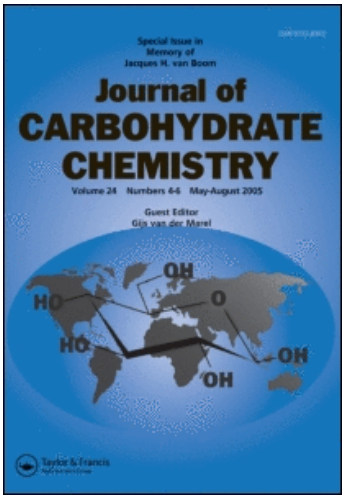

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COMMUNICATION

A HIGHLY EFFICIENT SYNTHETIC ROUTE TO α(2→3)/α(2→6) DISIALYL LEWIS A AS A CANCER ASSOCIATED CARBOHYDRATE ANTIGEN[1]

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The carbohydrate determinants, sialyl Lewis A and sialyl Lewis X, which are frequently expressed on human cancer cells,[2,3] serve as ligands for a cell adhesion molecule of the selectin family.[4] These carbohydrate determinants are also involved in the adhesion of cancer cells to vascular endothelium and thus contribute to hematogenous metastasis of cancer.[5,6] We have synthesized a series of the derivatives and the analogs of sialyl Lewis X[7] and sialyl Lewis A[8] gangliosides as the versatile probes for elucidation of their biological functions.

The title compound α(2→3) / α(2→6) disialyl Lewis A (**1**, Figure 1) was first isolated from human colonic adenocarcinoma,[9] and the determination of the (2→3) sialylated Lewis A to (2→3) / (2→6) disialylated Lewis A ratio in patients with pancreas disease may be helpful for differential diagnosis of pancreas cancer and nonmalignant pancreatic disorders.[10–12] This paper describes the first, efficient synthetic route to the title compound **1** as its peracetylated derivative **10**, which contains the tri-antennary structure at *O*-3, *O*-4, and *O*-6 of the GlcNAc residue as a structural feature.

The synthetic strategy is illustrated in Figure 1. The crucial point in the synthetic route to the target heptasaccharide **1** was successive glycosylations of a GlcNAc unit of an appropriate trisaccharide in the following order: (A) α-stereo- and regioselective sialylation at *O*-6, (B) regioselective introduction of the sialyl-α-(2→3)-galactose structure to *O*-3, and (C) fucosylation of the remaining 4-OH of the GlcNAc residue, to give the tri-antennary structure. The order of the glycosylations was decided based on results obtained by our ongoing studies on synthesis of sialoglycoconjugates. It was decided that sialylation should be carried out at the early stage of the synthesis to make isolation of the product less difficult, as sialy-

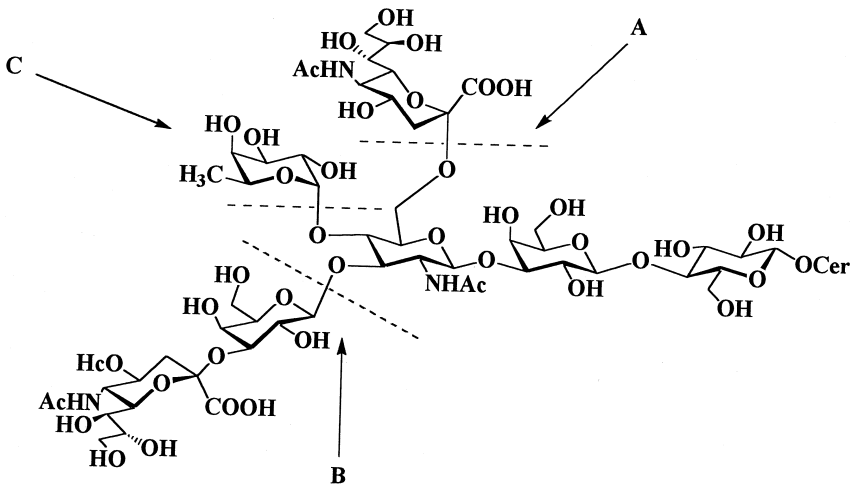


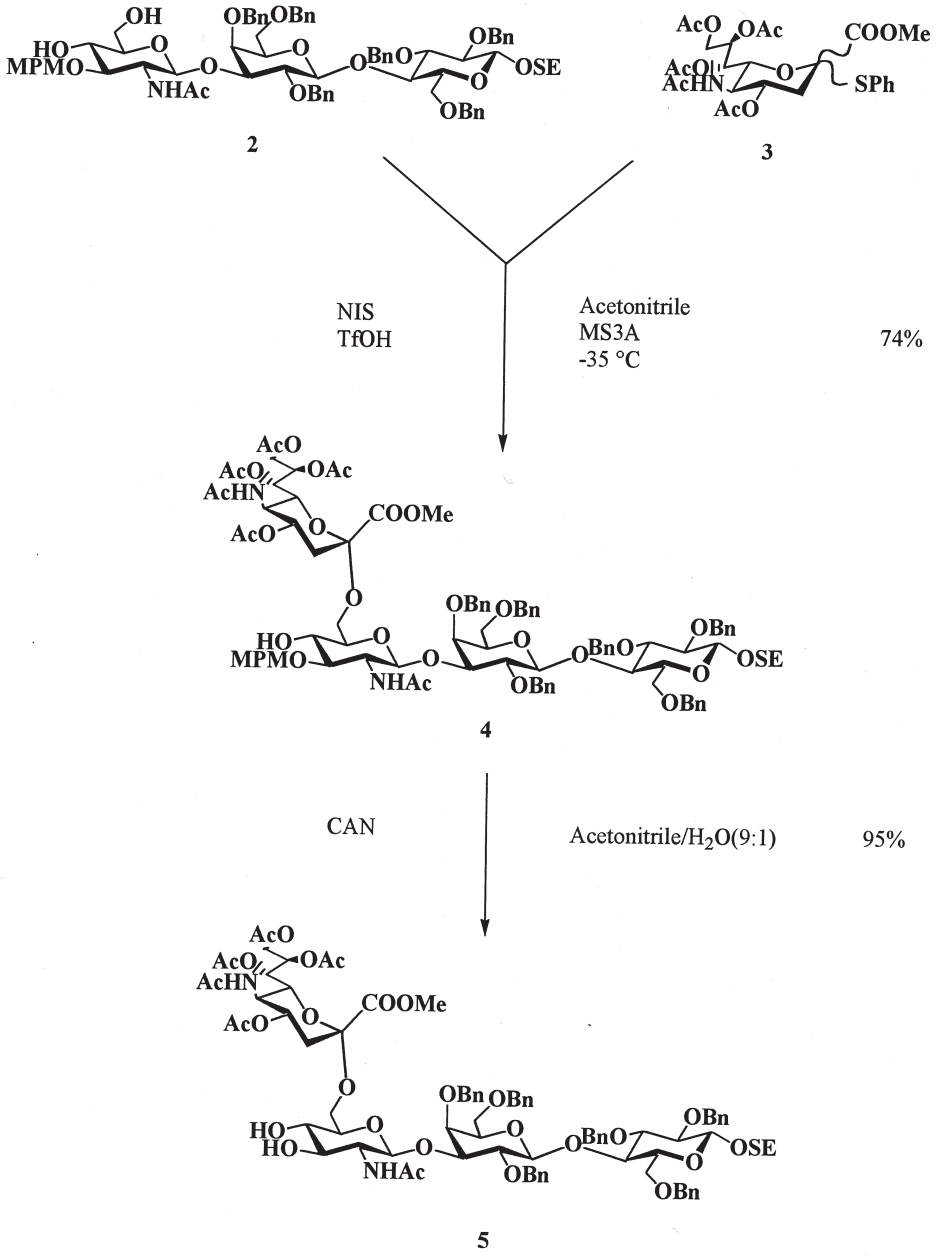
Figure 1. α(2 → 3)/α(2 → 6) disialyl Lewis A (1).

lation of primary hydroxyls often gives anomeric mixtures with relatively low selectivity. Fucosylation was expected to be successfully performed, even at the last stage of the synthesis, because of the observed potency of this reaction.

The α-stereo- and regioselective sialylation of the key trisaccharide acceptor **2**[13] with **3**,[14] was performed in the presence of *N*-iodosuccinimide (NIS)- trifluoromethanesulfonic acid (TfOH) at −35 °C in acetonitrile to give the desired sialyl-α-(2→6)-GlcNAc-β-(1→3)-Gal-β-(1→4)-Glc tetrasaccharide **4** in 74% yield, accompanied by the corresponding β-sialoside (16%) (Scheme 1). The most significant signal in the ^{1}H NMR spectrum of **4** was a one-proton doublet of doublets (J_{gem} = 13.0, $J_{3eq,4}$ = 4.8 Hz) at δ 2.60 due to H-3eq of the newly introduced α-(2→6)-linked sialyl residue.[15] In the spectrum of the β-sialoside, the H-3eq was observed at δ 2.47 (J_{gem} = 12.8, $J_{3eq,4}$ = 4.76 Hz).

Treatment of **4** with ceric ammonium nitrate (CAN) in acetonitrile-H_2O (9:1) gave the 3,4-diol tetrasaccharide acceptor **5**, which was glycosylated with the sialyl-α-(2→3)-galactose trichloroacetimidate donor **6**[16] in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) to afford the desired β-(1→3)-linked derivative **7** (53%), accompanied by the corresponding β-(1→4)-linked hexasaccharide (13%) (Scheme 2). A significant signal in the ^{1}H NMR spectrum of **7** was a one-proton doublet of doublets at δ 5.48 ($J_{1,2}$ = 10.3, $J_{2,3}$ = 8.01 Hz, H-2 of Gal) indicating the newly formed glycosidic linkage to be β. The regioselectivity of the glycosylation was confirmed after acetylation of the remaining OH of the GlcNAc residue. The high regioselective glycosylation at O-3 of the GlcNAc residue may be due to steric hindrance at O-4 caused by the (2→6)-linked sialic acid.

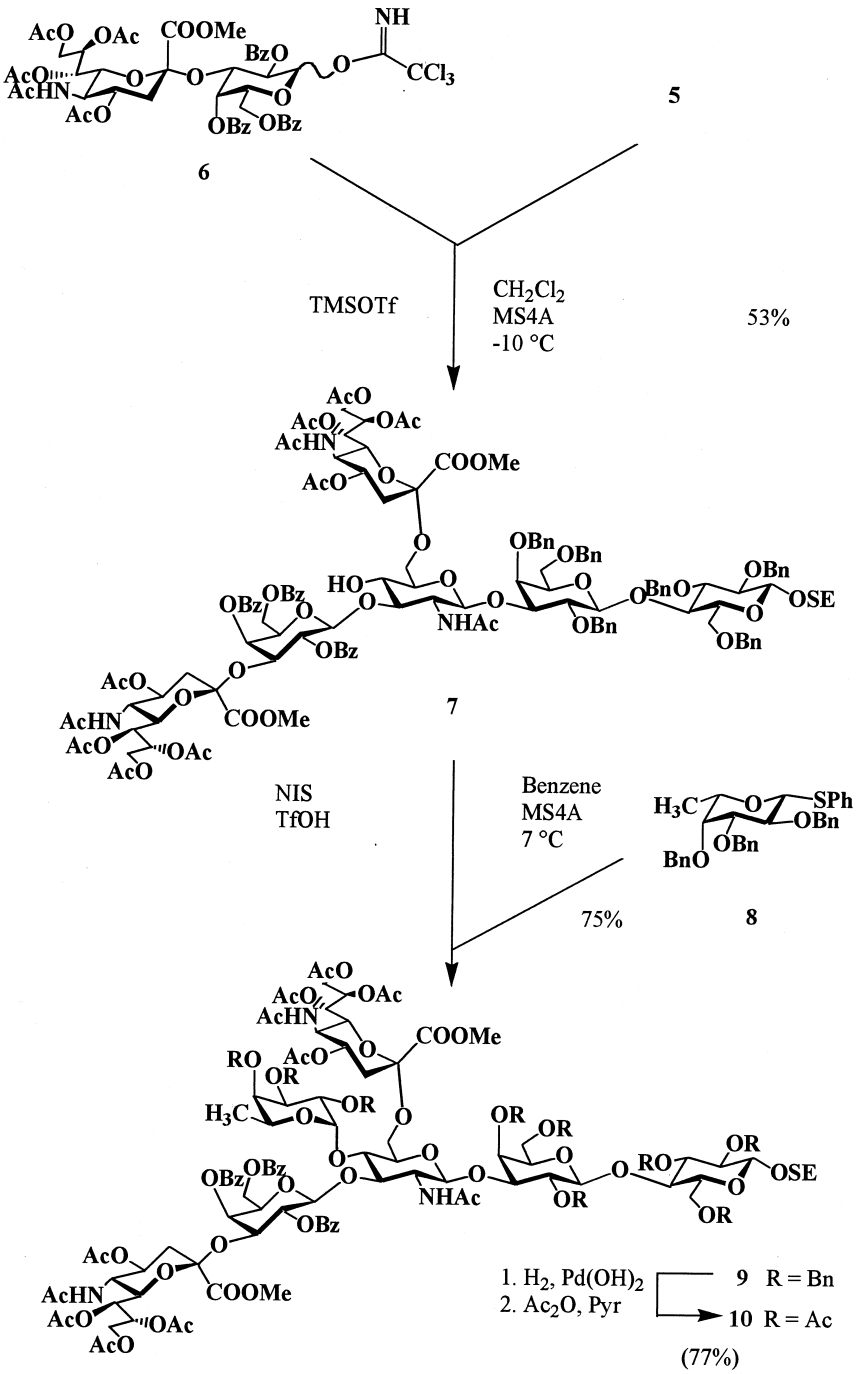
Finally, the remaining, sterically hindered 4-OH of the GlcNAc residue in **7** was efficiently fucosylated with the thiophenyl glycoside of fucose (**8**)[13] by using the NIS/TfOH-promoted glycosylation procedure in benzene at 7 °C. The desired



Scheme 1.

heptasaccharide **9** containing the tri-antennary structure based on the GlcNAc residue, was obtained in 75% yield.

Hydrogenolytic removal of the benzyl groups in **9** over $Pd(OH)_2$ in ethanol, followed by treatment with Ac_2O in pyridine, afforded the peracetylated heptasaccharide **10** in 77% yield.



Scheme 2.

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In conclusion, an efficient synthetic route to a derivative form of α(2→3)/α(2→6) disialyl Lewis A as a cancer associated carbohydrate antigen was achieved for the first time.

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