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C-Mannose Derivatives as Potent Mimics of Sialyl Lewis X

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Abstract: The synthesis of five sialyl Lewis X mimetics was described. Mimetics **2** - **6** were easily synthesized from readily available starting materials. Mimics **4** and **6** showed activities five-fold better than sialyl Lewis X. Copyright © 1996 Elsevier Science Ltd

In continuation of our interest in development of carbohydrate mimics,[1] we describe herein rationally designed C-linked mannose derivatives as mimics of sialyl Lewis X (SLe^x), a tetrasaccharide ligand of E- and P-selectin associated with inflammation[2] and cancer.[3]

Recent studies indicate that SLe^x is active *in vivo* as an anti-inflammatory agent[4] due to its inhibitory activity against E- and P-selectin of endothelial cells, which interact with SLe^x-expressing neutrophils and leukocytes in the rolling adhesion step of inflammatory reactions. Several drawbacks are encountered,

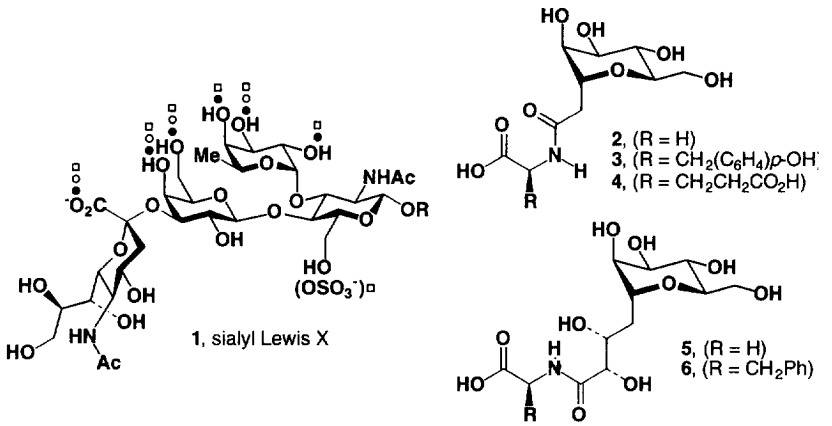


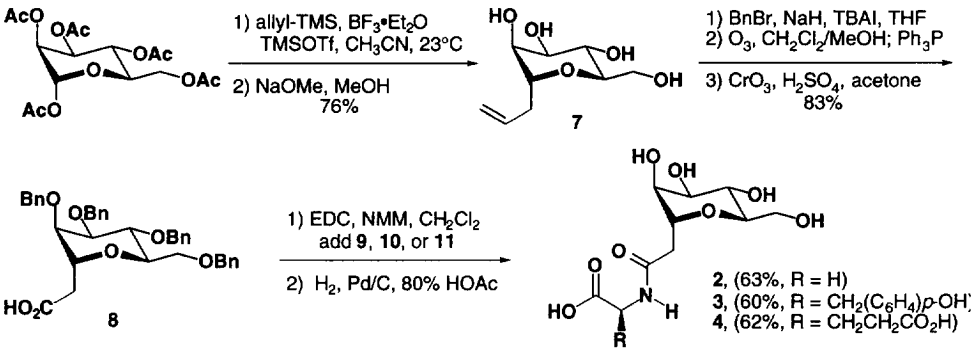
Figure 1. Sialyl Lewis X (**1**) and the funtional groups essential for E-(•), P-(○), and L-selectins (▫), and the mimetics **2** - **6**.

however, when considering SLe^x as a drug candidate: the activity is relatively low (IC_{50} for E- and P-selectin is 0.5 mmol and >3 mM respectively)[5]; the rotational barrier is relatively high (5 kcal/mole) for the free sugar binding to E-selectin; SLe^x is difficult to synthesize on large scales; it is relatively unstable and orally inactive. Development of SLe^x mimics which are easy to synthesize, more stable and more active than SLe^x, and preferably orally active is therefore of current interest.

Figure 1 shows the structure of SLe^x and the functional groups essential for interaction with E-, P-, and L-selectins. The 2-, 3-, and 4-hydroxyl groups of the L-fucose,[6] the 4-, and 6-hydroxyl groups of the D-

galactose,[7] and the carboxylate residue from the sialic acid[8] are critical for binding to E-selectin. P-selectin also requires these groups except that the 2- and 4-hydroxyl groups of the fucose are not critical.[6] L-selectin recognizes all the groups for E-selectin binding and additionally requires a sulfate at the 6-position of the galactose[9] or more likely of the N-acetylglucoseamine[10] to enhance binding.

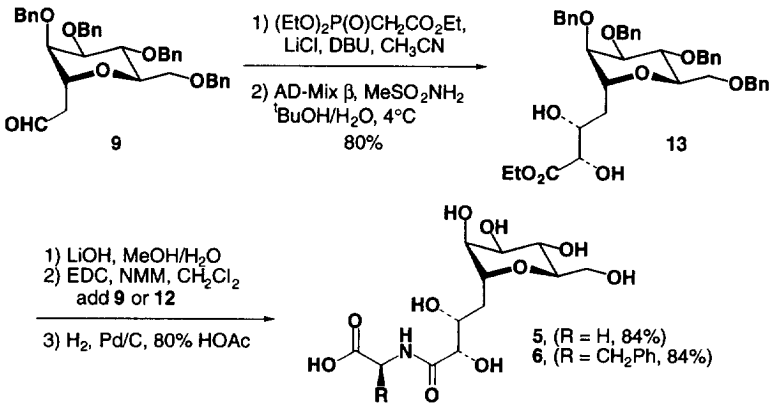
Mimics **2** - **6** utilize a D-mannose residue to mimic the L-fucose residue. This substitution has been used successfully in the design of SLe^X mimics.[1c,1g] Mimics **5** and **6** use a 1,2-diol as a galactose mimic and all of the mimics utilize the carboxyl group from readily available amino acids as the sialic acid surrogate.



Scheme 1. Synthesis of SLe^X mimics **2** - **4**.

The C-mannose core is common to all of the mimics and is readily available from commercially available mannose pentaacetate. Lewis acid catalyzed (BF_3•Et_2O, TMSOTf) allyltrimethylsilane addition to D-mannose pentaacetate in acetonitrile afforded the crude C-allyl glycoside which was deacylated directly to yield tetraol **7** in excellent yield (76%) and selectivity (8:1 α:β).[11] Perbenzylation followed by ozonolysis of the terminal olefin and oxidation of the crude aldehyde using Jones' reagent afforded carboxylic acid **8** in 83% yield for this three step conversion. EDC coupling of **8** with BnO-Gly-NH_2•TsOH (**9**), BnO-Tyr-NH_2•TsOH (**10**), or BnO-Glu(OBn)-NH_2•TsOH (**11**) followed by exhaustive hydrogenolysis of the benzyl groups afforded mimics **2**, **3**, and **4** in good yield (63%, 60%, 62% respectively from **8**).

Mimics **5** and **6** were synthesized from aldehyde **9** (scheme 2), which was an intermediate in the synthesis of mimics **2** - **4** . Treatment of aldehyde **9** with $(EtO)_2P(O)CH_2CO_2Et$ following the conditions outlined by Roush and Masamune[12] introduced the unsaturated ester with complete selectivity. Sharpless asymmetric dihydroxylation[13] of the α,β-unsaturated ester afforded the desired diol with excellent diastereoselectivity (>95:5) and yield (80% from **9**). Hydrolysis of the ethyl ester (LiOH, MeOH-H_2O) gave the requisite carboxylic acid which was coupled (EDC/HOBt) with BnO-Gly-NH_2•TsOH (**9**) or BnO-Phe-NH_2•TsOH (**12**). Hydrogenolysis of the benzyl protecting groups afforded mimics **5** and **6** in good yield (84% and 84% from **13**).



Scheme 2. Synthesis of SLe^x mimcs **5** - **6**.

Compounds **2** - **6** were fully characterized[14] and the IC_{50} values were determined[5c]; SLe^x (0.5 mmol), **2** (70% inhibition at 3 mM), **3** (73% inhibition at 3 mM), **4** (0.1 mM), **5** (0.16 mM), **6** (inactive). Mimic **5** shows activity 3-fold better than SLe^x for E-selectin. Introduction of the hydrophobic phenylalanine residue (e.g. **6**) resulted in complete loss of activity. Mimic **4** is 5-fold more active than SLe^x in spite of the fact that no hydroxyl groups are present to mimic the D-galactose. Mimics **2** and **3** show only modest inhibitory activity. Interestingly, mimic **5** does not inhibit P- and L-selectin at 3 mM, while 0% and 50% inhibition respectively were observed with 3 mM SLe^x. Current research in our laboratory is focused on the design and synthesis of SLe^x mimetics which show greater potency and increased selectivity for individual selectins.

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14. Data for **2**: ^{1}H NMR (D_2O, 400 MHz) δ 4.33 (m, 1 H), 3.68-4.0 (m, 6 H), 3.64 (t, *J* = 3.1 Hz, 1 H), 3.50-3.60 (m, 1 H), 2.81 (dd, *J* = 10.0, 14.7 Hz, 1 H), 2.57 (dd, *J* = 4.4, 14.7 Hz, 1 H); HRMS (FAB) calcd for $C_{10}H_{18}O_8N$ (M + H) 280.1032, fouund 280.1034. Data for **3**: ^{1}H NMR (D_2O, 400 MHz) δ 7.11 (d, *J* = 8.4 Hz, 2 H), 6.82 (d, *J* = 8.1 Hz, 2 H), 4.53 (dd, *J* = 5.2, 8.4 Hz, 1 H), 4.21 (dd, *J* = 6.8, 6.8 Hz, 1 H), 3.58-3.79 (m, 5 H), 3.44-3.47 (m, 1 H), 3.12 (dd, *J* = 4.8, 13.9 Hz, 1 H), 2.87 (dd, *J* = 8.4, 14.0 Hz, 1 H), 2.70 (dd, *J* = 9.2, 15.2 Hz, 1 H), 2.44 (dd, *J* = 5.7, 15.2 Hz, 1 H); MS calcd for $C_{17}H_{22}O_9N$ (M - H) 384, found 384. Data for **4**: ^{1}H NMR (D_2O, 400 MHz) δ 4.37-4.42 (m, 1 H), 4.32 (ddd, *J* = 1.8, 5.0, 5.0 Hz, 1 H), 3.87 (t, *J* = 2.9 Hz, 1 H), 3.79 (dd, *J* = 3.3, 9.0 Hz, 1 H), 3.71-3.77 (m, 2 H), 3.67 (dd, *J* = 9.2, 9.2 Hz, 1 H), 3.53-3.60 (m, 1 H), 2.80 (dd, *J* = 10.8, 14.8 Hz, 1 H), 2.55 (dd, *J* = 5.1, 14.9 Hz, 1 H), 2.46 (dd, *J* = 7.0, 7.0 Hz, 2 H), 2.11-2.20 (m, 1 H), 1.90-2.02 (m, 1 H); HRMS calcd for $C_{13}H_{22}O_{10}N$ (M + H) 352.1244, found 352.1238. Data for **5**: ^{1}H NMR (D_2O, 400 MHz) δ 4.16 (d, *J* = 2.6 Hz, 1 H), 4.06-4.15 (m, 2 H), 4.04 (d, *J* = 17.8 Hz, 1 H), 3.94 (d, *J* = 17.9 Hz, 1 H), 3.90 (dd, *J* = 2.9, 1.7 Hz, 1 H), 3.86 (dd, *J* = 12.2, 1.9 Hz, 1 H), 3.80 (dd, *J* = 9.3, 3.2 Hz, 1 H), 3.71 (dd, *J* = 12.1, 6.3 Hz, 1 H), 3.64 (t, *J* = 9.4 Hz, 1 H), 3.53 (ddd, *J* = 9.4, 6.0, 1.6 Hz, 1 H), 2.08 (m, 1 H), 1.70 (ddd, *J* = 14.2, 10.4, 3.1 Hz, 1 H); Electrospray Ionisation (ESI) MS calcd for $C_{12}H_{21}NO_{10}$ (M) 339, found (pos.: $M+H^+$) 340, (neg.: $[M-H]^-$) 338. Data for **6**: ^{1}H NMR (D_2O, 500 MHz) δ 7.19-7.29 (m, 5 H), 4.54 (br s, 1 H), 4.00-4.03 (m, 1 H), 4.01 (d, *J* = 11.1 Hz, 1 H), 3.93 (br d, *J* = 7.7 Hz, 1 H), 3.77 (m, 1 H), 3.76 (d, *J* = 11.3 Hz, 1 H), 3.68 (br d, *J* = 7.0 Hz, 1 H), 3.62, (dd, *J* = 11.7, 5.9 Hz, 1 H), 3.54 (t, *J* = 9.3 Hz, 1 H), 3.40 (dd, *J* = 7.3, 7.0 Hz, 1 H), 3.13 (br d, *J* = 10.8 Hz, 1 H), 3.02 (br s, 1 H), 1.89 (br t, *J* = 12.9 Hz, 1 H), 1.47 (br t, *J* = 11.5 Hz, 1 H); HRMS (FAB) calcd for $NaC_{19}H_{27}NO_{10}$ (M+Na) 452.1533, found 452.1545.

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