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A Stereospecific Synthesis of β-Glycosides of N-Acetylneuraminic Acid and Secondary Alcohols[1)]

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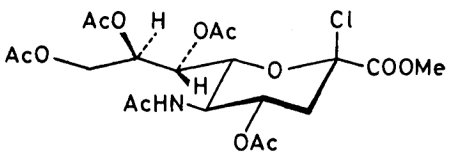
Glycosylation of secondary alcohols such as cholesterol, methyl 2,4,6-tri-O-benzylgalactopyranoside, and 2-deoxy-2,3-dehydro-NeuAc methyl ester with a new glycosyl donor, 2β,3α-dibromo-2-deoxy-NeuAc methyl ester, selectively gave the corresponding β-glycosides in high yields. The 3α-bromo-glycosides were debrominated with tri-n-butylstannane to the corresponding glycosides, which were deprotected to give the free glycosides having a β-NeuAc.

Glycosylation of N-acetylneuraminic acid (NeuAc) is one of the most important steps for the synthesis of gangliosides. The most common glycosyl donor in the glycosylation is the 2β-chloro derivative of pentaacetylneuraminic acid methyl ester, **1**, first prepared by Kuhn et al.[2)] Primary alcohols could be glycosylated with the chloroacetylneuraminic ester **1** to give a mixture of α- and β-glycosides in moderate yields accompanied by the dehydrohalogenated product, the protected 2-deoxy-2,3-dehydroneuraminic ester **2**.[3)] In the case of sugar derivatives having a hydroxy group, however, the major product was the dehydrated neuraminic ester **2** and the expected glycosylated product(s) was scarcely formed. We report here a new glycosylation method of secondary alcohols by the use of 2,3-dibromoneuraminic acid derivative **3** to produce only β-glycosylated products in high yields.



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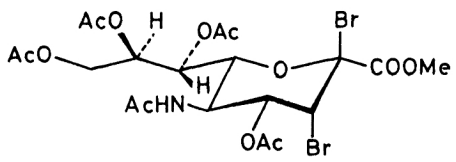

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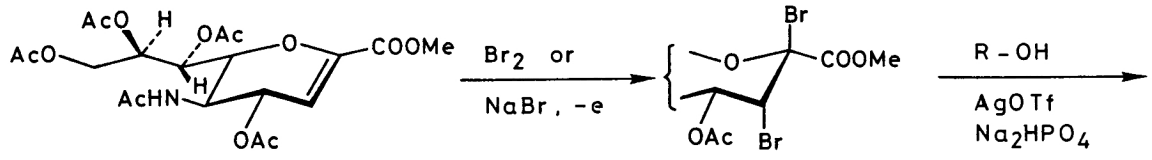
The protected 2-deoxy-2,3-dehydroneuraminic ester **2**[3)] (mp 126-127 °C) was brominated by treatment with bromine in dichloromethane or by the electrochemical oxidation of sodium bromide[4)] in acetonitrile-water (Pt-Pt electrodes) system to

give the dibromide **3**[5,6] (mp 156-157 °C) in 93 or 98% yield, respectively. The dibromide **3** is suitable for the glycosylation with the secondary alcohols since 3-axial position of **3** was blocked by the bromo group so as to prevent the dehydrobromination reaction.[7] Glycosylation of cholesterol with the dibromide **3** (1.0 equiv.) was carried out in benzene in the presence of silver triflate (1.0 equiv.) and disodium hydrogen phosphate to give the protected 3-O-(3α-bromo-2β-neuraminyl)cholesterol **7**[6] (mp 224-225 °C) in 88% yield. Reduction of the bromo-glycoside **7** with tri-n-butylstannane gave in 96% yield the debrominated compound **8**,[6] (mp 119-120 °C) which was identical with the β-glycoside **8** prepared by glycosylation of cholesterol with the chloroneuraminic acid derivative **1** followed by separation of the produced mixture of the α- and β-glycosides.[8] The anomeric configuration of the glycosides was deduced from the empirical rule of Paulsen et al.[9] The similar glycosylation of methyl 2,4,6-tri-O-benzyl-β-D-galactopyranoside **11**[10] with the dibromide **3** gave in 50% yield the protected 3-O-(3α-bromo-2β-neuraminyl)galactopyranoside **12**,[6] which was easily debrominated with tri-n-butylstannane to give the 3-glycoside derivative of galactose, **13**,[6] in 96% yield. Since the glycosylation of the galactopyranoside **11** with chloride **1** gave no glycosides, the configuration of the anomeric position of **13** was deduced as β by analysis of its ^{1}H-NMR spectrum; the H-4 of NeuAc unit of **13** appears in 4.98 ppm and the $J_{7,8}$ coupling constant was 2.1 Hz. These values agreed with those deduced from the empirical rule.[9]

The glycosylation of the protected 2-deoxy-2,3-dehydroneuraminic ester **19**[11] having a hydroxyl group at 8-position with the dibromide **3** gave in 58% yield only the bromo-β-glycoside **20**,[6] which was debrominated with tri-n-butylstannane to **21**[6] in 95% yield. In the ^{1}H-NMR spectrum of **21**, H-4 of the first NeuAc unit appeared at 5.09 ppm and the $J_{7,8}$ coupling constant was 2.7 Hz, and also H-8 of the 2,3-dehydro-NeuAc unit appeared in 4.53 ppm. These data confirmed the structure of **21** as β configuration.

The protected glycosides **8**, **13**, and **21** were deprotected quantitatively by hydrogenolysis (10% Pd-C in MeOH) and/or hydrolysis (i, t-BuOK in MeOH; ii, 1 mol dm^{-3} NaOH in MeOH) to give the free glycosides **10**, **14**, and **22**,[6] respectively. The NeuAc(β2-8)NeuAc derivative **20** still has a 2,3-unsaturated bond in the second NeuAc part, which could be converted to the corresponding tribromide **23**[6] in 98% yield. Glycosylation of the glucose derivative **4** with the tribromide **23** afforded in 42% yield the NeuAc(β2-8)NeuAc(β2-6)Glc derivative **24**,[6] which was debrominated in the same manner as above to give the corresponding trisaccharide **25** in 90% yield.

In conclusion we found that the glycosylation of the dibromide **3** with secondary alcohols gave only β-glycoside owing to steric hindrance of the axial bromo group at C-3, whereas the bromo group prevented the elimination reaction. In this procedure we could first construct the NeuAc(β2-8)NeuAc linkage.



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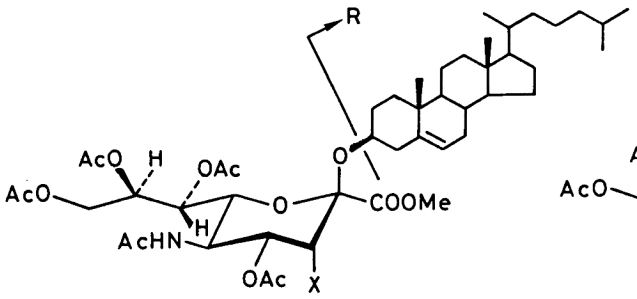
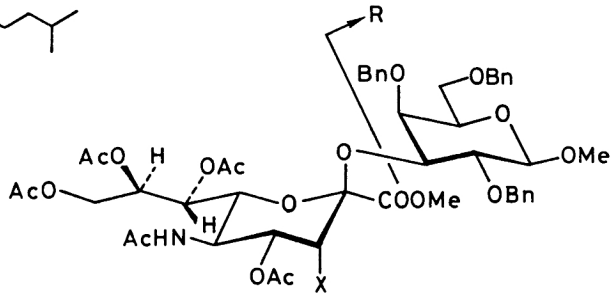


7: X = Br

8: X = H

10: deprotected 8

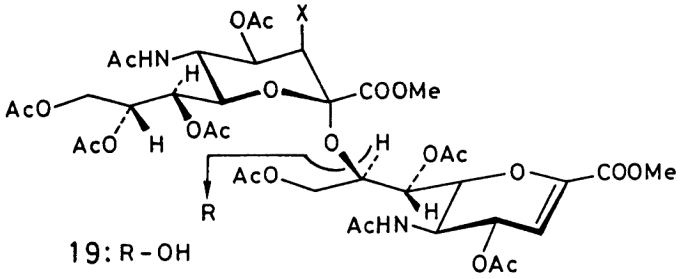


11: R-OH

12: X = Br

13: X = H

14: deprotected 13

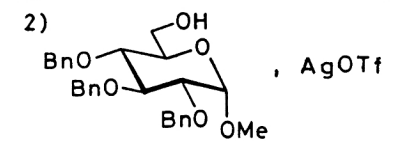


19: R-OH

20: X = Br

21: X = H

22: deprotected 21



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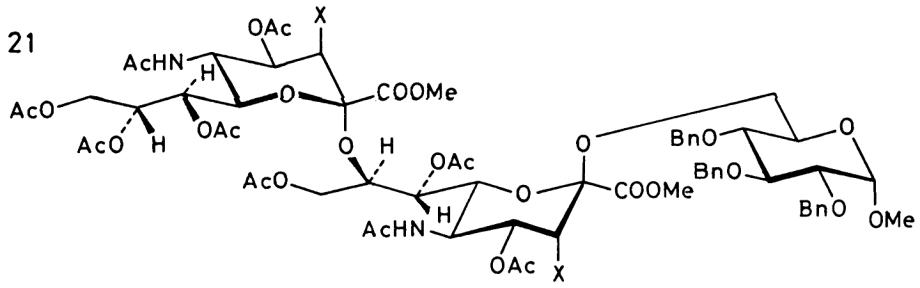

24: X = Br

25: X = H

References

1) Synthetic Studies on Gangliosides 1.
2) R. Kuhn, P. Lutz, and D. L. MacDonald, Chem. Ber., 99, 611 (1966).
3) P. Meindl and H. Tuppy, Monatsh. Chem., 100, 1295 (1969).
4) S. Torii, K. Uneyama, H. Tanaka, T. Yamanaka, T. Yasuda, M. Ono, and Y. Kohmoto, J. Org. Chem., 46, 3312 (1981).
5) The dibromide **3**: MS(FAB) m/z 634 (M+H).
6) Satisfactory elemental analyses were obtained for these compounds. $[\alpha]_D$ and ^{1}H-NMR (NeuAc unit in chloroform-d) data are shown below.

Compound	$[\alpha]_D$[a]	Chemical shifts, δ and coupling constants, Hz in ^{1}H-NMR												
		H-3eq (dd)	H-3ax (dd)	H-4 (dd)	H-5 (ddd)	H-6 (dd)	H-7 (dd)	H-8 (ddd)	H-9 (dd)	H-9' (dd)	Me ester (s)	NH (d)	$J_{7,8}$
3	-57.7°	5.05[b]		5.77[c]	4.51	4.46	5.42	5.25	4.15	4.45	3.91	5.54	7.0
5	+49.6°	4.64[b]		5.35[c]	4.53	4.49	5.34	5.27	4.16	5.19	3.75	5.53	2.0
6	+23.3°	2.47	1.88	5.16	4.11	4.27	5.38	5.27	4.13	5.07	3.72	5.49	2.2
7	-15.0°	4.64[b]		5.52[c]	4.26	4.26	5.32	5.17	4.22	4.84	3.82	5.38	2.4
8	-40.0°	2.52	d)	5.25	4.09	4.11	5.38	5.06	4.15	4.88	3.80	5.52	2.0
10[e]	-41.5°[f]	2.45	1.57	4.02	d)	d)	d)	d)	d)	d)			d)
12	+34.4°	4.73[b]		5.05[c]	4.51	3.87	5.09	5.19	4.03	5.23	3.53	3.51	2.0
13	+ 5.3°	2.70	1.80	4.98	3.99	3.91	5.15	5.15	4.00	4.99	3.54	3.86	2.1
14[g]	-18.3°[f]	2.50	1.73	4.20	d)	d)	d)	d)	d)	d)			d)
19	+48.1°	5.95[b]		5.59[c]	4.39	4.56	5.20	4.25	4.14	4.19	3.81	5.74	7.9
20	+57.1°	4.58[b]		5.22[c]	4.62	4.56	5.29	5.33	4.07	5.05	3.80[h]	6.08	2.3
21	+31.2°	2.49	1.80	5.09	4.08	4.62	5.37	5.31	4.01	4.92	3.78[h]	6.06	2.7
22[g]	+42.6°[i]	2.31	2.15	4.05	3.90[c]	4.02	3.59	3.69	3.61	3.79			9.2
24	+31.7°	4.60[b]		5.21[c]	4.65	4.61	5.34	5.34	4.10	5.08	3.60[h]	6.20	1.9
25	- 2.0°	2.43	1.80	5.11	4.11	4.63	5.41	5.33	4.07	4.96	3.61[h]	6.12	2.4

a) Measured in chloroform. b) Multiplicity: d. c) Multiplicity: dd. d) Not assigned owing to the complexity of the spectrum. e) Measured in methanol-d_4. f) Measured in methanol. g) Measured in D_2O (t-BuOH=1.23 ppm). h) Assignments may be interchanged with reducing or center NeuAc unit. i) Measured in water.

7) Primary alcohols could be glycosylated more easily with the dibromide **3**; for example, methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside **4**[12] reacted with **3** to give only the β-glycoside **5**[6] in 70% yield. Debromination of **5** with tri-n-butylstannane afforded **6**[6,13] in 97% yield.
8) The α-glycoside **9** (mp 105-106 °C), 33% yield and the β-glycoside **8**, 37% yield.
9) H. Paulsen and H. Tietz, Angew. Chem., Int. Ed. Engl., 21, 927 (1982).
10) H. M. Flowers, Carbohydr. Res., 39, 245 (1975).
11) The glycosyl acceptor **19** having a hydroxyl group at 8-position was prepared from 2-deoxy-2,3-dehydro-NeuAc methyl ester **15**[3] in the following four steps: (i) Dowex50W-X8 and acetone at 40 °C for 5 h (8,9-O-acetonide **16**,[6] mp 166-167 °C, 73% yield); (ii) Ac_2O-pyridine at 60 °C for 6 h (**17**,[6] mp 77-78 °C, 98% yield); (iii) 80% AcOH at 60 °C for 1 h (8,9-diol **18**,[6] 81% yield); and (iv) AcCl-pyridine at -20 °C for 0.5 h (8-ol **19**,[6] 76% yield).
12) P. Kovac, J. Alfödi, and B. Kosik, Chem. Zveski, 28, 820 (1974).
13) H. Ogura, K. Furuhata, T. Osawa, S. Toyoshima, and M. Ito, Ger. Offen. DE3219209 (1982).

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