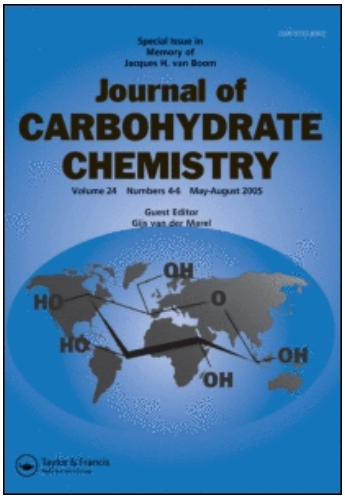

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Communication: Synthetic Studies on Sialoglycoconjugates 110: Efficient Assembly of α-Linked Tetrameric Sialoglycosides Coupled with Galactose and Lactose

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COMMUNICATION

SYNTHETIC STUDIES ON SIALOGLYCOCONJUGATES 110: EFFICIENT ASSEMBLY OF α-LINKED TETRAMERIC SIALOGLYCOSIDES COUPLED WITH GALACTOSE AND LACTOSE[1]

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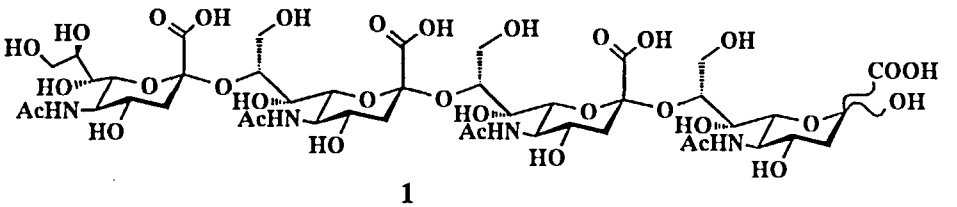
Polysialoglycoconjugates, such as polysialylated ganglio-series gangliosides and N-CAM (neural cell adhesion molecule), are of interest because of their important physiological functions in association with neural cell development, differentiation, neuron network formation, and so on.[2-4] Chemical synthesis of these glycoconjugates provides an effective method to elucidate their biological significance in nature at the molecular level, providing not only genuine original glycoconjugates but also their derivatives and analogs designed for biological investigation. We have established[5] an efficient method to construct dimeric and trimeric sialoglycosides by using the lactonated sialic acid derivatives as building blocks, and succeeded in the systematic synthesis of various polysialogangliosides such as GD3, GQ1b, GQ1bα and, very recently, GT3.[6] In this paper, as a part of our continuous synthetic approach directed toward the polysialoglycoconjugates, we report the first synthesis of α-linked tetrameric sialoglycosides coupled with a galactose and lactose residue.

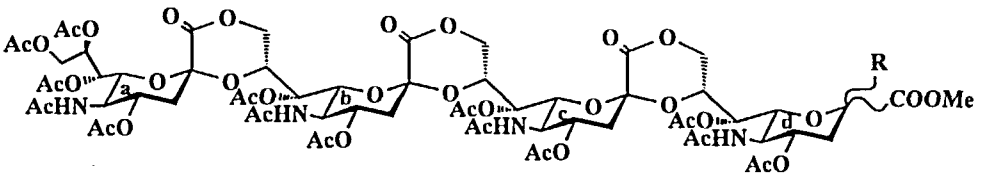
In the numerous studies of sialoglycoconjugates, there has been no reported synthesis of tetrameric sialoglycosides, owing to the difficulty in the chemical construction of α(2→8) glycosidic linkage between sialic acids, which arises from kinetic instability of α-sialoside and poor reactivity of the C-8 hydroxyl group in sialic acid. In this study, to avoid this difficulty, the fully lactonated tetrameric α(2→8) linked sialoglycoside donor (**3**) was efficiently prepared from the naked tetrameric sialic acid (**1**) obtained from colominic acid, and it was coupled with the suitably protected glycosyl acceptors (**4**[7] and **5**[8]) promoted by iodonium ion in acetonitrile.

Thus, methyl{phenyl 5-acetamido-8-*O*-[5-acetamido-8-*O*-(5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylono-1"',9"-lactone)-4,7-di-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylono-1",9'-lactone)-4,7-di-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylono-1',9-lactone]-4,7-di-*O*-acetyl-3,5-dideoxy-2-thio-D-*glycero*-D-*galacto*-2-nonulopyranosid}onate (**3**) was selected as the glycosyl donor, which underwent regio- and α-stereoselective glycosidation with 2-(trimethylsilyl)ethyl 2,6-di-*O*-benzyl-β-D-galactopyranoside (**4**) and 2-(trimethylsilyl)ethyl 2,3,6,2',6'-penta-*O*-benzyl-β-D-lactoside (**5**) in acetonitrile to give **6** and **8**, respectively.

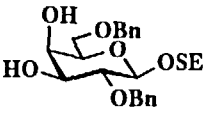
The inter-residue 1',9-lactonation of sialyl-α(2→8)sialyl-α(2→8)sialyl-α(2→8) sialic acid (**1**), which was prepared by a mild acid hydrolysis of colominic acid, was performed by treatment with Amberlite IR-120(H^+) resin and Drierite in *N*,*N*-dimethylformamide for 1 day at 40 °C. Methylation of the carboxyl group at the reducing terminal sialic acid with methyl *p*-toluenesulfonate and triethylamine, followed by acetylation with acetic anhydride and pyridine at 40 °C, gave an anomeric mixture (α:β ratio 1:3) of fully lactonated, acetylated tetrameric sialic acid derivative **2** in 55% overall yield. The compound **2** was then converted into the corresponding phenyl 2-thioglycoside **3** in 78% yield by treatment[6,9] with thiophenol and borane trifluoride diethyl etherate in dichloromethane at room temperature for 1 day (the α:β ratio was estimated as 1:4 from the relative intensities of MeO signals). Significant signals in the ^{1}H NMR spectrum of **3** (β-isomer) appeared at δ 1.76-1.89 (4s, 12H, 4AcN), 1.97-2.13 (10s, 30H, 10AcO), 2.30 (dd, $J_{3ax,3eq}$ = 13.2 Hz, $J_{3eq,4}$ = 5.1 Hz, H-3d*eq*), 2.43 and 2.67 (2m, 3H, H-3a*eq*, H-3b*eq* and H-3c*eq*), 3.56 (s, 3H, MeO), 5.31-5.52 (m,



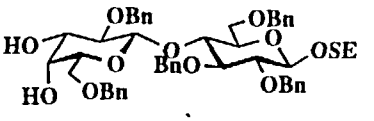
1



2 R = OAc
3 R = SPh



4



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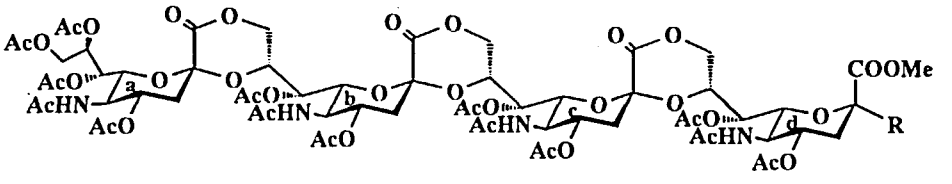
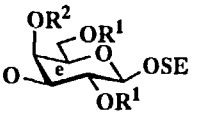
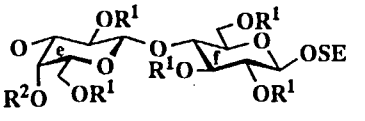


R =





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

8 R^1 = Bn, R^2 = H
9 R^1 = R^2 = Ac

SE = 2-(trimethylsilyl)ethyl
Bn = benzyl

4H, H-4a, H-4b, H-4c and H-4d) and 7.23-7.40 (m, 5H, Ph), showing the assigned structure.

The glycosylation[5,6,8,10,11] of **4** (2.5 mol equiv) with **3** (1 mol equiv) was carried out in acetonitrile at -35 °C for 2 days in the presence of *N*-iodosuccinimide (3 mol equiv) and trifluoromethanesulfonic acid (0.3 mol equiv) to give desired α-glycoside **6**, $[\alpha]_D$ -30.9° ($CHCl_3$), in 35% yield. Hydrogenolytic removal of the benzyl groups in **6** over palladium black in methanol at room temperature for 3 days, followed by acetylation of free hydroxyl groups at 40 °C, gave the per-acetylated pentasaccharide **7**, $[\alpha]_D$ -35° ($CHCl_3$), in 76% yield (2 steps). The ^{1}H NMR of **7** showed a series of characteristic signals at δ 2.55 (dd, $J_{3ax,3eq}$ = 12.8 Hz, $J_{3eq,4}$ = 4.8 Hz, H-3d*eq*), 5.04 (m, 1H, H-4d) and 5.16 (d, 1H, H-4e), indicating the newly established glycosidic linkage to be α at the C-3 position of the galactose residue.

According to the almost same way as described above, hexasaccharide **8**, $[\alpha]_D$ -20.6° ($CHCl_3$), was synthesized successfully, through the regio- and α-stereoselective coupling of **3** (1 mol equiv) and **5** (2.5 mol equiv) in 35% yield, and it was converted by debenzylation and subsequent acetylation into **9** (84% in 2 steps). Significant signals in the ^{1}H NMR spectrum of **9** appeared at δ 2.53 (dd, $J_{3ax,3eq}$ = 12.8 Hz, $J_{3eq,4}$ = 4.8 Hz, H-3d*eq*), 4.35 (dd, $J_{2,3}$ = 10.2 Hz, $J_{3,4}$ = 3.4 Hz, H-3e), 5.03 (m, 1H, H-4d) and 5.10 (d, 1H, H-4e), supporting the newly formed glycosidic linkage in the hexasaccharide **9** to be α(2"→3').

In conclusion, the first, stereocontrolled synthesis of α-linked tetrameric sialoglycosides coupled with a galactose and lactose residue was achieved by use of the phenyl 2-thioglycoside of fully lactonated tetrameric sialic acid as the key glycosyl donor (**3**) and the suitably protected galactose (**4**) and lactose (**5**) acceptors, promising a further development of the systematic synthesis of polysialoglycoconjugates. This method could also be useful for the synthesis of tetrameric sialoglycolipid found in nature.[12] All new compounds were fully characterized by elemental analyses, IR and ^{1}H NMR spectroscopy.

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