Synthesis P. K. Mandal Paper

Convergent Synthesis of the Pentasaccharide Repeating Unit of the *O*-Antigen of *Escherichia coli* O36

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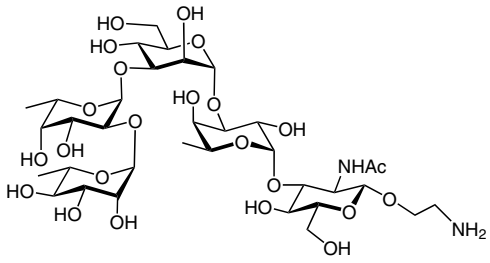


Received: 10.09.2014
Accepted after revision: 02.12.2014
Published online: 22.12.2014
DOI: 10.1055/s-0034-1379952; Art ID: ss-2014-n0558-op

Abstract An efficient synthesis of the pentasaccharide repeating unit of the *O*-antigen of *Escherichia coli* O36 is reported. A stereoselective [2 + 3] block glycosylation method has been exploited to obtain the target pentasaccharide derivative using thioglycoside, trichloroacetimidate, and halide-exchange glycosylation procedures. The 2-azidoethyl group has been used as the anomeric protecting group to make the glycone moiety with a readily available linker for its conjugation to a protein without destroying the cyclic structure at the reducing end. Yields were high in all the intermediate steps.

Key words *Escherichia coli*, pentasaccharide, glycosylation, lipopolysaccharide, *O*-antigen

Escherichia coli (*E. coli*) are a group of gram-negative bacteria that cause a variety of bacterial infections in humans and animals.[1] There are several *E. coli* infections, frequent in humans, including infections of the urinary tract,[2] sepsis, meningitis,[3] enteric/diarrheal disease blood stream,[4] and other anatomical diseases.[5,6]

Although *E. coli* strains are generally nonpathogenic members of the human colonic flora, certain clones develop specific virulence factors and they cause a broad spectrum of diseases in humans and animals. Based on intestinal types of diseases, there are six well-described pathotypes: enteropathogenic *E. coli* (EPEC), enterotoxigenic *E. coli* (ETEC), enteroinvasive *E. coli* (EIEC), enterohaemorrhagic *E. coli* (EHEC), enteroaggregative *E. coli* (EAEC), and diffusely adherent *E. coli* (DAEC).[7]

Recently, Perepelov et al. reported the structure of the cell wall *O*-antigen of *E. coli* O36 comprising of D-glucosamine, L-fucose, D-mannose, and L-rhamnose (Figure 1).[8] *E. coli* O36 strain is associated with diarrheal infections, respiratory tract disease, and broiler breeders with salpingitis.[9]

α-L-Rha*p*-(1→2)-α-L-Fuc*p*
1
↓
3
→ 4)-α-D-Man*p*-(1→3)-α-L-Fuc*p*-(1→3)-β-D-Glc*p*NAc-(1→

Figure 1 Structure of the repeating unit of the cell wall *O*-antigen of *Escherichia coli* O36

Bacterial cell wall *O*-antigens are unique polysaccharides and play important roles in the initial stage of bacterial adhesion with the host.[10] Due to the antigenic character of bacterial *O*-antigens in the form of glycoconjugates, biologists have made extensive efforts to develop antibacterial agents or vaccine candidates based on the cell wall glycoconjugate derivatives, and a number of reports appeared in the literature for the development of glycoconjugate vaccine candidates against several pathogenic bacteria.[11] However, it is impossible to collect adequate amounts of bacterial *O*-antigens from natural sources with high purity for making suitable glycoconjugates and for detailed biological evaluation. Therefore, the development of a chemical synthetic strategy would be useful to gain access to large-scale production of the *O*-antigen structure from commercially available sugars.

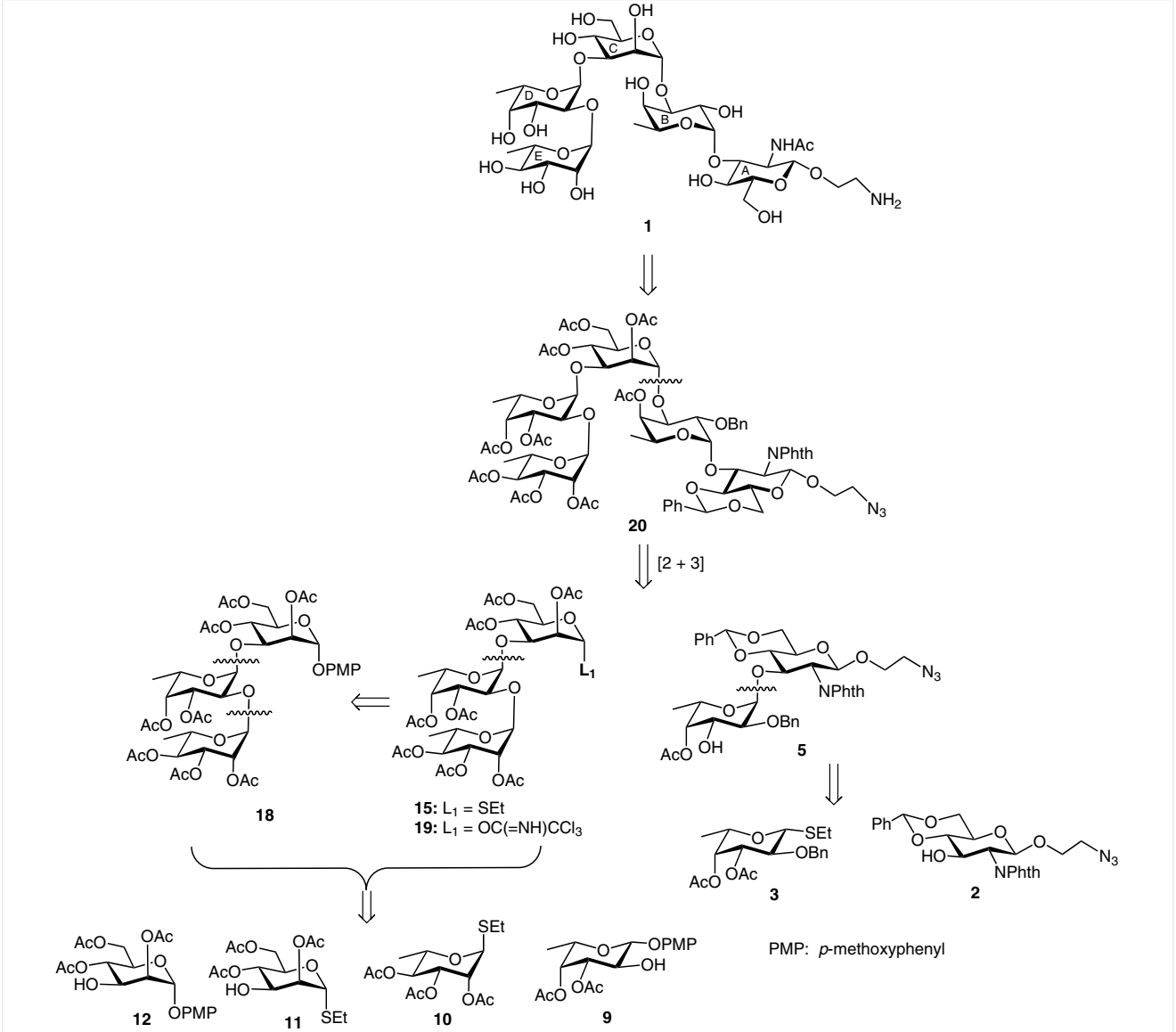
As a part of the ongoing studies on the synthesis of bacterial cell wall oligosaccharides[12] for their use in glycoconjugate preparation, the chemical synthesis of the pentasaccharide repeating unit of the *O*-antigen of *Escherichia coli* O36 as its 2-aminoethyl glycoside (Scheme 1) is presented herein.

The retrosynthetic analysis for the synthesis of pentasaccharide **1** showed a convergent [2 + 3] block synthetic strategy approach to be attractive (Scheme 1). Target structure **1** may be obtained from fully protected pentasaccharide **20** through a three-step deprotection sequence, includ-

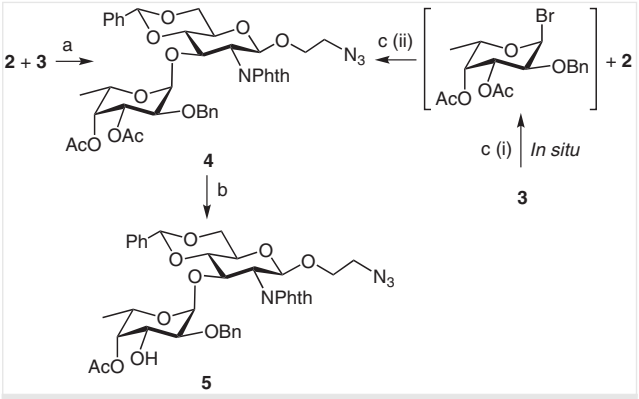
ing conversion of the *N*-phthaloyl group into the corresponding acetamide, deprotection of the ester groups, and hydrogenolysis.

Synthesis of the disaccharide acceptor **4** started with the known acceptor, 2-azidoethyl 4,6-*O*-benzylidene-2-deoxy-2-*N*-phthalimido-β-D-glucopyranoside (**2**)[13] and the halide donor 3,4-di-*O*-acetyl-2-*O*-benzyl-α-L-fucopyranosyl bromide,[14] prepared in situ by the addition of bromine to ethylthio fucoside **3**.[15] The stereoselective coupling (Scheme 2) under halide-assisted coupling conditions between the known acceptor **2** and the halide donor 3,4-di-*O*-acetyl-2-*O*-benzyl-α-L-fucopyranosyl bromide in the presence of tetraethylammonium bromide in the mixed solvent dichloromethane–*N*,*N*-dimethylformamide (4:1),[16] for three days at room temperature, furnished the protected disaccharide **4** in 56% yield.

Due to the low yield of this reaction an alternative method excluding the halide donor was utilized. Thioglycosides are commonly used as α-selective donors, as discussed in several reports.[17] An alternative approach involved the glycosylation of the thiofucoside donor **3** with known acceptor **2** using mixed solvent diethyl ether–dichloromethane (4:1) in the presence of *N*-iodosuccinimide/trimethylsilyl triflate[18] furnishing disaccharide derivative **4** in 83% yield together with a small quantity (~5%) of its other isomer, which was separated by column chromatography.



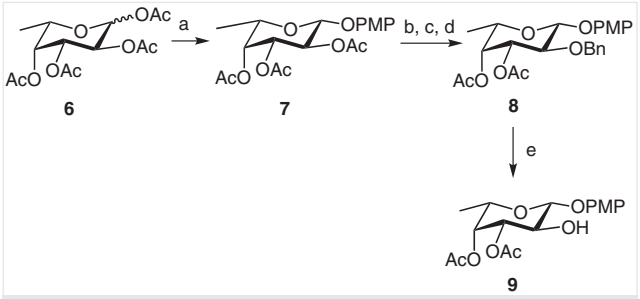
Scheme 1 Retrosynthetic analysis of pentasaccharide **1**



Scheme 2 *Reagents and conditions*: (a) NIS, TMSOTf, Et_2O–CH_2Cl_2 (4:1), 4 Å molecular sieves, –30 °C, 30 min, 83%; (b) (i) 0.1 M NaOMe, MeOH, r.t., 1 h; (ii) triethyl orthoacetate, TsOH, DMF, 2 h then 80% aq AcOH, r.t., 1 h, 90% overall; (c) (i) Br_2, CH_2Cl_2, 0 °C; (ii) Et_4NBr, CH_2Cl_2–DMF (4:1), 4 Å molecular sieves, r.t., 72 h, 56%.

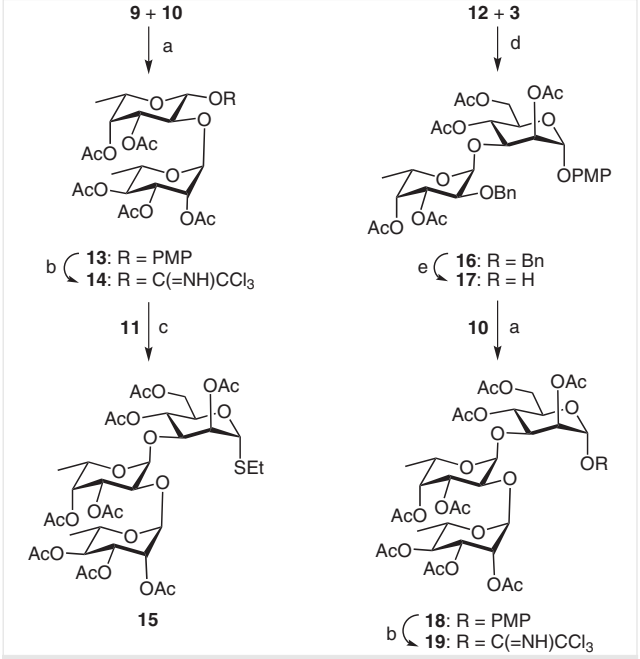
Therefore *N*-iodosuccinimide/trimethylsilyl triflate mediated glycosylation reaction should be preferred over halide-assisted coupling glycosylation. Stereoselective formation of compound **4** was supported by its spectral analysis [δ = 5.58 (PhC*H*), 5.33 (d, *J* = 8.5 Hz, 1 H, $H1_A$), 4.81 (d, *J* = 3.3 Hz, 1 H, $H1_B$) and at δ = 102.2 (PhCH), 99.1 ($C1_A$), 98.9 ($C1_B$) in the ^1H and ^{13}C NMR spectra, respectively]. Compound **4** was treated with sodium methoxide[19] in methanol followed by selective acetylation via the formation of an orthoester intermediate[20] resulting in the formation of disaccharide acceptor **5** in 90% yield (Scheme 2), which was used in the block glycosylation step for the preparation of the pentasaccharide derivative.

To synthesize trisaccharide **15**, a number of suitable functionalized monosaccharide intermediates **9**, **10**,[21] and **11**[22] were prepared from the reducing sugars following reported reaction conditions in the literature (Scheme 1). Transformation of L-fucose tetraacetate (**6**) into 4-methoxyphenyl 2,3,4-tri-*O*-acetyl-β-L-fucopyranoside (**7**) was carried out in 77% yield by treatment with 4-methoxyphenol and boron trifluoride–diethyl ether at 0 °C. Compound **7** was subjected to a series of reactions consisting of saponification, 3,4-*O*-isopropylidene ketal formation using 2,2-dimethoxypropane in the presence of 4-toluenesulfonic acid,[23] benzylation of the remaining hydroxy group using benzyl bromide and sodium hydroxide,[24] acid hydrolysis of the *O*-isopropylidene ring, and finally acetylation of the remaining hydroxy group to give 4-methoxyphenyl 3,4-di-*O*-acetyl-2-*O*-benzyl-β-L-fucopyranoside (**8**) in 85% yield. Compound **8** was transformed into 4-methoxyphenyl 3,4-di-*O*-acetyl-β-L-fucopyranoside (**9**) by hydrogenolysis in 88% yield using hydrogen over Pearlman's catalyst[25] (Scheme 3).



Scheme 3 *Reagents and conditions*: (a) 4-methoxyphenol, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C, 3 h, 77%; (b) 0.1 M NaOMe, MeOH, r.t., 2 h; (c) (i) 2,2-dimethoxypropane, TsOH, DMF, r.t., 6 h; (ii) BnBr, NaOH, TBAB, THF, r.t., 5 h; (d) (i) 80% aq AcOH, 80 °C, 1.5 h; (ii) Ac_2O, pyridine, r.t., 3 h, 85% overall; (e) H_2, 20% $Pd(OH)_2$/C, MeOH, r.t., 4 h; 88%.

The stereoselective glycosylation of 4-methoxyphenyl 3,4-di-*O*-acetyl-β-L-fucopyranoside (**9**) and ethyl 2,3,4-tri-*O*-acetyl-α-L-rhamnopyranoside (**10**) in the presence of *N*-iodosuccinimide/trimethylsilyl triflate[18] furnished disaccharide derivative **13** in 88% yield. Formation of compound **13** was confirmed by spectral analysis [δ = 5.25 (br s, 1 H, $H1_E$), 4.86 (d, *J* = 7.8 Hz, 1 H, $H1_D$) and δ = 102.8 ($C1_D$), 97.9 ($C1_E$) in the ^1H and ^{13}C NMR spectra, respectively] (Scheme 4).



Scheme 4 *Reagents and conditions*: (a) NIS, TMSOTf, CH_2Cl_2, 4 Å molecular sieves, –30 °C, 1 h, 88% for **13**, 85% for **18**; (b) (i) CAN, MeCN–H_2O (4:1), r.t., 2 h; (ii) CCl_3CN, DBU, CH_2Cl_2, –10 °C, 1 h; (c) $NOBF_4$, Et_2O–CH_2Cl_2 (4:1), – 30 °C, 30 min, 66%; (d) NIS, TMSOTf, Et_2O–CH_2Cl_2 (4:1), 4 Å molecular sieves, –30 °C, 30 min, 76%; (e) H_2, 20% $Pd(OH)_2$/C, MeOH, r.t., 5 h, 86%.

Removal of the anomeric 4-methoxyphenyl group of compound **13** using ammonium cerium(IV) nitrate (CAN)[26] in acetonitrile–water (4:1) followed by DBU[27] catalyzed reaction with trichloroacetonitrile furnished 2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl)-(1→2)-3,4-di-*O*-acetyl-β-L-fucopyranosyl disaccharide trichloroacetimidate donor **14** in 84% overall yield, and it was used directly without further purification.

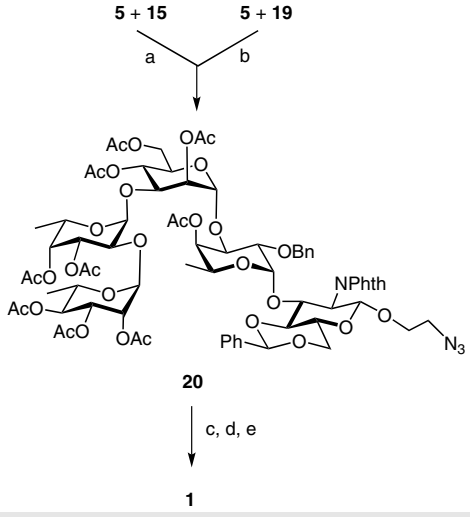
Because of its high reactivity, trichloroacetimidate donor **14** was coupled with ethyl 2,4,6-tri-*O*-acetyl-α-D-mannopyranosyl (**11**) in the presence of nitrosyl tetrafluoroborate[28] as a glycosyl activator in the mixed solvent diethyl ether–dichloromethane (4:1) furnishing trisaccharide thioglycoside derivative **15** in 66% moderate yield. Formation of compound **15** was confirmed from its spectral analysis [δ = 5.28 (br s, 1 H, $H1_C$), 5.09 (d, *J* = 2.3 Hz, 1 H, $H1_D$), 4.84 (br s, 1 H, $H1_E$) and δ = 95.7 ($C1_E$), 94.7 ($C1_D$), 82.4 ($C1_C$) in the ^{1}H and ^{13}C NMR spectra, respectively] (Scheme 4).

To circumvent the degradation pathways, an alternative retrosynthetic analysis was designed for the synthesis of another type of trisaccharide (Scheme 1). In this approach, another trisaccharide derivative **18** was synthesized using a sequential glycosylation strategy via stereoselective glycosylation of monosaccharide intermediates.

The stereoselective glycosylation of compound **12**[29] with thioglycoside derivative **3** in the presence of *N*-iodosuccinimide/trimethylsilyl triflate[18] in the mixed solvent diethyl ether–dichloromethane (4:1) furnished disaccharide derivative **16** in 76% yield together with a small quantity (~5%) of its other isomer, which was separated by column chromatography. Formation of compound **16** was confirmed from its spectral analysis [δ = 5.43 (d, *J* = 1.7 Hz, 1 H, $H1_C$), 5.02 (d, *J* = 3.4 Hz, 1 H, $H1_D$) and δ = 96.9 (2 C, $C1_C$, $C1_D$) in the ^{1}H and ^{13}C NMR spectra, respectively] (Scheme 4).

Hydrogenolysis of compound **16** using hydrogen over Pearlman's catalyst[25] furnished disaccharide acceptor derivative **17** in 86% yield. The following iodonium ion mediated stereoselective coupling of compound **17** with the thioglycoside donor **10** in the presence of *N*-iodosuccinimide/trimethylsilyl triflate[18] furnished trisaccharide derivative **18** in 85% yield. The presence of signals in the NMR spectra confirmed the formation of compound **18** [δ = 5.42 (d, *J* = 2.0 Hz, 1 H, $H1_C$), 5.17 (d, *J* = 2.2 Hz, 1 H, $H1_D$), 4.89 (d, *J* = 1.3 Hz, 1 H, $H1_E$) and δ = 96.9 ($C1_C$), 96.5 ($C1_D$), 96.1 ($C1_E$) in the ^{1}H and ^{13}C NMR spectra, respectively].

Finally the glycosylation of disaccharide acceptor **5** with thioglycoside trisaccharide donor **15** in the presence of *N*-iodosuccinimide/trimethylsilyl triflate[18] furnished pentasaccharide derivative **20** in 78% yield. In another approach 2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl-(1→2)-3,4-di-*O*-acetyl-α-L-fucopyranosyl-(1→3)-2,4,6-tri-*O*-acetyl-α-D-mannopyranosyl trichloroacetimidate derivative **19** was glycosylated with disaccharide acceptor **5** in the presence of nitrosyl tetrafluoroborate[28] furnishing pentaasaccharide derivative **20** in 81% yield (Scheme 5). Formation of compound **20** was supported by its spectral analysis [δ = 5.41 (s, 1 H, PhC*H*), 5.24 (d, *J* = 8.4 Hz, 1 H, $H1_A$), 4.87 (d, *J* = 2.3 Hz, 1 H, $H1_D$), 4.77 (d, *J* = 2.8 Hz, 1 H, $H1_B$), 4.66 (br s, 2 H, $H1_C$, $H1_E$) and δ = 101.4 (PhCH), 98.9 ($C1_A$), 98.0 ($C1_B$), 97.9 ($C1_C$), 95.5 ($C1_E$), 91.9 ($C1_D$) in the ^{1}H and ^{13}C NMR spectra, respectively]. Finally compound **20** was transformed to the target compound **1** in overall 51% yield following a sequence of reactions consisting of (a) conversion of *N*-phthaloyl group to the acetamido group;[30] (b) hydrogenolysis using hydrogen over Pearlmen's catalyst,[25] and (c) saponification using sodium methoxide.



Scheme 5 *Reagents and conditions*: (a) NIS, TMSOTf, CH_2Cl_2, 4 Å molecular sieves, –10 °C, 1 h, 78%; (b) $NOBF_4$, CH_2Cl_2, –10 °C, 30 min, 81%; (c) (i) $NH_2NH_2{\cdot}H_2O$, EtOH, 80 °C, 8 h; (ii) Ac_2O, pyridine, r.t., 1 h; (d) H_2, 20% $Pd(OH)_2/C$, MeOH, r.t., 12 h; (e) 0.1 M NaOMe, MeOH, r.t., 3 h, 51% overall yield.

Spectroscopic analysis of compound **1** unambiguously confirmed its formation [δ = 5.28 (br s, 1 H, $H1_D$), 5.03 (br s, 1 H, $H1_C$, $H1_B$), 5.02 (br s, 1 H, $H1_E$), 4.47 (d, *J* = 7.4 Hz, 1 H, $H1_A$) and δ = 101.1 ($C1_C$), 100.5 ($C1_A$), 99.8 ($C1_B$), 98.1 ($C1_E$), 96.1 ($C1_D$) in the ^{1}H and ^{13}C NMR spectra, respectively] (Scheme 5).

In summary, an efficient synthetic strategy has been developed for the synthesis of a pentasaccharide (**1**) as its 2-aminoethyl glycoside corresponding to the *O*-antigen of *E. coli* O36. Two model trisaccharide donors have been used to synthesize target compound using complementary glycosylation conditions.

All reactions were monitored by TLC (silica gel coated plates) visualized by warming 2% $Ce(SO_4)_2$ in 5% H_2SO_4 in EtOH 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, HSQC spectra were recorded on Bruker DPX-400 MHz spectrometers using $CDCl_3$ and D_2O as solvents and TMS as internal reference unless stated otherwise. ESI-MS were recorded on a Jeol spectrometer. Elementary analysis

was carried out on Carlo ERBA analyzer. IR spectra were recorded on Shimadzu spectrophotometers. Optical rotations were determined on Autopol III polarimeter. Commercially available grades of organic solvents of adequate purity were used in all reactions.

2-Azidoethyl *O*-(3,4-Di-*O*-acetyl-2-*O*-benzyl-α-L-fucopyranosyl)-(1→3)-4,6-*O*-benzylidene-2-deoxy-2-*N*-phthalimido-β-D-glucopyranoside (4)

Process I: Br_2 (56 μL, 1.09 mmol) was added to a solution of ethyl 3,4-di-*O*-acetyl-2-*O*-benzyl-1-thio-β-L-fucopyranoside **3** (236 mg, 0.65 mmol) in CH_2Cl_2 (4 mL) at 0 °C. After 20 min, the solution was concentrated and coevaporated with toluene, to which a solution of compound **2** (100 mg, 0.22 mmol), Et_4NBr (104 mg, 0.32 mmol) and 4 Å molecular sieves (100 mg) in anhyd CH_2Cl_2–DMF (4:1, 1.5 mL) were added and the mixture was stirred at r.t. After 72 h, TLC showed complete conversion of the starting materials. The crude mixture was concentrated and purified by column chromatography (silica gel; hexane–EtOAc, 4:1) to give **4** (95 mg, 56%).

Process II: To a solution of **2** (1 g, 2.15 mmol) and **3** (0.98 g, 2.58 mmol) in anhyd Et_2O–CH_2Cl_2 (4:1, 15 mL) was added 4 Å molecular sieves (1 g) and the mixture was stirred at r.t. for 30 min under argon and cooled to –30 °C. To the cooled mixture were added NIS (695 mg, 3.09 mmol) and TMSOTf (10 μL) and the mixture was stirred at this temperature for 30 min. The mixture was diluted with CH_2Cl_2 (50 mL) and filtered through Celite and it was washed with CH_2Cl_2. The combined organic layers were successively washed with 5% $Na_2S_2O_3$, sat. $NaHCO_3$, and water, dried (Na_2SO_4), and concentrated. The crude product was purified by chromatography (silica gel; hexane–EtOAc, 4:1) to give pure **4** (1.4 g, 83%) as a yellow oil; $[\alpha]_D^{25}$ +25 (*c* 1.0, $CHCl_3$).

IR (neat): 3451, 2924, 2117, 1777, 1742, 1721, 1507, 1387, 1250, 1102, 995, 796 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.71–7.62 (m, 4 H, H_{Ar}), 7.53–7.50 (m, 2 H, H_{Ar}), 7.39–7.34 (m, 3 H, H_{Ar}), 7.22–7.19 (m, 3 H, H_{Ar}), 6.91–6.88 (m, 2 H, H_{Ar}), 5.58 (s, 1 H, PhC*H*), 5.33 (d, *J* = 8.5 Hz, 1 H, $H1_A$), 5.12 (dd, *J* = 10.5, 3.3 Hz, 1 H, $H3_B$), 5.07 (dd, *J* = 3.2, 1.2 Hz, 1 H, $H4_B$), 4.81 (d, *J* = 3.3 Hz, 1 H, $H1_B$), 4.74 (dd, *J* = 8.6, 1.8 Hz, 1 H, $H3_A$), 4.45–4.39 (m, 2 H, $H2_A$, $H6_{aA}$), 4.27–4.24 (m, 1 H, $H5_B$), 4.08 (d, *J* = 12.9 Hz, 1 H, PhC*H*$_2$), 4.03–3.97 (m, 1 H, OCH_2), 3.95 (d, *J* = 12.9 Hz, 1 H, PhC*H*$_2$), 3.90–3.83 (m, 1 H, $H6_{aA}$), 3.78–3.70 (m, 2 H, $H4_A$, $H5_A$), 3.69–3.62 (m, 1 H, OCH_2), 3.52 (dd, *J* = 3.5 Hz, 1 H, $H2_B$), 3.38 (ddd, *J* = 13.3, 8.4, 3.5 Hz, 1 H, CH_2N_3), 3.23 (ddd, *J* = 13.3, 4.7, 3.4 Hz, 1 H, CH_2N_3), 1.95 (s, 3 H, COCH_3), 1.70 (s, 3 H, $COCH_3$), 0.54 (d, *J* = 6.5 Hz, 3 H, CCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.4 (*C*OCH_3), 169.6 (*C*OCH_3), 168.6, 168.2 (Phth), 137.9–126.5 (C_{Ar}), 102.2 (PhCH), 99.1 ($C1_A$), 98.9 ($C1_B$), 81.3 ($C4_A$), 75.1 ($C3_A$), 72.8 (PhCH_2), 72.7 ($C2_B$), 71.7 ($C4_B$), 70.4 ($C3_B$), 68.7 ($C6_A$), 68.4 (OCH_2), 66.6 ($C5_A$), 64.9 ($C5_B$), 55.7 ($C2_A$), 50.5 (CH_2N_3), 20.5 (CO*C*H_3), 20.4 (CO*C*H_3), 15.1 (C*C*H_3).

MS (ESI): *m*/*z* = 809.1 $[M + Na]^+$.

Anal. Calcd for $C_{40}H_{42}N_4O_{13}$ (786.27): C, 61.06; H, 5.38. Found: C, 60.92; H, 5.49.

2-Azidoethyl *O*-(4-*O*-Acetyl-2-*O*-benzyl-α-L-fucopyranosyl)-(1→3)-4,6-*O*-benzylidene-2-deoxy-2-*N*-phthalimido-β-D-glucopyranoside (5)

A solution of **4** (1 g, 1.27 mmol) in 0.1 M NaOMe in MeOH (20 mL) was stirred at r.t. for 1 h. The mixture was neutralized with Dowex 50W-X8 (H^+) resin, filtered, and evaporated to dryness. To a solution of the de-O-acetylated product in anhyd DMF (30 mL) was added triethyl orthoacetate (0.35 mL, 1.91 mmol) followed by TsOH (100 mg) and the mixture was stirred at r.t. for 2 h. The mixture was concentrated under reduced pressure and a solution of the crude product in 80% aq AcOH (40 mL) was stirred at r.t. for 1 h. The solvents were removed under reduced pressure and the crude product was purified by chromatography (silica gel; hexane–EtOAc, 3:1) to give pure **5** (0.85 g, 90%) as a yellow oil; $[\alpha]_D^{25}$ +17 (*c* 1.0, $CHCl_3$).

IR (neat): 3429, 3011, 2827, 2127, 1734, 1555, 1323, 1248, 1133, 1102, 979, 782, 698 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.78–7.75 (m, 2 H, H_{Ar}), 7.69–7.66 (m, 2 H, H_{Ar}), 7.52–7.49 (m, 2 H, H_{Ar}), 7.39–7.35 (m, 3 H, H_{Ar}), 7.24–7.22 (m, 3 H, H_{Ar}), 6.99–6.95 (m, 2 H, H_{Ar}), 5.57 (s, 1 H, PhC*H*), 5.37 (d, *J* = 8.5 Hz, 1 H, $H1_A$), 5.01 (dd, *J* = 3.2, 1.2 Hz, 1 H, $H4_B$), 4.87 (d, *J* = 3.3 Hz, 1 H, $H1_B$), 4.73 (dd, *J* = 8.6, 1.8 Hz, 1 H, $H3_A$), 4.46–4.39 (m, 2 H, $H2_A$, $H6_{aA}$), 4.26 (d, *J* = 12.4 Hz, 1 H, PhC*H*$_2$), 4.25–4.22 (m, 1 H, $H5_B$), 4.01–3.97 (m, 2 H, $H6_{bA}$, $H3_B$), 3.89 (d, *J* = 12.5 Hz, 1 H, PhC*H*$_2$), 3.88–3.84 (m, 1 H, OCH_2), 3.76–3.71 (m, 2 H, $H5_A$, $H4_A$), 3.68–3.63 (m, 1 H, OCH_2), 3.39–3.35 (m, 2 H, $H2_B$, CH_2N_3), 3.23 (ddd, *J* = 13.3, 4.7, 3.4 Hz, 1 H, CH_2N_3), 1.98 (s, 3 H, $COCH_3$), 0.70 (d, *J* = 6.5 Hz, 3 H, CCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0 (*C*OCH_3), 168.7, 168.3 (Phth), 137.7–123.4 (C_{Ar}), 101.9 (PhCH), 99.0 ($C1_A$), 98.1 ($C1_B$), 81.5 ($C4_A$), 75.5 ($C2_B$), 74.7 ($C3_A$), 73.4 ($C4_B$), 72.3 (PhCH_2), 68.7 (OCH_2), 68.5 ($C6_A$), 68.0 ($C3_B$), 66.5 ($C5_A$), 65.4 ($C5_B$), 55.8 ($C2_A$), 50.5 (CH_2N_3), 20.7 (CO*C*H_3), 15.6 (C*C*H_3).

MS (ESI): *m*/*z* = 767.1 $[M + Na]^+$.

Anal. Calcd for $C_{38}H_{40}N_4O_{12}$ (744.26): C, 61.28; H, 5.41. Found: C, 61.17; H, 5.51.

4-Methoxyphenyl 2,3,4-Tri-*O*-acetyl-β-fucopyranoside (7)

A solution of L-fucose tetraacetate (**6**, 5 g, 15.1 mmol), 4-methoxyphenol (2.2 g, 18.1 mmol), and 4 Å molecular sieves (2 g) in anhyd CH_2Cl_2 (30 mL) was cooled to 0 °C. To the cooled reaction was dropwise added $BF_3{\cdot}OEt_2$ (2.2 ml, 18.1 mmol) and the mixture was stirred this temperature for 3 h. The mixture was diluted with CH_2Cl_2 (50 mL) and the organic layer was washed with sat. $NaHCO_3$ and water in succession, dried (Na_2SO_4), and evaporated to dryness. The crude product was purified by chromatography (silica gel; hexane–EtOAc, 4:1) to give pure **7** (4.6 g, 77%) as a colorless liquid; $[\alpha]_D^{25}$ +22 (c 1.0, $CHCl_3$).

IR (neat): 2925, 2239, 1750, 1633, 1595, 1440, 1373, 1212, 1048, 760 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.95 (d, *J* = 9.0 Hz, 2 H, H_{Ar}), 6.82 (d, *J* = 9.0 Hz, 2 H, H_{Ar}), 5.43 (dd, *J* = 10.5, 3.0 Hz, 1 H, H3), 5.28 (d, *J* = 2.5 Hz, 1 H, H4), 5.09 (dd, *J* = 11.0, 3.5 Hz, 1 H, H2), 4.92 (d, *J* = 8.0 Hz, 1 H, H1), 3.92–3.89 (m, 1 H, H5), 3.77 (s, 3 H, OCH_3), 2.19 (s, 3 H, $COCH_3$), 2.07 (s, 3 H, $COCH_3$), 2.01 (s, 3 H, $COCH_3$), 1.26 (d, *J* = 6.5 Hz, 3 H, CCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8 (*C*OCH_3), 170.3 (*C*OCH_3), 169.6 (*C*OCH_3), 155.6–114.6 (C_{Ar}), 100.7 (C1), 71.3 (C4), 70.1 (C2), 69.4 (C3), 68.9 (C5), 55.6 (OCH_3), 20.8 (CO*C*H_3), 20.7 (CO*C*H_3), 20.6 (CO*C*H_3), 16.2 (C*C*H_3).

MS (ESI): *m*/*z* = 419.0 $[M + Na]^+$.

Anal. Calcd for $C_{19}H_{24}O_9$ (396.14): C, 57.57; H, 6.10. Found: C, 57.45; H, 6.25.

4-Methoxyphenyl 3,4-Di-*O*-acetyl-2-*O*-benzyl-β-L-fucopyranoside (8)

A solution of **7** (4 g, 10.1 mmol) in 0.1 M NaOMe in MeOH (30 mL) was stirred at r.t. for 2 h. The mixture was neutralized with Dowex 50W-X8 (H^+) resin, filtered, and evaporated to dryness. To a solution of the de-O-acetylated product in anhyd DMF (30 mL) were added 2,2-dimethoxypropane (1.9 mL, 15.2 mmol) and TsOH (150 mg) and the

mixture was stirred at r.t. for 6 h. To the mixture were added powdered NaOH (804 mg, 20.1 mmol), BnBr (1.4 mL, 12.0 mmol) and TBAB (3.9 g, 12.0 mmol) the mixture was stirred at r.t. for 5 h. The mixture was poured into water (200 mL) and extracted with EtOAc (100 mL). The organic layer was washed with water, dried (Na_2SO_4), and concentrated. A solution of the crude product in 80% aq AcOH (80 mL) was stirred at 80 °C for 1.5 h. The solvents were removed under reduced pressure and co-evaporated with toluene. To a solution of the crude product in anhyd pyridine (20 mL), Ac_2O (5 mL) was added and the solution was stirred at r.t. for 3 h when TLC (hexane–EtOAc, 6:1) showed complete conversion of the starting material to a faster moving spot. The solvents were evaporated in vacuo and co-evaporated with toluene to remove residual pyridine. The syrupy residue thus obtained was purified by chromatography (silica gel; hexane–EtOAc, 8:1) to give pure **8** (3.8 g, 85% overall) as a yellow oil; $[\alpha]_D^{25}$ +37 (*c* 1.0, $CHCl_3$).

IR (neat): 2925, 2339, 1750, 1663, 1595, 1440, 1373, 1222, 1048, 760 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.29 (m, 5 H, H_{Ar}), 7.02 (d, *J* = 9.0 Hz, 2 H, H_{Ar}), 6.83 (d, *J* = 9.0 Hz, 2 H, H_{Ar}), 5.25 (d, *J* = 2.5 Hz, 1 H, H4), 5.05 (dd, *J* = 10.5, 3.0 Hz, 1 H, H3), 4.97 (d, *J* = 8.0 Hz, 1 H, H1), 4.93 (d, *J* = 11.6 Hz, 1 H, PhC*H*$_2$), 4.73 (d, *J* = 11.6 Hz, 1 H, PhC*H*$_2$), 3.89–3.84 (m, 2 H, H5, H2), 3.78 (s, 3 H, OCH_3), 2.16 (s, 3 H, $COCH_3$), 1.98 (s, 3 H, $COCH_3$), 1.24 (d, *J* = 6.5 Hz, 3 H, CCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6 (*C*OCH_3), 170.1 (*C*OCH_3), 155.5–114.6 (C_{Ar}), 103.0 (C1), 76.3 (C2), 74.9 (C3), 72.7 (PhCH_2), 70.6 (C4), 69.1 (C5), 55.7 (OCH_3), 20.7 (2 C, *C*OCH_3), 16.2 (*C*CH_3).

MS (ESI): *m*/*z* = 467.1 [M + Na]+.

Anal. Calcd for $C_{24}H_{28}O_8$ (444.17): C, 64.85; H, 6.35. Found: C, 64.72; H, 6.47.

4-Methoxyphenyl 3,4-Di-*O*-acetyl-β-L-fucopyranoside (9)

To a solution of **8** (3.0 g, 6.76 mmol) in MeOH (20 mL) was added 20% $Pd(OH)_2/C$ (100 mg) and the mixture was stirred at r.t. for 4 h under a positive pressure of H_2. The mixture was filtered through Celite, the filter bed was washed with MeOH (20 mL), and the combined filtrates were concentrated under reduced pressure. The crude product was purified by chromatography (silica gel; hexane–EtOAc, 4:1) to give pure **9** (2.1 g, 88%) as a colorless oil; $[\alpha]_D^{25}$ +28 (*c* 1.0, $CHCl_3$).

IR (neat): 2925, 2349, 1760, 1653, 1595, 1430, 1373, 1232, 1048, 767 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.03 (d, *J* = 9.0 Hz, 2 H, H_{Ar}), 6.84 (d, *J* = 9.0 Hz, 2 H, H_{Ar}), 5.27 (dd, *J* = 10.5, 3.0 Hz, 1 H, H3), 5.00 (d, *J* = 2.5 Hz, 1 H, H4), 4.83 (d, *J* = 7.6 Hz, 1 H, H1), 4.06–4.01 (m, 1 H, H5), 3.92–3.88 (m, 1 H, H2), 3.78 (s, 3 H, OCH_3), 2.18 (s, 3 H, $COCH_3$), 2.07 (s, 3 H, $COCH_3$), 1.24 (d, *J* = 6.5 Hz, 3 H, CCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.7 (*C*OCH_3), 170.5 (*C*OCH_3), 155.6–114.6 (C_{Ar}), 102.5 (C1), 72.9 (C2), 70.3 (C3), 69.4 (C4), 68.9 (C5), 55.6 (OCH_3), 20.8 (*C*OCH_3), 20.6 (*C*OCH_3), 16.2 (*C*CH_3).

MS (ESI): *m*/*z* = 377.1 [M + Na]+.

Anal. Calcd for $C_{17}H_{22}O_8$ (354.13): C, 57.62; H, 6.26. Found: C, 57.48; H, 6.38.

4-Methoxyphenyl *O*-(2,3,4-Tri-*O*-acetyl-α-L-rhamnopyranosyl)-(1→2)-3,4-di-*O*-acetyl-α-L-fucopyranoside (13)

To a solution of **9** (2.0 g, 5.65 mmol) and **10** (2.3 g, 6.78 mmol) in anhyd CH_2Cl_2 (50 mL) was added 4 Å molecular sieves (2.0 g) and the mixture was stirred at r.t. for 30 min under argon. The mixture was cooled to –30 °C. To the cooled mixture were added NIS (1.8 g, 8.13 mmol) and TMSOTf (30 µL) and the mixture was stirred at this temperature for 1 h. The mixture was diluted with CH_2Cl_2 (50 mL) and filtered through Celite and it was washed with CH_2Cl_2. The combined organic layers were successively washed with 5% $Na_2S_2O_3$, sat. $NaHCO_3$, and water, dried (Na_2SO_4), and concentrated. The crude product was purified by chromatography (silica gel; hexane–EtOAc, 6:1) to give pure **13** (3.1 g, 88%) as a yellow oil; $[\alpha]_D^{25}$–39 (*c* 1.0, $CHCl_3$).

IR (neat): 3445, 2918, 1863, 1736, 1507, 1452, 1263, 1052, 1068, 1026, 709 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.01 (d, *J* = 9.1 Hz, 2 H, H_{Ar}), 6.80 (d, *J* = 9.1 Hz, 2 H, H_{Ar}), 5.28–5.26 (m, 2 H, $H3_D$, $H3_E$), 5.25 (br s, 1 H, $H1_E$), 5.17 (dd, *J* = 10.0, 3.2 Hz, 1 H, $H4_E$), 5.08–5.04 (m, 1 H, $H2_E$), 5.01 (dd, *J* = 10.2, 3.3 Hz, 1 H, $H4_D$), 4.86 (d, *J* = 7.8 Hz, 1 H, $H1_D$), 4.08 (dd, *J* = 10.2, 7.8 Hz, 1 H, $H2_D$), 4.03–3.96 (m, 1 H, $H5_E$), 3.90–3.85 (m, 1 H, $H5_D$), 3.75 (s, 3 H, OCH_3), 2.16 (s, 3 H, $COCH_3$), 2.14 (s, 3 H, $COCH_3$), 2.02 (s, 3 H, $COCH_3$). 2.01 (s, 3 H, $COCH_3$), 1.95 (s, 3 H, $COCH_3$), 1.23 (d, *J* = 6.4 Hz, 3 H, CCH_3), 1.21 (d, *J* = 6.4 Hz, 3 H, CCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6 (*C*OCH_3), 169.9 (*C*OCH_3), 169.8 (*C*OCH_3), 169.7 (2 C, *C*OCH_3), 155.8–114.6 (C_{Ar}), 102.8 ($C1_D$), 97.9 ($C1_E$), 73.6 ($C2_D$), 71.9 ($C4_D$), 70.9 ($C2_E$), 70.4 ($C3_D$), 69.6 ($C3_E$), 69.1 ($C5_D$), 68.9 ($C4_E$), 66.6 ($C5_E$), 55.6 (OCH_3), 20.8 (*C*OCH_3), 20.7 (*C*OCH_3), 20.6 (3 C, *C*OCH_3), 17.4 (*C*CH_3), 16.1 (*C*CH_3).

MS (ESI): *m*/*z* = 649.1 [M + Na]+.

Anal. Calcd for $C_{29}H_{38}O_{15}$ (626.22): C, 55.59; H, 6.11. Found: C, 55.42; H, 6.23.

Ethyl *O*-(2,3,4-Tri-*O*-acetyl-α-L-rhamnopyranosyl)-(1→2)-*O*-(3,4-di-*O*-acetyl-α-L-fucopyranosyl)-(1→3)-2,4,6-tri-*O*-acetyl-1-thio-α-D-mannopyranoside (15)

To a solution of **13** (3 g, 4.79 mmol) in MeCN–H_2O (4:1, 40 mL) was added CAN (3.2 g, 5.75 mmol) and the mixture stirred at r.t. for 2 h. The mixture was diluted with CH_2Cl_2 (70 mL) and the organic layer was washed with sat. $NaHCO_3$ and water, dried (Na_2SO_4), and evaporated to dryness to give disaccharide hemiacetal. To a solution of the hemiacetal in anhyd CH_2Cl_2 (30 mL) was added trichloroacetonitrile (0.72 mL, 7.2 mmol) and the mixture was cooled to –10 °C. To the cooled mixture was added DBU (0.2 mL, 1.3 mmol) and it was stirred at –10 °C for 1 h. The mixture was evaporated to dryness and the crude product was passed through a short pad of silica gel to give 2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl)-(1→2)-3,4-di-*O*-acetyl-β-L-fucopyranosyl trichloroacetimidate (**14**; 2.6 g, 84%). A solution of **11** (1.0 g, 2.9 mmol) and **14** (2.3 g, 3.4 mmol) in anhyd Et_2O–CH_2Cl_2 (4:1, 30 mL) was cooled to –30 °C. To the cooled mixture was added $NOBF_4$ (119 mg, 1.02 mmol) and it was stirred at –30 °C for 30 min. The mixture was diluted with CH_2Cl_2 (50 mL) and the organic layer was washed with sat. $NaHCO_3$ and water in succession, dried (Na_2SO_4), and evaporated to dryness. The crude product was purified by chromatography (silica gel; hexane–EtOAc, 3:1) to give pure **15** (1.6 g, 66%) as a yellow oil; $[\alpha]_D^{25}$– 28 (*c* 1.0, $CHCl_3$).

IR (neat): 3447, 2929, 2231, 1722, 1718, 1452, 1386, 1265, 1094, 957, 710 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.37–5.36 (m, 1 H, $H2_C$), 5.31–5.29 (m, 2 H, $H3_D$, $H3_E$), 5.28 (br s, 1 H, $H1_C$), 5.22–5.21 (m, 1 H, $H4_E$), 5.20–5.12 (m, 2 H, $H4_C$, $H2_E$), 5.09 (d, *J* = 2.3 Hz, 1 H, $H1_D$), 5.07–5.05 (m 1 H, $H4_D$), 4.84 (br s, 1 H, $H1_E$), 4.30–4.26 (m, 2 H, $H5_C$, $H6_{aC}$), 4.18–4.12 (m, 2 H, $H3_C$, $H5_D$), 4.11–4.07 (m, 3 H, $H6_{bC}$, $H2_D$, $H5_E$), 2.66–2.62 (m, 2 H, SCH_2CH$_3$), 2.17 (s, 3 H, $COCH_3$), 2.15 (s, 3 H, $COCH_3$), 2.13 (s, 3 H, CO-

CH_3), 2.12 (s, 3 H, $COCH_3$), 2.09 (s, 3 H, $COCH_3$), 2.02 (s, 3 H, $COCH_3$), 1.99 (s, 3 H, $COCH_3$), 1.96 (s, 3 H, $COCH_3$), 1.29 (t, *J* = 7.4 Hz, 3 H, SCH_2CH_3), 1.19 (d, *J* = 6.4 Hz, 3 H, CCH_3), 1.12 (d, *J* = 6.4 Hz, 3 H, CCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6 ($COCH_3$), 170.3 ($COCH_3$), 169.9 (2 C, $COCH_3$), 169.8 ($COCH_3$), 169.6 ($COCH_3$), 169.5 ($COCH_3$), 169.4 ($COCH_3$), 95.7 ($C1_E$), 94.7 ($C1_D$), 82.4 ($C1_C$), 73.1 ($C2_D$), 71.4 ($C3_D$), 70.8 ($C4_D$), 69.8 ($C2_E$), 69.6 ($C2_C$), 69.3 ($C4_E$), 69.2 ($C5_C$), 69.0 ($C3_C$), 68.5 ($C4_C$), 67.6 ($C3_E$), 66.4 ($C5_E$), 65.1 ($C5_D$), 62.6 ($C6_C$), 25.5 (SCH_2CH_3), 20.9 ($COCH_3$), 20.8 ($COCH_3$), 20.7 ($COCH_3$), 20.6 ($COCH_3$), 20.5 (2 C, $COCH_3$), 20.5 (2 C, $COCH_3$), 17.1 (SCH_2CH_3), 15.7 (CCH_3), 14.8 (CCH_3).

MS (ESI): *m*/*z* = 875.1 [M + Na]$^+$.

Anal. Calcd for $C_{36}H_{52}O_{21}S$ (852.27): C, 50.70; H, 6.15. Found: C, 50.53; H, 6.28.

4-Methoxyphenyl *O*-(3,4-Di-*O*-acetyl-2-*O*-benzyl-α-L-fucopyranosyl)-(1→3)-2,4,6-tri-*O*-acetyl-α-D-mannopyranoside (16)

To a solution of **12** (2 g, 4.85 mmol) and **3** (2.23 g, 5.83 mmol) in anhyd Et_2O–CH_2Cl_2 (4:1, 30 mL) was added 4 Å molecular sieves (1 g) and the mixture was stirred at r.t. for 30 min under argon and cooled to –30 °C. To the cooled mixture were added NIS (1.6 g, 6.99 mmol) and TMSOTf (30 μL) and it was stirred at this temperature for 30 min. The mixture was diluted with CH_2Cl_2 (50 mL) and filtered through Celite and it was washed with CH_2Cl_2. The combined organic layers were successively washed with 5% $Na_2S_2O_3$, sat. $NaHCO_3$, and water, dried (Na_2SO_4), and concentrated. The crude product was purified by chromatography (silica gel; hexane–EtOAc, 4:1) to give pure **16** (2.7 g, 76%) as a yellow oil; $[\alpha]_D^{25}$ –14 (*c* 1.0, $CHCl_3$).

IR (neat): 3057, 2856, 1712, 1625, 1520, 1365, 1229, 1173, 1097, 989, 911, 823, 745, 697 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.28 (m, 5 H, H_{Ar}), 7.01 (d, *J* = 9.2 Hz, 2 H, H_{Ar}), 6.84 (d, *J* = 9.2 Hz, 2 H, H_{Ar}), 5.48–5.47 (m, 1 H, $H2_C$), 5.43 (d, *J* = 1.7 Hz, 1 H, $H1_C$), 5.37 (t, *J* = 9.9 Hz, 1 H, $H4_C$), 5.28 (dd, *J* = 3.3, 1.2 Hz, 1 H, $H4_D$), 5.23 (dd. *J* = 10.5, 3.3 Hz, 1 H, $H3_D$), 5.02 (d, *J* = 3.4 Hz, 1 H, $H1_D$), 4.62 (br s, 2 H, $PhCH_2$), 4.29 (dd, *J* = 9.8, 3.4 Hz, 1 H, 3_C), 4.24–4.19 (m, 2 H, 6_{aC}, $H5_D$), 4.14–4.04 (m, 2 H, $H6_{bC}$, $H5_C$), 3.83 (dd, *J* = 10.4, 3.4 Hz, 1 H, $H2_D$), 3.78 (s, 3 H, OCH_3), 2.14 (s, 3 H, $COCH_3$), 2.11 (s, 3 H, $COCH_3$), 2.04 (s, 3 H, $COCH_3$), 2.01 (s, 3 H, $COCH_3$), 1.94 (s, 3 H, $COCH_3$), 1.14 (d, *J* = 6.4 Hz, 3 H, CCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6 (2 C, $COCH_3$), 170.4 ($COCH_3$), 169.9 ($COCH_3$), 169.6 ($COCH_3$), 155.4–114.6 (C_{Ar}), 96.9 (2 C, $C1_C$, $C1_D$), 73.4 ($PhCH_2$), 73.2 ($C2_D$), 73.1 ($C3_C$), 71.5 $C4_D$), 70.1 ($C3_D$), 69.3 ($C5_C$), 68.6 ($C2_C$), 67.4 ($C4_C$), 65.2 ($C5_D$), 62.5 ($C6_C$), 55.7 (OCH_3), 20.8 (2 C, $COCH_3$), 20.7 (2 C, $COCH_3$), 20.6 ($COCH_3$), 15.9 (CCH_3).

MS (ESI): *m*/*z* = 755.1 [M + Na]$^+$.

Anal. Calcd for $C_{36}H_{44}O_{16}$ (732.26): C, 59.01; H, 6.05. Found: C, 58.89; H, 6.17.

4-Methoxyphenyl *O*-(3,4-Di-*O*-acetyl-α-L-fucopyranosyl)-(1→3)-2,4,6-tri-*O*-acetyl-α-D-mannopyranoside (17)

To a solution of **16** (2.0 g, 2.73 mmol) in MeOH (50 mL) was added 20% $Pd(OH)_2$/C (500 mg) and the mixture was stirred at r.t. for 5 h under a positive pressure of H_2. The mixture was filtered through Celite, it was washed with MeOH (40 mL), and the combined filtrates were concentrated under reduced pressure. The crude product was purified by chromatography (silica gel; hexane–EtOAc, 3:1) to give pure **17** (1.5 g, 86%) as a colorless oil; $[\alpha]_D^{25}$ –24 (*c* 1.0, $CHCl_3$).

IR (neat): 3077, 2836, 1742, 1645, 1510, 1395, 1259, 1173, 1062, 989, 823, 678 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.02 (d, *J* = 9.2 Hz, 2 H, H_{Ar}), 6.84 (d, *J* = 9.2 Hz, 2 H, H_{Ar}), 5.55 (d, *J* = 1.6 Hz, 1 H, $H2_C$), 5.43 (br s, 1 H, $H1_C$), 5.32 (t, *J* = 9.9 Hz, 1 H, $H4_C$), 5.22 (d, *J* = 2.2 Hz, 1 H, $H4_D$), 5.07 (d, *J* = 3.4 Hz, 1 H, $H1_D$), 4.94 (dd, *J* = 10.5, 3.3 Hz, 1 H, $H3_D$), 4.33–4.25 (m, 2 H, H3C, $H6_{aC}$), 4.13–4.08 (m, 3 H, $H5_C$, $H5_D$, $H6_{bC}$), 3.97–3.93 (m, 1 H, $H2_D$), 3.79 (s, 3 H, OCH_3), 2.25 (s, 3 H, $COCH_3$), 2.17 (s, 3 H, $COCH_3$), 2.13 (s, 3 H, $COCH_3$), 2.07 (s, 3 H, $COCH_3$), 2.06 (s, 3 H, $COCH_3$), 1.13 (d, *J* = 6.4 Hz, 3 H, CCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.6 ($COCH_3$), 170.6 (2 C, $COCH_3$), 170.5 ($COCH_3$), 169.8 ($COCH_3$), 155.5–114.7 (C_{Ar}), 98.4 ($C1_D$), 96.9 ($C1_C$), 77.1 ($C3_C$), 71.3 ($C4_D$), 70.4 ($C3_D$), 69.5 ($C2_C$), 68.9 ($C5_C$), 67.4 ($C4_C$), 66.8 ($C2_D$), 66.1 ($C5_D$), 62.3 ($C6_C$), 55.7 (OCH_3), 21.1 ($COCH_3$), 20.9 ($COCH_3$), 20.8 ($COCH_3$), 20.7 ($COCH_3$), 20.6 ($COCH_3$), 15.9 (CCH_3).

MS (ESI): *m*/*z* = 665.1 [M + Na]$^+$.

Anal. Calcd for $C_{29}H_{38}O_{16}$ (642.21): C, 54.20; H, 5.96. Found: C, 54.08; H, 6.07.

4-Methoxyphenyl *O*-(2,3,4-Tri-*O*-acetyl-α-L-rhamnopyranosyl)-(1→2)-*O*-(3,4-di-*O*-acetyl-α-L-fucopyranosyl)-(1→3)-2,4,6-tri-*O*-acetyl-α-D-mannopyranoside (18)

To a solution of **17** (1 g, 1.56 mmol) and **10** (0.62 g, 1.87 mmol) in anhyd CH_2Cl_2 (10 mL) was added 4 Å molecular sieves (500 mg) and the mixture was stirred under argon at r.t. for 30 min and cooled to –30 °C. To the cooled mixture were added NIS (505 mg, 2.24 mmol) and TMSOTf (10 μL) and it was stirred at this temperature for 1 h. The mixture was filtered through Celite and it was washed with CH_2Cl_2 (50 mL). The combined organic layers were successively washed with 5% $Na_2S_2O_3$, sat. $NaHCO_3$, and water, dried (Na_2SO_4), and concentrated. The crude product was purified by chromatography (silica gel; hexane–EtOAc, 3:1) to give pure **18** (1.2 g, 85%) as a colorless oil; $[\alpha]_D^{25}$ –26 (*c* 1.0, $CHCl_3$).

IR (neat): 3027, 2806, 1762, 1615, 1509, 1355, 1239, 1173, 1042, 989, 813, 677 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.01 (d, *J* = 9.2 Hz, 2 H, H_{Ar}), 6.81 (d, *J* = 9.2 Hz, 2 H, H_{Ar}), 5.54–5.53 (m, 1 H, $H2_C$), 5.42 (d, *J* = 2.0 Hz, 1 H, $H1_C$), 5.41–5.39 (m, 1 H, $H4_C$), 5.31–5.30 (m, 1 H, $H4_E$), 5.28–5.25 (m, 1 H, $H3_E$), 5.21 (dd, *J* = 10.5, 3.3 Hz, 1 H, $H3_D$), 5.17 (d, *J* = 2.2 Hz, 1 H, $H1_D$), 5.16–5.15 (m, 1 H, $H2_E$), 5.10–5.05 (m, 1 H, $H4_D$), 4.89 (d, *J* = 1.3 Hz, 1 H, $H1_E$), 4.34 (dd, *J* = 9.8, 3.4 Hz, 1 H, 3_C), 4.27–4.23 (m, 2 H, $H6_{aC}$, $H5_D$), 4.15 (dd, *J* = 10.4, 3.4 Hz, 1 H, $H2_D$), 4.12–4.04 (m, 3 H, $H5_E$, $H6_{bC}$, $H5_C$), 3.77 (s, 3 H, OCH_3), 2.20 (s, 3 H, $COCH_3$), 2.17 (s, 3 H, $COCH_3$), 2.15 (s, 3 H, $COCH_3$), 2.13 (s, 3 H, $COCH_3$), 2.05 (s, 3 H, $COCH_3$), 2.01 (s, 6 H, $COCH_3$), 1.89 (s, 3 H, $COCH_3$), 1.21 (d, *J* = 6.5 Hz, 3 H, CCH_3), 1.14 (d, *J* = 6.5 Hz, 3 H, CCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6 ($COCH_3$), 170.4 ($COCH_3$), 170.2 ($COCH_3$), 170.0 ($COCH_3$), 169.9 ($COCH_3$), 169.6 ($COCH_3$), 155.4–114.5 (C_{Ar}), 96.9 ($C1_C$), 96.5 ($C1_D$), 96.1 ($C1_E$), 74.1 ($C3_C$), 71.5 ($C4_E$), 70.7 ($C4_D$), 70.5 ($C2_D$), 69.9 ($C3_E$), 69.4 ($C5_C$), 68.9 ($C3_D$), 68.8 ($C2_C$), 68.6 ($C2_E$), 67.5 ($C4_C$), 66.6 ($C5_E$), 65.5 ($C5_D$), 62.4 ($C6_C$), 55.6 (OCH_3), 20.9 (2 C. $COCH_3$), 20.7 (3 C, $COCH_3$), 20.6 (2 C, $COCH_3$), 20.5 ($COCH_3$), 17.2 (CCH_3), 15.8 (CCH_3).

MS (ESI): *m*/*z* = 937.2 [M + Na]$^+$.

Anal. Calcd for $C_{41}H_{54}O_{23}$ (914.31): C, 53.83; H, 5.95. Found: C, 53.71; H, 6.08.

2-Azidoethyl *O*-(2,3,4-Tri-*O*-acetyl-α-L-rhamnopyranosyl)-(1→2)-*O*-(3,4-di-*O*-acetyl-α-L-fucopyranosyl)-(1→3)-*O*-(2,4,6-tri-*O*-acetyl-α-D-mannopyranosyl)-(1→3)-*O*-(4-*O*-acetyl-2-*O*-benzyl-α-L-fucopyranosyl)-(1→3)-4,6-*O*-benzylidene-2-deoxy-2-*N*-phthalimido-β-D-glucopyranoside (20)

Process I: To a solution of **5** (500 mg, 0.67 mmol) and **15** (687 mg, 0.81 mmol) in anhyd CH_2Cl_2 (20 mL) was added 4 Å molecular sieves (500 mg) and the mixture was stirred under argon at r.t. for 30 min and cooled to –10 °C. To the cooled mixture were added NIS (217 mg, 0.97 mmol) and TMSOTf (10 μL) and it was stirred at this temperature for 1 h. The mixture was filtered through Celite and it was washed with CH_2Cl_2 (50 mL). The combined organic layers were successively washed with 5% $Na_2S_2O_3$, sat. $NaHCO_3$, and water, dried (Na_2SO_4), and concentrated. The crude product was purified by chromatography (silica gel; hexane–EtOAc, 1:1) to give pure **20** (800 mg, 78%).

Process II: To a solution of **18** (1 g, 1.09 mmol) in MeCN–H_2O (4:1, 20 mL) was added CAN (0.72 g, 1.31 mmol) and the mixture was stirred at r.t. for 2 h. The mixture was diluted with CH_2Cl_2 (40 mL) and the organic layer was washed with sat. $NaHCO_3$ and water, dried (Na_2SO_4), and evaporated to dryness to give the disaccharide hemiacetal. To a solution of the hemiacetal in anhyd CH_2Cl_2 (30 mL) was added trichloroacetonitrile (0.16 mL, 1.6 mmol) and the mixture was cooled to –10 °C. To the cooled mixture was added DBU (0.2 mL, 1.3 mmol) and it was stirred at –10 °C for 1 h. The mixture was evaporated to dryness and the crude product was passed through a short pad of silica gel to give 2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl-(1→2)-3,4-di-*O*-acetyl-α-L-fucopyranosyl-(1→3)-2,4,6-tri-*O*-acetyl-α-D-mannopyranosyl trichloroacetimidate (**19**; 0.90 g, 87%). A solution of **5** (500 mg, 0.67 mmol) and **19** (764 mg, 0.80 mmol) in anhyd CH_2Cl_2 (30 mL) was cooled to –10 °C. To the cooled mixture was added $NOBF_4$ (28 mg, 0.24 mol) and it was stirred at –10 °C for 30 min. The mixture was diluted with CH_2Cl_2 (50 mL) and the organic layer was washed with sat. $NaHCO_3$ and water in succession, dried (Na_2SO_4), and evaporated to dryness. The crude product was purified by chromatography (silica gel; hexane–EtOAc, 1:1) to give pure **20** (850 mg, 81%) as a colorless oil; $[\alpha]_D^{25}$ +12 (*c* 1.0, $CHCl_3$).

IR (neat): 3029, 2834, 2210, 2127, 1849, 1628, 1415, 1322, 1250, 1042, 988, 756, 667 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.33 (m, 2 H, H_{Ar}), 7.20–7.12 (m, 8 H, H_{Ar}), 7.06–7.04 (m, 2 H, H_{Ar}), 5.41 (s, 1 H, PhC*H*), 5.24 (d, *J* = 8.4 Hz, 1 H, $H1_A$), 5.13–5.13 (m, 2 H, $H2_C$, $H3_D$), 5.05 (m, 2 H, $H3_E$, $H4_E$), 4.93 (dd, *J* = 3.2, 1.2 Hz, 1 H, $H4_B$), 4.90–4.88 (m, 1 H, $H2_E$), 4.87 (d, *J* = 2.3 Hz, 1 H, $H1_D$), 4.86–4.84 (m, 4 H, PhCH_2, $H4_C$, $H4_D$), 4.77 (d, *J* = 2.8 Hz, 1 H, $H1_B$), 4.66 (br s, 2 H, $H1_C$, $H1_E$), 4.42 (dd, *J* = 8.6, 1.8 Hz, 1 H, $H3_A$), 4.29–4.17 (m, 3 H, $H6_{aA}$, $H6_{aC}$, $H2_A$), 4.15–4.059 (m, 4 H, $H3_C$, $H5_E$, $H5_C$, $H2_D$), 3.99–3.91 (m, 2 H, $H6_{bC}$, $H5_B$), 3.84–3.72 (m, 5 H, $H6_{bA}$, $H5_D$, $H3_B$, OCH_2, $H5_A$), 3.54–3.48 (m, 2 H, $H4_A$, OCH_2), 3.35 (m, 1 H, $H2_B$), 3.22–3.17 (m, 1 H, CH_2N_3), 3.06–3.03 (m, 1 H, CH_2N_3), 2.02 (s, 3 H, $COCH_3$), 1.99 (s, 3 H, $COCH_3$), 1.96 (s, 6 H, $COCH_3$), 1.84 (s, 9 H, $COCH_3$), 1.82 (s, 3 H, $COCH_3$), 1.78 (s, 3 H, $COCH_3$), 1.02 (d, *J* = 6.4 Hz, 6 H, CCH_3), 0.74 (d, *J* = 6.4 Hz, 3 H, CCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9 ($COCH_3$), 170.7 ($COCH_3$), 170.3 ($COCH_3$), 169.9 ($COCH_3$), 169.8 (2 C, $COCH_3$), 169.7 (2 C, $COCH_3$), 169.5 ($COCH_3$), 168.9, 168.7 (Phth), 155.1–114.5 (C_{Ar}), 101.4 (PhCH), 98.9 ($C1_A$), 98.0 ($C1_B$), 97.9 ($C1_C$), 95.5 ($C1_E$), 91.9 ($C1_D$), 82.2 ($C4_A$), 76.4 ($C2_B$), 75.9 ($C3_A$), 73.1 ($C4_B$), 72.5 (PhCH_2), 71.7 ($C2_D$), 70.8 ($C3_D$), 70.7 ($C4_D$), 69.7 ($C2_E$), 69.5 ($C2_C$), 69.4 (2 C, $C4_E$, $C5_C$), 68.6 (2 C, OCH_2, $C6_A$), 68.5 ($C3_B$), 67.8 ($C3_C$), 66.9 ($C4_C$), 66.5 ($C3_E$),, 66.3 ($C5_A$), 66.0 ($C5_D$), 65.7 ($C5_B$), 64.5 ($C5_E$), 62.9 ($C6_C$), 55.2 ($C2_A$), 50.4 (CH_2N_3), 20.9 (2 C, $COCH_3$), 20.7 (2 C, $COCH_3$), 20.6 ($COCH_3$), 20.5 (2 C, $COCH_3$), 20.5 (2 C, $COCH_3$), 17.1 (CCH_3), 15.7 (CCH_3), 15.5 (CCH_3).

MS (ESI): *m*/*z* = 1557.3 $[M + Na]^+$.

Anal. Calcd for $C_{72}H_{86}N_4O_{33}$ (1534.51): C, 56.32; H, 5.65. Found: C, 56.18; H, 5.79.

2-Aminoethyl *O*-(α-L-Rhamnopyranosyl)-(1→2)-*O*-(α-L-fucopyranosyl)-*O*-(1→3)-(α-D-mannopyranosyl)-(1→3)-*O*-(α-L-fucopyranosyl)-(1→3)-2-acetamido-2-deoxy-β-D-glucopyranoside (1)

To a solution of **20** (300 mg, 0.19 mmol) in EtOH (10 mL) was added hydrazine hydrate (2 mL) and the mixture was stirred at 80 °C for 8 h. The solvents were removed under reduced pressure and a solution of the crude mass in pyridine (5 mL) and Ac_2O (5 mL) was kept at r.t. for 1 h. The solvents were evaporated and co-evaporated with toluene under reduced pressure. To a solution of the acetylated product in MeOH (20 mL) was added 20% $Pd(OH)_2$/C (200 mg) and the mixture was stirred at r.t. under a positive pressure of H_2 for 12 h. The mixture was filtered through Celite, it was washed with MeOH (20 mL), and the combined filtrates were concentrated under reduced pressure. A solution of the hydrogenated product in 0.1 M NaOMe in MeOH (10 mL) was stirred at r.t. for 3 h. The mixture was neutralized with Dowex 50W-X8 (H^+) resin, filtered, and concentrated. The crude product was passed through a Sephadex LH20 column (MeOH–H_2O, 3:1) to give pure **1** (85 mg, 51%) as a white powder; $[\alpha]_D^{25}$ +10 (*c* 1.0, H_2O).

IR (KBr): 3456, 2935, 2722, 2117, 1622, 1356, 1256, 1165, 1067, 697 cm^{-1}.

^1H NMR (400 MHz, D_2O): δ = 5.28 (br s, 1 H, $H1_D$), 5.03 (br s, 1 H, $H1_C$, $H1_B$), 5.02 (br s, 1 H, H1E), 4.47 (d, *J* = 7.4 Hz, 1 H, $H1_A$), 4.33–4.23 (m, 2 H, $H5_D$, $H5_B$), 4.22–4.11 (m, 3 H, $H2_C$, $H3_C$, $H5_C$), 4.10–3.84 (m, 6 H, $H3_D$, OCH_2, $H2_E$, $H5_E$, $H6_{aA}$, $H2_A$), 3.78–3.70 (m, 8 H, $H6_{bA}$, $H6_{abC}$, OCH_2, $H3_A$, $H2_D$, $H2_B$, $H4_D$,), 3.69–3.60 (m, 3 H, $H4_B$, $H3_E$, $H4_C$), 3.51–3.39 (m, 2 H, $H4_E$, $H4_A$), 3.35–3.25 (m, 2 H, $H3_B$, $H5_A$), 3.24–3.21 (m, 1 H, CH_2N_3), 3.13–3.02 (m, 1 H, CH_2N_3), 1.95 (s, 3 H, $COCH_3$), 1.21 (d, *J* = 6.4 Hz, 3 H, CCH_3), 1.17 (d, *J* = 6.4 Hz, 3 H, CCH_3), 1.12 (d, *J* = 6.4 Hz, 3 H, CCH_3).

^{13}C NMR (100 MHz, D_2O): δ = 175.9 ($COCH_3$), 101.1 ($C1_C$), 100.5 ($C1_A$), 99.8 ($C1_B$), 98.1 ($C1_E$), 96.1 ($C1_D$), 80.1 ($C3_A$), 76.2 ($C3_B$), 75.4 ($C5_A$), 73.2 ($C3_C$), 72.2 (2 C, $C4_C$, $C4_D$), 72.0 ($C4_E$), 70.6 ($C4_B$), 70.3 ($C5_C$), 70.1 ($C2_D$), 69.0 ($C2_E$), 68.9 (2 C, $C3_E$, $C4_A$), 67.2 ($C5_B$), 67.0 ($C5_D$), 66.6 ($C2_B$), 66.4 ($C2_C$), 65.7 (2 C, $C5_E$, $C3_D$), 65.3 (OCH_2), 60.8 ($C6_A$), 60.7 ($C6_C$), 57.2 ($C2_A$), 39.9 (CH_2N_3), 23.2 ($COCH_3$), 16.8 (CCH_3), 15.1 (2 C, CCH_3).

MS (ESI): *m*/*z* = 865.2 $[M + H]^+$.

Anal. Calcd for $C_{34}H_{60}N_2O_{23}$ (864.36): C, 47.22; H, 6.99. Found: C, 47.08; H, 7.12.

Acknowledgment

Author gratefully acknowledges financial support by Department of Science and Technology (DST), India under Fast Track Proposal Scheme for Young Scientists (CS-127/2012) and SAIF Division of CSIR-CDRI for providing the spectroscopic and analytical data. CDRI communication no. 8863.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379952. Included are copies of 1D and 2D NMR spectra of compounds **1**, **4**, **5**, **7**, **8**, **9**, **13**, **15**, **16**, **17**, **18**, **20**.

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