3,3-dimethylacrylic, crotonic and sorbic acids, to give products **3**–**9** (from **1**) and **10**–**20** (from **2**).

The bulky 1,2-acetal in **1** and 4,5-acetal in **2** control the stereochemistry of addition of lithium dianions to the carbonyl group, by exerting steric hindrance from the *endo* face in two sugars [2b,4]. NMR shifts and coupling data for **1** and **2** are given in Tables 1 and 2, respectively.



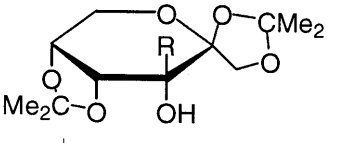
1 **2**

Scheme 1.



	R	
3		-CH_2CO_2H
4		-$CH(CH_3)CO_2H$
5	(1'S)	-$CH(Ph)CO_2H$
6	(1'R)	-$CH(Ph)CO_2H$
7		-$CH_2CH{=}CHCO_2H$
8		-$CH_2C(CH_3){=}CHCO_2H$
9		-$CH_2CH{=}CHCH{=}CHCO_2H$

Scheme 2.



	R	
10		-CH_2CO_2H
11	(3R)	-$CH(CH_3)CO_2H$
12		-$CH(CH_3)CO_2H$
13		-$CH(Ph)CO_2H$
14		-$CH(CO_2H)CH{=}CH_2$
15		-$CH_2CH{=}CHCO_2H$
16		-$CH(CO_2H)C(CH_3){=}CH_2$
17	(Z)	-$CH_2C(CH_3){=}CHCO_2H$
18	(E)	-$CH_2C(CH_3){=}CHCO_2H$
19		-$CH(CO_2H)CH{=}CHCH{=}CH_2$
20		-$CH_2CH{=}CHCH{=}CHCO_2H$

Scheme 3.

3. Experimental

General methods.—^{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 a Mettler FP 80 instrument. Thin-layer chromatography (TLC) was performed on E. Merck Kiesegel 60 F_{254} precoated plates (0.25 mm thickness), with detection by EtOH–H_2SO_4. Preparative TLC used on 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.

Procedure.—To a solution of LDA, prepared following the general method of Pfeffer et al. [5], and cooled to −78 °C, the carboxylic acid (10 mmol) dissolved in 15 mL of THF was added dropwise by syringe over a period of 30 min. This solution was stirred as indicated in Table 3. Then 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

Table 1
NMR data for products obtained from 1,2;5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose (**1**)

Compound	2 CMe_2	H-1	H-2	H-4	H-5	H-6a	H-6b	Others
Proton chemical shifts								
3	1.57, 1.43, 1.33	5.75	4.70	3.84	4.10	4.10	3.92	2.93 H-3^{1a}, 2.43 H-3^{1b}
4	1.62, 1.48, 1.40	5.75	4.88	3.84	4.23	4.18	3.95	3.27 H-3^{1}, 1.28 CH_3
5	1.56, 1.34, 1.21, 1.02	5.48	4.19	3.93	4.18	4.10	3.81	3.83 H-3^{1}, 7.53 H-*o*-Ph, 7.35 H-*o*,*p*-Ph, 4.30 OH
6	1.53, 1.46, 1.34	5.78	4.96	3.89	4.36	4.13	3.88	4.38
7	1.60, 1.47, 1.37, 1.35	5.71	4.26	3.81	4.10	4.10	3.94	2.82 H-3^{1a}, 2.34 H-3^{1b}, 7.25 H-3^{2}, 5.96 H-3^{3}
8	1.59, 1.47, 1.37, 1.35	5.70	4.32	3.76	4.15	4.15	3.95	2.79 H-3^{1a}, 2.19 H-3^{1b}, 2.36 H-3^{2}, 5.75 H-3^{3}
9	1.60, 1.40, 1.30	5.62	4.20	4.15–3.65				2.24 H-3^{1a}, 2.72 H3^{1b}, 6.4–6.15 H-3^{2} H-3^{3}, 7.30 H-3^{4}, 5.75 H-3^{5} 5.20 OH

Coupling data	$J_{1,2}$	$J_{4,5}$	$J_{4,3^{1a}}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$	
3	3.8	8.4			8.4	11.7	$J_{3^{1a},3^{1b}}$ 15.6
4	4.0	8.3			5.5	11.3	J_{3^{1},CH_3} 7.3
5	3.6	9.5		6.0	5.6	8.5	
6	4.1	9.3		6.0	5.3	8.6	
7	3.9	8.3	1.8				$J_{3^{1a},3^{1b}}$ 15.2, $J_{3^{1a},3^{2}}$ 5.4, $J_{3^{1b},3^{2}}$ 9.0, $J_{3^{2},3^{3}}$ 16.2
8	3.7	8.1			7.8	11.0	$J_{3^{1a},3^{1b}}$ 14.2
9	4.3						$J_{3^{1a},3^{1b}}$ 14.0, $J_{3^{1a},3^{2}}$ 6.5, $J_{3^{1b},3^{2}}$ 3.0, $J_{3^{3},3^{4}}$ 15.0, $J_{3^{4},3^{5}}$ 14.0

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), the acidic products were then extracted with satd aq $NaHCO_3$ (3 × 30 mL), freed by acidification with 0.1 N HCl to pH 4–5, and extracted with CH_2Cl_2 (4 × 30 mL). The combined organic layers were washed successively with water (2 × 30 mL) and brine (30 mL), and dried (anhyd Na_2SO_4). Evaporation of the solvent yielded the product (Schemes 1–3). When a mixture of isomers was obtained, they were separated by preparative TLC.

*Products from 1,2;5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose* (**1**).—*3-C-(Carboxymethyl)-1,2;5,6-di-O-isopropylidene-α-D-allofuranose)* (**3**). Yield 46%, syrup $[\alpha]_D^{21}$ + 34.3° (*c* 1.00, $CHCl_3$); TLC R_f 0.40. Anal. Calcd for $C_{14}H_{22}O_8$: C, 52.83; H, 6.97. Found: C, 52.95; H, 7.03.

3-C-(1-Carboxyethyl)-1,2;5,6-di-O-isopropylidene-α-D-allofuranose (**4**). Yield 61%, syrup, $[\alpha]_D^{26}$ + 18.52° (*c* 1.08, $CHCl_3$); TLC R_f 0.30. Anal. Calcd for $C_{15}H_{24}O_8$: C, 54.20; H, 7.28. Found: C, 54.25; H, 7.26.

(1′S)-3-C-(1-Carboxy-1-phenyl)methyl-1,2;5,6-di-O-isopropylidene-α-D-allofuranose (**5**). Yield 70%, mp 186.6–186.9 °C (toluene), $[\alpha]_D^{22}$ − 4.25° (*c* 1.01, $CHCl_3$). TLC R_f 0.50. Anal. Calcd for $C_{20}H_{26}O_8$: C, 60.90; H, 6.64. Found: C, 61.03; H, 6.75.

(1′R)-3-C-(1-Carboxy-1-phenylmethyl-1,2;5,6-di-O-isopropylidene-α-D-allofuranose (**6**). Yield 8%, mp 180.5–180.7 °C (benzene), $[\alpha]_D^{23}$ + 58.20° (*c* 0.70, $CHCl_3$). TLC R_f 0.41. Anal. Calcd for $C_{20}H_{26}O_8$: C, 60.90; H, 6.64. Found: C, 60.95; H, 6.70.

3-C-[(E)-(3-Carboxy)-2-propenyl]-1,2;5,6-di-O-isopropylidene-α-D-allofuranose (**7**). Yield 66%, mp 116.3–117.0 °C (toluene), $[\alpha]_D^{24}$ − 18.6° (*c* 0.60, $CHCl_3$). TLC R_f 0.34. Anal.

Table 2
NMR data for products obtained from 1,2;4,5-di-*O*-isopropylidene-β-D-*erythro*-hexlopyranos-3-ulose (**2**)

Compound	2 CMe_2	H-1a	H-1b	H-4	H-5	H-6a	H-6b	Others	OH	Me	Ph
Proton chemical shifts											
10	1.59, 1.48, 1.43, 1.38,	4.35	4.00	4.34	4.24	4.18	4.18	2.65 H-3^{1a}, 2.59 H-3^{1b}	3.55		
11	1.57, 1.49, 1.43, 1.39	4.39	4.03	5.05	4.23	4.14	4.03	2.73 H-3^{1}, 1.35 CH_3	3.35		
12	1.48, 1.44, 1.43	4.46	3.99	4.52	4.29	4.14	4.14	3.02 H-3^{1}, 1.25 CH_3	4.00	1.37	
13	1.51, 1.49, 1.36, 1.15	4.60	4.20	3.90	4.07	4.04	3.70	4.18 H-3^{1}, 7.50–7.30 H-Ph	1.85		7.50–7.30
14	1.62, 1.48, 1.43, 1.41	4.50	4.06	4.48	4.25	4.10	3.99	3.65 H-3^{1}, 5.37 H-3^{2}, 5.37 H-3^{3a}, 5.34 H-3^{3b}			7.45–7.29
15	1.58, 1.49, 1.38, 1.35	4.32	3.98	4.15	4.20	4.15	4.15	2.53 H-3^{1}, 7.30 H-3^{2}, 5.88 H-3^{3}	2.74		
16	1.53, 1.47, 1.35	4.50	4.17	4.25	4.17	4.00	3.96	3.73 H-3^{1}, 5.12 H-3^{3}, 1.96 CH_3	5.65		
17	1.55, 1.50, 1.48, 1.32	4.38	3.97	4.33	4.12	4.20	4.08	3.76 H-3^{1a}, 2.18 H-3^{1b}, 5.83 H-3^{3}, 2.11 CH_3	2.98	2.21	
18	1.55, 1.49, 1.46, 1.34	4.35	3.97	4.20–4.07	4.20–4.07	4.20–4.07	4.20–4.07	2.41 H-3^{1}, 5.76 H-3^{3}, 2.33 CH_3			
19	1.65, 1.48, 1.44, 1.43	4.50	4.04	4.51	4.27	4.09	3.88	3.68 H-3^{1}, 5.84 H-3^{2}, 2.30 H-3^{3}, H-3^{4}, 5.15 H-3^{5a}, 5.27 H-3^{5b}			
20	1.58, 1.49, 1.45, 1.38	4.35	3.98	4.16	4.20	4.15	4.10	2.50 H-3^{1}, 6.39 H-3^{2}, 6.27 H-3^{3}, 7.27 H-3^{4}, 5.82 H-3^{5}	2.69		

Coupling data	$J_{1a,1b}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$	
10	10.0	5.0				$J_{3^{1a},3^{1b}}$ 14.8
11	9.5	6.2	1.8		14.3	J_{3^{1},CH_3} 7.3
12	9.9	5.9	2.6			J_{3^{1},CH_3} 7.3
13	9.9	5.4	5.1	3.9	16.4	
14	10.2	6.1	4.2	2.4	13.4	$J_{3^{1},3^{2}}$ 8.1 $J_{3^{2},3^{3a}}$ 17.3 $J_{3^{2},3^{3b}}$ 10.3 $J_{3^{3a},3^{3b}}$ 1.2
15	9.8				13.0	$J_{3^{1a},3^{2}}$ 7.8 $J_{3^{2},3^{3}}$ 15.6
16	10.0	5.2	5.5	6.0	13.2	
17	9.6	5.4	3.2			$J_{3^{1a},3^{1b}}$ 13.0
18	9.6					
19	10.2	5.7		2.7	12.9	$J_{3^{1},3^{2}}$ 8.7 $J_{3^{2},3^{3}}$ 14.1 $J_{3^{4},3^{5a}}$ 7.5 $J_{3^{4},3^{5b}}$ 6.9 $J_{3^{5a},3^{5b}}$ 1.4
20	9.6	6.7	3.8	1.0	13.4	$J_{3^{1},3^{2}}$ 6.6 $J_{3^{1},3^{3}}$ 2.1 $J_{3^{2},3^{3}}$ 15.3 $J_{3^{2},3^{4}}$ 1.0 $J_{3^{3},3^{4}}$ 10.8 $J_{3^{4},3^{5}}$ 15.4

Table 3
Conditions for formation of dianions of the acids

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

Calcd for $C_{16}H_{24}O_8$: C, 55.81; H, 7.03. Found: C, 55.11; H, 7.40.

3-C-[(E)-(3-Carboxy-2-methyl)-2-propenyl]-1,2;5,6-di-O-isopropylidene-α-D-allofuranose (**8**). Yield 63%, mp 126.4–127.1 °C (toluene), $[\alpha]_D^{22} + 38.00°$ (*c* 0.54, $CHCl_3$). TLC R_f 0.55. Anal. Calcd for $C_{17}H_{26}O_8$: C, 56.97; H, 7.31. Found: C, 57.41; H, 7.14.

3-C-[(E,E)-(5-Carboxy)-2,4-pentadienyl]-1,2;5,6-di-O-isopropylidene-α-D-allofuranose (**9**). Yield 66%, syrup, $[\alpha]_D^{24} + 60.00°$ (*c* 1.00, $CHCl_3$). TLC R_f 0.49. Anal. Calcd for $C_{18}H_{26}O_8$: C, 58.37; H, 7.08. Found: C, 58.50; H, 7.10.

Products from 1,2;4,5-di-O-isopropylidene-β-D-erythro-2-hexulopyranos-3-ulose (**2**).—*3-C-(Carboxymethyl)-1,2;4,5-di-O-isopropylidene-β-D-psicopyranose* (**10**). Yield 56%, syrup, $[\alpha]_D^{24} - 20.25°$ (*c* 1.00, $CHCl_3$). TLC R_f 0.46. Anal. Calcd for $C_{14}H_{22}O_8$: C, 52.83; H, 6.97. Found: C, 52.80; H, 6.94.

(1′S)-3-C-(1-Carboxyethyl)-1,2;4,5-di-O-isopropylidene-β-D-psicopyranose (**11**). Yield 58%, syrup, $[\alpha]_D^{24} - 117.53°$ (*c* 0.97, $CHCl_3$). TLC R_f 0.38. Anal. Calcd for $C_{15}H_{24}O_8$: C, 54.20; H, 7.28. Found: C, 54.30; H, 7.34.

(1′R)-3-C-(1-Carboxyethyl)-1,2;4,5-di-O-isopropylidene-β-D-psicopyranose (**12**). Yield 5%, syrup, $[\alpha]_D^{25} - 56.12°$ (*c* 0.98, $CHCl_3$). TLC R_f 0.32. Anal. Calcd for $C_{15}H_{24}O_8$: C, 54.20; H, 7.28. Found: C, 54.23; H, 7.31.

3-C-(1-carboxy-1-phenylmethyl)-1,2;4,5-di-O-isopropylidene-β-D-psicopyranose (**13**). Yield 83%, mp 240.0 °C (toluene), $[\alpha]_D^{24} - 58.67°$ (*c* 1.00, $CHCl_3$). TLC R_f 0.33. Anal. Calcd for $C_{20}H_{26}O_8$: C, 60.90; H, 6.64. Found: C, 60.13; H, 6.63.

3-C-[(1-Carboxy)-2-propenyl]-1,2;4,5-di-O-isopropylidene-β-D-psicopyranose (**14**). Yield 76%, mp 161.0 °C (ether), $[\alpha]_D^{22} - 64.00°$ (*c* 0.65, $CHCl_3$). TLC R_f 0.45. Anal. Calcd for $C_{16}H_{24}O_8$: C, 55.81; H, 7.03. Found: C, 56.28; H, 7.26.

3-C-[(E)-(3-Carboxy)-2-propenyl]-1,2;4,5-di-O-isopropylidene-β-D-psicopyranose (**15**). Yield 76%, mp 140.0 °C (ether–hexane), $[\alpha]_D^{22} - 118.40°$ (*c* 0.25, $CHCl_3$). TLC R_f 0.53. Anal. Calcd for $C_{16}H_{24}O_8$: C, 55.81; H, 7.03. Found: C, 55.24; H, 7.28.

3-C-[(1-Carboxy-2-methyl)-2-propenyl]-1,2;4,5-di-O-isopropylidene-β-D-psicopyranose (**16**). Yield 9%, mp 199.0 °C (ether), $[\alpha]_D^{24} + 35.51°$ (*c* 1.07, $CHCl_3$); TLC R_f 0.35. Anal. Calcd for $C_{17}H_{26}O_8$: C, 56.97; H, 7.31. Found: C, 57.00; H, 7.27.

3-C-[(Z)-(3-Carboxy-2-methyl)-2-propenyl]-1,2;4,5-di-O-isopropylidene-β-D-psicopyranose (**17**). Yield 28%, mp 164.0–164.4 °C (hexane), $[\alpha]_D^{23} - 925.00°$ (*c* 0.20, $CHCl_3$). TLC R_f 0.50. Anal. Calcd for $C_{17}H_{26}O_8$: C, 56.97; H, 7.31. Found: C, 57.13; H, 7.89.

3-C-[(E)-(3-Carboxy-2-methyl)-2-propenyl]-1,2;4,5-di-O-isopropylidene-β-D-psicopyranose (**18**). Yield 18%, mp 159.0–159.6 °C (ether–hexane), $[\alpha]_D^{24} - 150.79°$ (*c* 0.63, $CHCl_3$). TLC R_f 0.50. Anal. Calcd for $C_{17}H_{26}O_8$: C, 56.97; H, 7.31. Found: C, 56.84; H, 7.59.

3-C-[(E)-(1-Carboxy)-2,4-pentadienyl]-1,2;4,5-di-O-isopropylidene-β-D-psicopyranose (**19**). Yield 69%, syrup, $[\alpha]_D^{21} - 80.75°$ (*c* 1.00, $CHCl_3$). TLC R_f 0.44. Anal. Calcd for $C_{18}H_{26}O_8$: C, 58.37; H, 7.08. Found: C, 58.55; H, 7.19.

3-C-[(E,E)-(5-Carboxy)-2,4-pentadienyl]-1,2;4,5-di-O-isopropylidene-β-D-psicopyranose (**20**). Yield 11%, mp 211.0 °C (toluene), $[\alpha]_D^{21} - 45.60°$ (*c* 1.00, $CHCl_3$). TLC R_f 0.48. Anal. Calcd for $C_{18}H_{26}O_8$: C, 58.37; H, 7.08. Found: C, 58.28; H, 7.11.

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