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Convergent synthesis of a common pentasaccharide-repeating unit corresponding to the O-specific polysaccharide of *Escherichia coli* O4:K3, O4:K6, and O4:K12

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ABSTRACT

A convergent chemical synthesis of a pentasaccharide found in the O-specific polysaccharide of *Escherichia coli* O4:K3, O4:K6, and O4:K12 has been achieved in excellent yield. A [3+2] block synthetic strategy has been adopted to couple a disaccharide donor **11** with a trisaccharide acceptor **10** for the construction of the pentasaccharide derivative **12** which on deprotection furnished target pentasaccharide **1** as its 4-methoxyphenyl glycoside. Disaccharide thioglycoside donor **11** and trisaccharide acceptor **10** were prepared from suitably protected monosaccharide intermediates. Yields were excellent in all steps.

1. Introduction

Escherichia coli is an extremely diverse bacterial species, which colonizes in numerous niches in both the environment and animal hosts. Although, *E. coli* and other commensal intestinal microorganisms form a beneficial symbiotic relationship with their host,[1] some strains of *E. coli* behave in a pathogenic nature and cause serious disease both within the intestinal tract and elsewhere within the host.[2] Among several virulent *E. coli* strains, Shiga-toxin-producing *E. coli* (STEC) has emerged as a major cause of foodborne infections. They are associated with outbreaks or sporadic cases of bloody diarrhea, hemorrhagic colitis (HC), hemolytic uremic syndrome (HUS), and thrombotic thrombocytopenic purpura (TTP).[3] In the past, several epidemics arose due to the infection of STEC strains of serotype O157:H7.[4] Besides *E. coli* O157, a number of diarrhea-causing STEC strains have been characterized which include, *E. coli* O4, O26, O55, O103, O111, and O145.[5] Jann et al. reported the structure of a pentasaccharide-repeating unit present in the O-specific polysaccharide of *E. coli* O4:K3, O4:K6, and O4:K12 (Fig. 1).[6] O-Specific polysaccharides (O-antigens) present in the outer membrane of Gram-negative bacteria plays a critical role during the initial stage of infection and immune responses in the host. Therefore, glycoconjugates corresponding to the O-antigen could be very useful in the immunochemical studies for their bioevaluation as possible glyco-vaccine candidates.[7] For the extensive biochemical studies of glycoconjugates of the bacterial O-antigens it is essential to have substantial quantities of oligosaccharides in hand. Since, the natural source cannot provide a large quantity of the oligosaccharides, chemical synthesis of oligosaccharides is extremely useful in this context. As a part of the ongoing program on the synthesis of microbial oligosaccharides,[8] we describe herein a convergent chemical synthesis of the pentasaccharide-repeating unit corresponding to the O-specific polysaccharide from enterohemorrhagic *E. coli* O4:K3, O4:K6, and O4:K12 as its 4-methoxyphenyl (PMP) glycoside using a block synthetic approach (Fig. 2). The PMP group has been chosen as a temporary anomeric protecting group[9] for its easy removal at the end of the chemical synthesis under oxidative condition to furnish hexasaccharide hemiacetal useful in the preparation of glycoconjugates.

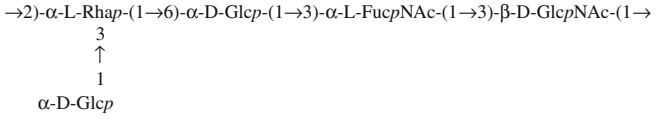

Figure 1. Structure of the pentasaccharide-repeating unit corresponding to the O-specific polysaccharide of *Escherichia coli* O4:K3, O4:K6, and O4:K12.

2. Results and discussion

Synthesis of the target pentasaccharide as its PMP glycoside (Fig. 2) has been achieved using a [3+2] block synthetic strategy. The synthetic strategy comprises a number of notable points, which are (a) α-selective glycosylation of 2-azido-L-fucosamine derivative **3**, prepared from L-fucose; (b) application of 'armed–disarmed' concept in the iodonium ion-mediated glycosylation of two thioglycoside derivatives tuning one as donor and the other as acceptor;[10] (c) exclusively stereoselective glycosylation of a disaccharide donor **11** with a trisaccharide acceptor **10**, and (d) use of the PMP group as a temporary anomeric protecting group.

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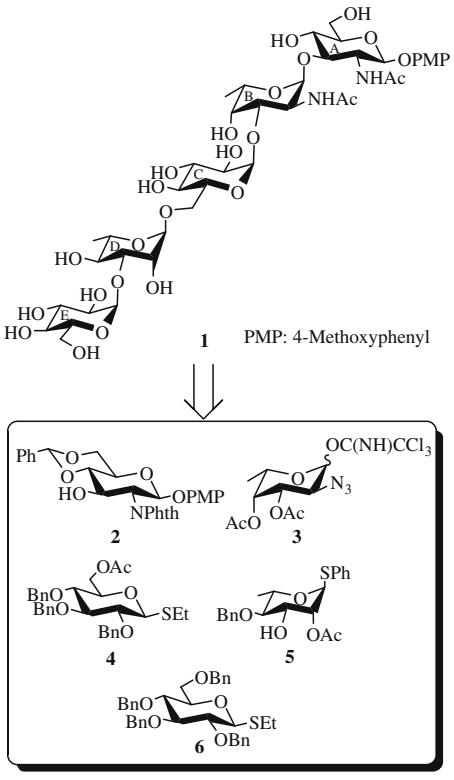
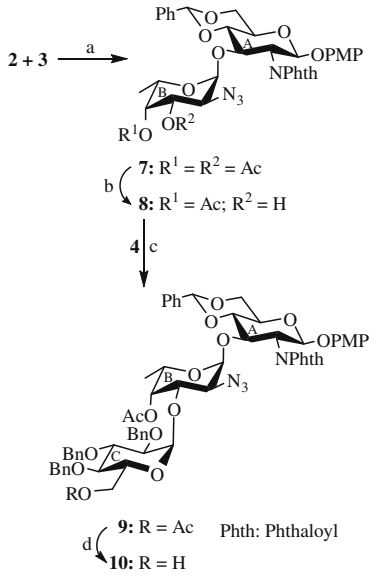


Figure 2. Chemical structure of the synthesized pentasaccharide as its PMP glycoside (**1**).

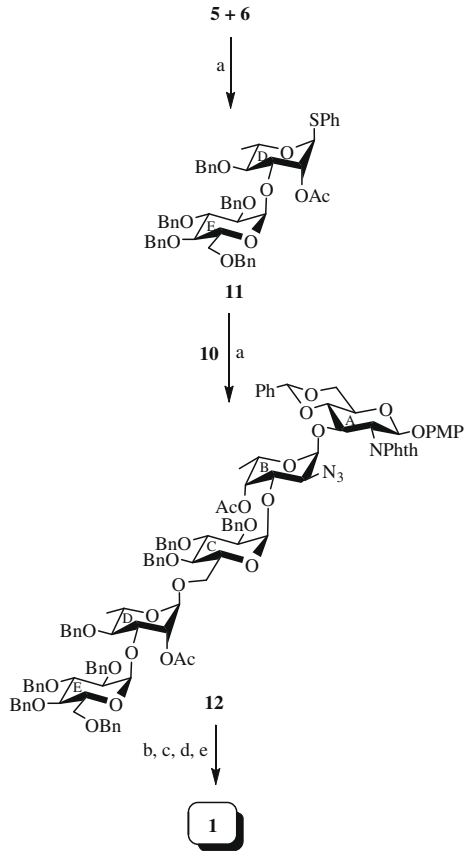
The trisaccharide derivative **10** was synthesized by sequentially assembling three suitably protected monosaccharide derivatives **2**,[11] **3**,[12] and **4**.[13] 4-Methoxyphenyl 4,6-*O*-benzylidene-2-deoxy-2-*N*-phthalimido-β-D-glucopyranoside **2** (prepared from D-glucosamine hydrochloride in five steps) was allowed to condense with 3,4-di-*O*-acetyl-2-azido-2-deoxy-α/β-L-fucopyranosyl trichloroacetimidate **3** (prepared from L-fucose in four steps following Roy et al.[12]) under Schmidt's glycosylation condition[14] to furnish exclusively 4-methoxyphenyl (3,4-di-*O*-acetyl-2-azido-2-deoxy-α-L-fucopyranosyl)-(1→3)-4,6-*O*-benzylidene-2-deoxy-2-*N*-phthalimido-β-D-glucopyranoside **7** in 73% yield. Presence of signals in the NMR spectra [δ 5.66 (d, J = 8.5 Hz, H-1_A), 5.55 (s, PhC*H*), 4.66 (d, J = 3.6 Hz, H-1_B) in the ^{1}H NMR and δ 102.9 (Ph*C*H), 99.3 (C-1_B) and 98.7 (C-1_A) in the ^{13}C NMR spectra] unambiguously confirmed the formation of compound **7**. Saponification of compound **7** followed by orthoesterification[15] and hydrolysis of the resulting orthoester resulted in the formation of 4-methoxyphenyl (4-*O*-acetyl-2-azido-2-deoxy-α-L-fucopyranosyl)-(1→3)-4,6-*O*-benzylidene-2-deoxy-2-*N*-phthalimido-β-D-glucopyranoside **8** in 90% yield. Iodonium ion-mediated glycosylation of compound **8** with thioglycoside donor **4** in the presence of a combination of *N*-iodosuccinimide (NIS) and trifluoromethanesulfonic acid (TfOH)[16] furnished 4-methoxyphenyl (6-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl)-(1→3)-(4-*O*-acetyl-2-azido-2-deoxy-α-L-fucopyranosyl)-(1→3)-4,6-*O*-benzylidene-2-deoxy-2-*N*-phthalimido-β-D-glucopyranoside **9** in 70% yield together with minor amount of its β-isomer (~10%), which on deacetylation afforded the trisaccharide derivative **10** in 96% yield. Formation of compound **9** was confirmed through spectral analysis [δ 5.68 (d, J = 8.5 Hz, H-1_A), 5.55 (s, PhC*H*), 4.87 (br s, H-1_B), 4.74 (d, J = 3.7 Hz, H-1_C) in the ^{1}H NMR and δ 103.0 (PhCH), 100.0 (C-1_B), 99.8 (C-1_C), 98.7 (C-1_A) in the ^{13}C NMR spectra] (Scheme 1).

In another experiment, phenyl 2-*O*-acetyl-4-*O*-benzyl-1-thio-α-L-rhamnopyranoside **5**[17] was allowed to condense with ethyl



Scheme 1. Reagents and conditions: (a) TMSOTf, CH_2Cl_2, −20 °C, 45 min, 73%; (b) (i) 0.01 M CH_3ONa, CH_3OH, room temperature, 30 min; (ii) triethylorthoacetate, *p*-TsOH, DMF, room temperature, 2 h; (iii) 80% AcOH, 30 min, room temperature, 90%; (c) NIS, TfOH, CH_2Cl_2, −40 °C, 30 min, 70%; (d) 0.01 M CH_3ONa, CH_3OH, room temperature, 30 min, 96%.

2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside **6**[18] using a combination of NIS and TfOH[16] applying 'arm-disarmed' strategy[10]



Scheme 2. Reagents and conditions: (a) NIS, TfOH, CH_2Cl_2, −40 °C, 30 min, 81% for **11** and 76% for **12**; (b) ethylene diamine, *n*-BuOH, 90 °C, 8 h; (c) acetic anhydride, pyridine, room temperature, 3 h; (d) H_2, 20% $Pd(OH)_2$–C, CH_3OH–AcOH, room temperature, 24 h; (e) (i) acetic anhydride, pyridine, room temperature, 3 h; (ii) 0. 1 M CH_3ONa, CH_3OH, room temperature, 3 h, over all 70%.

to furnish phenyl (2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-(1→3)-2-*O*-acetyl-4-*O*-benzyl-1-thio-α-L-rhamnopyranoside **11** in 81% yield together with its β-isomer (<10%). Stereoselective formation of compound **11** was confirmed through spectral analysis [δ 5.37 (br s, H-1_D), 5.14 (d, J = 3.4 Hz, H-1_E), 1.37 (d, J = 6.2 Hz, CCH_3) in the ^{1}H NMR and δ 93.0 (C-1_E), 86.4 (C-1_D), 18.2 (CCH_3) in the ^{13}C NMR spectra of compound **11**]. Stereoselective glycosylation of trisaccharide derivative **10** with disaccharide thioglycoside **11** in the presence of a combination of NIS and TfOH furnished 4-methoxyphenyl (2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-(1→ 3)-(2-*O*-acetyl-4-*O*-benzyl-α-L-rhamnopyranosyl)-(1→6)-(2,3, 4-tri-*O*-benzyl-α-D-glucopyranosyl)-(1→3)-(4-*O*-acetyl-2-azido-2-deoxy-α-L-fucopyranosyl)-(1→3)-4,6-*O*-benzylidene-2-deoxy-2-*N*-phthalimido-β-D-glucopyranoside **12** in 76% yield. Spectral analysis of compound **12** confirmed its formation [δ 5.71 (d, J = 8.4 Hz, H-1_A), 5.53 (s, PhC*H*), 5.15 (d, J = 3.4 Hz, H-1_E), 4.79 (d, J = 3.5 Hz, H-1_C), 4.76 (d, J = 3.5 Hz, H-1_B), 4.66 (br s, H-1_D) in the ^{1}H NMR and δ 102.8 (PhCH), 99.8 (C-1_C), 99.7 (C-1_B), 98.7 (C-1_D), 98.6 (C-1_A), 93.2 (C-1_E) in the ^{13}C NMR spectra of compound **12**]. Finally, transformation of *N*-phthalimido and azido groups to acetamido group[19,20] followed by deprotection of the pentasaccharide derivative furnished target compound **1** in 70% yield. Compound **1** was characterized by the appearance of signals in the ^{1}H NMR [δ 4.87 (br s, H-1_E), 4.85 (br s, H-1_C), 4.82 (br s, H-1_B), 4.68 (br s, H-1_D), 4.65 (br s, H-1_A)] and in the ^{13}C NMR spectra [δ 102.0 (C-1_B), 100.4 (3C, C-1_A, C-1_C, C-1_D), 95.3 (C-1_E)] (Scheme 2).

3. Conclusion

In summary, a convergent synthetic strategy for the preparation of the common pentasaccharide-repeating unit corresponding to the O-specific polysaccharide of *E. coli* O4:K3, O4:K6, and O4:K12 has been developed successfully. A successful stereoselective [3+2] glycosylation allowed to achieve the target pentasaccharide in minimum number of steps. A 'armed–disarmed' approach has been applied for the preparation of disaccharide thioglycoside derivative. All intermediate steps were reasonably high yielding and reproducible for a scale-up preparation.

4. Experimental

4.1. General methods

All the reactions were monitored by thin layer chromatography over silica gel-coated TLC plates. The spots on TLC were visualized by warming ceric sulfate (2% $Ce(SO_4)_2$ in 2 N H_2SO_4)-sprayed plates on a hot plate. Silica gel 230–400 mesh was used for column chromatography. ^{1}H and ^{13}C NMR, DEPT 135, 2D COSY, and HMQC spectra were recorded on Brucker Avance DRX 500 MHz using $CDCl_3$ and CD_3OD as solvents and TMS as internal reference unless stated otherwise. Chemical shift values are expressed in δ ppm. ESI-MS were recorded on a Micromass Quttro II mass spectrometer. Elementary analysis was carried out on Carlo Erba-1108 analyzer. Optical rotations were measured at 25 °C on a Perkin Elmer 341 polarimeter. Commercially available grades of organic solvents of adequate purity are used in many reactions.

4.2. 4-Methoxyphenyl (3,4-di-*O*-acetyl-2-azido-2-deoxy-α-L-fucopyranosyl)-(1→3)-4,6-*O*-benzylidene-2-deoxy-2-*N*-phthalimido-β-D-glucopyranoside 7

To a solution of compound **2** (2.0 g, 3.97 mmol) and compound **3** (2.0 g, 4.76 mmol) in anhydrous CH_2Cl_2 (15 mL) was added trimethylsilyl trifluoromethane sulfonate (TMSOTf; 50 μL) at −20 °C under argon and the reaction mixture was allowed to stir at the same temperature for 45 min. The reaction was quenched with Et_3N (0.1 mL) and the reaction mixture was diluted with CH_2Cl_2 (50 mL). The organic layer was successively washed with satd $NaHCO_3$ and water, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified over SiO_2 using hexane–EtOAc (6:1) as eluant to give pure compound **7** (2.2 g, 73%). Colorless oil; $[\alpha]_D^{25} = -16.8$ (c 1.0, $CHCl_3$); ν_{max} (neat): 2937, 2111, 1751, 1715, 1507, 1389, 1220, 1101, 1036, 967, 722 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87–7.84 (m, 9H, Ar-H), 6.81 (d, J = 9.0 Hz, 2H, Ar-H), 6.71 (d, J = 9.0 Hz, 2H, Ar-H), 5.66 (d, J = 8.5 Hz, 1H, H-1_A), 5.55 (s, 1H, PhC*H*), 5.15 (dd, J = 11.0, 3.2 Hz, 1H, H-3_B), 5.06 (d, J = 2.6 Hz, 1H, H-4_B), 4.70 (t, J = 10.4 Hz each, 1H, H-3_A), 4.66 (d, J = 3.6 Hz, 1H, H-1_B), 4.54 (dd, J = 8.5, 8.5 Hz, 1H, H-2_A), 4.39 (dd, J = 10.8, 3.9 Hz, 1H, H-6_{aA}), 4.17–4.16 (m, 1H, H-5_B), 3.86 (t, J = 10.6 Hz each, 1H, H-6_{bA}), 3.78–3.74 (m, 2H, H-5_A, H-4_A), 3.70 (s, 3H, OCH_3), 3.45 (dd, J = 11.0, 3.6 Hz, 1H, H-2_B), 2.0 (s, 3H, COCH_3), 1.93 (s, 3H, COCH_3), 0.41 (d, J = 6.5 Hz, 3H, CCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 169.8 (2COCH$_3$), 167.0, 167.1 (Phth), 156.0–114.9 (Ar-*C*), 102.9 (PhCH), 99.3 (C-1_B), 98.7 (C-1_A), 80.7 (C-4_A), 75.8 (C-3_A), 71.0 (C-4_B), 69.7 (C-3_B), 69.1 (C-6_A), 67.1 (C-5_A), 65.5 (C-5_B), 58.1 (C-2_B), 55.8 (C-2_A), 53.1 (OCH_3), 20.9, 20.8 (2COCH_3), 10.6 (CCH_3); ESI-MS: m/z 781.2 [M+Na]$^+$; Anal. Calcd for $C_{38}H_{38}N_4O_{13}$ (758.24): C, 60.15; H, 5.05. Found: C, 60.0; H, 5.30.

4.3. 4-Methoxyphenyl (4-*O*-acetyl-2-azido-2-deoxy-α-L-fucopyranosyl)-(1→3)-4,6-*O*-benzylidene-2-deoxy-2-*N*-phthalimido-β-D-glucopyranoside 8

A solution of compound **7** (2.0 g, 2.63 mmol) in 0.01 M CH_3ONa in CH_3OH (25 mL) was allowed to stir at room temperature for 30 min. The reaction mixture was neutralized with Dowex 50W X-8 (H^+) resin, filtered, and evaporated to dryness. To a solution of the dry mass in dry DMF (10 mL) were added triethylorthoacetate (3.0 mL, 16.36 mmol) and *p*-TsOH (100 mg) and the reaction mixture was allowed to stir at room temperature for 2 h. It was neutralized with Et_3N (1.0 mL) and the solvents were removed under reduced pressure. A solution of the crude mass in 80% aq AcOH (20 mL) was allowed to stir at room temperature for 30 min. The reaction mixture was evaporated and co-evaporated with toluene to give the crude product, which was purified over SiO_2 using hexane–EtOAc (5:1) as eluant to furnish pure compound **8** (1.7 g, 90%). Colorless oil; $[\alpha]_D^{25} = -19.4$ (c 1.0, $CHCl_3$); ν_{max} (neat): 2936, 2112, 1776, 1744, 1714, 1508, 1396, 1230, 1102, 1032, 966, 756 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75–7.34 (m, 9H, Ar-H), 6.84 (d, J = 9.0 Hz, 2H, Ar-H), 6.74 (d, J = 9.0 Hz, 2H, Ar-H), 5.72 (d, J = 8.5 Hz, 1H, H-1_A), 5.56 (s, 1H, PhC*H*), 4.97 (d, J = 2.5 Hz, 1H, H-4_B), 4.69 (t, J = 10.3 Hz each, 1H, H-3_A), 4.67 (d, J = 3.8 Hz, 1H, H-1_B), 4.55 (dd, J = 8.5, 8.5 Hz, 1H, H-2_A), 4.42 (dd, J = 10.5, 3.9 Hz, 1H, H-6_{aA}), 4.15–4.08 (m, 2H, H-5_B, H-3_B), 3.90–3.86 (m, 1H, H-6_{bA}), 3.77–3.75 (m, 2H, H-4_A, H-5_A), 3.71 (s, 3H, OCH_3), 3.29 (dd, J = 10.5, 3.5 Hz, 1H, H-2_B), 2.04 (s, 3H, COCH_3), 0.50 (d, J = 6.5 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.6 (*C*OCH$_3$), 167.1, 167.2 (Phth), 156.0–114.9 (Ar-*C*), 102.7 (PhCH), 99.6 (C-1_B), 98.7 (C-1_A), 81.2 (C-4_A), 76.2 (C-3_A), 73.8 (C-4_B), 69.0 (C-6_A), 68.2 (C-3_B), 67.1 (C-5_B), 65.8 (C-5_A), 61.2 (C-2_B), 56.2 (C-2_A), 55.8 (OCH_3), 21.0 (COCH_3), 15.6 (CCH_3); ESI-MS: m/z 739.2 [M+Na]$^+$; Anal. Calcd for $C_{36}H_{36}N_4O_{12}$ (716.23): C, 60.33; H, 5.06. Found: C, 60.10; H, 5.38.

4.4. 4-Methoxyphenyl (6-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl)-(1→3)-(4-*O*-acetyl-2-azido-2-deoxy-α-L-fucopyranosyl)-(1→3)-4,6-*O*-benzylidene-2-deoxy-2-*N*-phthalimido-β-D-glucopyranoside 9

To a solution of compound **8** (1.2 g, 1.67 mmol) and compound **4** (1.1 g, 2.05 mmol) in anhydrous CH_2Cl_2 (10 mL) was added MS

4 Å (1 g) and the reaction mixture was allowed to stir at room temperature for 30 min under argon. It was cooled to −40 °C and *N*-iodosuccinimide (NIS; 550 mg, 2.44 mmol) followed by TfOH (5 μL) was added to it. After stirring at the same temperature for 30 min, the reaction was quenched with Et_3N (50 μL) and the reaction mixture was filtered through a Celite® bed and washed with CH_2Cl_2 (50 mL). The combined organic layer was washed with 5% $Na_2S_2O_3$, satd $NaHCO_3$, water in succession, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified over SiO_2 using hexane–EtOAc (8:1) as eluant to give pure **9** (1.4 g, 70%). Colorless oil; $[\alpha]_D^{25} = +15.2$ (*c* 1.0, $CHCl_3$); ν_{max} (neat): 2925, 2112, 1744, 1713, 1507, 1392, 1227, 1100, 1027, 827 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.49–7.21 (m, 24H, Ar-H), 6.83 (d, *J* = 9.0 Hz, 2H, Ar-H), 6.73 (d, *J* = 9.0 Hz, 2H, Ar-H), 5.68 (d, *J* = 8.5 Hz, 1H, H-1_A), 5.55 (s, 1H, PhC*H*), 5.04 (d, *J* = 2.4 Hz, 1H, H-4_B), 4.89 (d, *J* = 11.2 Hz, 1H, PhCH_2), 4.87 (br s, 1H, H-1_B), 4.78 (t, *J* = 10.8 Hz each, 1H, H-3_A), 4.74 (d, *J* = 3.7 Hz, 1H, H-1_C), 4.72–4.69 (m, 3H, PhCH_2), 4.66 (m, 1H, PhCH_2), 4.62 (dd, *J* = 8.5, 8.5 Hz, 1H, H-2_A), 4.52 (d, *J* = 11.1 Hz, 1H, PhCH_2), 4.42 (dd, *J* = 12.5, 3.9 Hz, 1H, H-6_{aA}), 4.18 (m, 1H, H-6_{abC}), 4.05 (m, 1H, H-5_B), 3.88 (m, 2H, H-3_B, H-6_{bA}), 3.80–3.77 (m, 3H, H-4_A, H-4_C, H-5_A), 3.72 (m, 1H, H-5_C), 3.71 (s, 3H, OCH_3), 3.47 (dd, *J* = 10.7, 3.5 Hz, 1H, H-2_B), 3.44 (m, 2H, H-2_C, H-3_C), 2.0 (s, 3H, COCH_3), 1.9 (s, 3H, COCH_3), 0.36 (d, *J* = 6.5 Hz, 3H, CCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.0, 170.6 (2*C*OCH_3), 167.0, 167.1 (Phth), 156.1–114.9 (Ar-*C*), 103.0 (PhCH), 100.0 (C-1_B), 99.8 (C-1_C), 98.7 (C-1_A), 81.7 (C-4_A), 81.1 (C-4_C), 79.5 (C-3_C), 77.0 (C-2_C), 76.1 (C-3_A), 75.9 (C-3_B), 75.8, 75.0, 73.2 (3PhCH_2), 73.0 (C-4_B), 70.0 (C-5_C), 69.2 (C-6_A), 67.1 (C-5_A), 66.4 (C-5_B), 63.0 (C-6_C), 60.9 (C-2_B), 56.2 (C-2_A), 56.0 (OCH_3), 21.2, 21.1 (2$COCH_3$), 15.7 (CCH_3); ESI-MS: *m/z* 1213.4 $[M+Na]^+$; Anal. Calcd for $C_{65}H_{66}N_4O_{18}$ (1190.43): C, 65.54; H, 5.58. Found: C, 65.35; H, 5.82.

4.5. 4-Methoxyphenyl (2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl)-(1→3)-(4-*O*-acetyl-2-azido-2-deoxy-α-L-fucopyranosyl)-(1→3)-4,6-*O*-benzylidene-2-deoxy-2-*N*-phthalimido-β-D-glucopyranoside 10

A solution of compound **9** (1.2 g, 1.0 mmol) in 0.01 M CH_3ONa in CH_3OH (20 mL) was allowed to stir at room temperature for 30 min. The reaction mixture was neutralized with Dowex 50W X-8 (H^+) resin, filtered, and evaporated to dryness. The crude product was passed through a short pad of SiO_2 using hexane–EtOAc (4:1) as eluant to give pure compound **10** (1.1 g, 96%). Colorless oil; $[\alpha]_D^{25} = -1.6$ (*c* 1.0, $CHCl_3$); ν_{max} (neat): 2931, 2112, 1715, 1507, 1390, 1230, 1100, 1029, 970, 722 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.50–7.25 (m, 24H, Ar-H), 6.83 (d, *J* = 9.0 Hz, 2H, Ar-H), 6.72 (d, *J* = 9.0 Hz, 2H, Ar-H), 5.71 (d, *J* = 8.5 Hz, 1H, H-1_A), 5.55 (s, 1H, PhC*H*), 5.07 (d, *J* = 2.5 Hz, 1H, H-4_B), 4.86 (d, *J* = 10.9 Hz, 1H, PhCH_2), 4.81 (d, *J* = 11.1 Hz, 1H, PhCH_2), 4.77 (d, *J* = 3.6 Hz, 1H, H-1_B), 4.75 (d, *J* = 3.6 Hz, 1H, H-1_C), 4.70 (d, *J* = 11.1 Hz, 1H, PhCH_2), 4.71–4.66 (m, 1H, H-3_A), 4.66–4.65 (m, 2H, PhCH_2), 4.61 (t, *J* = 8.5, 8.5 Hz, 1H, H-2_A), 4.56 (d, *J* = 11.1 Hz, 1H, PhCH_2), 4.41 (dd, *J* = 10.5, 3.9 Hz, 1H, H-6_{aA}), 4.07–4.05 (m, 1H, H-5_B), 3.91–3.88 (m, 2H, H-3_B, H-6_{bA}), 3.81 (t, *J* = 9.3, 9.3 Hz, 1H, H-4_C), 3.77–3.72 (m, 3H, H-4_A, H-5_A, H-6_{aC}), 3.71 (s, 3H, OCH_3), 3.55–3.51 (m, 3H, H-2_B, H-5_C, H-6_{bC}), 3.40 (dd, *J* = 9.8, 3.4 Hz, 1H, H-2_C), 3.38 (t, *J* = 10.4, 10.4 Hz, 1H, H-3_C), 2.0 (s, 3H, COCH_3), 0.43 (d, *J* = 6.5 Hz, 3H, CCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.2 ($COCH_3$), 167.0, 167.1 (Phth), 156.1–114.9 (Ar-*C*), 102.8 (PhCH), 99.8 (C-1_B), 99.6 (C-1_C), 98.7 (C-1_A), 81.5 (C-4_A), 81.2 (C-4_C), 79.9 (C-3_C), 77.8 (C-2_C), 76.2 (C-3_A), 75.8 (PhCH_2), 75.7 (C-3_B), 75.1, 73.3 (2PhCH_2), 73.0 (C-4_B), 72.5 (C-5_C), 69.1 (C-6_A), 67.1 (C-5_A), 66.4 (C-5_B), 62.5 (C-6_C), 60.9 (C-2_B), 56.1 (C-2_A), 56.0 (OCH_3), 21.2 ($COCH_3$), 15.8 (CCH_3); ESI-MS: *m/z* 1171.4 $[M+Na]^+$; Anal. Calcd for $C_{63}H_{64}N_4O_{17}$ (1148.43): C, 65.84; H, 5.61. Found: C, 65.63; H, 5.86.

4.6. Phenyl (2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-(1→3)-2-*O*-acetyl-4-*O*-benzyl-1-thio-α-L-rhamnopyranoside 11

To a solution of compound **5** (1.0 g, 2.57 mmol) and compound **6** (1.6 g, 2.74 mmol) in anhydrous CH_2Cl_2 (10 mL) was added MS 4 Å (1 g) and the reaction mixture was allowed to stir at room temperature for 30 min under argon. It was cooled to −40 °C and *N*-iodosuccinimide (NIS; 620 mg, 2.75 mmol) followed by TfOH (5 μL) was added to it. After stirring at the same temperature for 30 min, the reaction was quenched with Et_3N (50 μL) and the reaction mixture was filtered through a Celite® bed and washed with CH_2Cl_2 (50 mL). The combined organic layer was washed with 5% $Na_2S_2O_3$, satd $NaHCO_3$, water in succession, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified over SiO_2 using hexane–EtOAc (8:1) as eluant to give pure **11** (1.9 g, 81%). Colorless oil; $[\alpha]_D^{25} = +3.2$ (*c* 1.0, $CHCl_3$); ν_{max} (neat): 2918, 1742, 1584, 1496, 1454, 1367, 1234, 1216, 1090, 911, 847, 748 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.33–7.04 (m, 30H, Ar-H), 5.58 (br s, 1H, H-2_D), 5.37 (br s, 1H, H-1_D), 5.14 (d, *J* = 3.4 Hz, 1H, H-1_E), 4.97 (d, *J* = 11.0 Hz, 1H, PhCH_2), 4.91 (d, *J* = 10.2 Hz, 1H, PhCH_2), 4.84 (d, *J* = 11.0 Hz, 1H, PhCH_2), 4.80 (d, *J* = 10.9 Hz, 1H, PhCH_2), 4.67–4.63 (2d, *J* = 12.2 Hz, 2H, PhCH_2), 4.60–4.58 (m, 2H, PhCH_2), 4.45 (d, *J* = 10.9 Hz, 1H, PhCH_2), 4.34 (d, *J* = 12.0 Hz, 1H, PhCH_2), 4.21–4.18 (m, 1H, H-5_D), 4.13 (dd, *J* = 9.4, 3.1 Hz, 1H, H-3_D), 4.04 (t, *J* = 9.3 Hz each, 1H, H-4_E), 4.02–3.99 (m, 1H, H-5_E), 3.69 (t, *J* = 9.4 Hz each, H-3_E), 3.62–3.52 (m, 4H, H-2_E, H-4_D, H-6_{abE}), 1.9 (s, 3H, COCH_3), 1.37 (d, *J* = 6.2 Hz, 3H, CCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5 ($COCH_3$), 139.0–127.8 (Ar-*C*), 93.0 (C-1_E), 86.4 (C-1_D), 82.4 (C-4_E), 80.2 (C-2_E), 79.6 (C-4_D), 78.2 (C-3_E), 76.6, 75.9, 75.3, 73.6, 73.4 (5PhCH_2), 72.9 (C-3_D), 70.6 (C-5_E), 69.7 (C-2_D), 69.6 (C-5_D), 68.6 (C-6_E), 21.2 ($COCH_3$), 18.2 (CCH_3); ESI-MS: *m/z* 933.3 $[M+Na]^+$; Anal. Calcd for $C_{55}H_{58}O_{10}S$ (910.37): C, 72.50; H, 6.42. Found: C, 72.27; H, 6.60.

4.7. 4-Methoxyphenyl (2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-(1→3)-(2-*O*-acetyl-4-*O*-benzyl-α-L-rhamnopyranosyl)-(1→6)-(2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl)-(1→3)-(4-*O*-acetyl-2-azido-2-deoxy-α-L-fucopyranosyl)-(1→3)-4,6-*O*-benzylidene-2-deoxy-2-*N*-phthalimido-β-D-glucopyranoside 12

To a solution of compound **10** (1.0 g, 0.87 mmol) and compound **11** (950 mg, 1.04 mmol) in anhydrous CH_2Cl_2 (10 mL) was added MS 4 Å (1 g) and the reaction mixture was allowed to stir at room temperature for 30 min under argon. It was cooled to −40 °C and *N*-iodosuccinimide (NIS; 260 mg, 1.15 mmol) followed by TfOH (3 μL) was added to it. After stirring at the same temperature for 30 min the reaction was quenched with Et_3N (50 μL) and the reaction mixture was filtered through a Celite® bed and washed with CH_2Cl_2 (50 mL). The combined organic layer was washed with 5% $Na_2S_2O_3$, satd $NaHCO_3$, water in succession, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified over SiO_2 using hexane–EtOAc (8:1) as eluant to give pure **12** (1.3 g, 76%). Colorless oil; $[\alpha]_D^{25} = +10.8$ (*c* 1.0, $CHCl_3$); ν_{max} (neat): 2928, 2870, 2111, 1779, 1745, 1716, 1508, 1388, 1233, 1100, 1028, 915, 738 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.36–7.05 (m, 49H, Ar-H), 6.82 (d, *J* = 9.0 Hz, 2H, Ar-H), 6.74 (d, *J* = 9.0 Hz, 2H, Ar-H), 5.71 (d, *J* = 8.4 Hz, 1H, H-1_A), 5.53 (s, 1H, PhC*H*), 5.30 (s, 1H, H-2_D), 5.15 (d, *J* = 3.4 Hz, 1H, H-1_E), 5.04 (d, *J* = 3.1 Hz, 1H, H-4_B), 4.99–4.80 (m, 7H, PhCH_2), 4.79 (d, *J* = 3.5 Hz, 1H, H-1_C), 4.76 (d, *J* = 3.5 Hz, 1H, H-1_B), 4.70–4.68 (m, 1H, H-3_A), 4.66 (br s, 1H, H-1_D), 4.71–4.52 (m, 8H, H-2_A, PhCH_2), 4.44–4.26 (m, 2H, H-5_B, PhCH_2), 4.26 (d, *J* = 11.2 Hz, 1H, PhCH_2), 4.18 (dd, *J* = 9.1, 3.0 Hz, 1H, H-3_D), 4.10–4.07 (m, 2H, H-4_E, H-5_D), 4.05–4.00 (m, 1H, H-5_E), 3.85–3.68 (m, 8H, H-3_B, H-3_E, H-4_A, H-4_C, H-5_A, H-6_{aC}, H-6_{abA}), 3.69 (s, 3H, OCH_3), 3.58–3.51 (m, 7H, H-2_B, H-2_E, H-4_D, H-5_C, H-6_{bC}, H-6_{abE}), 3.52–3.50 (m, 1H, H-3_C), 3.42 (dd, *J* = 9.5,

3.5 Hz, 1H, H-2_C), 1.98 (s, 3H, COCH_3), 1.92 (s, 3H, COCH_3), 1.37 (d, J = 6.3 Hz, 3H, CCH_3), 0.44 (d, J = 6.4 Hz, 3H, CCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.8, 170.6 (2COCH$_3$), 167.0, 167.1 (Phth), 156.1–114.9 (Ar-*C*), 102.8 (PhCH), 99.8 (C-1_C), 99.7 (C-1_B), 98.7 (C-1_D), 98.6 (C-1_A), 93.2 (C-1_E), 82.5 (C-4_E), 81.6 (C-4_A), 81.2 (C-4_C), 80.5 (C-2_E), 80.1 (C-3_C), 79.6 (C-4_D), 78.1 (C-3_E), 77.6 (C-2_C), 76.6 (PhCH_2), 76.2 (C-3_A), 75.9 (PhCH_2), 75.8 (C-3_B), 75.7, 75.3, 75.1, 73.7, 73.4, 73.3 (6PhCH_2), 73.0 (C-4_B), 72.7 (C-5_C), 71.2 (C-3_D), 70.6 (C-5_E), 69.1 (C-6_C), 68.8 (C-6_A), 68.6 (C-6_E), 68.3 (C-5_A), 68.1 (C-5_B), 67.1 (C-2_D), 66.5 (C-5_D), 61.0 (C-2_B), 56.1 (C-2_A), 56.0 (OCH_3), 21.3, 21.2 (2COCH_3), 18.2, 15.9 (2CCH_3); MALDI-MS: *m/z* 1971.8 $[M+Na]^+$; Anal. Calcd for $C_{112}H_{116}N_4O_{27}$ (1948.78): C, 68.98; H, 6.00. Found: C, 68.80; H, 6.30.

4.8. 4-Methoxyphenyl (α-D-glucopyranosyl)-(1→3)-(α-L-rhamnopyranosyl)-(1→6)-(α-D-glucopyranosyl)-(1→3)-(2-acetamido-2-deoxy-α-L-fucopyranosyl)-(1→3)-2-acetamido-2-deoxy-β-D-glucopyranoside 1

To a solution of compound **12** (1.0 g, 0.51 mmol) in *n*-butanol (10 mL) was added ethylene diamine (0.2 mL) and the reaction mixture was allowed to stir at 90 °C for 8 h. The solvents were removed under reduced pressure and a solution of the crude product in acetic anhydride-pyridine (2 mL; 1:1 v/v) was kept at room temperature for 3 h. The reaction mixture was evaporated and co-evaporated with toluene and passed through a short pad of SiO_2 using hexane–EtOAc (1:1) as eluant. To a solution of the crude product in CH_3OH–AcOH (10 mL; 8:1 v/v) was added 20% $Pd(OH)_2$–C (150 mg) and the reaction mixture was allowed to stir at room temperature under a positive pressure of hydrogen for 24 h. It was filtered through a Celite® bed and evaporated to dryness. A solution of the crude product in acetic anhydride–pyridine (2 mL; 1:1 v/v) was kept at room temperature for 3 h. The reaction mixture was evaporated and co-evaporated with toluene and passed through a short pad of SiO_2 using hexane–EtOAc (1:1) as eluant. Finally, a solution of the product in 0.1 M CH_3ONa (5 mL) was allowed to stir at room temperature for 3 h, neutralized using Dowex 50W X-8 (H^+) resin, filtered, and concentrated under reduced pressure. The crude product was purified over Sephadex® LH-20 column using CH_3OH–H_2O (8:1 v/v) as eluant to give pure compound **1** (350 mg, 70%). Glass; $[\alpha]_D$ = +9.2 (*c* 1.0, CH_3OH); ν_{max} (KBr): 2926, 2372, 1738, 1661, 1550, 1516, 1429, 1377, 1030, 679 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD): δ 6.75–6.63 (m, 4H, Ar-H), 4.87 (br s, 1H, H-1_E), 4.85 (br s, 1H, H-1_C), 4.82 (br s, 1H, H-1_B), 4.68 (br s, 1H, H-1_D), 4.65 (br s, 1H, H-1_A), 4.55–4.36 (m, 2H, H-2_A, H-3_A), 4.35–4.21 (m, 2H, H-3_B, H-3_D), 4.11 (br s, 1H, H-4_B), 4.05–3.76 (m, 5H, H-2_D, H-3_C, H-5_C, H-6_{aA}, H-6_{aC}), 3.70–3.58 (m, 9H, H-2_E, H-3_E, H-4_A, H-5_D, H-5_E, H-6_{bA}, H-6_{bC}, H-6_{abE}), 3.57 (s, 3H, OCH_3), 3.56–3.21 (m, 7H, H-2_B, H-2_C, H-4_C, H-4_D, H-4_E, H-5_A, H-5_B), 2.08, 1.91 (2s, 6H, 2COCH_3), 1.32, 1.20 (2d, J = 6.0 Hz, 6H, 2CCH_3); ^{13}C NMR (125 MHz, CD_3OD): δ 169.6 (2C, 2COCH$_3$), 156.0–114.7 (Ar-C), 102.0 (C-1_B), 100.4 (3C, C-1_A, C-1_C, C-1_D), 95.3 (C-1_E), 80.4 (C-3_A), 77.6 (C-3_B), 77.4 (C-5_A), 76.6 (C-3_D), 73.9 (3C, C-2_D, C-3_C, C-3_E), 72.5 (C-2_E), 72.4 (3C, C-4_D, C-4_E, C-5_E), 72.3 (2C, C-4_B, C-5_C), 72.0 (C-2_C), 71.0 (C-4_A), 70.6 (C-5_D), 70.2 (C-5_B), 68.5 (C-4_C), 67.0 (C-6_C), 61.5 (2C, C-6_A, C-6_E), 56.9 (C-2_A), 55.1 (OCH_3), 48.5 (C-2_B), 20.2 (2C, 2COCH_3), 17.2, 15.2 (2CCH_3); ESI-MS: *m/z* 1007.38 $[M+Na]^+$; Anal. Calcd for $C_{41}H_{64}N_2O_{25}$ (984.38): C, 50.00; H, 6.55. Found: C, 49.77; H, 6.81.

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