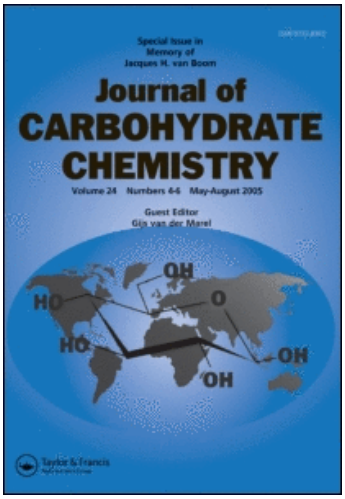

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Synthesis of Two Lewis^X Trisaccharides Using Regiospecific Glycosylation Reactions

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Synthesis of Two Lewis^x Trisaccharides Using Regiospecific Glycosylation Reactions

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Synthesis of two Lewis^X trisaccharides, namely, 2-(trimethylsilyl)ethyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl-(1 $\rightarrow$ 4)-6-*O*-benzyl-2-deoxy-3-*O*-(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)-2-phthalimido-β-D-glucopyranoside and 2-(trimethylsilyl)ethyl 2,3,4-tri-*O*-acetyl-6-*O*-*t*-butyldiphenylsilyl-β-D-galactopyranosyl-(1 $\rightarrow$ 4)-6-*O*-benzyl-2-deoxy-3-*O*-(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)-2-phthalimido-β-D-glucopyranoside, has been achieved using a regiospecific glycosylation strategy under NIS-TfOH activation. Two trisaccharides were prepared from monosaccharides without any protecting group manipulation.

Keywords Synthesis, Trisaccharide, Lewis^X, *N*-Iodosuccinimide, Trifluoromethanesulfonic acid

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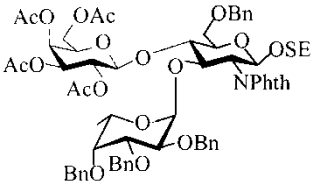
INTRODUCTION

Lewis^x and sulfated Lewis^x oligosaccharides have been attractive targets for synthesis owing to the important biological role of these compounds as potential ligands for selectins.[1] In all of these oligosaccharides sialic acid is present as NAcNeu α-(2 $\rightarrow$ 3)-Galp and is important for the trisaccharide to maintain a high affinity for E-Selectins.[2] However, replacement of this sialic acid residue with a sulfate group retains its affinity.[3] Therefore, synthesis of this suitably protected Lewis^x trisaccharide is very important so that the sialic acid or sulfate group can be introduced in proper position. Various groups[4–17] synthesized this trisaccharide backbone using different glycosylation strategies. Most of the synthetic strategy involves mainly two procedures: (1) galactosylation or fucosylation of the suitably protected glucosamine derivatives, having 3-OH or 4-OH unprotected, and (2) regioselective galactosylation or fucosylation of a glucosamine acceptor, having both 3-OH and 4-OH unprotected. The first synthetic strategy requires an elaborate protection of the acceptor while the second requires high regioselectivity. Different groups have synthesized the *N*-acetyllactosamine derivative by this regioselective glycosylation strategy[13,18,19] but either the regioselectivity of the glycosylation[18] was low or the yield of the reaction was not very good.[19]

In this paper, we describe the regioselective synthesis of *N*-acetyllactosamine derivatives under NIS-TfOH activation and their conversion to Lewis^x trisaccharides, which are suitable for the synthesis of silyl Lewis^x or sulfated anologues.



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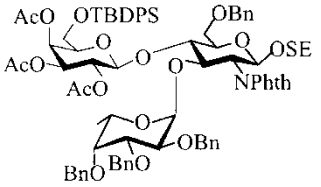

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RESULTS AND DISCUSSION

The known glucosamine acceptor 2-(trimethylsilyl)ethyl 6-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (**3**)[20] has two unprotected hydroxyl groups (3-OH and 4-OH) with different reactivities. We observed that disarmed galactopyranosyl donors **1** and **2** react regioselectively with the acceptor **3** under NIS-TfOH activation and the yield of the glycosidation reaction was high. The donor **1** reacts with the acceptor **3** to afford the disaccharide 2-(trimethylsilyl) ethyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl-(1 $\rightarrow$ 4)-6-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (**4**) in 80% yield, whereas the donor, phenyl 2,3,4-tri-*O*-acetyl-6-*O*-*t*-butyldiphenylsilyl-1-thio-β-D-galactopyranoide (**2**), under similar condition of glycosidation reaction afforded the disaccharide

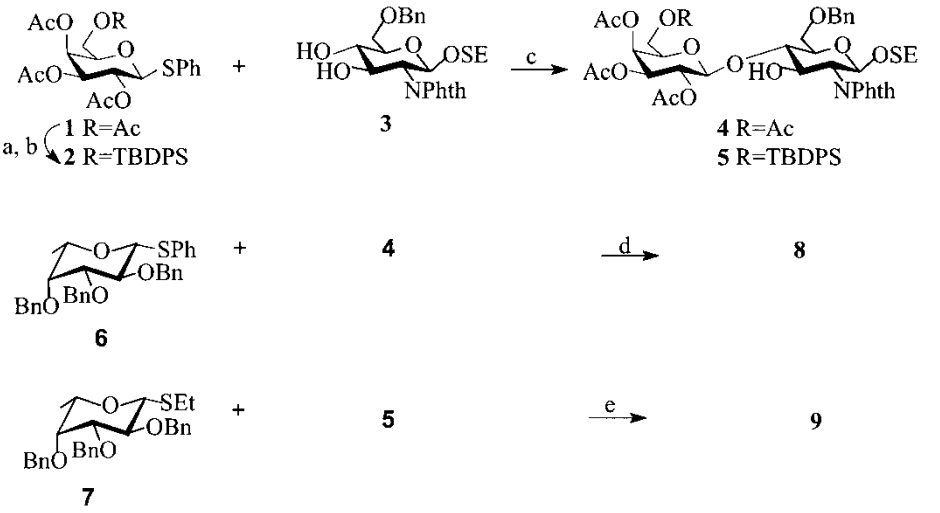
2-(trimethylsilyl)ethyl 2,3,4-tri-*O*-acetyl-6-*O*-*t*-butyldiphenylsilyl-β-D-galactopyranosyl-(1 → 4)-3-*O*-acetyl-6-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (**5**) in 88% yield. No undesired (1 → 3)-linked disaccharide was detected in the reaction mixture. Acetylation of the disaccharide (**4**) afforded the corresponding 3-*O*-acetate derivative, which shows a downfield shift of the H-3^A signal at δ 5.62 (dd, $J_{2,3} = 8.9$ Hz, $J_{3,4} = 10.6$ Hz) in its ^{1}H NMR spectrum. The downfield shift of the H-3^A signal also confirms that the disaccharide (**4**) is (1 → 4)-linked. The yield of these reactions clearly indicates that the 6-*O*-TBDPS group in the galactose residue has influence on the regioselectivity of glycosylation. For α-fucosylation, we have used phenyl 2,3,4-tri-*O*-benzyl-1-thio-β-L-fucopyranoside (**6**). The disaccharide acceptor **4** was reacted with the donor (**6**) under NIS-TfOH activation to afford the trisaccharide (2-trimethylsilyl)ethyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl-(1 → 4)-6-*O*-benzyl-2-deoxy-3-*O*-(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)-2-phthalimido-β-D-glucopyranoside (**8**) in good yield (65%). In spite of the steric hindrance of the phthalimido group, we were successful in introducing fucosyl group at 3-OH of the disaccharide acceptor **4** in good yield. Ellervik and Magnusson[13] reported that fucosylation at this hindered 3-OH was difficult under various reaction conditions. The α-anomeric configuration of this newly formed glycosidic linkage of trisaccharide **8** was confirmed from the signal at δ 4.75 ($J_{1,2} = 3.3$ Hz) in the ^{1}H NMR spectrum and the signal at δ 97.5 in the ^{13}C NMR spectrum. Mass spectroscopy of **8** also confirmed the formation of this trisaccharide. However, under similar glycosylation conditions, the donor **7** was reacted with the acceptor **5** to afford the trisaccharide (2-trimethylsilyl)ethyl 2,3,4-tri-*O*-acetyl-6-*O*-*t*-butyldiphenylsilyl-β-D-galactopyranosyl-(1 → 4)-6-*O*-benzyl-2-deoxy-3-*O*-(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)-2-phthalimido-β-D-glucopyranoside (**9**) in poor yield (35%). Under $CuBr_2$-TBAB activation the yield of compound **9** slightly improved (44%). From this glycosylation reaction we can conclude that the 6-*O*-TBDPS group at the galactose moiety has influence in the glycosylation at 3-OH of the glucosamine acceptor. The compound was characterized from ^{1}H, ^{13}C, and DEPT-135 NMR and mass spectroscopic data.

In conclusion, we have synthesized two Lewis^x trisaccharides using a minimal number of synthetic steps. These oligosaccharides are suitable for introducing sialic acid residues for conversion to the corresponding 3/6-*O*-sulphate analogues (Sch. 1).

EXPERIMENTAL

General Methods

Reactions were monitored by TLC on Silica Gel $60F_{254}$ (E. Merck). Column chromatography was performed on 100–200 mesh Silica Gel (SRL, India). The



Scheme 1: (a) NaOMe, MeOH, 30°C, 30 min, then IR-120 H^+ resin; (b) TBDPS-Cl, pyridine, 30°C, 2 hr, then Ac_2O, 0–30°C, 16 hr; (c) NIS,TfOH,CH_2Cl_2, –20°C, 1 hr; (d) NIS, TfOH, CH_2Cl_2, –20°C, 2 hr; (e) $CuBr_2$, TBAB, $ClCH_2CH_2Cl$-DMF(5:1), 30°C, 16 hr.

organic extracts were dried over anhydrous Na_2SO_4. All solvents were distilled and/or dried before use and all evaporations were conducted at or below 50°C under reduced pressure unless stated otherwise. Optical rotations were measured at 25°C with a JASCO DIP 360 polarimeter. The ^1H and ^{13}C NMR spectra were recorded with a Bruker DPX 300 spectrometer at 300 MHz using $CDCl_3$ as solvent and tetramethylsilane as the internal standard unless stated otherwise. Mass spectra were recorded on a Q-Tof of micromass spectrometer using electron spray ionization (ESI). Compound **1**,[23] **3**,[20] **6**,[22] and **7**[21] were synthesized as described in the literature.

Phenyl 2,3,4-tri-*O*-acetyl-6-*O*-*t*-butyldiphenylsilyl-1-thio-β-D-galacto-pyranoside (2). Compound **1** (5 g) was dissolved in MeOH (30 mL) and 50 mg NaOMe (in 5 mL MeOH) was added. The mixture was stirred for 30 min, neutralized by IR-120 H^+ resin, and filtered. The filtrate was coconcentrated twice with toluene to give phenyl 1-thio-β-D-galactopyranoside. The solid residue (3.6 g) was dissolved in pyridine (60 mL), and TBDPSCl (5 mL, 19.5 mmol) was added at rt. The mixture was stirred for 2 hr at 30°C and then Ac_2O (6.2 mL, 65 mmol) was added at 0°C. The mixture was kept overnight at rt and then coconcentrated twice with toluene. The residue was chromatographed (4:1 petroleum ether-EtOAc) to afford **2** (6 g, 82%) as an amorphous solid; $[\alpha]_D^{28} + 5.51$ (*c* 2.5, $CHCl_3$). ^1H NMR δ 7.65–7.25 (m, 15H, aromatic protons), 5.56 (d, 1H, $J_{3,4} = 3.2$ Hz, H-4), 5.22 (t, 1H, $J_{1,2} = J_{2,3} = 9.9$ Hz, H-2), 5.07 (dd, 1H, $J_{2,3} = 9.9$ Hz, $J_{3,4} = 3.2$ Hz, H-3), 4.71

(d, 1H, $J_{1,2} = 9.9$ Hz, H-1), 3.84–3.76 (m, 2H, H-6), 3.68–3.62 (m, 1H, H-5), 2.08, 1.99, 1.97 (s, 9H, 3 COCH_3), 1.03 [s, 9H, (CH_3)$_3$CSiPh$_2$]; ^{13}C NMR δ 170.0, 169.9, 169.4 (3 *C*OCH$_3$), 135.5–127.7 (aromatic carbons), 86.7 (C-1), 77.2, 72.3, 67.4, 67.4, 61.4 (C-6), 26.6 [(*C*H$_3$)$_3$CSiPh$_2$], 20.8, 20.6, 20.5 (3 CO*C*H$_3$), 18.9 [(CH$_3$)$_3$*C*SiPh$_2$]. TOF MS (ESI +) Found: 659[M + Na]$^+$.

Anal. Calcd for $C_{34}H_{40}SSiO_8$ (636.22): C, 64.12; H, 6.33. Found: C, 64.01; H, 6.23.

2-(Trimethylsilyl)ethyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl-(1 → 4)-6-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (4). A mixture of donor **1** (109 mg, 0.24 mmol), acceptor **3** (100 mg, 0.2 mmol), and 4 Å MS (250 mg) in CH_2Cl_2 (2 mL) was allowed to stir at rt for 2 hr. The mixture was then cooled to −20°C and NIS (64.8 mg, 0.288 mmol) and TfOH (2 μL, 0.024 mmol) were added. After stirring for 45 min, when TLC (7:1 toluene-EtOAc) showed optimum conversion, reaction was quenched with the addition of Et_3N, and then diluted with CH_2Cl_2 (25 mL) and filtered through a Celite bed. The filtrate was washed successively with aq. $Na_2S_2O_3$, saturated aqueous $NaHCO_3$, and water. The organic layer was dried (Na_2SO_4) and evaporated to a syrup. Column chromatography with 6:1 toluene-EtOAc yielded **4** (132 mg, 80%) as a glassy syrup; $[\alpha]_D^{28} + 13.71$ (*c* 1.05, $CHCl_3$). ^{1}H NMR δ 7.24–7.82 (m, 9H, aromatic protons), 5.30 (d, 1H, $J_{3,4} = 3.1$ Hz, H-4^B), 5.19 (d, 1H, $J_{1,2} = 8.5$, H-1^A), 5.17 (t, $J = 8.2$ Hz, H-2^B), 4.91 (dd, 1H, $J_{2,3} =$ 10.5 Hz, $J_{3,4} = 3.39$ Hz, H-4^B), 4.73, 4.52 (2 d, 2H, $J = 12.1$ Hz, CH_2Ph), 4.47 (d, 1H, $J_{1,2} = 8.0$ Hz, H-1^B), 4.39 (m, 1H, H-3^A), 4.13 (m, 1H, H-2^A), 3.89 (m, 1H, H-5^A), 3.59–3.74 (m, 5H, H-5^B, H-6^A, H-6^B), 3.49 (m, 2H, OCH_2CH$_2$SiMe$_3$), 2.13, 2.00, 1.95, 1.89 (s, 12H, 4 COCH_3), 0.82 (m, 2H, OCH$_2$CH_2SiMe$_3$), −1.5 (s, 9H, SiMe$_3$); ^{13}C NMR δ 170.4, 170.0, 169.9, 169.1 (4 *C*OCH$_3$), 138.1–127.5 (aromatic carbons), 101.5 (C-1^B), 97.7 (C-1^A), 74.1, 73.6, 73.6 (O*C*H$_2$CH$_2$Si), 71.1, 69.7, 68.7, 67.9 (C-6^A), 66.9, 66.8, 65.9, 61.4 (C-6^B), 56.0 (C-2^B), 20.6, 20.6, 20.5, 20.5 (4CO*C*H$_3$), 17.7 (OCH$_2$*C*H$_2$Si), −1.5 (SiMe$_3$); TOF MS (ESI +) Found: 852[M + Na]$^+$.

Anal. Calcd for $C_{40}H_{51}SiNO_{16}$ (829.30): C, 57.89; H, 6.19; N, 1.69. Found: C, 57.67; H, 6.32; N, 1.61.

2-(Trimethylsilyl)ethyl 2,3,4-tri-*O*-acetyl-6-*O*-*t*-butyldiphenylsilyl-β-D-galactopyranosyl-(1 → 4)-3-*O*-acetyl-6-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (5). The donor **2** (152.4 mg, 0.24 mmol) was reacted with the acceptor **3** (100 mg, 0.2 mmol) in the same manner as in the case of **4** and the resulting product was purified by column chromatography with 7:1 toluene-EtOAc to afford the disaccharide **5** (184 mg, 88%) as amorphous solid. $[\alpha]_D^{28}$ −11.21 (*c* 2.14, $CHCl_3$). ^{1}H NMR δ 7.65–7.32 (m, 19H, aromatic protons), 5.35 (d, 1H, $J_{3,4} = 3.2$ Hz, H-4^B), 5.17 (d, 1H, $J_{1,2} = 8.6$ Hz, H-1^B), 5.14 (t, 1H, $J = 8.1$ Hz, H-2^B), 4.91 (dd, 1H, $J_{2,3} = 10.5$ Hz, $J_{3,4} = 3.3$ Hz,

H-3^{B}), 4.73, 4.53 (2 d, 2H, $J = 12.1$ Hz, CH_2Ph), 4.52 (d, 1H, $J_{1,2} = 7.9$ Hz, H-1^{A}), 4.44 (t, 1H, $J = 8.8$ Hz, H-3^{A}), 4.13 (dd, 1H, $J_{1,2} = 8.6$ Hz, $J_{2,3} = 10.7$ Hz, H-2^{A}), 4.02 (d, 1H, $J = 1.3$ Hz, 3-OH), 3.92 (m, 1H, H-5^{A}), 3.76–3.61 (m, 5H, H-5^{B}, H-6^{A}, H-6^{B}), 3.47 (m, 2H, OCH_2CH_2Si), 1.98, 1.94, 1.94 (3 s, 9H, 3 COCH_3), 0.83 [s, 9H, (CH_3)$_3$CPh$_2$Si], 0.75 [M, 2H, OCH$_2$CH_2Si], −0.15 [s, 9H, Si(CH_3)$_3$]; ^{13}C NMR δ 170.0, 169.9, 169.3 (3 COCH$_3$), 138.3–127.7 (aromatic carbons), 101.5 (C-1^{B}), 97.8 (C-1^{A}), 81.9 (C-4^{A}), 74.3, 73.8, 73.7 (OCH$_2$CH$_2$Si), 71.0, 69.9, 69.1, 68.1 (C-6^{A}), 66.9, 66.9, 61.4 (C-6^{B}), 55.8 (C-2^{B}), 26.5 [(CH$_3$)$_3$CPh$_2$Si], 20.7, 20.6, 20.5 (3 COCH$_3$), 18.7 [(CH$_3$)$_3$$CPh_2$Si], 17.7 [OCH$_2$$CH_2$Si], −1.5 [Si($CH_3$)$_3$]. TOF MS (ESI +) Found: 1048[M + Na]$^+$.

Anal. Calcd for $C_{54}H_{67}Si_2NO_{15}$(1025.40): C, 63.20; H, 6.58; N, 1.36. Found: C, 63.02; H, 6.41; N 1.45.

2-(Trimethylsilyl)ethyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl-(1 → 4)-6-*O*-benzyl-2-deoxy-3-*O*-(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)-2-phthalimido-β-D-glucopyranoside (8). The donor **6** (102 mg, 0.19 mmol) was reacted with the acceptor **4** (134 mg, 0.16 mmol) in the same manner as in the case of **4** and the product was purified on column chromatography with 3:1 toluene-EtOAc to yield trisaccharide **8** (130 mg, 65%). $[\alpha]_D^{28} + 3.35$ (*c* 1.8, $CHCl_3$); ^{1}H NMR δ 7.41–7.03 (m, 24 H, aromatic protons), 5.23 (d, 1H, $J = 3.4$ Hz, H-4^{B}), 5.08 (d, 1H, $J = 8.4$ Hz, H-1^{A}), 5.01 (t, $J = 8.4$, H-2^{B}), 4.75 (d, 1H, $J = 3.2$, H-1^{C}), 4.67 (d, 1H, $J = 7.9$, H-1^{B}), 2.01, 2.00, 1.94, 1.85 (4 s, 12 H, 4 COCH_3), 1.20 (d, 3H, $J = 6.3$ Hz, H-6^{C}), 0.72 (m, 2H, OCH$_2$CH_2Si), −0.15 [s, 9H, SiMe$_3$]; ^{13}C NMR δ 170.2, 170.1, 170.0, 168.8 (4 COCH$_3$), 140.9–127.0 (aromatic carbons), 99.5 (C-1^{B}), 97.8 (C-1^{A}), 97.5 (C-1^{C}), 79.8, 77.2, 75.4, 75.3, 74.6 (5 CH), 74.2, 73.6, 72.9 (3 CH$_2$Ph), 72.6 (CH), 72.4 (PhCH$_2$), 71.0, 70.4, 69.1 (3 CH), 67.8 [OCH$_2$CH$_2$Si], 66.8 (C-6^{A}), 66.4 (CH), 60.3 (C-6^{B}), 56.4 (C-2^{A}), 20.7, 20.6, 20.5 (3 COCH$_3$), 17.8 (OCH$_2$$CH_2$Si), 16.7 (C-$CH_3$), −1.5 [Si($CH_3$)$_3$]. TOF MS (ESI +) Found: 1268[M + Na]$^+$.

Anal. Calcd for $C_{67}H_{79}NSiO_{20}$(1245.50): C, 64.56; H, 6.69; N, 1.12. Found: C, 64.82; H, 6.74; N, 1.18.

2-(Trimethylsilyl)ethyl 2,3,4-tri-*O*-acetyl-6-*O*-*t*-butyldiphenylsilyl-β-D-galactopyranosyl-(1 → 4)-6-*O*-benzyl-2-deoxy-3-*O*-(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)-2-phthalimido-β-D-glucopyranoside (9). A solution of **5** (100 mg, 0.095 mmol) and **7** (91 mg, 0.19 mmol) in 2 mL ClCH$_2$CH$_2$Cl-DMF (5:1) was added to a stirred mixture of $CuBr_2$ (52 mg, 0.23 mmole), tetrabutylammonium bromide (74 mg, 23 mmole), and freshly activated powdered MS 4A (200 mg) under nitrogen. The reaction was stirred for 50 hr at rt. The reaction mixture was filtered through Celite and washed with CH_2Cl_2. The combined filtrate and washings were washed with saturated $NaHCO_3$ solution and then with water, dried (Na_2SO_4), and concentrated.

Column chromatography of the residue with ethyl acetate-pet ether (3:7) yielded the solid product **9** (61 mg, 44%). $[\alpha]_D^{28}$ −19.9 (*c* 1.6, $CHCl_3$); ^{1}H NMR δ 7.49–6.86 (m, 34 H, aromatic protons), 5.50 (d, 1H, $J = 2.93$ Hz, H-4^B), 5.03 (d, 1H, $J = 8.51$ Hz, H-1^A), 4.82 (d, 1H, $J = 4.17$ Hz, H-1^C), 4.62 (d,1H, $J =$ 5.66 Hz, H-1^B), 2.02, 1.96, 1.74 (s, 12H, 4 COCH_3), 1.11 (d, 1H, $J = 6.5$ Hz, H-6^C), 0.98 (s, 9H, Me_3CPh_2Si), 0.79 (m, 2H, OCH_2CH_2Si), −0.15 (s, 9H, $SiMe_3$); ^{13}C NMR δ 170.1, 169.7, 168.8 (3 COCH_3), 138.4–123.5 (aromatic carbons), 99.7 (C-1^B), 97.8 (C-1^A), 97.3 (C-1^C), 79.5, 77.2, 75.4, 75.3, 74.4, 74.3 (6 ring CH), 73.5, 72.8, 72.7, 72.6, 72.4, 71.4, 69.4, 67.7, 66.8, 66.8 [OCH_2CH_2Si], 66.2 (C-6^A), 59.9 (C-6^B), 56.4 (C-2^A), 26.7, 21.0, 20.8, 20.7 (3 COCH_3), 18.9 (OCH_2CH_2Si), 17.8, 16.5 (C-CH_3), −1.5 [Si(CH_3)$_3$]. TOF MS (ESI +) Found: 1464[M + Na]$^+$.

Anal. Calcd for $C_{81}H_{95}Si_2NO_{19}$ (1441.60): C, 67.43; H, 6.64; N, 0.97. Found: C, 67.65; H 6.81; N, 1.11.

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