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Carbohydrate Research 260 (1994) 233–241

CARBOHYDRATE RESEARCH

Some derivatives of 3-deoxy-D-*glycero*-D-*galacto*-non-2-ulosonic acid (KDN)

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(Received October 18th, 1993, accepted in final form February 24th, 1994)

Abstract

Treatment of a solution of 3-deoxy-D-*glycero*-D-*galacto*-non-2-ulosonic (KDN) in 11 N aqueous hydrochloric acid with an excess of ethanethiol gave in 52% yield the diethyl dithioacetal of the corresponding 1,4-lactone, which was further characterized as its peracetate. With 1,3-propanedithiol, only one thiol function reacted and the product, isolated in 18% yield as its peracetate, was a vinyl thioether of the α,β-unsaturated 1,4-lactone. The methyl ester methyl β-glycopyranoside derivative of KDN could be converted to the 8,9-isopropylidene ketal **7** (69%). Conditions were found which allow selective silylation at C-4 with *tert*-butylchlorodimethylsilane, giving the 4-*O*-*tert*-butylsilyl derivative in 91% yield. Heating it with bis(tributyltin) oxide afforded the 1,7-lactone with inversion of the ring conformation. Lithium aluminium hydride reduction of **7** afforded the corresponding methyl non-2-ulopyranoside, which was converted to the 1,4-bis(silyl) ether. Bromination of 1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol in aqueous solution at 0°C with *N*-bromophthalimide gave a mixture of bromodeoxy hexoses from which 2-bromo-2-deoxy-D-mannose was isolated in 60% yield by crystallization. Its incubation with pyruvate in the presence of sialyl aldolase gave 5-bromo-3,5-dideoxy-D-*glycero*-D-*galacto*-non-2-ulosonic acid **16** in 70% yield.

1. Introduction

3-Deoxy-D-*glycero*-D-*galacto*-non-2-ulosonic (KDN, **1**), a trace component of rainbow trout egg polysialoglycoprotein, was prepared in high yield, and on a large scale by the aldol condensation of D-mannose and pyruvate catalyzed by sialyl aldolase [1]. Considering that this enzyme is readily available, KDN is then among

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SSDI 0008-6215(94)00070-V

the most readily available higher sugars. This prompted us to make a preliminary exploration of its chemistry, which is now reported.

2. Discussion

It has been claimed that dithioacetals of ketonic sugars cannot be prepared directly [2]. For instance, the preparation of D-fructose dithioacetals starts from the acyclic pentaacetate. However, Kuhn and Brossmer succeeded in obtaining, in good yield, the diethyl dithioacetal 2 of *N*-acetylneuraminic acid 1,4-lactone [3]. Under the same conditions, with a great excess of ethanethiol in 11 N hydrochloric acid for 2 days at 0°C, we obtained a crystalline, high-melting dithioacetal derivative of KDN (**3**) in 52% yield. Lead carbonate was used for the neutralization, and some of the product may have been lost by adsorption. In a modified procedure, the mixture was neutralized with ammonia, and the final residue was directly *O*-acetylated. The crystalline pentaacetate **4** was obtained in 75% overall yield from KDN. The structure of **3** relies on its centesimal composition and on ^{1}H NMR spectroscopy evidence (Table 1). The signal of H-4 in the spectrum of the dithioacetal **3** does not shift downfield on acetylation, and the spectrum of the peracetate **4** is almost similar to that of the peracetate [4] of **2**. Zemplén *O*-deacetylation converted **4** back into **3** in 77% yield. Thus, ring-closure of the lactone occurred during work up.

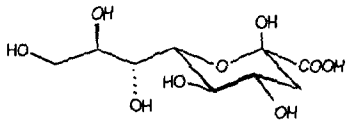
No reaction of KDN occurred with thiophenol. However, treatment with 1,3-propanedithiol gave a derivative which could be isolated as the peracetate **5** obtained in 18% yield by acetylation of the crude mixture. The unusual structure of **5** was confirmed by comparison of its ^{1}H NMR spectrum with that of the peracetate **4** (Table 1). The signals of H-5–H-9 are almost identical, but the highly characteristic signal at low field for H-3,3′ is not seen in the spectrum of **5**. Instead, a one proton signal at δ 6.63 (J 2 Hz) indicates the presence of an ethylenic proton. The allylic proton H-4 in **5** resonates at slightly lower field as compared to H-4 in the peracetate **4**. In the spectrum of the hexaacetate **5**, the signals of the five *O*-acetyl groups appear at δ 1.99, 2.05, 2.07, 2.12, and 2.15 ppm, and that of the *S*-acetyl group at 2.36 ppm. Furthermore, the signal of the trimethylene unit is quite different from the well-known pattern for a dithiane unit, with signals at δ 1.90 ($^3J_{H,H}$ 7 and 7 Hz, $CH_2CH_2CH_2$), 2.89 ($^3J_{H,H}$ 7 Hz, $C=CSCH_2$), 2.95 ($^3J_{H,H}$ 7 Hz, CH_2SAc). Obviously, the elimination of water from a protonated intermediate was preferred to the formation of a spiro compound.

We then considered as starting material the known methyl ester methyl glycoside **6**, which is easily prepared [5] from KDN. Treatment with acetone and 2,2-dimethoxypropane, in the presence of Dowex 50 (H^+) resin, gave in 69% yield a crystalline isopropylidene monoketal **7**. Acetylation gave the triacetate **8** with the signals for H-4, H-5, and H-7 shifted downfield by $\geqslant$ 1.6 ppm on acetylation. Initially, we planned to prepare a derivative fully protected except at OH-7, a position which is known for its lack of reactivity in the analogous *N*-acetylneuraminic acid derivatives [6]. We first treated **7** with two equivalents of *tert*-

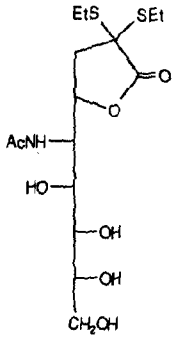
Table 1
^{1}H NMR data for skeletal protons (250 MHz, δ, J in parentheses)

Proton no.	3 [a]	4	5	6 [b]	7 [c]	8	9	11 [c]	12	13	14	16 [b]	10
1								3.38	4.03	3.70			
								(11)	(12)	(10)			
1′								3.45	4.32	3.73			
								(11)	(12)	(10)			
3*ax*	2.26	2.35	6.63	1.71	1.43	1.85	1.66	1.53	1.73	1.49	1.61	1.71	2.02
	(14)	(8) [d]	(2)	(13.5)	(13)	(12.5)	(13)	(13)	(13)	(13)	(13)	(13)	(14)
	(6)			(11.5)	(11.5)	(11.5)	(11)	(12)	(12)	(12)	(11)	(11)	(3)
3*eq*	2.70	2.38		2.30	2.14	2.52	2.22	1.96	2.35	2.17	2.23	2.14	2.15
	(14)	(8) [d]		(13.5)	(13)	(12.5)	(13)	(13)	(13)	(13)	(13)	(13)	(14)
	(11)			(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(3.5)
4	4.78	4.63	5.00	3.95	3.73	5.33		3.72	5.31			4.04	
	(0.5)	(2)	(1.5)	(9)	(9)	(10)	(8)	(10)	(10)	(10)	(10)	(11)	(1.5)
5		5.04	5.07	3.54	3.35	4.94	3.60	3.31	4.89	3.50	4.82	3.78	3.56 [e]
		(10)	(10)	(10)	(10)	(10)	(9)	(9)	(10)	(10)	(10)	(11)	(1.5)
6		5.63	5.70	3.79	3.66	4.08	3.88	3.72	4.08		3.45	4.12	
		(2)	(2)	(0.8)	(1)	(2.5)	(1)	(1)	(2)		(1)	(1)	
7		5.38	5.42	3.86	3.53	5.28	3.76	3.51	5.21	3.41	5.20	3.91	4.56
		(10)	(10)		(10)	(6.5)	(10)	(9)	(7)	(11)	(6.5)	(9)	(0)
8		5.01	5.40		4.09	4.36		4.08	4.28		4.26	3.57	
		(3)	(3)	(5)	(5.5)	(6.5)		(5.5)	(6)		(6.5)	(2)	
		(5)	(5)		(8)	(6.5)		(6)	(6)		(6.5)	(6)	
9		4.21	4.22	3.68	3.84	3.91		3.83	3.84			3.67	
		(12.5)	(12.5)	(12)	(8)	(9)		(8.5)	(8.5)			(11.5)	
9′		4.01	4.04		4.09	4.06		3.99	3.99			3.46	
		(12.5)	(12.5)		(8)	(9)		(8.5)	(8.5)			(11.5)	

[a] In CD_3SOCD_3. [b] In D_2O. [c] In CD_3OD. [d] $J_{3,4}$. [e] $J_{5,OH}$ 8 Hz.



1



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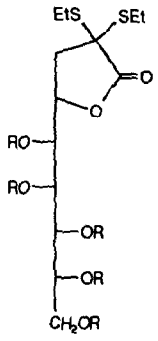
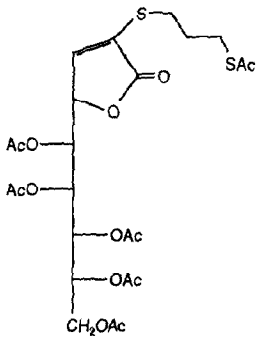


3 R=H

4 R=Ac



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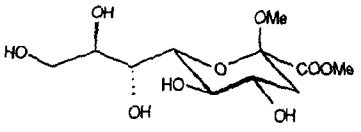
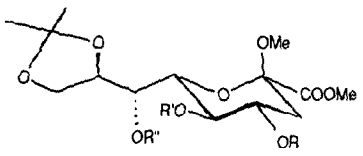


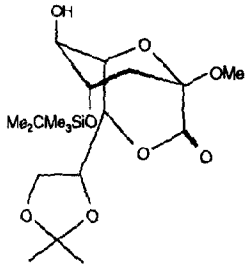
6



7 R=R'=R''=H

8 R=R'=R''=Ac

9 R=$SiMe_2CMe_3$ R'=R''=H



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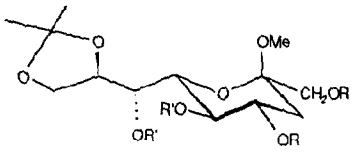
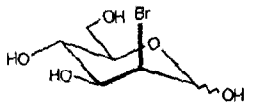


11 R=R'=H

12 R=R'=Ac

13 R=$SiMe_2CMe_3$ R'=H

14 R=$SiMe_2CMe_3$ R'=Ac



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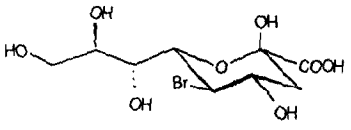

16

butylchlorodimethylsilane in the presence of imidazole, for one day at room temperature. TLC indicated the presence of one major and two minor, less polar products. The main product (54%) was the 4-*O*-silyl ether **9**; by adjustment of the conditions, it was obtained in 91% yield.

We then attempted selective substitution at O-5 or O-7 in the silyl ether **9** by the stannylene method. After a 16-h reflux in toluene in the presence of dibutyltin oxide, tetrabutylammonium bromide and benzyl bromide were added with additional heating for 1.5 h. TLC indicated the formation of a major product (**10**), which was obtained crystalline after subsequent purification in 31% yield. Proof of its structure came from its elemental analysis, which agreed with the loss of one methanol molecule from **9**, a fact which correlated with the disappearance of the CO_2Me signal from the ^1H NMR spectrum. The small couplings of H-4 (3, 3.5, and 1.5 Hz) indicated its equatorial orientation. The signal of H-5 showed small couplings (1.5 and 1.5 Hz) to H-4 and H-6, together with a large coupling to the hydroxyl proton, which could be interpreted as a stabilization of the *anti* conformation by hydrogen bonding to the ring oxygen. Finally, intramolecular acylation of O-7 in **10** moved the signal of H-7 by 1 ppm downfield. Thus, it appeared that the addition of benzyl bromide had been of no use. Finally, lactone **10** was prepared in 55% yield by a 16-h reflux of **9** in toluene in the presence of bis(tributyltin) oxide. The peracetylated derivative of **10** had been previously reported as the product, in 10% yield, of a fairly complex series of reactions [5] of KDN.

It was of interest to see what happened when the lactonization was not possible. We prepared the non-2-ulopyranoside **11** by lithium aluminium hydride reduction of the ester group in **7**. The unexpectedly low yield (41%) was probably due to the difficulty in extracting this highly polar compound from the aqueous phase and inorganic precipitate. This glycoside was further characterized as the tetraacetate **12**. Treatment with *tert*-butylchlorodimethylsilane gave the 1,4-bis(silyl) ether **13**. Acetylation of **13**, catalyzed with 4-dimethylaminopyridine gave the diacetate **14**. In the NMR spectrum, the signals of H-5 and H-7 were displaced by ca. 1.4 ppm. Thus, again, HO-5 and HO-7 had failed to react. Organotin-mediated benzylation was attempted in two ways, first as described above for **9** and dibutyltin oxide, and afterward with bis(tributyltin) oxide. In both cases, there was almost quantitative recovery of starting material. Likewise, almost no benzoylation occurred at room temperature, even with extended times of reaction or with the addition of dimethylaminopyridine. It is likely that one factor in the unreactivity of HO-5 is the steric protection by the bulky substituent on the proximate silicium atom. The lack of reactivity of HO-7 in the related ketals of *N*-acetylneuraminic acid has been already noticed by Zbiral and co-workers [6].

Thus, it appears that selective modifications at C-5 of KDN would be best achieved by de novo synthesis from a modified D-mannose precursor and, with this objective in mind, we prepared the 5-bromo-5-deoxy derivative of KDN from 2-bromo-2-deoxy-D-mannose (**15**). The feasibility of this approach has already been briefly reported [7]. The starting material, a free sugar, has already been prepared [8] from 1,5-anhydro-2-deoxy-*arabino*-hex-1-enitol (D-glucal) or its triacetate, but

always in several steps. We found that it could be prepared efficiently in a one-step procedure by treatment of D-glucal in aqueous solution at 0°C by *N*-bromophthalimide. This reagent is insoluble in water, and the reaction was heterogeneous. Despite that, the reaction was practically instantaneous, and the phthalimide by-product, also insoluble, could be easily removed by filtration. A quantitative yield of a 85:15 mixture of D-*manno* and D-*gluco* derivatives was obtained from the aqueous phase and, from the mixture, 2-bromo-2-deoxy-D-mannose (**15**) was obtained by crystallization in 60% yield from D-glucal. Working at higher temperature decreased the proportion of the D-*manno* isomer but the effect was not dramatic.

Condensation of the bromo sugar **15** with pyruvate in the presence of sialyl aldolase gave, in 70% yield, the crystalline 5-bromo-3,5-dideoxy-D-*glycero*-D-*galacto*-non-2-ulosonic acid (**16**).

3. Experimental

General methods.—Silica gel (Chromagel 60, 6–35 μm, SDS) columns were used for the chromatographic separations. Unless otherwise stated, the solvent for ^{1}H NMR spectroscopy was $CDCl_3$. Results are tabulated in ppm downfield from Me_4Si. Only skeletal protons are reported in Table 1.

3-Deoxy-D-glycero-D-galacto-*non-2-ulosonic acid-1,4-lactone diethyl dithioacetal* (**3**).—A solution of KDN **1** (ref [1]; 868 mg; 3.24 mmol) and EtSH (8 mL) in 11 N aq HCl (8 mL) was stirred for 2 days at 0°C. The acid was neutralized with $PbCO_3$, the solid was separated by filtration and washed with hot water. The filtered solution and the washings were evaporated to dryness, the residue was suspended in EtOH (5 mL) and the suspension was again filtered. Evaporation to dryness gave **3** (595 mg, 52%); mp 216–217°C (from water); $[\alpha]_D^{20}$ −1.3° (*c* 0.78, MeOH). Anal. Calcd for $C_{13}H_{24}O_7S_2$: C, 43.81; H, 6.79; O, 31.42; S, 17.99. Found: C, 44.10; H, 6.95; O, 31.31; S, 17.90.

5,6,7,8,9-Penta-O-*acetyl-3-deoxy*-D-glycero-D-galacto-*non-2-ulosonic acid 1,4-lactone diethyl dithioacetal* (**4**).—A solution of **1** (268 mg; 1 mmol) and EtSH (2.5 mL) in 11 N aq HCl (2.5 mL) was stirred for 2 days at 0°C, then neutralized with NH_3 and evaporated to dryness. The residue was dried by several co-evaporations with EtOH, and then pyridine (10 mL) and Ac_2O (5 mL) were added. The solution was kept for 16 h at room temperature, then poured into water and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), evaporated to dryness, and co-evaporated several times with toluene. Chromatography (3:1 hexane–EtOAc) allowed recovery of the pentaacetate **4** (426 mg, 75%); mp 91–92°C (from hexane); $[\alpha]_D^{20}$ −0.7° (*c* 1.51, CH_2Cl_2); ^{1}H NMR: δ 1.23, 1.26 (2 t, 6 H, 2 SCH_2CH_3), 2.06, 2.08, 2.09, 2.12, 2.14 (5 s, 15 H, 5Ac), 2.50–2.94 (m, 4 H, 2 SCH_2CH_3). Anal. Calcd for $C_{23}H_{34}O_{12}S_2$: C, 48.75; H, 6.05; O, 33.88; S, 11.32. Found: C, 48.49; H, 5.92; O, 34.02; S, 11.32.

Zemplén deacetylation of **4** (0.4 g) with 0.2 M NaOMe in MeOH, followed by the usual separation, gave a crystalline product (196 mg, 77%) identical in all respects with **3** as prepared above.

*5,6,7,8,9-Penta-*O*-acetyl-2,3-dideoxy-2-en-2-(3-acetylthiopropylthio)-*D*-glycero-*D*-galacto-non-2-ulosonic acid 1,4-lactone* (**5**).—A solution of KDN (536 mg, 2 mmol) in 1:1 HCl–EtOH (5.4 mL) was stirred for 16 h at room temperature in the presence of 1,3-propanedithiol (0.24 mL), then neutralized with aq NH_3 and evaporated to dryness. Pyridine (5 mL), Ac_2O (2.5 mL), and DMAP (10 mg) were added to the residue. After 16 h at room temperature, the mixture was poured into aq $NaHCO_3$ and extracted with CH_2Cl_2. Chromatography of the extract (2:1 hexane–EtOAc) separated first a mixture of at least two compounds which was not further examined (205 mg), and then **5** (219 mg, 18%); mp 123–124°C (EtOAc–hexane); $[\alpha]_D^{20}$ +6° (*c* 0.4, CH_2Cl_2). Anal. Calcd for $C_{24}H_{32}O_{13}S_2$: C, 48.64; H, 5.45; S, 10.80. Found: C, 48.91; H, 5.58; S, 10.77.

*Methyl (methyl 3-deoxy-8,9-*O*-isopropylidene-*D*-glycero-β-*D*-galacto-non-2-ulopyranosid)onate* (**7**).—Dowex 50 (H^+) resin (0.6 g) was added to a solution of **6** (ref [5]; 695 mg; 2.35 mmol) in acetone (20 mL) containing 2,2-dimethoxypropane (1.2 mL). After 30 min at room temperature, the resin was removed by filtration, and the solution evaporated to dryness. Chromatography of the residue (95:5 CH_2Cl_2–MeOH) separated the ketal **7** (543 mg, 69%); mp 135–136°C (from hexane–EtOAc); $[\alpha]_D^{20}$ −58° (*c* 1.24, MeOH); ^{1}H NMR: δ 1.30, 1.40 (2 s, 6 H, CMe_2), 3.23 (s, 3 H, OMe), 3.81 (s, 3 H, CO_2Me). Anal. Calcd for $C_{14}H_{24}O_9$: C, 49.98; H, 7.20; O, 42.83. Found: C, 49.82; H, 7.07; O, 43.10.

A solution of **7** (32 mg) in Ac_2O (1 mL) and pyridine (1 mL) was kept for 24 h at room temperature and then processed in the usual way to give in quantitative yield, as a syrup, a derivative considered to be the triacetate **8**. ^{1}H NMR: δ 1.32, 1.38 (2 s, 6 H, CMe_2), 2.00, 2.02, 2.12 (3 s, 9 H, 3 Ac), 3.30 (s, 3 H, OMe), 3.82 (s, 3 H, CO_2Me).

*Methyl [methyl 4-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-8,9-*O*-isopropylidene-*D*-glycero-β-*D*-galacto-non-2-ulopyranosid]onate* (**9**).—A solution of **7** (1.07 g, 3.2 mmol), *tert*-butylchlorodimethylsilane (670 mg, 4.46 mmol), and imidazole (608 mg, 8.96 mmol) in DMF (16 mL) was kept for 16 h at room temperature, poured into water, and extracted with ether. The organic phase was washed with water, dried, and evaporated to give a residue from which the silyl ether **9** was isolated by chromatography (2:1 hexane–EtOAc) as a syrup (1.31 g, 91%); $[\alpha]_D^{20}$ −25.5° (*c* 2.16, CH_2Cl_2); ^{1}H NMR: δ 0.10, 0.12 (2 s, 6 H, $SiMe_2$), 0.89 (s, 9 H, Me_3C), 1.31, 1.41 (2 s, 6 H, CMe_2), 3.24 (s, 3 H, OMe), 3.80 (s, 3 H, CO_2Me). Anal. Calcd for $C_{20}H_{38}O_9Si$: C, 53.31; H, 8.51. Found: C, 53.55; H, 8.79.

*Methyl 4-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-8,9-*O*-isopropylidene-*D*-glycero-β-*D*-galacto-non-2-ulopyranosidono-1,7-lactone* (**10**).—A solution of **9** (0.3 g; 0.67 mmol) and bis(tributyltin) oxide (0.19 mL, 0.55 equiv) in toluene (20 mL) was heated at reflux with a Dean–Stark condenser for 16 h, and then the volatiles were removed by evaporation. Chromatography of the residue (2:1 hexane–EtOAc) gave the lactone **10** (155 mg, 55%); mp 147–148°C (from ether–hexane); $[\alpha]_D^{20}$ +89° (*c* 0.5, CH_2Cl_2); ^{1}H NMR: δ 0.09, 0.10 (2 s, 6 H, $SiMe_2$), 0.89 (s, 9 H, Me_3C), 1.37, 1.41 (2 s, 6 H, CMe_2), 2.43 (d, 1 H, $J_{5,OH}$ 8Hz, OH), 3.38 (s, 3 H, OMe). Anal. Calcd for $C_{19}H_{34}O_8Si$: C, 54.52; H, 8.19. Found: C, 54.68; H, 8.28.

*Methyl 1,4,5,7-tetra-O-acetyl-3-deoxy-8,9-O-isopropylidene-*D-glycero-*β*-D-galacto-*non-2-ulopyranoside* (**12**).—A mixture of **7** (1.00 g, 3 mmol) and $LiAlH_4$ (456 mg, 12 mmol) in anhyd THF (20 mL) was stirred for 2 h at room temperature. Then water (0.46 mL), 15% aq NaOH (0.46 mL), and water (1.38 mL) were successively added. Filtration of the solution and evaporation of volatiles gave the glycoside **11** as an oil (375 mg, 41%); ^{1}H NMR (CD_3OD): δ 1.18, 1.27 (2 s, 6 H, CMe_2), 3.13 (s, 3 H, OMe). This was further characterized by conversion of a portion (20 mg) to the tetraacetate by treatment with Ac_2O (1 mL), pyridine (1 mL), and 4-dimethylaminopyridine (5 mg) for 24 h at room temperature. Evaporation of volatiles, followed by chromatography of the residue (4:1 hexane–EtOAc) gave the tetraacetate **12** in quantitative yield as an oil; $[\alpha]_D^{20}$ −44° (*c* 0.8 CH_2Cl_2); ^{1}H NMR: δ 1.32, 1.40 (2 s, 6 H, CMe_2), 2.00, 2.02, 2.10, 2.11 (4 s, 12 H, 4 Ac), 3.30 (s, 3 H, OMe). Anal. Calcd for $C_{21}H_{32}O_{12}$: C, 52.92; H, 6.77; O, 40.31. Found: C, 52.94; H, 6.81; O, 40.39.

*Methyl 1,4-di-*O-(tert-*butyldimethylsilyl)-3-deoxy-8,9-O-isopropylidene-*D-glycero-*β*-D-galacto-*non-2-ulopyranoside* (**13**).—A solution of **11** (375 mg, 1.22mmol), *tert*-butylchlorodimethylsilane (402 mg, 2.68 mmol), and imidazole (364 mg, 5.35 mmol) in DMF (6 mL) was kept for 16 h at room temperature, poured into water, and extracted with ether. The extract was washed with water, dried, and the volatiles were evaporated. Chromatography of the residue (3:1 hexane–EtOAc) gave the bis(silyl) ether **13** as a syrup (438 mg, 67%); ^{1}H NMR: δ 0.07, 0.10, 0.12 (3 s, 2 $SiMe_2$), 0.90 (s, 18 H, 2 Me_3C), 1.32, 1.41 (2 s, 6 H, CMe_2), 2.24 (br, OH), 2.51 (br, OH), 3.21 (s, 3 H, OMe). Anal. Calcd for $C_{25}H_{52}O_8Si_2$: C, 55.94; H, 9.77. Found: C, 56.12; H, 9.55.

Treatment of a portion (25 mg) of **13** with pyridine and Ac_2O in the presence of 4-dimethylaminopyridine gave, in quantitative yield, the diacetate **14** as an oil; ^{1}H NMR: δ 0.09 (2 $SiMe_2$), 0.85, 0.91 (2 s, 2 Me_3C), 1.33, 1.38 (2 s, CMe_2), 2.30, 2.90 (2 s, 2 Ac), 3.24 (OMe). Anal. Calcd for $C_{29}H_{56}O_{10}Si_2$: C, 56.10; H, 9.10. Found: C, 56.40; H, 9.01.

*2-Bromo-2-deoxy-*D-*mannose* (**15**).—A solution of 3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol (2.72 g, 10 mmol) in MeOH (10 mL) containing a trace of NaOMe was kept for 16 h at room temperature, then neutralized with Dowex 50 (H^+) ion-exchange resin, and evaporated to dryness. The residue was dissolved in water (10 mL) and cooled to 0°C. *N*-Bromophthalimide was added (2.49 g, 11 mmol) and the suspension was kept for 5 min at 0°C. The solution was separated from the solids by filtration, and extracted with ether. The aqueous phase was evaporated to dryness, the residue was dried for 7 days over P_2O_5, and dissolved in warm EtOH (10 mL). Crystallization occurred after a few days to give **15** (880 mg, 60%); mp 125°C (lit. [9] 128°C); ^{1}H NMR (D_2O): δ 5.47 (0.46 H, d, $J_{1,2}$ 1.5 Hz, H-1α), 4.92 (0.54 H, d, $J_{1,2}$ 1 Hz, H-1β), 4.53 (0.54 H, d, $J_{2,3}$ 4 Hz, H-2β), 4.41 (0.46 H, d, $J_{2,3}$ 4 Hz, H-2α), 3.4–4.0 (m, 5 H, H-3 to H-6′); ^{13}C NMR (62.9 MHz, CD_3OD): δ 95.85 (C-1α), 93.46 (C-1β), 79.02 (C-5β), 74.78 (C-5α), 73.46 (C-3β), 70.07 (C-3α), 69.28 (C-4α), 68.78 (C-4β), 62.84 (C-6), 62.38 (C-2β), 58.08 (C-2α).

5-Bromo-3,5-dideoxy-D-glycero-D-galacto-*non-2-ulosonic acid* (**16**).—Bromomannose **15** (290 mg, 2 mmol), sodium pyruvate (1.1 g, 10 mmol), dithiothreitol (1 mg), and NaN_3 (1 mg) were dissolved in 0.1 M phosphate buffer (10 mL, pH 7); sialylaldolase (10 units), immobilized on agarose gel, was added, and the suspension was stirred at 37°C for 5 days. The suspension was filtered and the aqueous solution chromatographed on a column of Dowex 1 (formate) resin. The column was washed with water and then elution with M aq formic acid to give the acid **16** (460 mg, 1.4 mmol, 70%) as a gum, which crystallized from EtOAc; mp 156–157°C (dec); ^{13}C NMR (62.9 MHz, CD_3OD): δ 173.31 (C-1), 96.54 (C-2), 73.51, 72.30, 71.06, 70.50 (C-4, C-6, C-7, and C-8), 64.84 (C-9), 56.26 (C-5), 42.36 (C-3). Anal. Calcd for $C_9H_{15}BrO_8$: C, 32.73; H, 4.58; O, 38.78; Br, 23.92. Found: C, 32.67; H, 4.58; O, 38.95; Br, 23.84.

Acknowledgment

The authors are indebted to Professor A. Lubineau, director of the URA 462 (CNRS), for his help in the pursuit of this work.

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