Carbohydrate Research, 184 (1988) c1–c4
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

Preliminary communication

A facile regio- and stereo-selective synthesis of α-glycosides of *N*-acetylneuraminic acid*

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(Received June 15th, 1988; accepted for publication, July 13th, 1988)

Sialic acids[1,2] are well known as constituents of glycoproteins and glycolipids of cell membranes, and they play a role in biological recognition. It is also known that naturally occurring sialo compounds contain sialic acids in α-glycosidic linkage, except for CMP-*N*-acetylneuraminic acid. Therefore, a facile regio- and α-selective glycoside synthesis of *N*-acetylneuraminic acid (Neu5Ac) is critically important, in order to investigate the structure–function relationships of such sialoglycoconjugates as glycoproteins and glycolipids.

Glycosidation of methyl (5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-β-D-*galacto*-2-nonulopyranosyl chloride)onate[3] as the glycosyl donor with sugar derivatives usually gives a mixture of α- and β-glycosides. When reacting with secondary hydroxyl groups of sugar derivatives, this donor affords the expected α-glycosides in very low yields.

Recently, new efforts[4,5] have been made at obtaining mainly α-glycosides, using 3-substituted Neu5Ac derivatives as glycosyl donors. However, the stereoselectivity and yields of the glycosidation reactions, especially of those involving secondary alcohols, were still unsatisfactory.

Previously[6], we demonstrated that the methyl α- and β-2-thioglycosides[6] of Neu5Ac are useful glycosyl donors to afford glycosides of Neu5Ac by use of dimethyl(methylthio)sulfonium triflate[7] (DMTST). We report here a facile α-stereoselective synthesis of glycosides of Neu5Ac, using methyl (methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-2-thio-D-*glycero*-α-D-*galacto*-2-nonulopyranosid)onate[6] (**10**) as the glycosyl donor, and the suitably protected D-galactosides (**2** and **5**) and lactoside **9** as the glycosyl acceptors, in the presence of DMTST in acetonitrile as the solvent.

Selective benzoylation of 2-(trimethylsilyl)ethyl β-D-galactopyranoside[8] (**1**) with benzoyl chloride (1.2 equiv.) in pyridine–dichloromethane at −50° gave the

*Synthetic Studies on Sialoglycoconjugates, Part 1.
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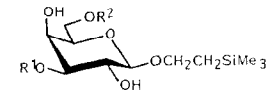
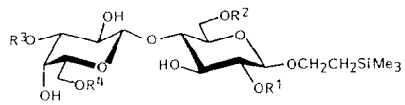
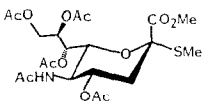


1 $R^1 = R^2 = H$
2 $R^1 = Bz$, $R^2 = H$
3 $R^1 = Bn$, $R^2 = H$
4 $R^1 = Bn$, $R^2 = Bz$
5 $R^1 = H$, $R^2 = Bz$

Bn = benzyl
Bz = benzoyl



6 $R^1 = R^2 = R^3 = R^4 = H$
7 $R^1 = R^2 = R^4 = H$ $R^3 = Bn$
8 $R^1 = R^2 = R^4 = Bz$ $R^3 = Bn$
9 $R^1 = R^2 = R^4 = Bz$ $R^3 = H$



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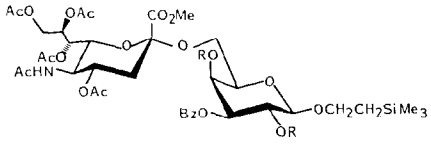
3-benzoate **2** (67%, $[\alpha]_D$ +31°), which was used as the acceptor for the synthesis of the α-Neu5Ac-(2→6)-D-Gal derivative; significant signals in the n.m.r. spectrum were a one-proton doublet of doublets at δ 5.04 ($J_{2,3}$ 10.26, $J_{3,4}$ 3.21 Hz, H-3) and a five-proton multiplet at δ 7.38–8.08 (one Ph). On the other hand, selective benzylation[9] at O-3 in compound **1** and at O-3′ in 2-(trimethylsilyl)ethyl β-D-lactoside[8] (**6**), using dibutyltin oxide, tetrabutylammonium bromide, and benzyl bromide in benzene, afforded the corresponding 3-*O*-benzyl-D-galactose derivative **3** (77%, $[\alpha]_D$ +5.6°), and 3′-*O*-benzyllactose derivative **7** (75%, m.p. 167°, $[\alpha]_D$ −0.14°) respectively, which, on selective benzoylation according to the method described for **2**, gave the 6-benzoate **4** (71%, $[\alpha]_D$ −1.6°) and 2,6,6′-tri-*O*-benzoyllactose derivative **8** (67%, $[\alpha]_D$ +14.0°). Removal of the benzyl groups in compounds **4** and **8** by hydrogen-transfer reduction with Pd–C catalyst in methanol, in the presence of formic acid as hydrogen donor, gave the desired glycosyl acceptors **5** (67%, $[\alpha]_D$ −3.7°) and **9** (70%, $[\alpha]_D$ +11.0°), respectively. The n.m.r. spectrum of **9** exhibited multiplets at δ 7.40–8.17, integrating for 15 protons, which demonstrated the presence of three benzoyl groups; H-2 appeared at δ 5.33 ($J_{1,2}$ 8.06, $J_{2,3}$ 9.61 Hz) as a doublet of doublets, H-1 at δ 4.74 ($J_{1,2}$ 8.06 Hz), and H-1′ at δ 4.50 ($J_{1',2'}$ 7.88 Hz), indicating the structure assigned.

The glycosidation of **2** with the methyl α-2-thioglycoside **10** (2.0 equiv., relative to the acceptor) of Neu5Ac in acetonitrile for 15 h at −15° in the presence of DMTST (4.0 equiv., relative to the donor), gave the expected α-glycoside of Neu5Ac, 2-(trimethylsilyl)ethyl *O*-(methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonate)-(2→6)-3-*O*-benzoyl-β-D-galactopyranoside (**11**; $[\alpha]_D$ −6.4°) in 68% yield (based on the weight of acceptor employed), together with the 2,3-dehydro derivative **13** of Neu5Ac and some unreacted acceptor; no β-glycoside of Neu5Ac was isolated. The observed chemical shifts and coupling constants (δ 2.56, $J_{3a,3e}$ 12.73, $J_{3e,4}$ 4.68 Hz, δ 4.76, and δ 5.27, $J_{7,8}$ 7.51 Hz) for H-3*e*, H-4, and H-7 in the Neu5Ac moiety are characteristic for α-glycoside linkages[4–6,10–13]. Other ^{1}H-n.m.r. data (see Table I) are consistent with structure **11**.



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12 R = Ac

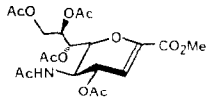

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TABLE I

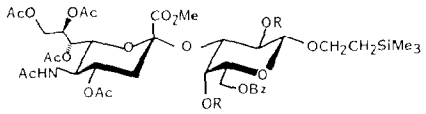
SELECTED ^{1}H-N.M.R. DATA[a] FOR α-GLYCOSIDES OF *N*-ACETYLNEURAMINIC ACID

Compound	*Chemical shifts (δ)[b] (coupling constants, in Hz)*		
	Neu5Ac unit	D-*Galactose unit*	D-*Glucose unit*
11	H-3*e* 2.56 ($J_{3a,3e}$ 12.73) H-4 4.76 ($J_{3e,4}$ 4.68) H-7 5.27 ($J_{7,8}$ 7.51)	H-3 4.99 ($J_{2,3}$ 7.88) H-4 4.15 ($J_{3,4}$ 3.30)	
12	H-3*e* 2.50 ($J_{3a,3e}$ 12.82) H-4 4.83 ($J_{3e,4}$ 4.58) H-7 5.27 ($J_{7,8}$ 10.01)	H-2 5.35 ($J_{1,2}$ 7.88) H-3 5.22 ($J_{2,3}$ 10.44) H-4 5.62 ($J_{3,4}$ 2.39)	
14	H-3*e* 2.60 ($J_{3a,3e}$ 12.6) H-4 4.90 ($J_{3e,4}$ 4.71) H-7 5.37 ($J_{7,8}$ 8–9)		
16	H-3*e* 2.81 ($J_{3a,3e}$ 12.73) H-4 4.97 ($J_{3e,4}$ 4.49) H-7 5.38 ($J_{7,8}$ 8.24)		H-2 5.36 ($J_{1,2}$ 8.24) ($J_{2,3}$ 9.52)
17	H-3*e* 2.68 ($J_{3a,3e}$ 12.64) H-4 4.94 ($J_{3e,4}$ 4.76) H-7 5.46 ($J_{7,8}$ 8.80)	H-2 5.13 ($J_{1,2}$ 7.88) H-3 4.74 ($J_{2,3}$ 10.17) H-4 5.13 ($J_{3,4}$ 3.30)	H-2 5.32 ($J_{1,2}$ 7.88) H-3 5.59 ($J_{2,3}$ 9.71)

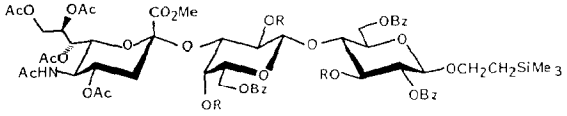
[a]The spectra were recorded with a Jeol JNM-GX270 (270 MHz) spectrometer for solutions in $CDCl_3$, and the assignments were confirmed by use of decoupling techniques. [b]From Me_4Si.

In the same way, when treated with the glycosyl acceptors **5** and **9**, compound **10** yielded the corresponding α-glycosides (**14**, $[\alpha]_D$ −6.0°; and **16**, $[\alpha]_D$ +10.9°) at O-3 or O-3′ in the acceptor moiety, in 43 and 40% yields, respectively; again, no β-glycoside was isolated. Acetylation of the glycosides **11, 14,** and **16** thus obtained gave the acetates (**12**, $[\alpha]_D$ −7.2°; **15**, $[\alpha]_D$ −24.5°; and **17**, $[\alpha]_D$ +5.74°) in quantitative yields, respectively. The structures of the glycosides were determined from the ^{1}H-n.m.r.-spectral data (see Table I), i.r. spectral data, and elemental analysis. Specific rotations were determined with a Union MP-201 polarimeter at 25° for solutions in chloroform.

In conclusion, regio- and α-stereoselective glycosidation of Neu5Ac was achieved by using the methyl α-2-thioglycoside (**10**) of Neu5Ac as the glycosyl



14 R = H
15 R = Ac



16 R = H
17 R = Ac

donor and suitably protected acceptors, with DMTST in acetonitrile under kinetically controlled conditions.

This procedure might be useful for the synthesis of a variety of sialoglycoconjugates. The α-glycosides described herein could be used as intermediates suitable for ganglioside synthesis, and they are also important as building units for glycoconjugate syntheses.

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