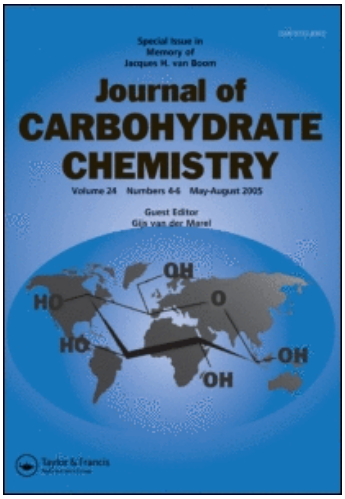

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Synthetic Studies on Sialoglycoconjugates 49: Novel Disaccharides and Lactams Composed of Sialic Acid and 1-Deoxynojirimycin-Potential for Biomedical Application

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COMMUNICATION

SYNTHETIC STUDIES ON SIALOGLYCOCONJUGATES 49: NOVEL DISACCHARIDES AND LACTAMS COMPOSED OF SIALIC ACID AND 1-DEOXYNOJIRIMYCIN—POTENTIAL FOR BIOMEDICAL APPLICATION

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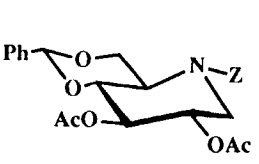
Sialic acid-containing glycoconjugates participate in a variety of biological functions on cell surfaces, not only serving as receptors for hormones, viruses and bacteria but also as mediators in cell growth, differentiation, adhesion, oncogenesis and so on. For example, influenza virus[1,2] and *tripanosoma cruzi*[3,4] recognize sialic acid in the time of infection to animal cells. Recently, the sialyl-Le^x (sLe^x) and sialyl-Le^a (sLe^a) carbohydrate epitopes have been highlighted as the ligands for selectins, a family of cell adhesion molecules involved in leukocyte traffic[5,6] and tumor metastasis.[7] 1-Deoxynojirimycin (DNJ) and related compounds are well known[8] as the potent inhibitors of α-glycosidases and glycoprotein-processing enzymes. Some of the *N*-substituted DNJ derivatives have been noted as antidiabetic and anti-HIV agents.

We have systematically synthesized a variety of gangliosides including their analogs[9] and DNJ-containing oligosaccharides[10] not only to elucidate their biological functions but also to evaluate their biomedical usefulness. New inhibitors of influenza virus sialidase have been found[11] among the ganglioside analogs containing thioglycosidically bound sialic acid. The DNJ-containing sLe^x and sLe^a epitopes[10a,10c] recognized by selectins may become very useful for biomedical application. We report here the synthesis of novel disaccharides and their lactams composed of sialic acid and



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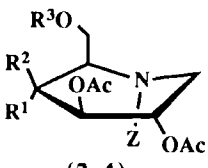

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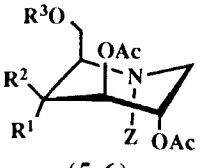
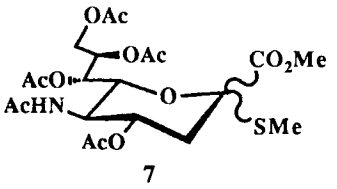


(5,6)

	R^1	R^2	R^3
2	OH	H	H
3	OH	H	TBDPS
4	OTf	H	TBDPS
5	H	OAc	TBDPS
6	H	OAc	H



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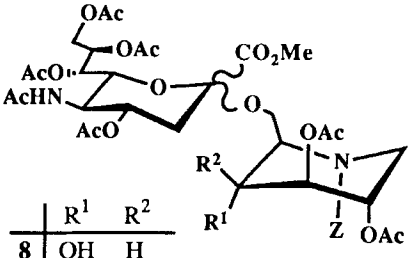
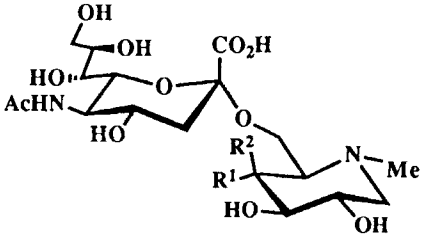
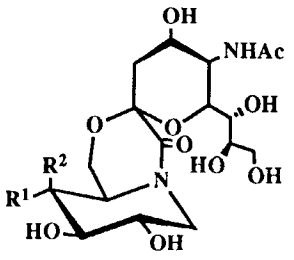


	R^1	R^2
8	OH	H
9	H	OAc



	R^1	R^2
10	OH	H
11	H	OH



	R^1	R^2
12	OH	H
13	H	OH

Z=benzyloxycarbonyl, TBDPS=*tert*-butyldiphenylsilyl, Tf=trifluoromethanesulfonyl

DNJ structurally related to ganglioside GM_4 which have significant immunosuppressive activity.[12]

Compound **1**, $[\alpha]_D$ -19° (CH_2Cl_2), ^1H NMR ($CDCl_3$) δ 3.32 (dd, Jgem = 14, $J_{1ax,2}$ = 8 Hz, H-1ax), 3.47 (ddd, J = 10, 10, and 4.6 Hz, H-5), 3.88 (~t, $J_{3,4} = J_{4,5}$ = 10 Hz, H-4), 4.07 (dd, $J_{1eq,2}$ = 4 Hz, H-1eq), 4.93 (m, $J_{2,3}$ = 6.6 Hz, H-2) and 5.16 (dd, H-

3), prepared by acetylation of 4,6-*O*-benzylidene-*N*-benzyloxycarbonyl-1,5-dideoxy-1,5-imino-D-glucitol,[10b] was treated with 80% acetic acid at 45 °C to give 2,3-di-*O*-acetyl-*N*-benzyloxycarbonyl-1,5-dideoxy-1,5-imino-D-glucitol (**2**), $[\alpha]_D$ -1.7° (CH_2Cl_2), quantitatively. In the ^1H NMR spectrum of **2**, H-2 and H-3 appeared at δ 4.86 (~q, $J_{1ax,2} = J_{1eq,2} = 4$, $J_{2,3} = 5.7$ Hz) and 5.03 (dd, $J_{3,4} = 7.3$ Hz), respectively, showing a significant conformational change involving the flexible skew-boat type conformations. 6-OH of **2** was selectively protected by the *tert*-butyldiphenylsilyl (TBDPS) group to afford a 93% yield of **3**: $[\alpha]_D$ +2.6° (CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 3.25 (dd, Jgem = 15.6, $J_{1ax,2} = 3$ Hz, H-1ax), 4.04 (m, $J_{3,4} = 7$, $J_{4,5} = 5.5$ Hz, H-4), 4.18 (~d, $J_{1eq,2} = 2$ Hz, H-1eq), 4.89 (broad s, H-2) and 4.98 (dd, $J_{2,3} = 4$ Hz, H-3). 4-*O*-Trifluoromethanesulfonylation of **3**, and successive treatment of **4** with cesium acetate and 1,4,7,10,13,16-hexaoxacyclooctadecane (18-Crown-6) at room temperature gave a 67% yield (two steps) of **5**: $[\alpha]_D$ +0.1° (CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.83, 1.90, 1.91 (3s, CH_3CO), 2.96 (dd, Jgem = 15.6, $J_{1ax,2} = 2$ Hz, H-1ax), 5.04 (~t, $J_{2,3} = J_{3,4} = 3$~4 Hz, H-3) and 5.34 (dd, $J_{3,4} = 3$, $J_{4,5} = 6$ Hz, H-4). The TBDPS group of **5** was removed by treatment with BF_3-etherate in dichloromethane to give **6** (81%): $[\alpha]_D$ +20° (CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 4.89 (narrow m, J = 2~4 Hz, H-2), 5.15 (~t, $J_{2,3} = J_{3,4} =$ 3~4 Hz, H-3) and 5.39 (dd, $J_{3,4} = 3$, $J_{4,5} = 6$ Hz, H-4). The preferred conformation of compounds **5** and **6** seems to be near $^1C_4$ rather than skew-boat form.

The glycosylation[13] of **2** with methyl (methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-2-thio-D-*glycero*-D-*galacto*-2-nonulopyranosid)onate (**7**) was performed in the presence of dimethyl(methylthio)sulfonium triflate (DMTST) in acetonitrile to give **8** in an 85% yield (α:β = 3:1). The desired α-glycoside (**8α**) had $[\alpha]_D$ -16° (CH_2Cl_2) and ^1H NMR ($CDCl_3$) δ 3.14 (d, $J_{4,OH} = 4.9$ Hz, 4-OH), 3.42 (dd, Jgem = 15.6, $J_{1ax,2}$ = 3.5 Hz, H-1ax), 4.18 (~d, $J_{1eq,2} = 2$ Hz, H-1eq), 4.92 (narrow m, J = 2~4 Hz, H-2), 5.03 (narrow m, H-3) for the DNJ part; δ 2.56 (dd, Jgem = 13, $J_{3eq,4} = 5$ Hz, H-3eq) and 3.73 (s, CO_2Me) for the sialic acid part. H-3eq of sialic acid in the β-glycoside (**8β**) appeared at δ 2.35 (dd, Jgem = 13, $J_{3eq,4} = 5$ Hz). Coupling[13b] of **6** with **7** in the presence of *N*-iodosuccinimide and trifluoromethanesulfonic acid in acetonitrile afforded an 80% yield of **9** (α:β = 7:3). The α-glycoside (**9α**) had $[\alpha]_D$ +24° (CH_2Cl_2) and ^1H NMR ($CDCl_3$) δ 3.48 (~d, Jgem = 15.6 Hz, H-1ax), 4.68 (m, H-5), 4.90 (narrow m, H-2), 5.16 (~t, $J_{2,3} = J_{3,4} = 3$~4 Hz, H-3) for the DNJ part; δ 2.47 (broad dd, H-3eq), and 3.74 (broad s, CO_2Me) for the sialic acid part. For the β-glycoside (**9β**), H-1ax of DNJ and H-3eq of sialic acid appeared at δ 3.39 (~d, Jgem = 14.5 Hz) and 2.35 (dd, Jgem = 13, $J_{3eq,4} = 5$ Hz), respectively.

Compounds **8α** and **9α** were each hydrogenolyzed for 30 min over 10% palladium-carbon catalyst in methanol, and the products were successively treated with

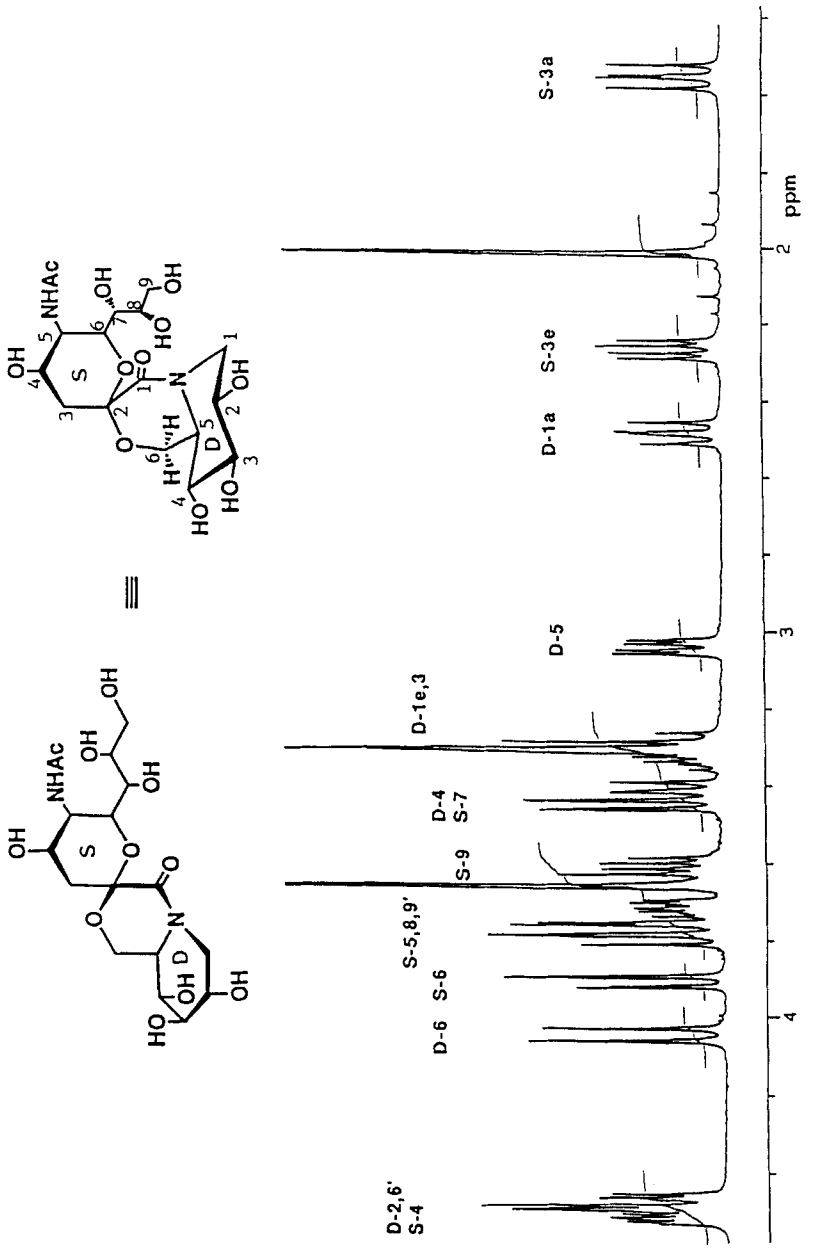


Fig. 1. ^{1}H NMR Spectrum of compound 12 in CD_3OD at 400 MHz.

sodium methoxide and then 0.2 M aq KOH in methanol. The fully deprotected products were chromatographed on a column of Sephadex LH-20 to give novel disaccharides (**10** and **11**; 10~20%) and lactams (**12** and **13**; 80~90%). The ion-spray mass spectrum (positive ion mode) of **12**, $[\alpha]_D$ +38° (MeOH), showed a significant base peak at m/z 437.2 (100%) corresponding to $(M+H)^+$ together with several smaller peaks at m/z 459.0 (33%) $(M+Na)^+$ and 419.2 (23%) $(M-H_2O+H)^+$. The average mass was determined as 436.42 ($C_{17}H_{28}N_2O_{11}$). Significant signals in the ^1H NMR spectrum of **12** (Fig.1) were at δ 1.56 (dd, Jgem = 13.5, $J_{3ax,4}$ = 10.7 Hz, H-3ax) and 2.27 (dd, $J_{3eq,4}$ = 5.5 Hz, H-3eq) for the sialic acid part, and δ 2.48 (dd, Jgem = 13, $J_{1ax,2}$ = 10.5 Hz, H-1ax) for the DNJ part. The lactam ring structure was determined based on the *gauche-gauche* conformation of the C-6 protons of DNJ ($J_{5,6}$ = ~0 and $J_{5,6'}$ = 3.9 Hz) confirmed by 2D NMR technique. Compound **13**, $[\alpha]_D$ +36° (MeOH) showed similar spectral paterns to those of **12**. The minor products **10**, $[\alpha]_D$ +10° (2:3 H_2O - EtOH) and **11**, $[\alpha]_D$ +11° (2:3 H_2O-EtOH) were also characterized from ion-spray mass and ^1H NMR spectra. In the mass spectrum of **10** (positive ion mode), a significant base peak appears at m/z 469.2 that corresponds to $(M+H)^+$ showing the average molecular weight is 468.46 ($C_{18}H_{32}N_2O_{12}$). The ^1H NMR (CD_3OD) spectrum clearly showed the presence of *N*-Me at δ 2.85 ppm. These disaccharides may be formed in the hydrogenolytic process of the *N*-benzyloxycarbonyl (Z) group as previously described.[10c]

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