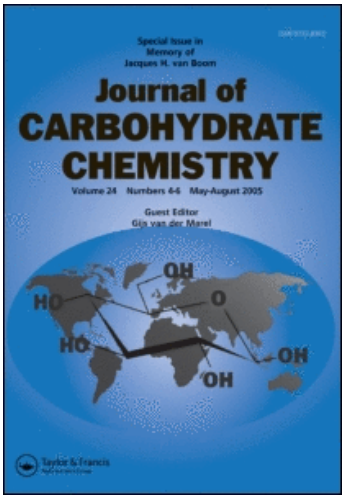

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COMMUNICATION

SYNTHETIC STUDIES ON SIALOGLYCOCONJUGATES 12: TOTAL SYNTHESIS OF SIALYL NEOLACTOTETRAOSYL CERAMIDE

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Sialoglycoconjugates such as glycoproteins and glycolipids are present as components of cell membranes and play important roles[1,2] in biological systems. Sialyl neolactotetraosyl ceramide (IV^3NeuAc-nLc_4Cer), a complex type of ganglioside, was isolated as the major ganglioside of human erythrocytes[3] and was shown to be a receptor of human influenza A virus.[4] Recently, it has been reported[5] that this glycolipid induces granulocytic differentiation of human premyelocytic leukemia cell.

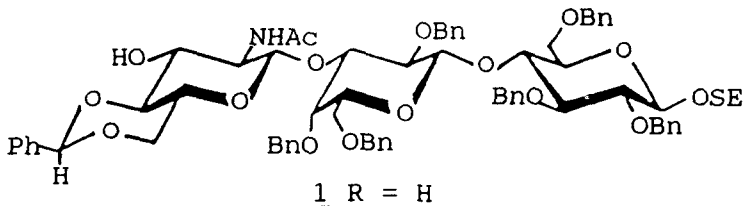
In view of these facts and in order to analyze the biological functions of gangliosides on the molecular level, a facile, regio- and stereo-selective synthesis is required. As a part of our project on the synthesis of sialoglycoconjugates, we describe here the first total synthesis of sialyl neolactotetraosyl ceramide.

For the synthesis of the title ganglioside, we began with compounds 3, 4, 9, and 10 as the suitably protected glycosyl acceptors and glycosyl donors.

Treatment of 2-(trimethylsilyl)ethyl O-(2-acetamido-4,6-O-benzylidene-2-deoxy-β-D-glucopyranosyl)-(1→3)-O-(2,4,6-tri-O-benzyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-O-benzyl-β-D-glucopyranoside[6] (1), with 4-methoxybenzyl chloride in N,N-dimethylformamide in the presence of sodium hydride for 3 h at 0 °C, gave the 4-methoxybenzyl derivative 2 [79.6%; $[\alpha]_D$ -10.8° (dichloromethane)]. Reductive ring-opening of the benzylidene group in 2 with sodium cyanoborohydride-hydrogen chloride in tetrahydrofuran, according to the method by Garegg et al.,[7] afforded the expected 6-O-benzyl derivative 3 [$[\alpha]_D$ -5.1° (chloroform)] as the glycosyl acceptor in a good yield.

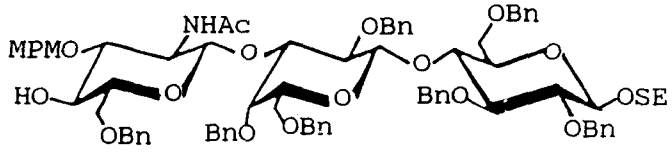
The glycosidation of 3 with methyl O-[methyl (5-acetamido-4,7,8,9-tetra-O-acetyl-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosyl)onate]-(2→3)-2,4,6-tri-O-benzoyl-1-thio-β-D-galactopyranoside[6] (4; 1.5 equiv to the glycosyl acceptor) in dichloromethane for 12 h at 0 °C in the presence of dimethyl(methylthio)sulfonium triflate[8] (DMTST) (4.0 equiv to the glycosyl donor) as a glycosyl promoter and molecular sieves 4A (MS-4A), yielded the pentasaccharide 5 [79%; $[\alpha]_D$ + 7.5° (chloroform)], which had the desired stereochemistry. Significant signals in ^{1}H NMR (270 MHz) spectrum of 5 were two three proton singlets at δ 1.44 and 1.49 (N-acetyl), four three-proton singlets at δ 1.78, 1.91, 1.95, and 2.14 (O-acetyl), two three-proton singlets at δ 3.64 and 3.82 (O-methyl), fifty four aromatic protons at δ 6.58-8.23 (10 Ph and MeOPh), and a one-proton doublet at δ 5.07 (J = 8.1 Hz) due to the newly formed β-glycosidic linkage.

Removal of the benzyl and 4-methoxybenzyl groups in compound 5 by catalytic hydrogenolysis over 10% Pd-C in ethanol-formic acid at 45 °C and subsequent acetylation gave compound 7 [$[\alpha]_D$ +10.7° (chloroform)] in 59.4% yield. Selective cleavage[8c,9] of the 2-(trimethylsilyl)ethyl group in 7 with boron trifluoride etherate in dichloromethane for 8 h at 0 °C gave compound 18 [$[\alpha]_D$ + 28.9° (chloroform)] in 78.3% yield after column chromatography. Treatment[9c,d, 10] of 8 with trichloroacetonitrile in dichloromethane for 4 h at 0 °C in the



1 R = H
2 R = MPM

MPM = 4-methoxybenzyl
SE = 2-(trimethylsilyl)ethyl
Bn = benzyl
Ph = phenyl



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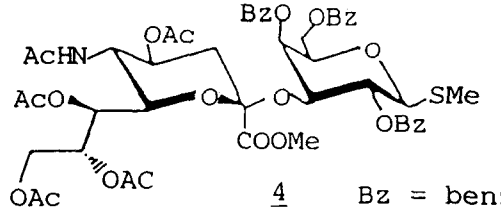
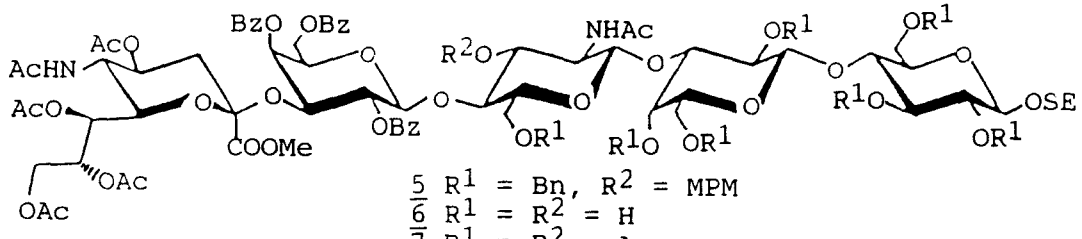
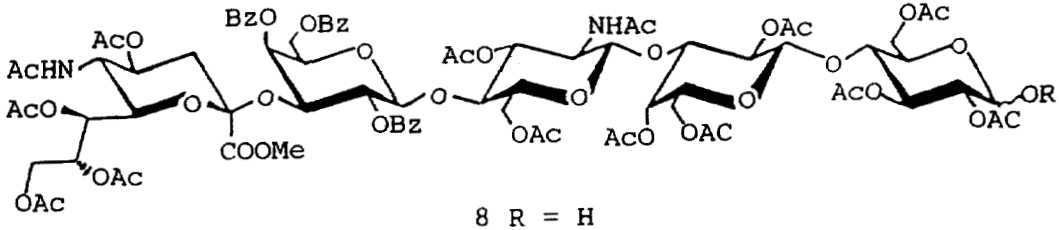


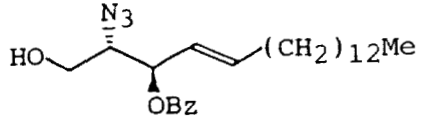
4 Bz = benzoyl



5 R^1 = Bn, R^2 = MPM
6 R^1 = R^2 = H
7 R^1 = R^2 = Ac



8 R = H
9 R = C(=NH)CCl$_3$



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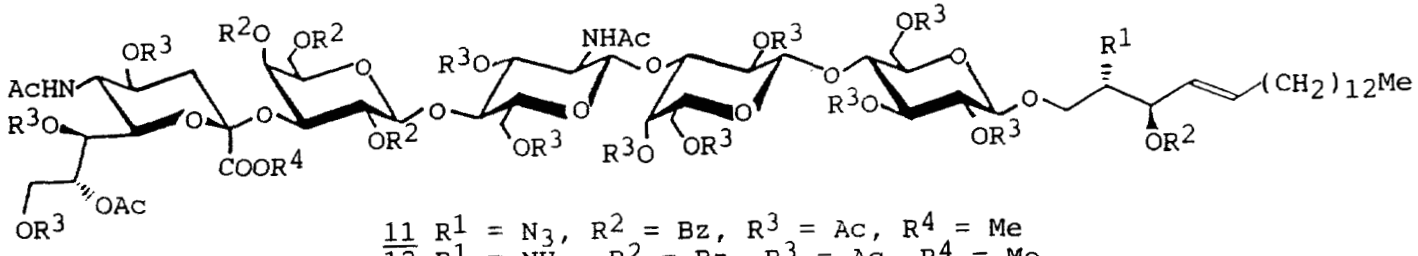

11 R^1 = N_3, R^2 = Bz, R^3 = Ac, R^4 = Me
12 R^1 = NH_2, R^2 = Bz, R^3 = Ac, R^4 = Me
13 R^1 = $NHCO(CH_2)_{16}Me$, R^2 = Bz, R^3 = Ac, R^4 = Me
14 R^1 = $NHCO(CH_2)_{16}Me$, R^2 = R^3 = R^4 = H

presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), gave the corresponding α-trichloroacetimidate 9 [$[\alpha]_D$ +42.8° (chloroform)] in 87.2% yield. There were two significant signals in the ^1H NMR spectrum of compound 9, a one-proton doublet at δ 6.47 ($J_{1,2}$ = 3.3 Hz, H-1) and a one-proton singlet at δ 8.64 (C=NH), indicating the α-trichloroacetimidate formation.

The glycosidation of (2S, 3R, 4E)-2-azido-3-O-benzoyl-4-octadecene-1,3-diol[11] (10) with 9 in the presence of boron trifluoride etherate for 8 h at 0 °C afforded only the expected β-glycoside 11 [$[\alpha]_D$ +5.4° (chloroform)] in 41.5% yield after column chromatography.

Selective reduction[9c,12] of the azido group in compound 11 with hydrogen sulfide in 83% aqueous pyridine gave the amine 12, which, on condensation with octadecanoic acid using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSC) in dichloromethane for 16 h at room temperature gave compound 13 [$[\alpha]_D$ +12.3° (chloroform)] in 83.7% yield.

Finally, O-deacetylation and O-debenzoylation of 13 with sodium methoxide in methanol, and subsequent saponification of the methyl ester yielded the title compound 14 [$[\alpha]_D$ -3.8° (water)] in 89.2% yield after Sephadex LH-20 column chromatography.

In conclusion, regio- and stereo-controlled total synthesis of sialyl neolactotetraosyl ceramide was first achieved by using a Neu5Ac-galactose disaccharide unit 4 as the important glycosyl donor. It was also shown that the 2-(trimethylsilyl)ethyl group employed here was an efficient protecting group for the anomeric hydroxyl group because of the easy and selective deprotection with boron trifluoride etherate, and of the stability toward many of the reagents used here.

New compounds obtained gave elemental analyses and IR and NMR data in agreement with the structures assigned.

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