Carbohydrate Research, 187 (1989) 35–42
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

STEREOSELECTIVE SYNTHESIS OF 2-THIOGLYCOSIDES OF *N*-ACETYLNEURAMINIC ACID

ALBERTO MARRA AND PIERRE SINAŸ*
Ecole Normale Supérieure, Laboratoire de Chimie, UA 1110, 24, Rue Lhomond, 75231 Paris 05 (France)
(Received August 16th, 1988; accepted for publication, October 7th, 1988)

ABSTRACT

Treatment of methyl 5-acetamido-2,4,7,8,9-penta-*O*-acetyl-3,5-dideoxy-β-D-*glycero*-D-*galacto*-2-nonulopyranosonate (**1**) severally with thiophenol, phenylmethanethiol, and ethanethiol in the presence of boron trifluoride etherate gave the corresponding 2-thio-β-glycosides **3–5**. Treatment of methyl (5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-β-D-*glycero*-D-*galacto*-2-nonulopyranosyl chloride)onate (**2**) severally with thiophenol in the presence of *N,N*-di-isopropylethylamine, *O*-ethyl *S*-potassium dithiocarbonate, and *O*-ethyl *S*-potassium thiocarbonate gave the corresponding 2-thio-α-glycosides **7, 10,** and **11**, of which **10** was converted into the ethyl 2-thio-α-glycoside **9** on heating with *N,N*-dimethylformamide–sodium iodide. The phenyl 2-thioglycosides **3** and **7** were converted into the corresponding sulfones.

INTRODUCTION

The condensation[1] of phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside with 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose in the presence of mercury(II) sulfate, to give a satisfactory yield of an α-linked disaccharide derivative, was the first example of the practical use of a thioglycoside as glycosyl donor in the synthesis of an oligosaccharide. The potential of alkyl or aryl 1-thioglycosides as glycosylating agents in the synthesis of oligosaccharides has been increased considerably by the development[2] of efficient methods for the activation of 1-thioglycosides.

As part of a programme on the synthesis of *N*-acetylneuraminic acid-containing oligosaccharides[3,4] and in order to evaluate the possible extension of the thioglycoside methodology, the stereoselective synthesis of a series of 2-thio-α- and -β-glycosides of *N*-acetylneuraminic acid has been investigated. Phenyl 1-thio-α- and -β-glycosides and methyl 1-thio-α-glycosides have been used as glycosyl donors[5–7].

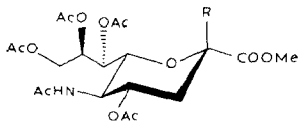
*Author for correspondence.

0008-6215/89/$ 03.50

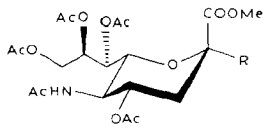
RESULTS AND DISCUSSION

Although Baggett and Marsden[8] showed that acetylation of the methyl ester of *N*-acetylneuraminic acid with acetic anhydride–perchloric acid[9] (Kuhn procedure) or with acetic anhydride–pyridine gave mainly crystalline methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-β-D-*glycero*-D-*galacto*-2-nonulopyranosonate, **1** continues to be prepared by acetylation of the methyl ester of *N*-acetylneuraminic acid[6,10]. The method of choice appears to be the acetylation[11,12] (acetic anhydride–pyridine) of *N*-acetylneuraminic acid followed by esterification with diazomethane[12,13]. When this procedure was used without purification of the intermediate acetylated acid, 94% of pure **1** was obtained.

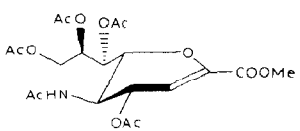
Treatment of **1** with thiophenol in the presence of boron trifluoride etherate gave methyl (phenyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-2-thio-β-D-*glycero*-D-*galacto*-2-nonulopyranosid)onate (**3**, 81%) together with 7% of the α-anomer **7** (isolated by flash chromatography[14] on silica gel). Compound **3** has been described by Kirchner *et al.*[6], but the physical properties reported {m.p. 84–87°, $[\alpha]_D^{20}$ −99.6° (chloroform)} are at variance with our data {m.p. 181–182°, $[\alpha]_D$ −132° (chloroform)}. Similarly, treatment of **1** with either phenylmethanethiol or ethanethiol gave the β-anomer **4** (84%) or **5** (72%) together with α-anomers **8** (4%) and **9** (3%), respectively.



1 R = OAc
2 R = Cl
3 R = SPh
4 R = SCH_2Ph
5 R = SEt
6 R = SO_2Ph



7 R = SPh
8 R = SCH_2Ph
9 R = SEt
10 R = S—C(=S)—OEt
11 R = S—C(=O)—OEt
12 R = SO_2Ph



13

The structures of the above acetylated 2-thioglycosides were indicated by their ^{1}H-n.m.r. spectra (C_6D_6). Thus, the signal of H-4 of **7** is at higher field (4.81 p.p.m.) than for the corresponding β-glycoside **3** (5.35 p.p.m.). Furthermore, the value of $J_{7,8}$ for the β-glycoside **3** is much smaller (2.1 Hz) than for the α-anomer **7** (7.0 Hz)[15]. These differences apply to all the derivatives described subsequently (see Table I) and will not be discussed further.

No reaction occurred when **1** was treated with trimethyl(methylthio)silane[16] in the presence of boron trifluoride etherate. Thus, the treatment of **1** with various thiols is a convenient and stereoselective approach to 2-thio-β-glycosides of *N*-acetylneuraminic acid.

TABLE I

SELECTED CHEMICAL SHIFTS (δ, P.P.M.) AND J VALUES (Hz)

	3	**4**	**5**	**6**	
$\delta_{H\text{-}4}$	5.35[a]	5.22[a]	5.26[a]	5.79[a]	5.66[b]
$J_{7,8}$	2.1[a]	2.4[a]	2.6[a]	n.d.[c]	4.6[b]

	7	**8**	**9**	**10**	**11**	**12**	
$\delta_{H\text{-}4}$	4.81[a]	4.79[a]	4.81[a]	4.81[a]	4.86[a]	4.85[a]	4.90[d]
$J_{7,8}$	7.0[a]	8.3[a]	8.2[a]	6.4[a]	6.6[a]	n.d.[c]	8.2[d]

[a]In C_6D_6. [b]In $CDCl_3$. [c]Not determined in C_6D_6. [d]In $(CD_3)_2CO$.

Attention was then turned to the stereoselective synthesis of 2-thio-α-glycosides. In addition to being potential glycosyl donors, these compounds are of biological interest, either as competitive inhibitors of neuraminidase[17] or as photoaffinity probes of sialidases and sialic acid-binding proteins[18], presumably because the thio-α-glycosyl linkage is resistant to enzyme degradation.

Acetylated 2-thio-α-glycosides of the methyl ester of *N*-acetylneuraminic acid have been prepared mainly by *S*-alkylation of methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-2-thio-α-D-*glycero*-D-*galacto*-2-nonulopyranosonate. Privalova and Khorlin[19] used the thiouronium procedure which we and others[20] found to be unsatisfactory. Problems were experienced also in attempting selective *S*-deacetylation[7,21] of methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-2-*S*-acetyl-3,5-dideoxy-2-thio-α-D-*glycero*-D-*galacto*-2-nonulopyranosonate.

The penta-acetate **1** was converted into the glycosyl chloride **2** (HCl–acetyl chloride) which was used without purification. Treatment of **2** with thiophenol in dichloromethane in the presence of *N,N*-di-isopropylethylamine readily gave methyl (phenyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-2-thio-α-D-*glycero*-D-*galacto*-2-nonulopyranosid)onate (**7**, 68% from **1**). Compound **7** has been obtained (60%) from **2** by Kirchner *et al.*[6], but the physical properties reported {m.p. 97–102°, $[\alpha]_D^{20}$ +10.1° (chloroform)} are at variance with our data {m.p. 139–140°, $[\alpha]_D$ +21° (chloroform)}. Ethanethiol did not react with **2** under these conditions.

Reaction of **2** with *O*-ethyl *S*-potassium dithiocarbonate in ethanol gave **10** (71% from **1**), which, on heating at 110° in *N,N*-dimethylformamide containing sodium iodide, was transformed with retention of configuration into methyl (ethyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-2-thio-α-D-*glycero*-D-*galacto*-2-nonulopyranosid)onate (**9**, 57%). Some glycal **13** was also formed in this reaction. The use of acetone[22] instead of *N,N*-dimethylformamide resulted in incomplete reaction.

Likewise, the thiocarbonate **11** was prepared by reaction of **2** with *O*-ethyl *S*-potassium thiocarbonate[23] (Bender's salt). In each of these reactions with **2**, some unsaturated derivative **13** was formed and removed by flash chromatography.

S-Methyl *O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl) dithiocarbonate has been used as glycosyl donor[24], but the chemical properties of *O*-alkyl *S*-glycosyl dithiocarbonates and *O*-alkyl *S*-glycosyl thiocarbonates remain to be evaluated.

Glycosyl phenyl sulfones have recently been used as glycosyl donors[25]. The 2-thioglycosides **3** and **7** were converted in excellent yields into the sulfones **6** and **12**, respectively, using ruthenium trichloride hydrate and sodium metaperiodate in the biphasic system carbon tetrachloride–acetonitrile–water[26].

EXPERIMENTAL

General methods. — Melting points were determined with a Büchi Model 510 capillary apparatus and are uncorrected. Optical rotations were measured at 20 ±2° with a Perkin–Elmer Model 241 polarimeter. C.i. (ammonia) mass spectra were obtained with a Nermag R10-10 spectrometer. Elemental analyses were performed at University Pierre et Marie Curie (Paris VI). ^{1}H-N.m.r. spectra were recorded for solutions in C_6D_6 (internal Me_4Si) with a Bruker AM-400 spectrometer. ^{13}C-N.m.r. spectra were recorded for solutions in $CDCl_3$, adopting δ 77.0 for the central line of $CDCl_3$. Assignments were aided by the J-MOD technique[27,28]. Reactions were monitored by t.l.c. on Silica Gel 60 F_{254} (Merck), using 6:1 toluene–methanol and/or 20:1 chloroform–methanol and detection by charring with sulphuric acid. Flash column chromatography[14] was performed on Silica Gel 60 (230–400 mesh; Merck).

*Methyl (phenyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-2-thio-β-*D*-glycero-*D*-galacto-2-nonulopyranosid)onate* (**3**). — A mixture of **1** (533 mg, 1 mmol), anhydrous dichloromethane (10 mL), thiophenol (110 μL, 1.1 mmol), and boron trifluoride etherate (300 μL, 2.5 mmol) was kept overnight at room temperature, then diluted with dichloromethane (150 mL), washed with saturated aqueous sodium hydrogencarbonate (30 mL), dried ($MgSO_4$), and concentrated. The residue was eluted from a column of silica gel with 70:1 toluene–methanol to give, first, **3** (472 mg, 81%), m.p. 181–182° (from ethyl acetate–hexane), $[\alpha]_D$ −132° (*c* 1, chloroform); lit.[6] m.p. 84–87°, $[\alpha]_D^{20}$ −99.6° (chloroform). ^{1}H-N.m.r. data: δ 7.64, 7.10, and 6.99 (3 m, 5 H, Ph), 5.72 (dd, 1 H, $J_{6,7}$ 2.5, $J_{7,8}$ 2.1 Hz, H-7), 5.44 (ddd, 1 H, $J_{8,9a}$ 2.1, $J_{8,9b}$ 8.6 Hz, H-8), 5.35 (ddd, 1 H, $J_{3a,4}$ 11.7, $J_{3e,4}$ 4.8, $J_{4,5}$ 10.2 Hz, H-4), 5.00 (dd, 1 H, $J_{9a,9b}$ 12.4 Hz, H-9a), 4.61 (m, 1 H, H-6), 4.52–4.43 (m, 2 H, H-5 and NH), 4.38 (dd, 1 H, H-9b), 3.26 (s, 3 H, MeO), 2.80 (dd, 1 H, $J_{3a,3e}$ 14.0 Hz, H-3*e*), 2.01 (dd, 1 H, H-3*a*), 1.92, 1.88, 1.67, 1.63, and 1.60 (5 s, 15 H, 5 Ac).

Anal. Calc. for $C_{26}H_{33}NO_{12}S$: C, 53.51; H, 5.70; N, 2.40. Found: C, 53.59; H, 5.68; N, 2.36.

Further elution gave **7** (40 mg, 7%), identical with the compound obtained from **2**.

When the reaction was conducted on a larger scale, **3** (~60%) was obtained directly by crystallization.

*Methyl (benzyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-2-thio-β-* (**4**) *and -α-*D*-glycero-*D*-galacto-2-nonulopyranosid)onate* (**8**). — Reaction of **1** (533 mg, 1 mmol) with phenylmethanethiol (130 μL, 1.1 mmol), as for the preparation of **3**, gave, after similar work-up and purification, first **4** (502 mg, 84%), $[\alpha]_D$ −108° (*c* 1, chloroform). ^{1}H-N.m.r. data: δ 7.48, 7.17, and 7.03 (3 m, 5 H, Ph), 5.74 (ddd, 1 H, $J_{7,8}$ 2.4, $J_{8,9a}$ 2.1, $J_{8,9b}$ 8.5 Hz, H-8), 5.72 (m, 1 H, H-7), 5.45 (dd, 1 H, $J_{9a,9b}$ 12.4 Hz, H-9a), 5.22 (ddd, 1 H, $J_{3a,4}$ 11.8, $J_{3e,4}$ 5.0, $J_{4,5}$ 9.7 Hz, H-4), 4.56 (dd, 1 H, H-9b), 4.51–4.42 (m, 2 H, H-5 and H-6), 4.27 (m, 1 H, NH), 4.08 and 4.00 (2 d, 2 H, *J* 13.0 Hz, PhCH_2), 3.23 (s, 3 H, MeO), 2.62 (dd, 1 H, $J_{3e,3a}$ 14.0 Hz, H-3*e*), 2.00 (dd, 1 H, H-3*a*), 1.96, 1.88, 1.69, 1.59, and 1.58 (5 s, 15 H, 5 Ac).

Anal. Calc. for $C_{27}H_{35}NO_{12}S$: C, 54.26; H, 5.90; N, 2.34. Found: C, 54.03, H, 6.06; N, 2.27.

Further elution gave **8** (24 mg, 4%), $[\alpha]_D$ +60° (*c* 0.9, chloroform). ^{1}H-N.m.r. data: δ 7.40, 7.10, and 6.99 (3 m, 5 H, Ph), 5.91 (ddd, 1 H, $J_{7,8}$ 8.3, $J_{8,9a}$ 2.5, $J_{8,9b}$ 6.0 Hz, H-8), 5.51 (dd, 1 H, $J_{6,7}$ 2.2 Hz, H-7), 4.79 (ddd, 1 H, $J_{3a,4}$ 11.8, $J_{3e,4}$ 4.7, $J_{4,5}$ 10.2 Hz, H-4), 4.70 (dd, 1 H, $J_{9a,9b}$ 12.5 Hz, H-9a), 4.42 (ddd, 1 H, $J_{5,6}$ 10.6, $J_{5,NH}$ 10.5 Hz, H-5), 4.35 (dd, 1 H, H-9b), 4.16 and 4.11 (2 d, 2 H, *J* 13.5, PhCH_2), 4.07 (d, 1 H, NH), 3.90 (dd, 1 H, H-6), 3.19 (s, 3 H, MeO), 2.80 (dd, 1 H, $J_{3a,3e}$ 12.7 Hz, H-3*e*), 1.99 (dd, 1 H, H-3*a*), 2.17, 1.94, 1.77, 1.60, and 1.58 (5 s, 15 H, 5 Ac).

Anal. Calc. for $C_{27}H_{35}NO_{12}S$: C, 54.26; H, 5.90; N, 2.34. Found: C, 53.97; H, 5.89; N, 2.26.

*Methyl (ethyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-2-thio-β-*D*-glycero-*D*-galacto-2-nonulopyranosid)onate* (**5**). — Reaction of **1** (533 mg, 1 mmol) with ethanethiol (80 μL, 1.1 mmol), as for the preparation of **3**, gave, after similar work-up and purification, first **5** (385 mg, 72%), $[\alpha]_D$ −74° (*c* 1, chloroform). ^{1}H-N.m.r. data: δ 5.69 (dd, 1 H, $J_{6,7}$ 2.5, $J_{7,8}$ 2.6 Hz, H-7), 5.59 (ddd, 1 H, $J_{8,9a}$ 2.4, $J_{8,9b}$ 8.5 Hz, H-8), 5.33 (dd, 1 H, $J_{9a,9b}$ 12.5 Hz, H-9a), 5.26 (ddd, 1 H, $J_{3a,4}$ 11.6, $J_{3e,4}$ 5.0, $J_{4,5}$ 10.0 Hz, H-4), 4.53 (dd, 1 H, H-9b), 4.44 (ddd, 1 H, $J_{5,6}$ 10.5, $J_{5,NH}$ 10.0 Hz, H-5), 4.38 (d, 1 H, NH), 4.35 (dd, 1 H, H-6), 3.34 (s, 3 H, MeO), 2.79–2.65 (m, 2 H, CH_3CH_2), 2.61 (dd, 1 H, $J_{3a,3e}$ 13.8 Hz, H-3*e*), 2.00 (dd, 1 H, H-3*a*), 1.95, 1.87, 1.71, and 1.60 (4 s, 15 H, 5 Ac), 1.15 (t, 3 H, *J* 7.5 Hz, CH_3CH_2).

Anal. Calc. for $C_{22}H_{33}NO_{12}S$: C, 49.34; H, 6.21; N, 2.61. Found: C, 49.04; H, 6.25; N, 2.57.

Further elution gave **9** (16 mg, 3%), identical with the compound obtained from **10**.

*Methyl (phenyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-2-thio-α-*D*-glycero-*D*-galacto-2-nonulopyranosid)onate* (**7**). — To a cooled (0°) solution of **1** (533 mg, 1 mmol) in acetyl chloride (10 mL) was added an ice-cold saturated solution of hydrogen chloride in acetyl chloride (5 mL). The mixture was kept overnight at room temperature and then concentrated, and toluene was evaporated from the residue to leave crude glycosyl chloride **2**, a solution of which in anhydrous dichloromethane (5 mL) was treated with thiophenol (154 μL, 1.5 mmol) and *N,N*-

di-isopropylethylamine (260 μL, 1.5 mmol). The mixture was kept overnight at room temperature in the dark, then added to a column of silica gel, and eluted with 60:1 toluene–methanol to give **7** (396 mg, 68% from **1**), m.p. 139–140° (from benzene–hexane), $[\alpha]_D$ +21° (*c* 0.9, chloroform); lit.[6] m.p. 97–102°, $[\alpha]_D^{20}$ +10.1° (chloroform). ^{1}H-N.m.r. data: δ 7.64, 7.16, and 7.07 (3 m, 5 H, Ph), 5.67 (ddd, 1 H, $J_{7,8}$ 7.0, $J_{8,9a}$ 2.7, $J_{8,9b}$ 5.8 Hz, H-8), 5.51 (dd, 1 H, $J_{6,7}$ 2.2 Hz, H-7), 4.81 (ddd, 1 H, $J_{3a,4}$ 12.0, $J_{3e,4}$ 4.7, $J_{4,5}$ 10.5 Hz, H-4), 4.77 (dd, 1 H, $J_{9a,9b}$ 12.5 Hz, H-9a), 4.46 (dd, 1 H, H-9b), 4.35 (ddd, 1 H, $J_{5,6}$ 10.7, $J_{5,NH}$ 10.5 Hz, H-5), 4.10 (d, 1 H, NH), 3.94 (dd, 1 H, H-6), 3.21 (s, 3 H, MeO), 2.98 (dd, 1 H, $J_{3a,3e}$ 12.8 Hz, H-3*e*), 2.03 (dd, 1 H, H-3*a*), 1.96, 1.94, 1.79, 1.57, and 1.56 (5 s, 15 H, 5 Ac).

Anal. Calc. for $C_{26}H_{33}NO_{12}S$: C, 53.51; H, 5.70; N, 2.40. Found: C, 53.57; H, 5.66; N, 2.44.

[*Methyl (5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-β-*D*-glycero-*D*-galacto-2-nonulopyranosyl)onate*] *phenyl sulfone* (**6**). — A catalytic amount of ruthenium trichloride hydrate (~3 mg) was added to a vigorously stirred biphasic solution of **3** (292 mg, 0.5 mmol) and sodium metaperiodate (430 mg, 2 mmol) in carbon tetrachloride (2 mL), acetonitrile (2 mL), and water (3 mL). After 5 min at room temperature, the yellow mixture was diluted with dichloromethane (100 mL), washed with water (20 mL), dried ($MgSO_4$), and concentrated. The residue was eluted from a column of silica gel with ethyl acetate to give **6** (280 mg, 91%), $[\alpha]_D$ −55° (*c* 1, chloroform). Mass spectrum: *m/z* 616 $(M + 1)^+$, 633 $(M + 18)^+$. ^{1}H-N.m.r. data: δ 7.97, 7.00, and 6.94 (3 m, 5 H, Ph), 5.79 (ddd, 1 H, $J_{3a,4}$ 10.6, $J_{3e,4}$ 4.8, $J_{4,5}$ 10.0 Hz, H-4), 5.76–5.70 (m, 2 H, H-7,8), 5.23 (dd, 1 H, $J_{6,7}$ 2.5, $J_{5,6}$ 10.7 Hz, H-6), 4.89 (dd, 1 H, $J_{8,9a}$ 2.4, $J_{9a,9b}$ 12.5 Hz, H-9a), 4.72 (d, 1 H, $J_{5,NH}$ 10.2 Hz, NH), 4.50 (ddd, 1 H, H-5), 4.39 (dd, 1 H, H-9b), 3.36 (dd, 1 H, $J_{3a,3e}$ 15.0 Hz, H-3*e*), 3.05 (s, 3 H, MeO), 2.14 (dd, 1 H, H-3*a*), 2.00, 1.91, 1.71, 1.61, and 1.60 (5 s, 15 H, 5 Ac).

Anal. Calc. for $C_{26}H_{33}NO_{14}S$: C, 50.73; H, 5.40; N, 2.28. Found: C, 50.55; H, 5.49; N, 2.19.

[*Methyl (5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-α-*D*-glycero-*D*-galacto-2-nonulopyranosyl)onate*] *phenyl sulfone* (**12**). — Treatment of **7** (292 mg, 0.5 mmol) as for the preparation of **6** gave **12** (283 mg, 92%), m.p. 201–203° (from benzene–hexane), $[\alpha]_D$ +26° (*c* 1, chloroform). Mass spectrum: *m/z* 616 $(M + 1)^+$, 633 $(M + 18)^+$. ^{1}H-N.m.r. data: δ 8.00 and 7.12–7.04 (2 m, 5 H, Ph), 5.32–5.26 (m, 2 H, H-7,8), 4.85 (m, 1 H, H-4), 4.57 (m, 1 H, H-9a), 4.21 (m, 1 H, H-9b), 4.09 (m, 1 H, NH), 4.04–3.95 (m, 2 H, H-5,6), 3.42 (s, 3 H, MeO), 3.28 (dd, 1 H, $J_{3e,4}$ 4.5, $J_{3a,3e}$ 12.8 Hz, H-3*e*), 2.36 (dd, 1 H, $J_{3a,4}$ 11.7 Hz, H-3*a*), 2.01, 1.77, 1.76, 1.55, and 1.51 (5 s, 15 H, 5 Ac).

Anal. Calc. for $C_{26}H_{33}NO_{14}S \cdot 0.5\ C_6H_6$: C, 53.20; H, 5.54; N, 2.14. Found: C, 53.04; H, 5.47; N, 2.15.

O-Ethyl S-[*methyl (5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-α-*D*-glycero-*D*-galacto-2-nonulopyranosyl)onate*] *dithiocarbonate* (**10**). — A solution of crude **2** (1 mmol), prepared as for the synthesis of **7**, and *O*-ethyl *S*-potassium

dithiocarbonate (240 mg, 1.5 mmol) in anhydrous ethanol (10 mL) was left overnight at room temperature in the dark, then diluted with dichloromethane (150 mL), washed with water (30 mL), dried ($MgSO_4$), and concentrated. The residue was eluted from a column of silica gel with 70:1 toluene–methanol to give **10** (423 mg, 71% from **1**), $[\alpha]_D$ +79° (*c* 1, chloroform). N.m.r. data: ^1H, δ 5.69 (ddd, 1 H, $J_{7,8}$ 6.4, $J_{8,9a}$ 2.7, $J_{8,9b}$ 6.1 Hz, H-8), 5.55 (dd, 1 H, $J_{6,7}$ 2.2 Hz, H-7), 4.81 (ddd, 1 H, $J_{3a,4}$ 11.5, $J_{3e,4}$ 4.6, $J_{4,5}$ 10.3 Hz, H-4), 4.69 (dd, 1 H, $J_{5,6}$ 10.2 Hz, H-6), 4.68 (dd, 1 H, $J_{9a,9b}$ 12.4 Hz, H-9a), 4.65 and 4.45 (2 m, 2 H, CH_3CH_2), 4.43 (dd, 1 H, H-9b), 4.34 (ddd, 1 H, $J_{5,NH}$ 10.5 Hz, H-5), 4.28 (d, 1 H, NH), 3.31 (s, 3 H, MeO), 2.54 (dd, 1 H, $J_{3a,3e}$ 13.0 Hz, H-3*e*), 1.79 (dd, 1 H, H-3*a*), 2.02, 1.91, 1.75, 1.59, and 1.57 (5 s, 15 H, 5 Ac), 1.10 (t, 3 H, *J* 7.0 Hz, CH_3CH_2); ^{13}C, δ 207.12 (C=S), 170.74, 170.45, 170.19, 170.16, 169.99, and 168.60 (6 C=O), 86.44 (C-2), 75.08, 70.15, 68.77, and 67.67 (C-4,6,7,8), 70.37 (CH_3CH_2), 61.98 (C-9), 53.21 (CH_3O), 49.02 (C-5), 37.03 (C-3), 23.03, 20.98, 20.72, 20.69, and 20.66 (5 CH_3CO), 13.23 (CH_3CH_2). Mass spectrum: *m/z* 596 $(M + 1)^+$, 613 $(M + 18)^+$.

Anal. Calc. for $C_{23}H_{33}NO_{13}S_2$: C, 46.38; H, 5.58; N, 2.35. Found: C, 46.64; H, 5.65; N, 2.29.

O-*Ethyl* S-[*methyl (5-acetamido-4,7,8,9-tetra*-O-*acetyl-3,5-dideoxy-α*-D-glycero-D-galacto-*2-nonulopyranosyl)onate*] *thiocarbonate* (**11**). — A solution of crude **2** (1 mmol), prepared as for the synthesis of **7**, and *O*-ethyl *S*-potassium thiocarbonate[23] (216 mg, 1.5 mmol) in anhydrous ethanol (10 mL) was left overnight at room temperature in the dark, then diluted with dichloromethane (150 mL), washed with water (30 mL), dried ($MgSO_4$), and concentrated. The residue was eluted from a column of silica gel with 70:1 toluene–methanol to give **11** (300 mg, 52% from **1**), $[\alpha]_D$ +55° (*c* 1, chloroform). N.m.r. data: ^1H, δ 5.67 (ddd, 1 H, $J_{7,8}$ 6.6, $J_{8,9a}$ 2.6, $J_{8,9b}$ 6.0 Hz, H-8), 5.60 (dd, 1 H, $J_{6,7}$ 2.4 Hz, H-7), 4.86 (ddd, 1 H, $J_{3a,4}$ 12.0, $J_{3e,4}$ 4.5, $J_{4,5}$ 10.3 Hz, H-4), 4.85 (dd, 1 H, $J_{9a,9b}$ 12.5 Hz, H-9a), 4.82 (dd, 1 H, $J_{5,6}$ 11.0 Hz, H-6), 4.43 (ddd, 1 H, $J_{5,NH}$ 10.2 Hz, H-5), 4.36 (dd, 1 H, H-9b), 4.23 (d, 1 H, NH), 4.11 and 3.88 (2 m, 2 H, CH_3CH_2), 3.46 (s, 3 H, MeO), 2.59 (dd, 1 H, $J_{3a,3e}$ 12.8 Hz, H-3*e*), 1.88 (dd, 1 H, H-3*a*), 2.11, 1.92, 1.77, 1.60, and 1.59 (5 s, 15 H, 5 Ac), 0.88 (t, 3 H, *J* 7.2 Hz, CH_3CH_2); ^{13}C, δ 170.74, 170.53, 170.28, 170.21, 170.01, and 168.95 (6 C=O), 165.66 (S–C=O), 84.99 (C-2), 75.22, 70.56, 68.94, and 67.71 (C-4,6,7,8), 64.19 (CH_3CH_2), 62.21 (C-9), 53.25 (CH_3O), 48.77 (C-5), 37.49 (C-3), 22.97, 20.85, 20.68, and 20.63 (5 CH_3CO), 13.96 (CH_3CH_2). Mass spectrum: *m/z* 580 $(M + 1)^+$, 597 $(M + 18)^+$.

Anal. Calc. for $C_{23}H_{33}NO_{14}S$: C, 47.66; H, 5.74; N, 2.42. Found: C, 47.47; H, 5.81; N, 2.39.

Methyl (ethyl 5-acetamido-4,7,8,9-tetra-O-*acetyl-3,5-dideoxy-2-thio-α*-D-glycero-D-galacto-*2-nonulopyranosid)onate* (**9**). — A mixture of **10** (300 mg, 0.5 mmol) and NaI (300 mg, 2 mmol) in *N,N*-dimethylformamide (10 mL) was stirred for 6 h at 110°, then cooled to room temperature, concentrated, diluted with dichloromethane (150 mL), washed with water (30 mL), dried ($MgSO_4$), and concentrated. The residue was eluted from a column of silica gel with 70:1 toluene–methanol to give **9** (154 mg, 57%), m.p. 80° (softening at 65°) (from benzene–hexane), $[\alpha]_D$

+21° (*c* 1, chloroform). ^{1}H-N.m.r. data: δ 5.81 (ddd, 1 H, $J_{7,8}$ 8.2, $J_{8,9a}$ 2.7, $J_{8,9b}$ 5.7 Hz, H-8), 5.48 (dd, 1 H, $J_{6,7}$ 2.4 Hz, H-7), 4.81 (ddd, 1 H, $J_{3a,4}$ 11.6, $J_{3e,4}$ 4.6, $J_{4,5}$ 10.7 Hz, H-4), 4.68 (dd, 1 H, $J_{9a,9b}$ 12.5 Hz, H-9a), 4.39 (ddd, 1 H, $J_{5,6}$ 10.8, $J_{5,NH}$ 10.4 Hz, H-5), 4.32 (dd, 1 H, H-9b), 4.00 (d, 1 H, NH), 3.83 (dd, 1 H, H-6), 3.37 (s, 3 H, MeO), 2.99 and 2.70 (2 m, 2 H, CH_3CH_2), 2.83 (dd, 1 H, $J_{3a,3e}$ 12.6 Hz, H-3*e*), 2.01 (dd, 1 H, H-3*a*), 2.16, 1.90, 1.77, 1.59, and 1.58 (5 s, 15 H, 5 Ac), 1.12 (t, 3 H, *J* 7.5 Hz, CH_3CH_2).

Anal. Calc. for $C_{22}H_{33}NO_{12}S$: C, 49.34; H, 6.21; N, 2.61. Found: C, 49.40; H, 6.26; N, 2.54.

ACKNOWLEDGMENT

We thank the MECT Corporation (Tokyo, Japan) for a generous gift of *N*-acetylneuraminic acid.

REFERENCES

1 R. J. FERRIER, R. W. HAY, AND N. VETHAVIYASAR, *Carbohydr. Res.*, 27 (1973) 55–61.
2 P. FÜGEDI, P. J. GAREGG, H. LÖNN, AND T. NORBERG, *Glycoconjugate J.*, 4 (1987) 97–108, and references therein; S. SATO, M. MORI, Y. ITO, AND T. OGAWA, *Carbohydr. Res.*, 155 (1986) c6–c10; Y. ITO AND T. OGAWA, *Tetrahedron Lett.*, 28 (1987) 4701–4704; V. POZSGAY AND H. J. JENNINGS, *J. Org. Chem.*, 52 (1987) 4635–4637.
3 F. PAQUET AND P. SINAŸ, *Tetrahedron Lett.*, 25 (1984) 3071–3074.
4 A. MARRA AND P. SINAŸ, *Gazz. Chim. Ital.*, 117 (1987) 563–566.
5 Y. ITO AND T. OGAWA, *Tetrahedron Lett.*, 29 (1988) 1061–1064.
6 E. KIRCHNER, F. THIEM, R. DERNICK, J. HEUKESHOVEN, AND J. THIEM, *J. Carbohydr. Chem.*, 7 (1988) 453–486.
7 O. KANIE, M. KISO, AND A. HASEGAWA, *J. Carbohydr. Chem.*, 7 (1988) 501–506.
8 N. BAGGETT AND B. J. MARSDEN, *Carbohydr. Res.*, 110 (1982) 11–18.
9 R. KUHN, P. LUTZ, AND D. L. MACDONALD, *Chem. Ber.*, 99 (1966) 611–617.
10 M. N. SHARMA AND R. EBY, *Carbohydr. Res.*, 127 (1984) 201–210.
11 P. MEINDL AND H. TUPPY, *Monatsh. Chem.*, 96 (1965) 802–815.
12 R. W. MYERS, R. T. LEE, Y. C. LEE, G. H. THOMAS, L. W. REYNOLDS, AND Y. UCHIDA, *Anal. Biochem.*, 101 (1980) 166–174.
13 H. PAULSEN AND H. TIETZ, *Carbohydr. Res.*, 125 (1984) 47–64.
14 W. C. STILL, M. KAHN, AND A. MITRA, *J. Org. Chem.*, 43 (1978) 2923–2925.
15 H. PAULSEN AND H. TIETZ, *Angew. Chem. Int. Ed. Engl.*, 21 (1982) 927–928.
16 V. POZSGAY AND H. J. JENNINGS, *Tetrahedron Lett.*, 28 (1987) 1375–1376.
17 A. YA KHORLIN, I. M. PRIVALOVA, L. YA ZAKSTELSKAYA, E. V. MOLIBOG, AND N. A. EVSTIGNEEVA, *FEBS Lett.*, 8 (1970) 17–19.
18 T. G. WARNER AND L. A. LEE, *Carbohydr. Res.*, 176 (1988) 211–218.
19 I. M. PRIVALOVA AND A. YA. KHORLIN, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 12 (1969) 2614–2619.
20 M. M. PONPIPOM, R. L. BUGIANESI, AND T. Y. SHEN, *Can. J. Chem.*, 58 (1980) 214–220.
21 A. HASEGAWA, J. NAKAMURA, AND M. KISO, *J. Carbohydr. Chem.*, 5 (1986) 11–19; 5 (1986) 21–31; A. HASEGAWA, *Jpn. Kokai Tokkyo Koho JP* 61,282,390 [86,282,390]; *Chem. Abstr.*, 108 (1988) 75782p.
22 M. SAKATA, M. HAGA, AND S. TEJIMA, *Carbohydr. Res.*, 13 (1970) 379–390; H. PAULSEN, W. RAUWALD, AND U. WEICHERT, *Liebigs Ann. Chem.*, (1988) 75–86.
23 C. N. MURPHY AND G. WINTER, *Aust. J. Chem.*, 26 (1973) 755–760.
24 J. R. POUGNY, *J. Carbohydr. Chem.*, 5 (1986) 529–535.
25 D. S. BROWN, S. V. LEY, AND S. VILE, *Tetrahedron Lett.*, 29 (1988) 4873–4876.
26 H. J. CARLSEN, T. KATSUKI, V. S. MARTIN, AND K. B. SHARPLESS, *J. Org. Chem.*, 46 (1981) 3936–3938.
27 C. LE COQ AND J. Y. LALLEMAND, *J. Chem. Soc., Chem. Commun.*, (1981) 150–152.
28 D. L. RABENSTEIN AND T. T. NAKASHIMA, *Anal. Chem.*, 51 (1979) 1465A.