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Expedient synthesis of a pentasaccharide related to the O-specific polysaccharide of *Escherichia coli* O117:K98:H4 strain†

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A convenient synthetic strategy has been developed for the synthesis of a pentasaccharide, related to the O-specific polysaccharide of *Escherichia coli* O117:K98:H4 strain, using sequential glycosylations of functionalized monosaccharide moieties. The application of a one-pot reaction condition for two glycosylations and *in situ* PMB group removal reduced the number of reaction steps significantly. All glycosylation reactions were stereoselective with satisfactory yield.

Introduction

Escherichia coli (*E. coli*) strains are found in the human gastrointestinal tract as commensal organisms. However, on many occasions, they acquire virulence properties in a host with poor immunity.[1] A number of infections in humans have been reported till date, which are caused by pathogenic *E. coli*. *E. coli* infections are classified in three general clinical symptoms, such as urinary tract infections (UTI),[2] septicaemia[3] or meningitis[4] and diarrheal infections.[5] Several strains of *E. coli* have been identified, which are associated with each clinical symptom. *E. coli* O117:K98:H4 strain has been found to cause septicaemia in children.[6] It also produces verocytotoxin (VT) and causes diarrhoea, particularly among travellers.[7] This strain is also occasionally responsible for acute urinary tract infections in women.[8] The structure of the O-specific polysaccharide present in the cell wall of *E. coli* O117:K98:H4 strain has been reported by Ruth Leslie *et al.*, which is composed of D-galactosamine, D-glucose, D-galactose and L-rhamnose.[9] The emergence of multidrug resistant bacterial strains is a serious concern for controlling bacterial infections using antibiotics. Since cell wall polysaccharides are involved in various stages of bacterial infections to the host, they have been used in the development of vaccines for long term protection from infectious diseases.[10] Conventionally, glycoconjugate vaccines are prepared by isolating polysaccharides from the bacterial cell wall and coupling with a career protein.[10,11] However, the isolation of oligosaccharides from the bacterial cells with adequate purity and structural integrity is quite tedious. On the contrary, chemical synthesis could provide oligosaccharide fragments with appropriate structure and purity. In the recent past, several successful attempts were made in the development of vaccine candidates using synthetic oligosaccharide fragments for the preparation of glycoconjugate derivatives by conjugating with a carrier protein.[12–14] In an ongoing program, focusing the concise chemical synthesis oligosaccharides related to the bacterial cell wall,[15] a linear synthetic strategy for the synthesis of a pentasaccharide related to the O-specific polysaccharide of *E. coli* O117:K98:H4 is presented herein.

→ 4)-β-D-Gal*p*NAc-(1 → 3)-α-L-Rha*p*-(1 → 4)-α-D-Glc*p*-(1 → 4)-β-D-Gal*p*-(1 → 3)-α-D-Gal*p*NAc-(1 →

Structure of the repeating unit of the O-specific polysaccharide of *E. coli* O117:K98:H4.

Results and discussion

The strategy for the synthesis of the pentasaccharide as *p*-methoxyphenyl (PMP) glycoside (**1**) involves sequential glycosylations of suitably functionalized monosaccharide intermediates (Fig. 1). The selection of PMP group at the anomeric position of the reducing end of the pentasaccharide could provide the option for conjugation of the pentasaccharide with an appropriate protein or aglycon moiety after oxidative removal of the PMP group.[16] As per the requirement of the synthetic strategy, monosaccharide intermediates **2**, **3**,[17] **4**,[18] **5** (ref. 19) and **6** (ref. 20) were prepared in good yield from the commercially available reducing sugars, using earlier reported reaction conditions. A number of recently developed reaction methodologies have been used in the synthesis of the target pentasaccharide.

p-Methoxyphenyl-2-azido-4,6-*O*-benzylidene-2-deoxy-α-D-galactopyranoside (**7**)[21] (prepared from D-galactal) was treated with sodium cyanoborohydride[22] in the presence of HCl in Et_2O to give 3,4-dihydroxy derivative, which on treatment with triethyl orthoacetate in the presence of *p*-toluenesulfonic acid,[23] followed by acid hydrolysis of the orthoester, furnished

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† Electronic supplementary information (ESI) available: Copies of 1D and 2D NMR spectra of compounds **2**, **8–13**, and **1**. See DOI: 10.1039/c4ra10538a

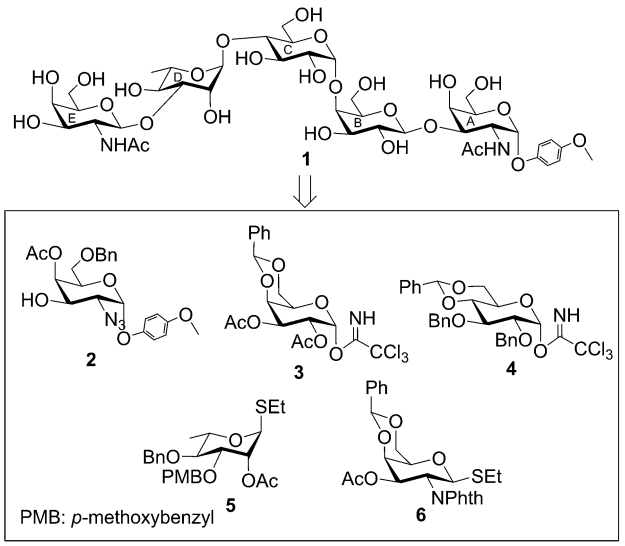
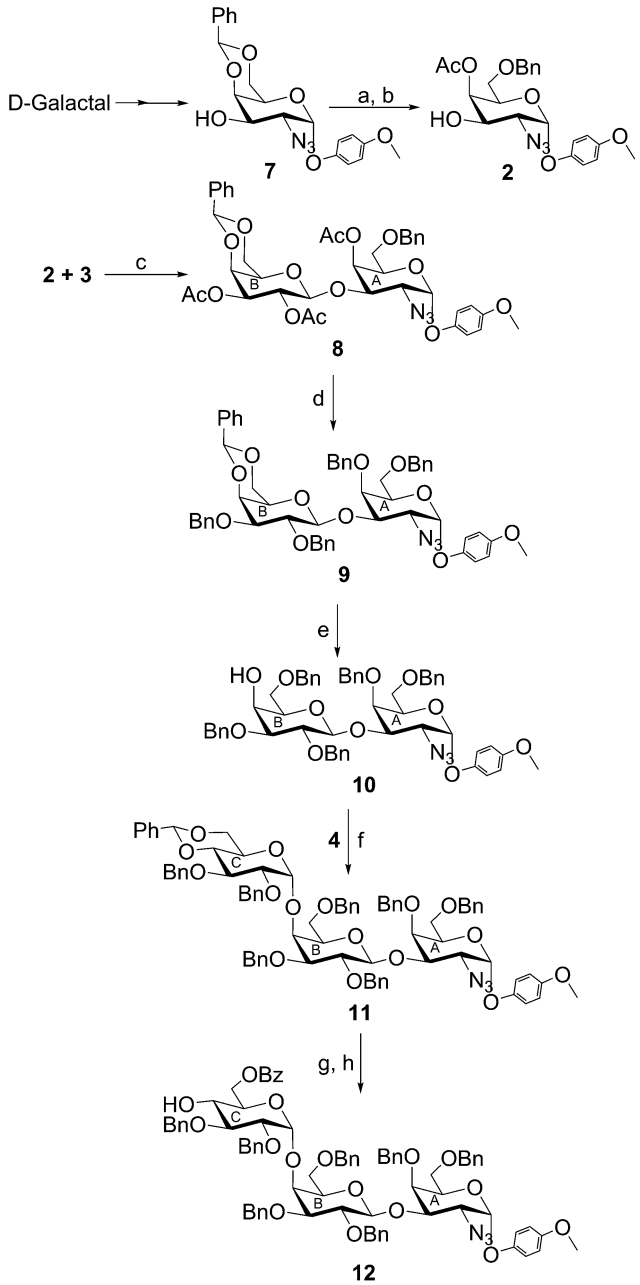


Fig. 1 Structure of the synthesized pentasaccharide with its synthetic intermediates.

p-methoxyphenyl-4-*O*-acetyl-2-azido-6-*O*-benzyl-2-deoxy-α-D-galactopyranoside (**2**) in 72% over all yield. Nitrosyl tetrafluoroborate ($NOBF_4$)[24] mediated stereoselective glycosylation of compound **2** with trichloroacetimidate derivative **3** furnished disaccharide derivative **8** in 79% yield, which was characterized by NMR spectroscopy [signals at δ 5.34 (d, $J = 3.5$ Hz, H-1_A), 4.67 (d, $J = 8.0$ Hz, H-1_B) in the ^{1}H NMR and at δ 101.2 (C-1_B), 98.7 (C-1_A) in the ^{13}C NMR spectra]. Direct conversion of acetoxy groups in compound **8** into benzyloxy group using benzyl bromide and solid sodium hydroxide[25] afforded compound **9** in 90% yield. Regioselective ring opening[22] of the benzylidene acetal in compound **9** using sodium cyanoborohydride in the presence of HCl in Et_2O gave 4-hydroxylated disaccharide acceptor **10** in 75% yield. In order to confirm the regioselective ring opening of the benzylidene acetal, compound **10** was conventionally acetylated using acetic anhydride and pyridine and subjected to NMR spectral analysis. Appearance of a broad singlet at δ 5.71 in the ^{1}H NMR spectrum of the acetylated compound confirmed the downfield shift of 4-hydroxy group of the D-galactopyranosyl moiety after acetylation, and hence formation of compound **10**. $NOBF_4$ mediated stereoselective 1,2-*cis* glycosylation[24] of compound **10** with trichloroacetimidate derivative **4** furnished trisaccharide derivative **11** in 75% yield together with the other isomeric product (~5%), which was separated by column chromatography. The formation of 1,2-*cis* linkage in compound **11** was confirmed by NMR spectroscopy [signals at δ 5.34 (d, $J = 3.5$ Hz, H-1_A), 4.90 (d, $J = 3.0$ Hz, H-1_C), 4.70 (d, $J = 8.0$ Hz, H-1_B) in ^{1}H NMR and at δ 105.5 (C-1_B), 100.6 (C-1_C), 99.3 (C-1_A) in ^{13}C NMR spectra]. The treatment of compound **11** with perchloric acid on silica ($HClO_4$–SiO_2)[26,27] in acetonitrile furnished a trisaccharide diol derivative, which was selectively benzoylated at the primary hydroxyl group using benzoyl cyanide[28] and pyridine to give trisaccharide acceptor **12** in 76% yield in two steps (Scheme 1).



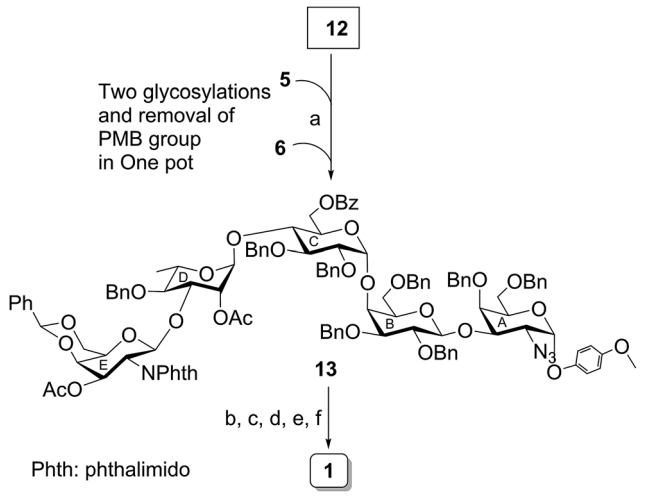
Scheme 1 Reagents and conditions: (a) $NaBH_3CN$, HCl–Et_2O, THF, MS-3Å, 5 °C, 1 h; (b) $CH_3C(OEt)_3$, *p*-TsOH, DMF, room temperature, 2 h, then H_2O, room temperature, 30 min, 72%; (c) **3**, $NOBF_4$, CH_2Cl_2, −20 °C, 45 min, 79%; (d) benzyl bromide, NaOH, TBAB, THF, room temperature, 5 h, 90%; (e) $NaBH_3CN$, HCl–Et_2O, THF, MS-3Å, 5 °C, 1 h, 75%; (f) **4**, $NOBF_4$, CH_2Cl_2–Et_2O (1 : 4 v/v), −10 °C, 30 min, 75%; (g) $HClO_4$–SiO_2, CH_3CN, room temperature, 25 min; and (h) benzoyl cyanide, pyridine, CH_2Cl_2, 0 °C, 4 h, over all 76%.

Compound **13** was synthesised in a 3-step-one-pot-sequence starting from trisaccharide acceptor **12**. Thus, acceptor **12** and 3-PMB protected L-fucosyl donor **5** were reacted in the presence of NIS and $HClO_4$–SiO_2 at a low temperature,[29] providing the expected tetrasaccharide intermediate. Slowly raising the reaction temperature in the reaction vessel initiated the hydrolysis ($HClO_4$–SiO_2) of the PMB group and produced the desired

tetrasaccharide acceptor. The reaction mixture was once again cooled, and a mixture of galactosamine donor **6** and fresh NIS was added to eventually furnish pentasaccharide **13** in 65% over all yield. The formation of compound **13** was unambiguously confirmed by NMR spectroscopy [signals at δ 5.52 (d, $J = 7.5$ Hz, H-1_E), 5.44 (d, $J = 3.5$ Hz, H-1_A), 5.08 (br s, H-1_D), 5.00 (d, $J = 3.0$ Hz, H-1_C), 4.77 (d, $J = 8.0$ Hz, H-1_B) in ^{1}H NMR and δ 105.8 (C-1_B), 99.3 (C-1_C), 99.1 (C-1_A), 98.1 (C-1_E), 97.2 (C-1_D) in ^{13}C NMR spectra]. Carrying out three reactions in a one pot setup significantly reduced the number of steps. The PMB ether acted as an *in situ* removable temporary protecting group for the hydroxy functionality.[30] The pentasaccharide derivative **13** was subjected to a sequence of reactions consisting of (a) treatment with hydrazine hydrate,[31] followed by acetylation using acetic anhydride and pyridine for the conversion of phthalimido group into acetamido group; (b) treatment with thioacetic acid[32] to convert azido group to acetamido group; (c) removal of benzyl ethers and benzylidene acetal under a catalytic transfer hydrogenation condition using triethylsilane and 20% Pd(OH)–C,[33] and finally and (d) saponification using sodium methoxide[34] to furnish desired pentasaccharide PMP glycoside **1** in 52% over all yield. The NMR spectrum of compound **1** unambiguously supported its structure [signals at δ 5.51 (d, $J = 3.5$ Hz, H-1_A), 4.94 (d, $J = 3.5$ Hz, H-1_C), 4.88 (br s, H-1_D), 4.64 (d, $J = 8.0$ Hz, H-1_B), 4.62 (d, $J = 7.5$ Hz, H-1_E) in ^{1}H NMR and at δ 104.9 (C-1_B), 103.3 (C-1_E), 100.4 (C-1_D), 100.0 (C-1_C), 97.2 (C-1_A) in ^{13}C NMR spectra] (Scheme 2).

Conclusions

In conclusion, a straightforward linear synthesis of a pentasaccharide has been developed, applying a one pot reaction condition for two stereoselective glycosylation reactions and removal of PMB group *in situ*. High stereoselective outcome was observed in most of the glycosylation reactions. Thioglycosides and glycosyl trichloroacetimidate derivatives have been used in the glycosylation reactions using recently developed reaction conditions.



Scheme 2 Reagents and conditions: (a) **5**, NIS, $HClO_4$–SiO_2, CH_2Cl_2, MS-4Å, −45 °C, 30 min; then 10 °C, 30 min; then **6**, NIS, −30 °C, 1 h, 65%; (b) $NH_2NH_2 \cdot H_2O$, EtOH, 80 °C, 8 h; (c) acetic anhydride, pyridine, room temperature, 1 h; (d) CH_3COSH, pyridine, room temperature, 18 h; (e) Et_3SiH, 20% $Pd(OH)_2$–C, CH_3OH, room temperature, 24 h; and (f) 0.1 M CH_3ONa, CH_3OH, room temperature, 4 h, over all 52%.

Experimental

General methods

All reactions were monitored by thin layer chromatography over silica gel coated TLC plates. The spots on TLC were visualized by warming ceric sulphate (2% $Ce(SO_4)_2$ in 2 N H_2SO_4) sprayed plates in hot plate. Silica gel 230–400 mesh was used for column chromatography. NMR spectra were recorded on Brucker Avance 500 MHz using $CDCl_3$ as the solvent and TMS as the internal reference, unless stated otherwise. The chemical shift value is expressed in δ ppm. The complete assignment of proton and carbon spectra was carried out using a standard set of NMR experiments, *e.g.* ^{1}H NMR, ^{13}C NMR, ^{13}C DEPT 135, 2D COSY and 2D HSQC. MALDI-MS were recorded on a Bruker Daltonics mass spectrometer. Optical rotations were recorded in a Jasco P-2000 spectrometer. Commercially available grades of organic solvents of adequate purity were used in all reactions.

***p*-Methoxyphenyl-4-*O*-acetyl-2-azido-6-*O*-benzyl-2-deoxy-α-D-galactopyranoside (2).** To a solution of compound 7 (2 g, 5.01 mmol) in dry THF (15 mL) MS-3Å (2 g) and $NaBH_3CN$ (1.8 g, 28.64 mmol) were added, and the reaction mixture was stirred at 0 °C for 20 min. To the cold reaction mixture, HCl in Et_2O (~10 mL) was added dropwise till the solution became acidic (pH ~ 2), and the reaction mixture was allowed to stir at 5 °C for 1 h. The reaction mixture was filtered through a Celite bed, and the filtering bed was washed with CH_2Cl_2 (100 mL). The combined filtrate was successively washed with satd $NaHCO_3$ and water, dried (Na_2SO_4) and concentrated. The crude product was purified over SiO_2 using hexane–EtOAc (3 : 1) as eluent to give 3,4-diol derivative. To a solution of the diol derivative in anhydrous DMF (10 mL), $CH_3C(OEt)_3$ (3 mL, 16.36 mmol) and *p*-TsOH (250 mg) were added, and the reaction mixture was allowed to stir at room temperature for 2 h. After complete consumption of the starting material (TLC; hexane–EtOAc 3 : 1), H_2O (10 mL) was added to the reaction mixture, and it was stirred at room temperature for 30 min. The solvents were removed under reduced pressure, and the crude product was purified over SiO_2 using hexane–EtOAc (4 : 1) as the eluent to give pure compound **2** (1.6 g, 72%). White solid; m.p. 64–65 °C [EtOH]; $[\alpha]_D^{25}$ −11.7 (*c* 1.0, $CHCl_3$); IR (KBr): 3027, 2363, 2110, 1713, 1589, 1218, 1042, 760 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24–7.14 (m, 5H, Ar-H), 6.96 (d, $J = 9.0$ Hz, 2H, Ar-H), 6.70 (d, $J = 9.0$ Hz, 2H, Ar-H), 5.37 (d, $J = 2.5$ Hz, 1H, H-4), 5.34 (d, $J = 3.0$ Hz, 1H, H-1), 4.42 (d, $J = 11.5$ Hz, 1H, PhCH_2), 4.35 (dd, $J = 10.5$, 3 Hz, 1H, H-3), 4.32 (d, $J = 11.5$ Hz, 1H, PhCH_2), 4.25–4.22 (m, 1H, H-5), 3.67 (s, 3H, OCH_3), 3.48 (dd, $J = 10.5$, 3.0 Hz, 1H, H-2), 3.43–3.41 (m, 2H, H-6_{ab}), 2.01 (s, 3H, COCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.2 (*C*OCH_3), 156.6–114.6 (Ar-C), 98.3 (C-1), 73.4 (Ph*C*H$_2$), 70.5 (C-4), 68.5 (C-5), 68.0 (C-6), 67.4 (C-3), 60.1 (C-2), 55.5 (O*C*H$_3$), 20.7 (CO*C*H$_3$); ESI-MS: 466.1 [M +

Na]$^+$; anal. calcd for $C_{22}H_{25}N_3O_7$ (443.17): C, 59.59; H, 5.68; found: C, 59.46; H, 5.85.

***p*-Methoxyphenyl-(2,3-di-*O*-acetyl-4,6-*O*-benzylidene-β-D-galactopyranosyl)-(1 → 3)-4-*O*-acetyl-2-azido-6-*O*-benzyl-2-deoxy-α-D-galactopyranoside (8).** A solution of compound **2** (1.3 g, 2.93 mmol) and compound **3** (1.6 g, 3.22 mmol) in anhydrous CH_2Cl_2 (20 mL) was cooled to −20 °C under argon. To the cooled reaction mixture, $NOBF_4$ (0.4 g, 3.42 mmol) was added, and the reaction mixture was allowed to stir at the same temperature for 45 min. The reaction mixture was diluted with CH_2Cl_2 (100 mL), and the organic layer was successively washed with satd $NaHCO_3$ and water, dried (Na_2SO_4) and concentrated. The crude product was purified over SiO_2 using hexane–EtOAc (5 : 1) as the eluent to give pure compound **8** (1.8 g, 79%). White solid; m.p. 164–165 °C [EtOH]; $[\alpha]_D^{25}$ +147.6 (*c* 1.0, $CHCl_3$); IR (KBr): 3027, 2935, 2366, 2100, 1755, 1378, 1218, 1042, 761 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43–7.16 (m, 10H, Ar-H), 6.98 (d, J = 9.0 Hz, 2H, Ar-H), 6.66 (d, J = 9.0 Hz, 2H, Ar-H), 5.46 (d, J = 3.5 Hz, 1H, H-4$_A$), 5.36 (s, 1H, PhC*H*), 5.34 (d, J = 3.5 Hz, 1H, H-1$_A$), 5.30 (dd, J = 7.5 Hz each, 1H, H-2$_B$), 4.84 (dd, J = 8.5, 3.5 Hz, 1H, H-3$_B$), 4.67 (d, J = 8.0 Hz, 1H, H-1$_B$), 4.39–4.36 (m, 2H, PhCH_2), 4.28–4.20 (m, 4H, H-3$_A$, H-4$_B$, H-5$_A$, H-6$_{aB}$), 3.88–3.85 (m, 1H, H-6$_{bB}$), 3.70 (dd, J = 10.5, 3.5 Hz, 1H, H-2$_A$), 3.66 (s, 3H, OCH_3), 3.54 (dd, J = 10.5, 4.0 Hz, 1H, H-6$_{aA}$), 3.43–3.38 (m, 2H, H-5$_B$, H-6$_{bA}$), 2.03, 2.02, 2.00 (3 s, 9H, 3 COCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.6, 170.4, 169.1 (*C*OCH$_3$), 155.7–114.6 (Ar-C), 101.4 (Ph*C*H), 101.2 (C-1$_B$), 98.7 (C-1$_A$), 75.2 (C-4$_B$), 73.4 (PhCH_2), 73.2 (C-5$_A$), 71.9 (C-3$_A$), 69.7 (C-4$_A$), 69.5 (C-6$_A$), 69.4 (C-3$_B$), 68.6 (C-2$_B$), 68.4 (C-6$_B$), 66.5 (C-5$_B$), 59.2 (C-2$_A$), 55.5 (O*C*H$_3$), 20.8 (2C, 2 CO*C*H$_3$), 20.7 (CO*C*H$_3$); MALDI-MS: 800.2 [M + Na]$^+$; anal. calcd for $C_{39}H_{43}N_3O_{14}$ (777.27): C, 60.23; H, 5.57; found: C, 60.09; H, 5.76.

***p*-Methoxyphenyl-(2,3-di-*O*-benzyl-4,6-*O*-benzylidene-β-D-galactopyranosyl)-(1 → 3)-2-azido-4,6-di-*O*-benzyl-2-deoxy-α-D-galactopyranoside (9).** To a solution of compound **8** (1.6 g, 2.06 mmol) in THF (25 mL), benzyl bromide (2.5 mL, 21.02 mmol), powdered NaOH (2 g, 50 mmol) and TBAB (100 mg) were added, and the reaction mixture was allowed to stir at room temperature for 5 h. The reaction mixture was diluted with CH_2Cl_2 (100 mL), and the organic layer was washed with water, dried (Na_2SO_4) and concentrated. The crude product was purified over SiO_2 using hexane–Et_2O (8 : 1) as the eluent to give pure compound **9** (1.7 g, 90%). Colorless oil; $[\alpha]_D^{25}$ +137 (*c* 1.0, $CHCl_3$); IR (neat): 3432, 3030, 2929, 2100, 1640, 1500, 1457, 1360, 1218, 1099, 1056, 697 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37–7.11 (m, 25H, Ar-H), 7.00 (d, J = 9.0 Hz, 2H, Ar-H), 6.69 (d, J = 9.0 Hz, 2H, Ar-H), 5.41 (s, 1H, PhC*H*), 5.38 (d, J = 3.5 Hz, 1H, H-1$_A$), 5.12 (d, J = 11.0 Hz, 1H, PhCH_2), 5.01 (d, J = 11.0 Hz, 1H, PhCH_2), 4.76 (d, J = 7.5 Hz, 1H, H-1$_B$), 4.73–4.61 (m, 4H, 2 PhCH_2), 4.35–4.25 (m, 3H, H-3$_A$, PhCH_2), 4.20 (d, J = 12.5 Hz, 1H, H-6$_{aB}$), 4.16–4.13 (m, 1H, H-5$_A$), 4.03 (d, J = 3.5 Hz, 1H, H-4$_B$), 3.95 (d, J = 12.5 Hz, 1H, H-6$_{bB}$), 3.84 (t, J = 7.5 Hz each, 1H, H-2$_B$), 3.79–3.77 (m, 1H, H-2$_A$), 3.67 (s, 3H, OCH_3), 3.55 (dd, J = 10.0, 3.0 Hz, 1H, H-3$_B$), 3.50–3.45 (m, 2H, H-6$_{abA}$), 3.35–3.34 (m, 1H, H-5$_B$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.5–114.6 (Ar-C), 105.2 (C-1$_B$), 101.5 (Ph*C*H), 99.3 (C-1$_A$), 79.0 (C-3$_B$), 78.6 (C-2$_B$), 77.1 (C-4$_B$), 76.8 (C-4$_A$), 75.4 (PhCH_2), 75.1 (Ph*C*H$_2$), 73.9 (C-3$_A$), 73.2 (Ph*C*H$_2$), 72.4 (Ph*C*H$_2$), 70.3 (C-5$_A$), 69.2 (C-6$_A$), 69.0 (C-6$_B$), 66.3 (C-5$_B$), 59.4 (C-2$_A$), 55.5 (O*C*H$_3$); MALDI-MS: 944.3 [M + Na]$^+$; anal. calcd for $C_{54}H_{55}N_3O_{11}$ (921.38): C, 70.34; H, 6.01; found: C, 70.18; H, 6.20.

***p*-Methoxyphenyl-(2,3,6-tri-*O*-benzyl-β-D-galactopyranosyl)-(1 → 3)-2-azido-4,6-di-*O*-benzyl-2-deoxy-α-D-galactopyranoside (10).** To a solution of compound **9** (1.6 g, 1.73 mmol) in dry THF (20 mL), MS-3Å (3 g) and $NaBH_3CN$ (0.8 g, 12.73 mmol) were added, and the reaction mixture was stirred at 0 °C for 20 min. To the cold reaction mixture, HCl in Et_2O (~7 mL) was added dropwise till the solution became acidic (pH ~ 2), and the reaction mixture was allowed to stir at 5 °C for 1 h. The reaction mixture was filtered through a Celite bed, and the filtering bed was washed with CH_2Cl_2 (100 mL). The combined filtrate was successively washed with satd $NaHCO_3$ and water, dried (Na_2SO_4) and concentrated. The crude product was purified over SiO_2 using hexane–EtOAc (6 : 1) as the eluent to give pure compound **10** (1.2 g, 75%). Colorless oil; $[\alpha]_D^{25}$ +67 (*c* 1.0, $CHCl_3$); IR (neat): 3526, 2927, 2100, 1500, 1374, 1217, 1022, 697 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32–7.10 (m, 25H, Ar-H), 6.98 (d, J = 9.0 Hz, 2H, Ar-H), 6.68 (d, J = 9.0 Hz, 2H, Ar-H), 5.37 (d, J = 3.0 Hz, 1H, H-1$_A$), 4.99 (d, J = 11.0 Hz, 1H, PhCH_2), 4.89 (d, J = 11.0 Hz, 1H, PhCH_2), 4.66 (d, J = 7.5 Hz, 1H, H-1$_B$), 4.65–4.57 (m, 4H, PhCH_2), 4.43–4.40 (m, 2H, PhCH_2), 4.35–4.24 (m, 3H, H-3$_A$, PhCH_2), 4.15 (br s, 1H, H-4$_A$), 4.13–4.10 (m, 1H, H-5$_A$), 3.93 (d, J = 2.5 Hz, 1H, H-4$_B$), 3.78–3.75 (m, 1H, H-2$_A$), 3.73–3.70 (m, 1H, H-6$_{aA}$), 3.68 (s, 3H, OCH_3), 3.67–3.57 (m, 3H, H-2$_B$, H-3$_B$, H-6$_{bA}$), 3.49–3.45 (m, 2H, H-5$_B$, H-6$_{aA}$), 3.42–3.38 (m, 1H, H-6$_{bA}$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.5–114.6 (Ar-C), 105.2 (C-1$_B$), 99.2 (C-1$_A$), 80.5 (C-3$_B$), 78.9 (C-2$_B$), 76.9 (C-4$_B$), 76.5 (C-4$_A$), 75.2 (Ph*C*H$_2$), 74.7 (Ph*C*H$_2$), 73.7 (Ph*C*H$_2$), 73.2 (Ph*C*H$_2$), 73.1 (C-3$_A$), 72.8 (Ph*C*H$_2$), 70.3 (C-5$_A$), 69.3 (C-6$_A$), 69.1 (C-6$_B$), 66.8 (C-5$_B$), 59.5 (C-2$_A$), 55.4 (O*C*H$_3$); MALDI-MS: 946.3 [M + Na]$^+$; anal. calcd for $C_{54}H_{57}N_3O_{11}$ (923.40): C, 70.19; H, 6.22; found: C, 70.05; H, 6.38.

***p*-Methoxyphenyl-(2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranosyl)-(1 → 4)-(2,3,6-tri-*O*-benzyl-β-D-galactopyranosyl)-(1 → 3)-2-azido-4,6-di-*O*-benzyl-2-deoxy-α-D-galactopyranoside (11).** A solution of compound **10** (1 g, 1.08 mmol) and compound **4** (0.7 g, 1.18 mmol) in anhydrous CH_2Cl_2–Et_2O (10 mL; 1 : 4 v/v) was cooled to −10 °C under argon. To the cooled reaction mixture, $NOBF_4$ (150 mg, 1.28 mmol) was added, and the reaction mixture was allowed to stir at the same temperature for 30 min. The reaction mixture was diluted with CH_2Cl_2 (100 mL), and the organic layer was successively washed with satd $NaHCO_3$ and water, dried (Na_2SO_4) and concentrated. The crude product was purified over SiO_2 using hexane–EtOAc (5 : 1) as the eluent to give pure compound **11** (1.1 g, 75%). Colorless oil; $[\alpha]_D^{25}$ +65 (*c* 1.0, $CHCl_3$); IR (neat): 3408, 3037, 2935, 2117, 1597, 1503, 1459, 1392, 1346, 1245, 1217, 1177, 1085, 1044, 998, 918, 697 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38–6.97 (m, 42H, Ar-H), 6.68 (d, J = 9.0 Hz, 2H, Ar-H), 5.38 (s, 1H, PhC*H*), 5.34 (d, J = 3.5 Hz, 1H, H-1$_A$), 4.98 (d, J = 11.5 Hz, 1H, PhCH_2), 4.91 (d, J = 11.5 Hz, 1H, PhCH_2), 4.90 (d, J = 3.0 Hz, 1H, H-1$_C$), 4.80 (d, J = 11.5 Hz, 1H, PhCH_2), 4.72 (d, J = 11.5 Hz, 1H, PhCH_2), 4.70 (d, J = 8.0 Hz, 1H, H-1$_B$), 4.68–4.45 (m, 6H, PhCH_2), 4.35–4.19 (m, 5H, H-3$_A$, PhCH_2), 4.17–4.06 (m, 4H, H-4$_A$, H-5$_A$, H-6$_{abC}$), 4.03–3.96 (m, 2H, H-4$_B$, H-5$_C$), 3.82 (t, J = 8.5 Hz each, 1H, H-4$_C$), 3.78

(t, J = 8.5 Hz each, 1H, H-2_B), 3.75–3.68 (m, 1H, H-2_A), 3.67 (s, 3H, OCH_3), 3.58–3.52 (m, 2H, H-3_B, H-6_{aA}), 3.47–3.40 (m, 4H, H-5_B, H-6_{bA}, H-6_{abB}), 3.38–3.30 (m, 2H, H-2_C, H-3_C); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.4–114.6 (Ar-C), 105.5 (C-1_B), 101.0 (PhCH), 100.6 (C-1_C), 99.3 (C-1_A), 82.8 (C-5_C), 80.6 (C-2_B), 79.7 (C-3_B), 79.3 (C-3_C), 78.4 (C-4_C), 77.1 (C-4_A),76.9 (C-4_B), 76.7 (C-5_B), 76.6 (C-5_C), 75.8 (C-3_A), 75.0 (PhCH_2), 74.9 (PhCH_2), 74.8 (PhCH_2), 74.2 (PhCH_2), 73.2 (PhCH_2), 73.1 (PhCH_2), 73.0 (PhCH_2), 70.3 (C-5_A), 69.8 (C-6_A), 69.4 (C-6_B), 68.0 (C-6_C), 63.0 (C-2_C), 59.3 (C-2_A), 55.5 (OCH_3); MALDI-MS: 1376.5 $[M + Na]^+$; anal. calcd for $C_{81}H_{83}N_3O_{16}$ (1353.58): C, 71.82; H, 6.18; found: C, 71.70; H, 6.35.

***p*-Methoxyphenyl-(6-*O*-benzoyl-2,3-di-*O*-benzyl-α-D-glucopyranosyl)-(1 → 4)-(2,3,6-tri-*O*-benzyl-β-D-galactopyranosyl)-(1 → 3)-2-azido-4,6-di-*O*-benzyl-2-deoxy-α-D-galactopyranoside (12).** To a solution of compound **11** (1 g, 0.74 mmol) in CH_3CN (20 mL), $HClO_4$–SiO_2 (0.3 g) was added, and the reaction mixture was stirred at room temperature for 25 min. The reaction mixture was filtered and concentrated under reduced pressure to give the 4,6-diol derivative. A solution of the diol derivative in CH_2Cl_2 (10 mL) was cooled to 0 °C. To the cooled reaction mixture, pyridine (1 mL) and benzoyl cyanide (150 mg, mmol) were added, and the reaction mixture was allowed to stir for 4 h at the same temperature. The reaction mixture was poured into water and extracted with CH_2Cl_2 (50 mL). The organic layer was washed with satd $NaHCO_3$, dried (Na_2SO_4) and concentrated. The crude product was purified over SiO_2 using hexane–EtOAc (7 : 1) as the eluent to give pure compound **12** (770 mg, 76%). Colorless oil; $[\alpha]_D^{25}$ +62 (*c* 1.0, $CHCl_3$); IR (neat): 3370, 3036, 2929, 2116, 1739, 1600, 1488, 1454, 1365, 1340, 1236, 1217, 1100, 1049, 999, 918, 666 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01–6.68 (m, 44H, Ar-H), 5.36 (d, J = 3.0 Hz, 1H, H-1_A), 5.05–4.95 (m, 2H, PhCH_2), 4.89 (br s, 1H, H-1_C), 4.79–4.76 (m, 1H, PhCH_2), 4.70–4.69 (m, 1H, PhCH_2), 4.68 (d, J = 3.0 Hz, 1H, H-1_B), 4.68–4.60 (m, 2H, PhCH_2), 4.60–4.55 (m, 2H, PhCH_2), 4.55–4.49 (m, 2H, PhCH_2), 4.35–4.30 (m, 3H, H-3_A, PhCH_2), 4.30–4.20 (m, 4H, H-4_A, H-5_A, PhCH_2), 4.13–4.11 (m, 2H, H-5_C, H-6_{aC}), 4.02–3.98 (m, 2H, H-4_B, H-4_C), 3.77–3.75 (m, 3H, H-2_A, H-2_B, H-6_{bC}), 3.67 (s, 3H, OCH_3), 3.65–3.64 (m, 1H, H-6_{aB}), 3.56 (m, 2H, H-3_B, H-6_{aA}), 3.45–3.43 (m, 3H, H-5_B, H-6_{bA}, H-6_{bB}), 3.35–3.33 (m, 2H, H-2_C, H-3_C); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.0 (PhCO), 155.4–114.6 (Ar-C), 105.7 (C-1_B), 99.7 (C-1_C), 99.3 (C-1_A), 81.5 (C-2_B), 80.3 (C-2_C), 80.2 (C-3_C), 78.6 (C-4_C), 77.3 (C-4_A), 76.7 (C-4_B), 75.5 (C-3_A), 75.3 (PhCH_2), 74.9 (2C, 2 PhCH_2), 73.8 (PhCH_2), 73.2 (2C, C-5_A, PhCH_2), 73.1 (2C, 2 PhCH_2), 70.6 (C-5_B), 70.3 (2C, C-3_B, C-5_C), 69.3 (C-6_A), 67.9 (C-6_B), 63.0 (C-6_C), 59.3 (C-2_A), 55.5 (OCH_3); MALDI-MS: 1392.5 $[M + Na]^+$; anal. calcd for $C_{81}H_{83}N_3O_{17}$ (1369.57): C, 70.98; H, 6.10; found: C, 70.82; H, 6.28.

***p*-Methoxyphenyl-(3-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-2-phthalimido-β-D-galactopyranosyl)-(1 → 3)-(2-*O*-acetyl-4-*O*-benzyl-α-L-rhamnopyranosyl)-(1 → 4)-(6-*O*-benzoyl-2,3-di-*O*-benzyl-α-D-glucopyranosyl)-(1 → 4)-(2,3,6-tri-*O*-benzyl-β-D-galactopyranosyl)-(1 → 3)-2-azido-4,6-di-*O*-benzyl-2-deoxy-α-D-galactopyranoside (13).** A solution of compound **12** (700 mg, 0.51 mmol), compound **5** (250 mg, 0.54 mmol) and MS-4Å (2 g) in anhydrous CH_2Cl_2 (10 mL) was cooled to −45 °C under argon. To the cooled reaction mixture, NIS (130 mg, 0.58 mmol) and $HClO_4$–SiO_2 (100 mg) were added, and it was allowed to stir at the same temperature for 30 min. After consumption of the starting materials (TLC; hexane–EtOAc, 2 : 1), the temperature of the reaction mixture was raised to 10 °C and stirred for 30 min. After the formation of a new spot in TLC (hexane–EtOAc, 2 : 1), again the reaction mixture was cooled to −30 °C. To the cooled reaction mixture, a solution of compound **6** (240 mg, 0.50 mmol) in CH_2Cl_2 (2 mL) and NIS (115 mg, 0.51 mmol) were added, and the reaction mixture was allowed to stir at −30 °C for another 1 h. The reaction mixture was filtered through a Celite bed, and the filtering bed was washed with CH_2Cl_2 (50 mL). The combined organic layer was successively washed with 5% $Na_2S_2O_3$, satd $NaHCO_3$ and water, dried (Na_2SO_4) and concentrated. The crude product was purified over SiO_2 using hexane–EtOAc (5 : 1) as the eluent to give pure compound **13** (685 mg, 65%). Colorless oil; $[\alpha]_D^{25}$ +14 (*c* 1.0, $CHCl_3$); IR (neat): 3089, 2866, 1722, 1625, 1524, 1377, 1242, 1176, 1097, 1076, 989, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.10–6.76 (m, 58H, Ar-H), 5.52 (d, J = 7.5 Hz, 1H, H-1_E), 5.50 (br s, 1H, H-2_D), 5.44 (d, J = 3.5 Hz, 1H, H-1_A), 5.37 (s, 1H, PhCH), 5.14 (t, J = 9.0 Hz each, 1H, H-3_E), 5.12–5.10 (m, 1H, PhCH_2), 5.08 (br s, 1H, H-1_D), 5.00 (d, J = 3.0 Hz, 1H, H-1_C), 4.92–4.79 (3 d, J = 11.0 Hz each, 3H, PhCH_2), 4.77 (d, J = 8.0 Hz, 1H, H-1_B), 4.75–4.72 (m, 2H, H-2_E, PhCH_2), 4.66–4.50 (m, 4H, 2 PhCH_2), 4.46–4.37 (m, 4H, PhCH_2, H-6_{aE}), 4.34–4.28 (m, 5H, H-3_A, H-6_{aC}, H-5_A, PhCH_2), 4.25–4.17 (m, 5H, H-4_A, H-5_C, H-4_E, PhCH_2), 4.10–4.01 (m, 4H, H-4_B, H-4_C, H-4_D, H-6_{bE}), 3.89–3.81 (m, 6H, H-3_D, H-2_A, H-2_B, H-6_{bC}, H-5_D, H-5_E), 3.74 (s, 3H, OCH_3), 3.64–3.58 (m, 2H, H-3_B, H-6_{aA}), 3.55–3.52 (m, 3H, H-6_{aB}, H-6_{bA}, H-5_B), 3.45–3.42 (m, 1H, H-6_{bB}), 3.38–3.35 (m, 2H, H-2_C, H-3_C), 2.01, 1.86 (2 s, 6H, 2 COCH_3), 0.89 (d, J = 4.0 Hz, 3H, CCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.0, 171.0 (2 *C*OCH$_3$), 168.0, 167.0 (PhthCO), 166.0 (PhCO), 155.5–114.6 (Ar-C), 105.8 (C-1_B), 100.8 (PhCH), 99.3 (C-1_C), 99.1 (C-1_A), 98.1 (C-1_E), 97.2 (C-1_D), 81.3 (C-2_B), 79.8 (C-2_C), 79.7 (C-3_C), 79.6 (C-4_C), 79.3 (C-3_E), 79.0 (C-5_D), 78.7 (C-3_D), 77.6 (C-4_A), 76.8 (C-4_B), 76.1 (C-4_E), 75.3 (C-5_A), 75.1 (C-3_A), 75.0 (PhCH_2), 74.7 (PhCH_2), 74.3 (2C, 2 PhCH_2), 73.8 (PhCH_2), 73.2 (PhCH_2), 73.0 (PhCH_2), 72.6 (C-2_D), 71.2 (PhCH_2), 70.3 (C-5_B), 69.4 (C-6_E), 69.3 (C-6_A), 69.0 (C-3_B), 68.7 (C-5_C), 67.9 (C-6_B), 67.8 (C-4_D), 65.8 (C-5_E), 62.6 (C-6_C), 59.3 (C-2_A), 55.5 (OCH_3), 51.1 (C-2_E), 21.0, 20.7 (2C, COCH_3), 17.6 (CCH_3); MALDI-MS: 2091.7 $[M + Na]^+$; anal. calcd for $C_{119}H_{120}N_4O_{29}$ (2068.80): C, 69.04; H, 5.84; found: C, 68.86; H, 6.00.

***p*-Methoxyphenyl-(2-acetamido-2-deoxy-β-D-galactopyranosyl)-(1 → 3)-(α-L-rhamnopyranosyl)-(1 → 4)-(α-D-glucopyranosyl)-(1 → 4)-(β-D-galactopyranosyl)-(1 → 3)-2-acetamido-2-deoxy-α-D-galactopyranoside (1).** A solution of compound **13** (600 mg, 0.29 mmol) and $NH_2NH_2 \cdot H_2O$ (0.2 mL) in EtOH (10 mL) was stirred at 80 °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 1 h. The solvents were removed under reduced pressure, and the crude product was dissolved in pyridine (1 mL). Thioacetic acid (0.2 mL) was added to the reaction mixture, and it was

allowed to stir at room temperature for 18 h. The solvents were removed under reduced pressure, and the crude product was passed through a short pad of SiO_2. To a solution of the *N*-acetylated product in CH_3OH (5 mL), 20% $Pd(OH)_2$–C (100 mg) and Et_3SiH (1 mL, 6.26 mmol) was added, and it was stirred at room temperature for 24 h. The reaction mixture was filtered through a Celite bed, and the filtering bed was washed with CH_3OH (50 mL). The combined filtrate was concentrated under reduced pressure. A solution of the hydrogenolyzed product in CH_3ONa (5 mL; 0.1 M in CH_3OH) was stirred at room temperature for 4 h. The reaction mixture was neutralized with Dowex 50W X8 (H^+) resin, filtered and concentrated. The deprotected product was passed through a Sephadex LH-20 column using CH_3OH–H_2O (3 : 1) as the eluent to give pure compound **1** (150 mg, over all 52%). White powder; $[\alpha]_D^{25}$ +54 (*c* 0.5, H_2O); IR (KBr): 3436, 2942, 1619, 1400, 1157, 1096, 669 cm^{-1}; ^1H NMR (500 MHz, D_2O): δ 7.13 (d, J = 9.0 Hz, 2H, Ar-H), 6.98 (d, J = 9.0 Hz, 2H, Ar-H), 5.51 (d, J = 3.5 Hz, 1H, H-1_A), 4.94 (d, J = 3.5 Hz, 1H, H-1_C), 4.88 (br s, 1H, H-1_D), 4.64 (d, J = 8.0 Hz, 1H, H-1_B), 4.62 (d, J = 7.5 Hz, 1H, H-1_E), 4.54 (dd, J = 10.0, 3.5 Hz, 1H, H-2_A), 4.34–4.27 (m, 2H, H-3_A, H-5_A), 4.25–4.16 (m, 3H, H-2_D, H-4_A, H-5_C), 4.12–4.05 (m, 1H, H-5_D), 4.03 (d, J = 3.0 Hz, 1H, H-4_E), 4.00–3.90 (m, 3H, H-2_E, H-4_B, H-6_{aB}), 3.78 (s, 3H, OCH_3), 3.76–3.65 (m, 12H, H-3_B, H-3_D, H-3_E, H-5_B, H-5_E, H-6_{abA}, H-6_{bB}, H-6_{abC}, H-6_{abE}), 3.63–3.60 (m, 2H, H-2_B, H-4_C), 3.59–3.50 (m, 3H, H-2_C, H-3_C, H-4_D), 2.06, 2.05 (2 s, 6H, 2 COCH_3), 1.26 (d, J = 6.0 Hz, 3H, CCH_3); ^{13}C NMR (125 MHz, D_2O): δ 175.1, 175.0 (2 *C*OCH$_3$), 155.2–115.0 (Ar-C), 104.9 (C-1_B), 103.3 (C-1_E), 100.4 (C-1_D), 100.0 (C-1_C), 97.2 (C-1_A), 80.0 (C-3_D), 77.4 (C-3_A), 76.9 (C-4_C), 76.8 (C-4_B), 75.1 (C-4_E), 74.8 (C-5_E), 72.0 (C-3_B), 71.9 (C-3_C), 71.4 (C-2_B), 71.3 (C-2_C), 70.9 (C-2_D), 70.8 (2C, C-3_E, C-4_D), 70.4 (C-5_C), 70.3 (C-5_D), 69.3 (C-5_A), 68.8 (C-5_B), 67.7 (C-4_A), 60.9 (2C, C-6_A, C-6_E), 59.9 (C-6_C), 59.6 (C-6_B), 55.8 (OCH_3), 52.5 (C-2_E), 48.8 (C-2_A), 22.2, 22.0 (2 CO*C*H$_3$), 16.5 (C*C*H$_3$); MALDI-MS: 1023.3 $[M + Na]^+$; anal. calcd for $C_{41}H_{64}N_2O_{26}$ (1000.37): C, 49.20; H, 6.44; found: C, 49.00; H, 6.60.

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