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Assembly of a Library of Trisaccharides as Mimics of Sialyl Lewis X *via* Random Combination Strategy

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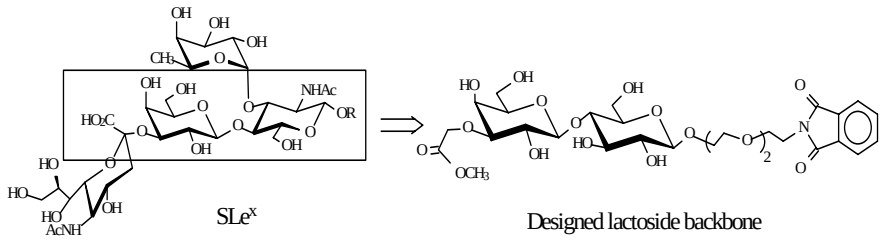
Abstract: A small library containing six positional isomers of fucosyl on the modified lactoside backbone as mimics of the Sialyl Lewis X was synthesized *via* random combinatorial glycosylation, which was charactered by ESI-MS and HPLC.

Keywords: SLe ^{x}, selectin, oligosaccharide synthesis, random combinatorial glycosylation.

The Sialyl Lewis X (SLe ^{x}) tetrasaccharide is not only the smallest recognizable ligand for all the three selectins, but also the tumor- associated carbohydrate antigen[1]. It plays a vital role in the progress of chronic inflammatory diseases and metastasis of malignant tumor cells, and provides a new approach for the research and development of anti-inflammatory and anti-metastatic drugs[2, 3].

According to the structure-activity relationship between SLe^{x} and selectins, we designed a series of trisaccharide analogues in which the acetamino lactoside scaffold of SLe^{x} was replaced by lactoside to simplify the synthesis[4]; a spacer-armed hydrophobic group introduced to the reducing terminal of the lactoside to enhance the binding activity with the selectins[5]; and the carboxyl methyl introduced on the non-reducing end to mimic the sialyl residue[6] (**Figure 1**). A small library containing six positional isomers of fucosyl on the modified lactoside backbone as mimics of the SLe^{x} was thus synthesized *via* random combinatorial glycosylation[7].

Figure 1 SLe^{x} *versus* designed lactoside backbone



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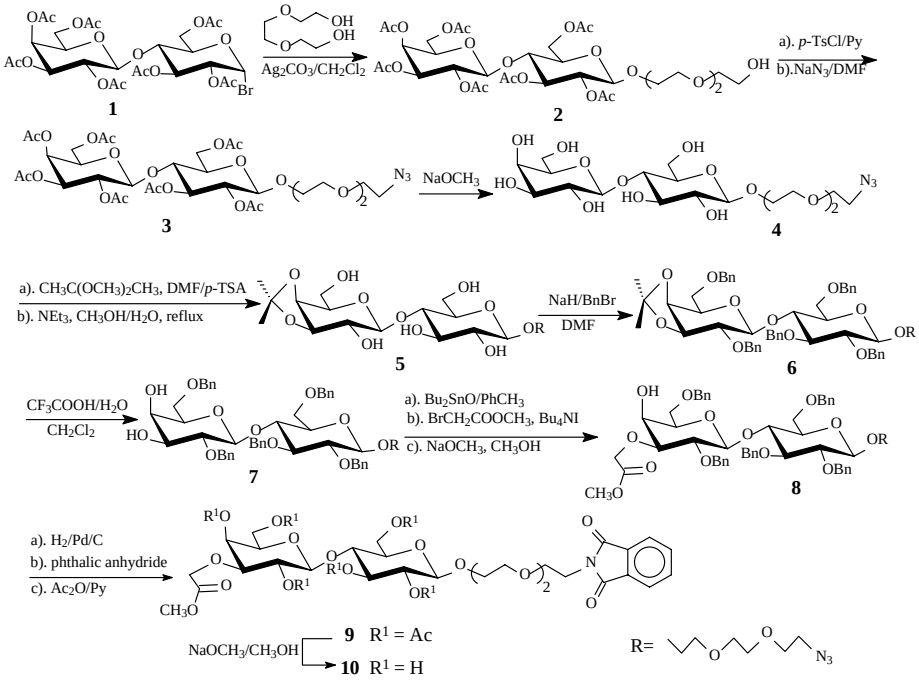
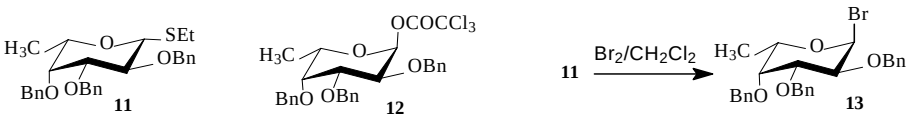
The modified lactoside backbone **10** was synthesized *via* mul material—lactosyl bromide **1** (**Scheme 1**). tisteps from the starting

Scheme 1 Synthesis of modified lactoside



Three fucosyl donors we selected including the thiofucoside **11**, fucopyranosyl trichloroacetate **12** and bromide **13** were prepared according to the literature reports respectively[8-10] (**Scheme 2**).

Scheme 2 Selected three fucosyl donors



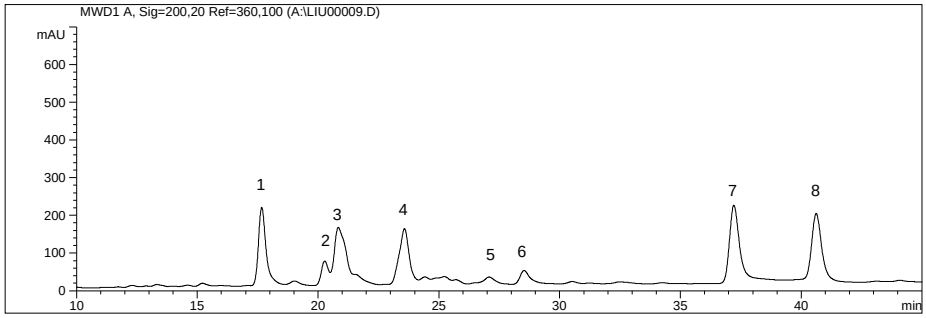
Random combinatorial glycosylation was carried out in anhydrous DMF, in which all the six free hydroxyls on the lactoside **10** show a similar nucleophilic reactivity toward the glycosyl donors. This strategy can afford a number of oligosaccharides within concise steps[7]. The reaction conditions of random glycosylation were investigated in detail (**Table 1**). The reaction was monitored by TLC and quenched with methanol. The desired library was separated by PTLC, assayed by ESI-MS and HPLC.

Table 1 Reaction conditions of random combinatorial glycosylation °C

Entry	Donor	Promoter (equiv.)	Temperature°C
Library **1**	**13**	AgOTf (2.2)	r.t.
Library **2**	**12**	TMSOTf (0.4)	r.t.
Library **3**	**11**	NIS/ TfOH (2.2/0.4)	0
Library **4**	**11**	NIS/ TfOH (2.2/0.4)	-20

The assembly of trisaccharides library was quite successful when thiofucoside **11** was used as a donor and NIS/TfOH as promoter at -20°C. After the workup, the intact disaccharide and multifucosylated products were readily separated by PTLC because of their appreciable polar difference from that of the main trisaccharide components, which was subsequently subjected to HPLC. The HPLC spectra of this trisaccharide library indicated that the ratio of six possible position isomeric trisaccharides is 12.2%, 4.0%, 16.4%, 11.8%, 22.3%, and 21.2%, respectively. The two less abundant peaks 5 (5.5%) and 6 (6.7%) are most probably to be the β-isomers (**Figure 2**) which usually are the minor products of fucosylations. Though it is possible to synthesize separately each trisaccharide isomer to confirm their structure *via* a tiresome multistep procedure, the advantage of combinatorial chemistry is to screen the mixture and determine the most biologically active component. A screening model for this trisaccharide library is being established and the result will be reported in another paper.

Figure 2 HPLC assay of library **4**



Note: HPLC (Aglilent 1100), column (Agilent Extend C–18, 250mm×4.6 mm), mobile phase (H_2O-CH_3CN), detector (UV).

In conclusion, a library containing six trisaccharides as mimics of SLe^x was synthesized *via* random combinatorial glycosylation.

Acknowledgment

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References and Notes

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11. Data for intermediate **10** and the library **4**:
    Compound **10**: ^{1}HNMR ($CDCl_3$, 300 MHz): δ 7.78 (dd, 2 H, J=3.0 Hz, J=5.1 Hz, Phth), 7.66(dd, 2 H, Phth), 4.30-4.44(m, 8 H), 3.80-3.84(m, 6 H), 3.68(s, 3 H, OCH_3), 3.39-3.66(m, 12 H). ^{13}CNMR: δ 172.72, 168.27(C=O), 133.98, 131.91, 123.21(Phth), 103.59, 102.78(C-1, C-1′), 83.16, 83.07, 79.89, 77.92, 77.21, 75.00, 74.68, 74.54, 73.04, 70.14, 69.87, 68.54, 67.74, 67.24, 66.63, 61.70, 61.47, 52.19(OCH_3), 37.16(NCH_2). MALDI-TOF-MS: 697.8$[M+Na]^+$, 713.7 $[M+K]^+$.
    Library **4**: ESI-TOF MS *(m/z)*: $C_{56}H_{71}O_{21}N$, 1094.28 $[M+H]^+$, 1106.30 $[M+NH_4]^+$.

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