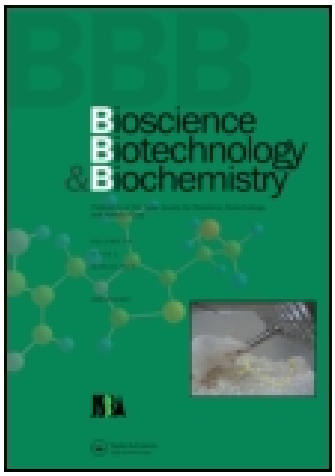

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Synthesis of 2-O-Fucosyl Sulfatide, a Blocker of L- and P-Selectin

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Short Communication

Synthesis of 2-*O*-Fucosyl Sulfatide, a Blocker of L- and P-Selectin†

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A new derivative of sulfatide, 2-*O*-α-L-fucopyranosyl sulfatide, was synthesized. The compound inhibited the binding of HL-60 cells, which express sialyl Lewis X, to P- and L-selectin more than the corresponding non fucosylated compound.

Key words: selectin blocker; sulfatide; inflammatory disease; cell adhesion

Selectin-ligand interactions are involved in various inflammatory diseases,[2] and much attention has been focused on the identification of carbohydrate ligands of the selectin family. Sulfatide, one of the most abundant acidic glycosphingolipid in mammalian tissues, is a good ligand for L- and P-selectin,[3,4] and protects against inflammatory lung injury caused by selectin.[5] Many mimetics[6] and analogs[7] of sialyl Lewis X (sLe^x) have been designed and synthesized as anti-inflammatory agents, but few attempts to develop a selectin blocker derived from sulfatide have been reported. The fucose moiety is needed if sLe^x is to be recognized by selectins.[8] Fucoidan, the sulfated fucose polymer, binds to L-selectin and inhibits lymphocyte adhesion mediated by this molecule to lymph-node endothelial venules.[9]

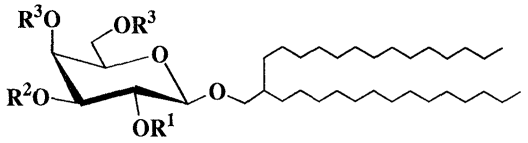
We describe here the synthesis of a new derivative of sulfatide, 2-*O*-α-L-fucopyranosyl sulfatide, anchored with 2-(tetradecyl)hexadecyl group in place of ceramide. It is a potent selectin blocker.

2-(Tetradecyl)hexadecyl β-D-galactopyranoside (**1**)[10] was selected as the starting material. Treatment of **1** with benzaldehyde dimethyl acetal in *N*,*N*-dimethylformamide containing 10-camphorsulfonic acid for 45 min at 45°C afforded the 4,6-*O*-benzylidene derivative **2** {78%, $[\alpha]_D^{20}$ −83° (*c* 1, $CHCl_3$)}, which was treated with levulinic anhydride in pyridine in the presence of 4-dimethylaminopyridine for 1 h at −50°C to give the 3-*O*-levulinyl derivative **3** {93%, $[\alpha]_D^{20}$ +126° (*c* 1, $CHCl_3$)}. The H-3 proton in the ^{1}H-NMR spectrum of **3** appeared at δ 4.99 ($J_{2,3}$ = 10, $J_{3,4}$ = 3.4 Hz), indicating the levulinylated position to be *O*-3. Glycosylation of **3** with phenyl 2,3,4-tri-*O*-benzyl-1-thio-β-L-fucopyranoside[11] in the presence of *N*-iodosuccinimide-trifluoromethanesulfonic acid[12] and molecular sieves 4A in toluene for 1 h at −20°C gave the desired disaccharide **5** {89%, $[\alpha]_D^{20}$ −25° (*c* 1, 2, $CHCl_3$)}, showing a signal in ^{1}H-NMR at δ 4.98 (d, $J_{1,2}$ = 2.2 Hz) characteristic of an α-L-fucopyranosyl unit. Removal of the benzyl and benzylidene group in **5** by catalytic hydrogenolysis over palladium hydroxide on carbon in ethanol for 10 h at 25°C and then acetylation with acetic anhydride and pyridine gave the per-*O*-acylated disaccharide **7** {quantitative, $[\alpha]_D^{20}$ −44° (*c* 0.8, $CHCl_3$)} *via* **6**.

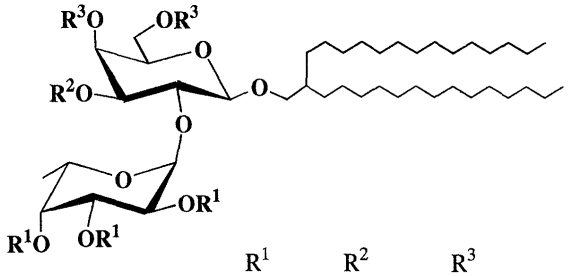
Selective removal of the levulinyl group at *O*-3 in the galactose moiety with hydrazine acetate[13] gave **8** in a yield of 87%, and **8** was then treated with complexes of sulfur trioxide and pyridine in *N*,*N*′-dimethylformamide.[14] The resulting 3-sulfate was treated with sodium methoxide, and chromatographic purification (Sephadex LH-20, CH_3OH) gave the desired 2-*O*-α-L-fucopyranosyl sulfatide with an artificial anchor of 2-(tetradecyl)hexadecyl groups, as a colorless solid {78%, $[\alpha]_D^{20}$ −66° (*c* 0.8, CH_3OH)}.

The structure of **10** thus obtained was identified by ion-spray MS. The molecular ion for **10** was detected in the negative ion mode (*m*/*z* 826.2 $[M-Na]^-$).

Compound **10** inhibited the binding of HL-60 cells (which express sLe^x) to selectins more (inhibition at 0.3 mM, 100% for P-selectin, and 99% for L-selectin) than the corresponding nonfucosylated sulfatide **4** (inhibition at 0.3 mM, 23%



	R^1	R^2	R^3
1	H	H	H
2	H	H	Bzd
3	H	Lev	Bzd
4	H	SO_3Na	H



	R^1	R^2	R^3
5	Bn	Lev	Bzd
6	H	Lev	H
7	Ac	Lev	Ac
8	Ac	H	Ac
9	Ac	SO_3Na	Ac
10	H	SO_3Na	H

† Synthetic Studies on Sialoglycoconjugates, Part 99. For Part 98, see ref. 1.
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for P-selectin, and 27% for L-selectin). (T. Ikami, manuscript in preparation).

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