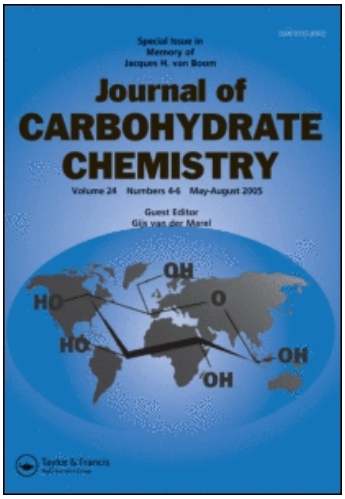

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ONE-POT SYNTHESIS OF LEWIS X OLIGOSACCHARIDE DERIVATIVES USING "ARMED–DISARMED" COUPLING METHOD[1]

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ABSTRACT

A stereocontrolled synthesis of Le^x oligosaccharide derivatives using a facile one-pot, two-step glycosylation based on the "Armed–Disarmed" concept are described. The first coupling of phenyl *O*-(2,6-di-*O*-benzoyl-3,4-*O*-isopropylidene-β-D-galacto-pyranosyl)-(1→ 4)-2,6-di-*O*-benzoyl-1-thio-β-D-glucopyranoside (**2**) with phenyl 2,3,4-tri-*O*-benzyl-1-thio-β-L-fucopyranoside (**3**) using *N*-iodosuccinimide (NIS)–trifluoro-methanesulfonic acid (TfOH) gave the trisaccharide (**8**) which was subjected to the second condensation without purification with several acceptors such as ethyl 2,4,6-tri-*O*-benzyl-β-D-galactopyranoside (**4**), ethyl 2,6-di-*O*-benzoyl-β-D-galactopyranoside (**5**), ethyl *O*-(2,6-di-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (**6**), and ethyl *O*-(2,6-di-*O*-benzoyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzoyl-β-D-glucopyranoside (**7**), to afford the desired Le^x tetra- and pentasaccharides in good yields, respectively.

INTRODUCTION

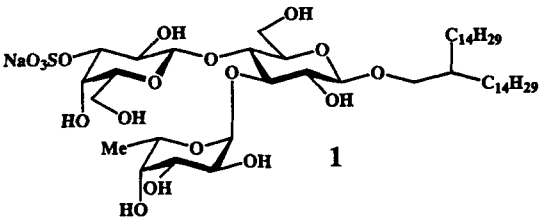
Selectins (E-, P-, and L-selectin)[2-4] are a family of calcium-dependent adhesion molecules that can mediate a specific rolling interaction between leukocytes and vascular endothelium prior to leukocyte extravasation. Although each selectin may have its own optimum carbohydrate ligand, it has been shown that all these selectins recognize oligosaccharides, such as sialyl Lewis^x (sLe^x) and sialyl Lewis^a (sLe^a) that linked to either glycoproteins or glycolipids.[5] Therefore, it has been of interest to elucidate more detailed structural requirements necessary for selectin recognitions. In addition, their involvement in inflammatory diseases makes the selectins attractive targets for the therapy of these diseases.[6]

Hasegawa's group reported[7] the syntheses of sLe^x gangliosides and their analogs, and examined[8] their structure–activity relationship. Their studies of sLe^x mimetics include an attractive 3'-sulfated Le^x analog (**1**), GSC-150, which has a potent inhibitory activity against E-, P-, and L-selectins binding.[9]

In spite of the several attractive biological activities of the Le^x, sLe^x, and sulfated Le^x derivatives, there are still limitations in their practical syntheses. One of the most difficult problems is the many steps required for their syntheses. We have recently reported[10] a highly practical synthesis of GSC-150 (**1**) using an "Armed–Disarmed" one-pot, two-step coupling method. In order to investigate applicability of our method reported previously, we have studied a practical synthesis of Le^x oligosaccharides, such as Le^x tetra-, and pentasaccharides, by one-pot, two-step glycosylation.

RESULTS AND DISCUSSION

An "Armed-Disarmed" strategy provides one of the most useful methods for the synthesis of oligosaccharides, because glycosylation using such a strategy allows for continuous glycosidic bond formation.[11] We have already reported[10] the practical synthesis of 3'-sulfated Le^x (**1**) with a branched alkyl chain, 2-tetradecylhexadecyl, using an "Armed–Disarmed" coupling method. Especially, the "Armed-Disarmed" method gave rise to the first synthesis of Le^x derivatives by one-pot glycosylation. Recently, several methods have been reported to perform sequential glycosylation as a one-pot



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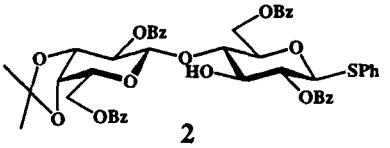

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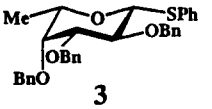

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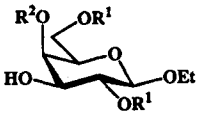
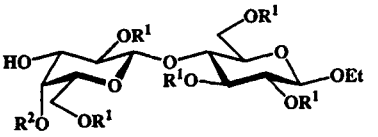
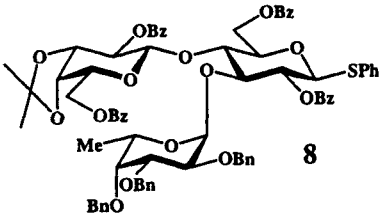


4 $R^1 = R^2 = Bn$
5 $R^1 = Bz, R^2 = H$



6 $R^1 = R^2 = Bn$
7 $R^1 = Bz, R^2 = H$



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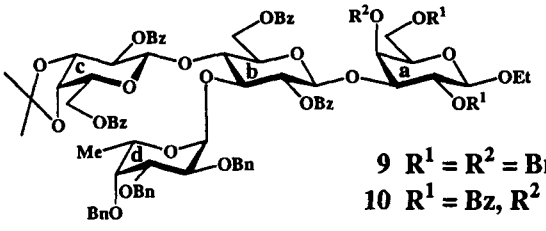
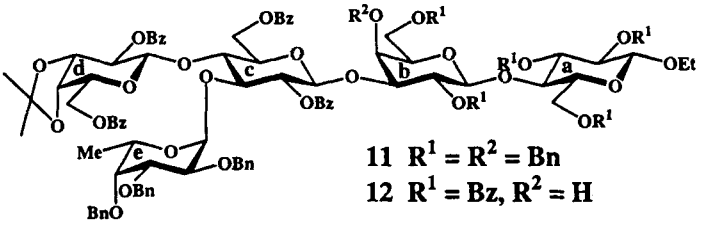


9 $R^1 = R^2 = Bn$
10 $R^1 = Bz, R^2 = H$



11 $R^1 = R^2 = Bn$
12 $R^1 = Bz, R^2 = H$

procedure.[12] There have been, however, few reports on a one-pot synthesis of an Le^x analog. Therefore, in order to investigate the applicability of "Armed-Disarmed" glycosylation in one-pot syntheses, we have synthesized Le^x analogs (**9**-**12**).

For the synthesis of Le^x oligosaccharides (**9**-**12**), we selected phenyl *O*-(2,6-di-*O*-benzoyl-3,4-*O*-isopropylidene-β-D-galactopyranosyl)-(1→4)-2,6-di-*O*-benzoyl-1-thio-β-D-glucopyranoside[10](**2**) and phenyl 2,3,4-tri-*O*-benzyl-1-thio-β-L-fucopyranoside[13](**3**) as acceptor and donor for the first coupling step, and ethyl 2,4,6-tri-*O*-benzyl-β-D-galactopyranoside[14](**4**), ethyl 2,6-di-*O*-benzoyl-β-D-galactopyranoside[15] (**5**), ethyl *O*-(2,6-di-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside[16](**6**), and ethyl *O*-(2,6-di-*O*-benzoyl-b-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzoyl-b-D-glucopyranoside[16] (**7**) as acceptors for the second coupling step.

Our synthetic strategy for the Le^x oligosaccharides **9**, **10**, **11**, and **12** is illustrated in Scheme 1. First, glycosylation of phenyl thiolactoside **2** with a donor phenyl thiofucoside **3** in chloroform for 1 h at -20 °C in the presence of *N*-iodosuccinimide (NIS)–trifluoromethanesulfonic acid (TfOH) gave the intermediate Le^x trisaccharide **8**. To this reaction mixture was added galactose acceptor **4** for the second glycosylation, and the mixture was activated under the same conditions to give a desired Le^x tetrasaccharide analog **9** in 83 % (two steps) based on acceptor **4**. In a same manner, desired Le^x oligosaccharides **10**, **11**, and **12** were obtained using acceptor **5**, **6**, and **7** for the replacement of **4** in 75 %, 53 % and 64 %, respectively, without purification (Table 1). This one-pot, two-step glycosylation is characterized by utilization of the same leaving group, the SPh group, and the same activator, NIS-TfOH.

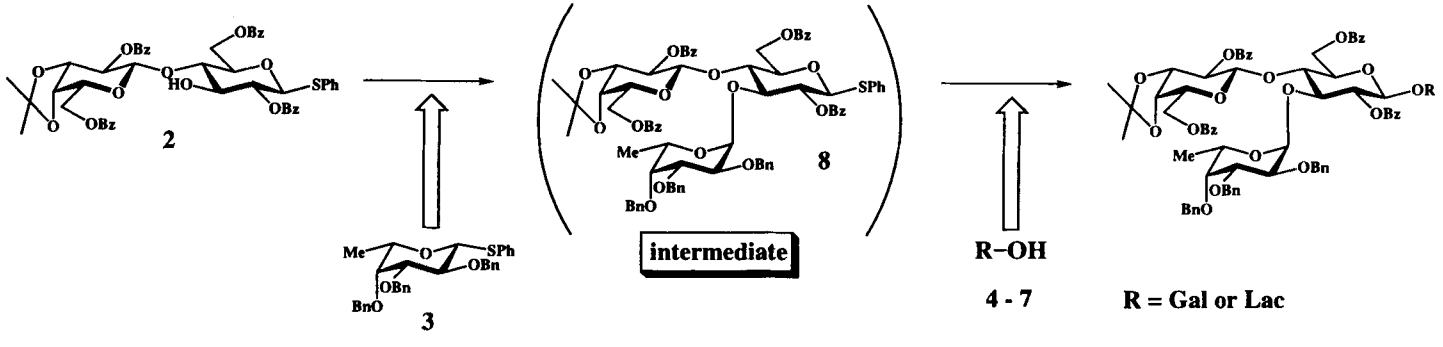
These results indicated that the disarmed phenyl *O*-(2,6-di-*O*-benzoyl-3,4-*O*-isopropylidene-β-D-galactopyranosyl)-(1→4)-2,6-di-*O*-benzoyl-1-thio-β-D-gluco-pyranoside (**2**) and the armed phenyl 2,3,4-tri-*O*-benzyl-1-thio-β-L-fucopyranoside (**3**) as the first step acceptor and donor could be useful materials for one-pot syntheses of Le^x oligosaccharides. In addition, one-pot synthesis using "Armed-Disarmed" coupling described here has allowed us to carry out a highly practical synthesis of Le^x oligosaccharides. As part of a series of studies of one-pot glycosylations, we are now investigating simple syntheses of several Le^x glycolipids.

Table 1

One–pot two–step glycosylation[a] for the synthesis of Le^x oligosaccharides

	first step				second step				
entry	acceptor (eq.)	donor (eq.)	NIS[b] (eq.)	TfOH[b] (eq.)	acceptor (1 eq.)	NIS[b] (eq.)	TfOH[b] (eq.)	product	yield (%)
1					4			9	83
2	2	3			5			10	75
3	(1.5 eq.)	(2.25 eq.)	1.5	0.5	6	1.5	0.5	11	53
4					7			12	64

a. All reactions were performed at -20 °C in chloroform.
b. Based on corresponding donor.



Scheme 1

EXPERIMENTAL

General Procedures. Specific rotations were determined with a Jasco DIP-370 digital polarimeter at 25 °C. ^{1}H NMR spectra were recorded with a BRUKER AVANCE DPX250 spectrometer. Elemental analyses were performed with a Yanagimoto CHN-CORDER MT-3. Concentrations were conducted in *vacuo*.

Ethyl *O*-(2,6-Di-*O*-benzoyl-3,4-*O*-isopropylidene-β-D-galactopyranosyl)-(1→4)-[*O*-(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)-(1→3)]-*O*-(2,6-di-*O*-benzoyl-β-D-gluco-pyranosyl)-(1→3)-2,4,6-tri-*O*-benzyl-β-D-galactopyranoside (9).

To a solution of phenyl *O*-(2,6-di-*O*-benzoyl-3,4-*O*-isopropylidene-β-D-galactopyranosyl)-(1→4)-2,6-di-*O*-benzoyl-1-thio-β-D-glucopyranoside (**2** 100 mg, 0.11 mmol) and phenyl 2,3,4-tri-*O*-benzyl-1-thio-β-L-fucopyranoside (**3** 89 mg, 0.17 mmol) in $CHCl_3$ (1 mL) were added molecular sieves 4Å (160 mg), and the mixture was stirred for 3 h at room temperature and then cooled to -20 °C. *N*-Iodosuccinimide (NIS 57 mg, 0.25 mmol) and trifluoromethanesulfonic acid (TfOH 8 μL, 0.09 mmol) were added to the stirred mixture, and this was stirred for 1 h at -20 °C. To the reaction mixture was added solution of ethyl 2,4,6-tri-*O*-benzyl-β-D-galactopyranoside (**4** 36 mg, 0.08 mmol) in $CHCl_3$ (1 mL), NIS (37 mg, 0.16 mmol), and TfOH (5 μL, 0.05 mmol), and the stirring was continued for 1 h at -20 °C; the course of the reaction was monitored by TLC. The precipitate was filtered off and washed with $CHCl_3$. The filtrate and washings were combined, and the solution was washed with sat. $Na_2S_2O_3$, M $NaHCO_3$, and water, dried ($MgSO_4$) and concentrated. The preparative TLC (20 x 20 cm, 2 mm, Merck Co., 1:3 AcOEt:hexane) of the residue gave **9** (104 mg, 83%) as an amorphous mass: $[\alpha]_D$ -20.3° (*c* 0.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.08 (t, 3H, *Me*CH_2O), 1.28, 1.51 (2s, 6H, Me_2C), 1.35 (d, 3H, $J_{5,6}$ = 6.6 Hz , H-6d), 3.46 (dd, 1H, $J_{1,2}$ = 7.9 Hz, $J_{2,3}$ = 9.4 Hz, H-2a), 3.93 (dd, 1H, $J_{1,2}$ = 3.5 Hz , $J_{2,3}$ = 10.2 Hz , H-2d), 4.14 (d, 1H, H-1a), 4.52 (d, 1H, $J_{1,2}$ = 8.1 Hz , H-1c), 4.92 (d, 1H, $J_{1,2}$ = 8.6 Hz , H-1b), 5.24 (t, 1H, $J_{2,3}$ = 8.1 Hz , H-2c), 5.45 (d, 1H, H-1d), 5.49 (t, 1H, $J_{2,3}$ = 8.6 Hz , H-2b), and 6.8-8.2 (m, 50H, 10Ph).

Anal. Calcd for $C_{99}H_{102}O_{24}$ (1675.9): C, 70.95; H, 6.13. Found: C, 70.94; H, 6.02.

Ethyl *O*-(2,6-Di-*O*-benzoyl-3,4-*O*-isopropylidene-β-D-galactopyranosyl)-(1→4)-[*O*-(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)-(1→3)]-*O*-(2,6-di-*O*-benzoyl-β-D-gluco-pyranosyl)-(1→3)-2,6-di-*O*-benzoyl-β-D-galactopyranoside (10). Coupling of **2** (100 mg, 0.11 mmol) with **3** (89 mg, 0.17 mmol) and ethyl 2,6-di-*O*-benzoyl-β-D-galacto-pyranoside (**5** 31 mg, 0.07 mmol), as described for **9**, yielded amorphous **10** (90 mg, 75%): $[\alpha]_D$ +2.7° (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$), after *O*-acetylation, δ 0.97 (t, 3H, J = 7.1 Hz, *Me*CH_2O), 1.25 (d, 3H, $J_{5,6}$ = 5.9 Hz , H-6d), 1.30, 1.48 (2s, 6H, Me_2C), 2.06 (s, 3H, AcO), 3.41 (dd, 1H, J_{gem} = 9.8 Hz, Me*CH*$_2$O), 3.72 (broad s, 1H, H-4d), 3.87 (dd, 1H, $J_{2,3}$ = 10.1 Hz , $J_{3,4}$ = 3.5 Hz , H-3a), 4.39 (d, 1H, $J_{1,2}$ = 8.0 Hz, H-1a), 4.47 (d, 1H, $J_{1,2}$= 8.7 Hz , H-1c), 4.56 (d, 1H, $J_{1,2}$ = 7.6 Hz , H-1b), 5.17-5.33 (m, 3H, H-2a, 2b, and 2c), 5.22 (d, 1H, $J_{1,2}$ = 4.0 Hz , H-1d), 5.49 (d, 1H, H-4a), and 6.8-8.2 (m, 45H, 9Ph).

Anal. Calcd for $C_{92}H_{92}O_{26}$ (1613.7): C, 68.48; H, 5.75. Found: C, 68.38; H, 5.46.

Ethyl *O*-(2,6-Di-*O*-benzoyl-3,4-*O*-isopropylidene-β-D-galactopyranosyl)-(1→4)-[*O*-(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)-(1→3)]-*O*-(2,6-di-*O*-benzoyl-β-D-gluco-pyranosyl)-(1→3)-*O*-(2,4,6-tri-*O*-benzyl-β-D-galacto-pyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (11). Coupling of **2** (80 mg, 0.09 mmol) with **3** (71 mg, 0.13 mmol) and ethyl *O*-(2,3,6-tri-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (**6** 54 mg, 0.06 mmol), as described for **9**, yielded amorphous **11** (66 mg, 53%): $[\alpha]_D$ -18.7° (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.21 (t, 3H, J = 7.0 Hz, *Me*CH_2O), 1.32, 1.51 (2s, 6H, Me_2C), 1.35 (d, 1H, $J_{5,6}$ = 6.6 Hz, H-6e), 4.20-4.25 (m, 2H, H-1 and H-1' of reducing end Lac), 4.55 (d, 1H, $J_{1,2}$ = 8.0 Hz, H-1d), 4.83 (d, 1H, $J_{1,2}$ = 7.8 Hz, H-1c), 5.25 (d, 1H, $J_{2,3}$ = 8.0 Hz, H-2d), 5.40 (d, 1H, $J_{1,2}$ = 3.7 Hz, H-1e), 5.50 (d, 1H, $J_{2,3}$ = 9.3 Hz, H-2c), and 6.8-8.2 (m, 65H, 13Ph).

Anal. Calcd for $C_{126}H_{130}O_{29}$ (2108.4): C, 71.78; H, 6.21. Found: C, 71.53; H, 6.07.

Ethyl *O*-(2,6-Di-*O*-benzoyl-3,4-*O*-isopropylidene-β-D-galactopyranosyl)-(1→4)-[*O*-(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)-(1→3)]-*O*-(2,6-di-*O*-benzoyl-β-D-gluco-pyranosyl)-(1→3)-*O*-(2,6-di-*O*-benzoyl-β-D-galacto-

pyranosyl)-(1→4)-2,3,6-tri-*O*-benzoyl-β-D-glucopyranoside (12). Coupling of **2** (100 mg, 0.11 mmol) with **3** (89 mg, 0.17 mmol) and ethyl *O*-(2,6-di-*O*-benzoyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzoyl-β-D-glucopyranoside (**7** 67 mg, 0.08 mmol), as described for **9**, yielded amorphous **12** (101 mg, 64%): $[\alpha]_D$ +18.4° (*c* 0.3, $CHCl_3$); ^1H NMR ($CDCl_3$), after *O*-acetylation, δ 1.04 (t, 3H, *Me*CH_2O), 1.23 (d, 1H, $J_{5,6}$ = 6.5 Hz, H-6e), 1.28, 1.47 (2s, 6H, Me_2C), 1.83 (s, 3H, AcO), 4.01 (t, 1H, $J_{3,4} = J_{4,5}$ = 9.6 Hz, H-4a), 4.04 (t, 1H, $J_{2,3} = J_{3,4}$ = 9.9 Hz, H-3c), 4.39-4.45 (3d, 3H, $J_{1,2}$ = 7.5 Hz, H-1b, 1c, and 1d), 4.57 (d, 1H, $J_{1,2}$ = 7.8 Hz, H-1a), 5.14-5.26 (m, 5H, H-1e, 2b, 2c, 2d, and 4b), 5.32 (dd, 1H, $J_{2,3}$ = 9.6 Hz, H-2a), 5.61 (t, 1H, H-3a), and 6.8-8.1 (m, 60H, 12Ph).

Anal. Calcd for $C_{119}H_{114}O_{34}$ (2088.2): C, 68.45; H, 5.50. Found: C, 68.30; H, 5.42.

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16. Compounds **6** and **7** could be easily synthesized from a lactose ethylglycoside. A.C. Schram, E.H. Byers, and R.H. Wilson, *Nature*, **197**, 1074 (1963). Compound **6**; ^{1}H NMR ($CDCl_3$) δ 1.27 (t, 3H, $\underline{Me}CH_2O$), 4.39 (d, 1H, $J_{1,2}$ = 8.1 Hz, H-1), 4.42 (d, 1H, $J_{1,2}$ = 8.1 Hz, H-1), 7.1 - 7.4 (m, 30H, 6Ph). Compound **7**; ^{1}H NMR ($CDCl_3$) δ 1.08 (t, 3H, $\underline{Me}CH_2O$), 4.14 (t, 1H, $J_{3,4}$ = 9.5 Hz, H-4 of Glc), 4.64 (d, 1H, $J_{1,2}$ = 7.9 Hz, H-1 of Gal), 4.65 (d, 1H, $J_{1,2}$ = 7.8 Hz, H-1 of Glc), 5.26 (dd, 1H, $J_{2,3}$ = 9.6 Hz, H-2 of Gal), 5.39 (dd, 1H, $J_{2,3}$ = 9.5 Hz, H-2 of Glc), 5.66 (t, 1H, H-3 of Glc), 7.2 - 8.1 (m, 25H, 5Ph).