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ARTICLE TYPE

Synthetic Routes Toward the Trisaccharide Related to the Lipopolysaccharide of *Burkholderia sp.* HKI-402 (B4)

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Stepwise as well as a three component one-pot sequential glycosylation reaction has been utilized for the synthesis of trisaccharide related to the LPS of *Burkholderia sp*. HKI-402 (B4) employing trichloroacetimidate and thio donors.

Introduction

The interactions between bacterial symbionts and their hosts (higher organisms) can either be beneficial or detrimental to the later.[1] In many cases, living organisms harbour endosymbiotic bacteria for providing improved defence mechanism, survival, and even acquired virulence.[2] The fungus *Rhizopus microsporus* offers endosymbiotic bacteria asylum for the production of the causal agent of rice seedling blight, rhizoxin. It has been proved that rhizoxin is not biosynthesized by the fungus itself, but by endosymbiotic bacteria of the genus *Burkholderia sp*. residing in it.[3] Rhizoxin, a lactone antibiotic, is a phytotoxin which exhibits strong antimitotic activity in most eukaryotic cells, including various human cancer cell lines. Owing to these, rhizoxin has attracted considerable interest as a potential antitumor drug.[4] Similarly there are innumerous antimitotic agents with different potentialities, produced by several types of bacteria which could unveil deadly effects such as chronic or acute toxic damage of internal organs and many more.

Lipopolysaccharides (LPSs) are one of the major components constructing the bacterial cell wall, and hence hugely responsible for every kind of host-bacteria interaction. So, it is of immense importance to identify and synthetically mimic the bacterial cell wall LPSs in order to understand and manipulate their survival ability and virulence property for vaccination purpose.

The synthesis of the trisaccharide related to the repeating unit (Figure 1) present in the O-antigen LPS portion of *Burkholderia sp*. HKI-402 (B4), [5] by stepwise and one-pot sequential glycosylation reactions, will be discussed. To the best of our knowledge, this is the first synthesis of this trisaccharide.

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† Electronic Supplementary Information (ESI) available: General experimental procedure, copies of ^{1}H-, ^{13}C-, COSY- HSQC-NMR spectra of compounds **1, 2** and HMBC-NMR spectra of **2**. See DOI: 10.1039/b000000x/

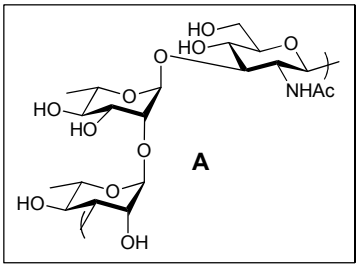


Figure 1. Trisaccharide repeating unit present in the LPS of Burkholderia sp. HKI-402 (B4).

Stepwise oligosaccharide syntheses[6] are generally expensive and tedious procedures since they demand extensive protecting group manipulation and purification after each step. On the contrary, one pot sequential oligosaccharide syntheses are more cost viable, expeditious and more environment friendly. Owing to these advantages many complex oligosaccharides have been synthesized utilising one pot protocol, such as Globo-H hexasaccharide, heparin pentasaccharide, Le^{y}, α-Gal epitopes and Gb_3 saccharides.[7] In continuation to our work on oligosaccharide syntheses,[8] we report herein the synthesis of the trisaccharide related to the repeating unit present in the LPS of *Burkholderia sp*. HKI-402 (B4) from the corresponding monosaccharide building blocks as 3-(*N*-benzyloxycarbonyl) propyl glycoside by stepwise and sequential one pot protocols.

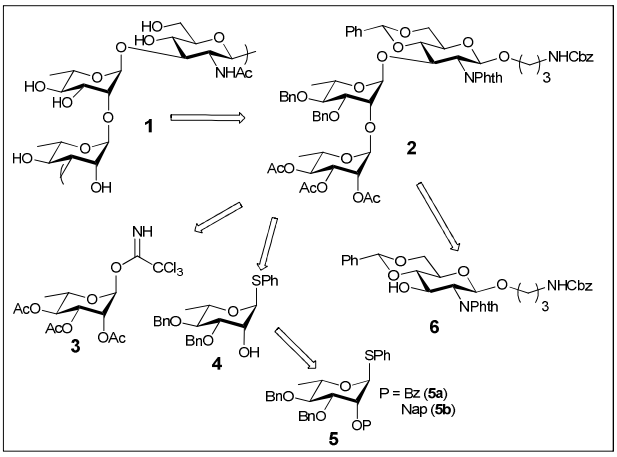
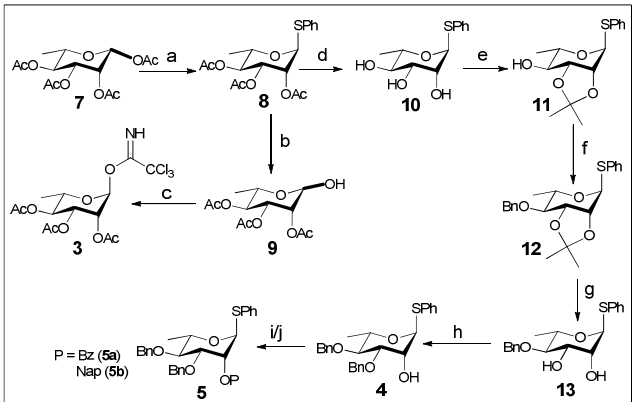


Figure 2. Retrosynthetic analysis of **1**.

Results and Discussion

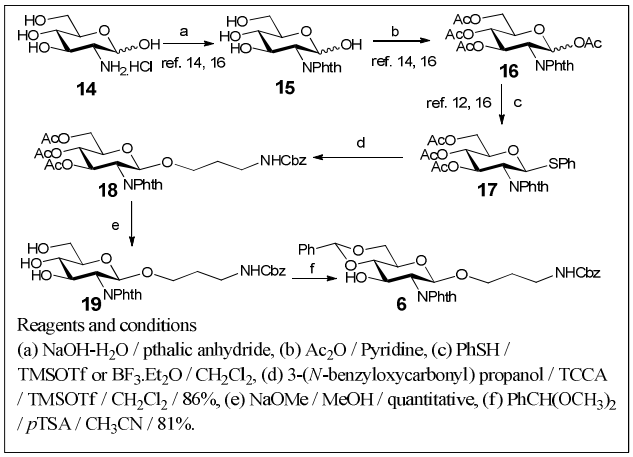
Retrosynthetic analysis of the fully protected trisaccharide **2** led to five monomeric sugar units, two orthogonal donors, L-rhamnose based trichloroacetimidate **3** and thioglycoside **4** along with donors **5a** and **5b**, and the glucosamine based acceptor **6** for exploiting stepwise as well as sequential one pot synthetic approaches (Figure 2).

Treatment of tetra acetylated L-rhamnose (**7**)[9] with thiophenol and $BF_3.Et_2O$ in dry CH_2Cl_2 furnished phenyl 2,3,4-tri-*O*-acetyl-1-thio-α-D-rhamanopyranoside (**8**)[9] in 91% yield after purification by column chromatography. Thioglycoside hydrolysis of **8** was carried out using TCCA[10] in aqueous $(CH_3)_2CO$ to give 2,3,4-tri-*O*-acetyl-L-rhamanopyranoside (**9**)[9] in 88% yield. Treatment of **9** with trichloroacetonitrile and DBU in dry CH_2Cl_2 provided the trichloroacetimidate donor **3**[9] in 89% yield. Zemplén deacetylation[11] of **8** resulted in quantitative formation of phenyl 1-thio-α-D-rhamanopyranoside (**10**).[9] 2,3-*O*-Isopropylidenation of **10** with 2,2-dimethoxypropane and catalytic camphorsulphonic acid in dry CH_3CN followed by O-benzylation of the resulting crude phenyl 2,3-*O*-isopropyl-1-thio-α-D-rhamanopyranoside (**11**)[12] with benzyl bromide and sodium hydride in dry DMF furnished phenyl 4-*O*-benzyl-2,3-*O*-isopropyl-1-thio-α-D-rhamanopyranoside (**12**).[12] 60% AcOH was used for 2,3-*O*-isopropylidene removal in the next step. After column chromatography, 71% phenyl 4-*O*-benzyl-1-thio-α-D-rhamanopyranoside (**13**)[12] was obtained over 3 steps from **10**. Next, 2,3-*O*-stannylene acetal formation of **13** was carried out by dibutyltinoxide in dry toluene. Then, benzyl bromide was added in the same reaction vessel to furnish eventually phenyl 3,4-*O*-benzyl-1-thio-α-D-rhamanopyranoside (**4**).[13] Thus L-rhamnose based monosaccharide units **3** and **4** were gathered. Next the 2-OH group of **4** was protected in various methods to furnish its *O*-benzyl (**5a**),[13a] and *O*-napthylmethyl (**5b**)[13b] derivatives (Scheme 1).

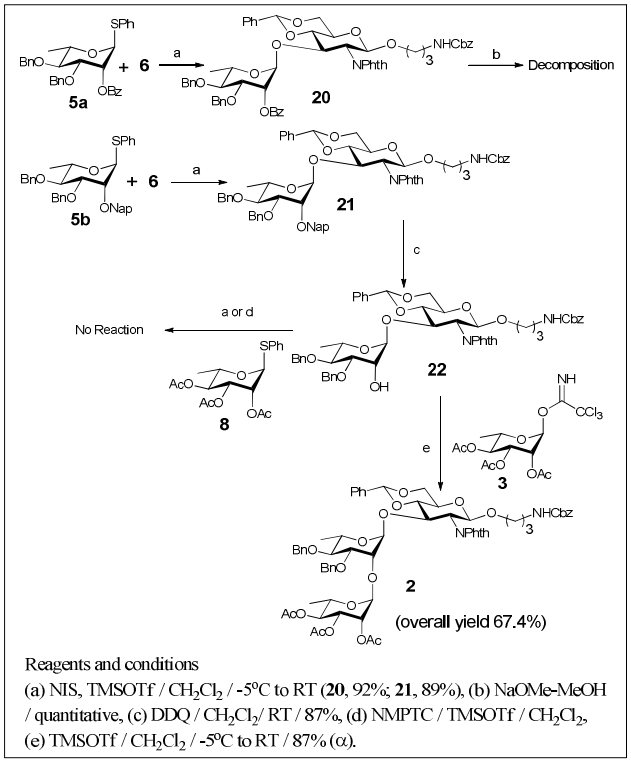


Scheme 1. Synthesis of L-rhamnopyranose based donor and acceptor.

The glucosamine based acceptor **6** was synthesized in six steps from D-glucosamine hydrochloride (Scheme 2). D-glucosamine hydrochloride (**14**) was converted to *N*-phth-protected tetra-*O*-acetyl-D-glucosamine **16**[14] as anomeric mixture following reported method. Thereafter, thiolation of **16** with thiophenol in the presence of trimethylsilyltrifluoromethanesulfonate (TMSOTf) or $BF_3.Et_2O$ in CH_2Cl_2 furnished 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (**17**)[12] in comparable yields (~85%). Glycosylation reaction was then carried out on **17** and 3-(*N*-benzyloxycarbonyl) propanol as donor and acceptor, respectively using TCCA / TMSOTf[15] activator system to provide **18**[15,16] in 86 % yield. It is to be noted that, this method[15] furnished a better yield (86%) compared to the other reported one[16] (65%). Zemplén deacetylation of **18** generated **19** in quantitative yield. Benzylidenation of deacetylated product was carried out using benzaldehyde dimethylacetal and catalytic camphorsulphonic acid in dry CH_3CN.



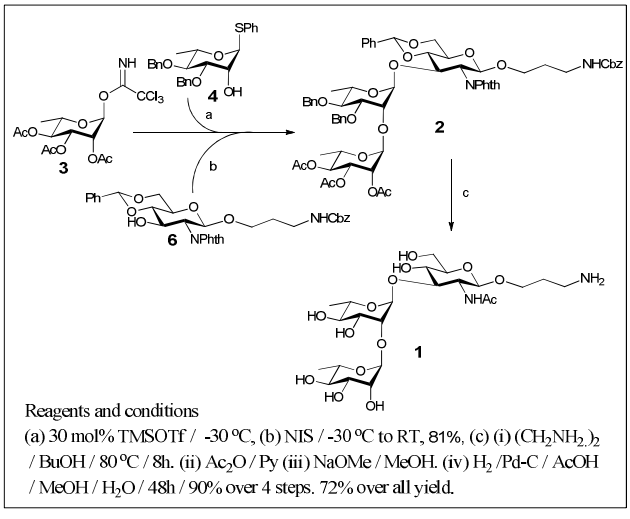
Scheme 2. Synthesis of D-glucosamine based acceptor.



Scheme 3. Stepwise synthesis of the desired trisaccharide.

With all the appropriately protected monomeric intermediates in hand, the glycosylation protocol leading to the protected trisaccharide (**2**) was first started from the non-reducing end of the same. For this purpose, *N*-phthalimido based acceptor **6** was reacted with phenyl 2-*O*-benzyl / 2-*O*-napthylmethyl-3,4-*O*-benzyl-1-thio-α-D-rhamanopyranosides, respectively in the presence of NIS/TMSOTf.[17] Both rhamnoside donors (**5a** and **5b**) led to fruitful respective glycosylations in 92 and 89% yields. Unfortunately, deacylation following Zémplen's method or based on NEt_3/MeOH/H_2O failed to give the corresponding desired product. Surprisingly both reactions proceeded with unusual decomposition. For exploration of another route **21** was denapthylmethylated with DDQ which progressed smoothly, yielding the desired disaccharide acceptor (**22**) in 87% yield. But, when the thiorhamnoside donor **8** was allowed to react with **22** in the presence of *N*-(*p*-methylphenylthio)-ε-caprolactam (NMPTC) -TMSOTf[18] or NIS/TMSOTf;[17] both of these reactions failed to produce the fully protected trisaccharide even after exploring different temperature controls. Later, use of trichloroacetimidate donor **3** instead of thiorhamnoside solved the problem yielding the desired trisaccharide **2** in 73% yield (Scheme 3).

After achieving the final protected trisaccharide *via* multistep synthesis, we set out for a reverse synthetic route starting from reducing end towards desired product now, by one pot sequential glycosylation reaction. Compound **3** and **4** were coupled by TMSOTf[19] in dry CH_2Cl_2 at -30 °C (Scheme 4). After completion of the initial reaction (indicated by TLC), acceptor **6** and NIS were added to the reaction mixture in the same vessel. Reaction temperature was then gradually increased to room temperature. After completion, the crude product was purified by flash chromatography to give 81% pure trisaccharide derivative (**2**). A comparison of the one pot synthesis (Scheme 4) of the protected trisaccharide (**2**) with the multistep one (Scheme 3) clearly indicates the efficacy of the first one (overall 81%) over the second one (overall 67.4%) in terms of reaction yield, atom economy and environmental ground.



Scheme 4. One-pot synthesis of the desired trisaccharide

The structure of **2** was confirmed by ^{1}H- and ^{13}C-NMR, COSY, HMBC, HSQC and HRMS techniques. Compound **2** showed three consecutive anomeric protons, listed from the non-reducing end at δ 3.87 (s), 4.56 (brs) and 5.17 (d, *J* 8.5 Hz), respectively, and the corresponding anomeric carbons at δ 98.7 ($^1J_{CH}$ 173.8 Hz), 99.7 ($^1J_{CH}$ 164.7 Hz) and 99.6 ($^1J_{CH}$ 173.6 Hz), respectively. The observed NMR spectral data indicate the presence of two α-linked rhamnopyranose and one *β*-linked glucopyranose residues in **2**.

The trisaccharide derivative was deprotected in a stepwise reaction scheme, starting with NPhth deprotection by ethylene diamine in butanol. Then acetylation using pyridine, acetic anhydride, followed by selective de-*O*-acetylation under Zémplen condition and finally global de-benzylation using hydrogen and palladium-charcoal in a mixture of acetic acid, water and methanol ultimately produced the desired product (**1**) in overall 72 % yield (Scheme 4). Compound **1** was characterized by ^{1}H- and ^{13}C-NMR, DEPT, COSY, HSQC and HRMS techniques. The three consecutive anomeric protons of **1** from the non-reducing end appeared at δ 4.85 (s), 5.07 (s) and 4.58 (d, *J* = 8.5 Hz) respectively.

Conclusion

In summary, our endeavor to reach the targeted trisaccharide via a stepwise glycosylation approach with chain extension from the non-reducing end as well as exploiting a sequential one-pot glycosylation route has been successful. Our effort has been rewarded particularly with the highly expeditious and high yielding stereoselective one pot protocol of the desired trisaccharide unit similar to repeating unit of the LPS of Burkholderia sp. HKI-402 (B4). The NMR data recorded for the synthetic target is in good agreement with the reported one, with slight deviations due to the incorporation of the 3-(*N*-benzyloxycarbonyl) propyl as the aglycon moiety.

Experimental

NMR spectra were recorded on Bruker DPX 300 NMR spectrometer operating at 300 MHz and 75 MHz for ^{1}H- and ^{13}C-NMR, respectively, in $CDCl_3$. HRMS data were recorded on a Q-tof-Micro mass spectrometer by electron spray ionization method. Specific rotations were measured on Jasco J-815 spectrometer.

*2, 3, 4-Tri-O-acetyl-L-rhamnopyranose (**9**)*[9]

To a solution of compound **8** (2 g, 5.24 mmol) in aqueous $(CH_3)_2CO$ (4:1), TCCA (1.2 g, 5.24 mmol) was added at 0 °C and kept on stirring for 40 min. Then the white precipitate was filtered, and the bed was washed with CH_2Cl_2 (3×5 mL). The combined filtrate and washings was evaporated, and the resulting mass was again dissolved in CH_2Cl_2. This organic part was washed subsequently with saturated $NaHCO_3$ solution (200 mL) and water (200 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated under vacuum to furnish compound **9**. Column filtration of the crude product furnished pure compound as white solid (**9**, 1.34 g, 88 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.24 (d, *J* = 6.0 Hz, 3H), 1.99 (s, 3H, COCH_3), 2.06 (s, 3H, COCH_3), 2.16 (s, 3H, COCH_3), 3.19 (d, *J* = 3.0 Hz, 1H), 4.13 (m, 1H), 5.08 (t, *J* = 10.0 Hz, 1H), 5.17 (s, 1H), 5.28 (m, 1H), 5.36 (m, 1H).

*2,3,4-Tri-O-acetyl-L-rhamnopyranosyl trichloroacetimidate (**3**)*[9]

To a solution of compound **9** (1 g, 3.45 mmol) and CCl_3CN (0.52 mL, 5.18 mmol) in dry CH_2Cl_2 (15 mL) DBU (0.1 mL, 0.69

mmol) was added at -5 °C, and the reaction was kept on stirring at that temperature. After 5 h, excess solvent was removed, and the resulting mass was purified through flash column chromatography (PE/EtOAc, 3:1) to furnish pure compound **3** as colorless syrup (1.33 g, 89 %). ^{1}H (200 MHz, $CDCl_3$): δ 1.26 (s, *J* = 6.2 Hz, 3H, C*H*$_3$), 2.00 (s, 3H, COC*H*$_3$), 2.06 (s, 3H, COC*H*$_3$), 2.18 (s, 3H, COC*H*$_3$), 4.08 (m, 1H), 5.17 (t, *J* = 10.0 Hz, 1H), 5.36 (dd, *J* = 3.4, 10.2 Hz, 1H), 5.45 (m, 1H), 6.19 (d, *J* = 1.5 Hz, 1H, C-1), 8.72 (s, 1H, N*H*).

*Phenyl -1-thio-α-L-rhamnopyranoside (**10**)*[9]

A suspension of compound **8** (2 g, 5.24 mmol) in 0.1 M NaOMe in dry MeOH (10 mL) was stirred overnight at room temperature. After completion of the reaction (indicated by TLC), Dowex 50(H^+) resin was poured into the clear solution, and it was swirled occasionally. After 30 min the resin was filtered, and the bed was washed with distilled MeOH (3×5 mL). The combined filtrate and washings was evaporated to dryness to furnish the title compound **10** in quantitative yield. It was dried thoroughly and directly used without characterization for the next step.

Synthesis of *phenyl 4-O-benzyl-1-thio-α-L-rhamnopyranoside* (***13***)[12] from ***10***

To a solution of compound **10** (1 g, 3.9 mmol) and 2,2-dimethoxypropane (0.72 mL, 5.85 mmol) in dry CH_3CN, CSA (271.8 mg, 1.17 mmol) was added at 0 °C. The reaction mixture was kept on stirring for 5 h. After completion (indicated by TLC), the reaction was quenched by addition of Et_3N. Excess solvent was removed in vacuum, and the resulting mass was dissolved in CH_2Cl_2. The organic solution was washed subsequently with saturated $NaHCO_3$ solution (100 mL) and water (100 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated under vacuum to furnish crude product **11**. This was used for the next step without purification. To crude **11**, 60 % oil suspension of NaH (234.0 mg, 5.85 mmol) and BnBr (0.7 mL, 5.85 mmol) were added subsequently in dry DMF at 0 °C. After completion (indicated by TLC), the reaction was quenched by MeOH, and excess solvent was removed in vacuum. The resulting white paste was dissolved in CH_2Cl_2 and washed with water (100 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated under vacuum to furnish crude product **12**. Compound **12** was treated with 80% AcOH (15 mL) at 60 °C for 6 h. Then excess AcOH was co-evaporated with toluene, furnishing thick brown syrup. This was dissolved in CH_2Cl_2 and washed subsequently with saturated $NaHCO_3$ solution (100 mL) and water (100 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated under vacuum to furnish crude product **13**. Purification of **13** by silica gel column chromatography (PE/EtOAc, 2:1) yielded phenyl 4-*O*-benzyl-1-thio-α-L-rhamnopyranoside as white solid (**13**, 0.96 g, 71% over 3 steps). M.p. 110-112 °C. $[\alpha]^{25}_D$ -187.5 (*c* 1.5, $CHCl_3$). Lit[12] m.p. 111-113 °C. $[\alpha]_D$ -201 (*c* 0.9, $CHCl_3$). ^{1}H (500 MHz, $CDCl_3$): δ 1.36 (d, *J* = 6.0Hz, 3H, C*H*$_3$), 3.41 (t, *J* = 9.5 Hz, 1H), 3.94 (dd, *J* = 3.0, 9.0 Hz, 1H), 4.19 (m, 1H), 4.22 (m, 1H), 4.76 (s, 2H), 5.47 (d, *J* = 1.0 Hz, 1H, C-1), 7.24-7.34 (m, 4H, ArH), 7.36-7.38 (m, 4H, ArH), 7.45-7.47 (m, 2H, ArH). ^{13}C (125 MHz, $CDCl_3$): δ 18.0, 68.7, 71.9, 72.6, 75.1, 81.8, 87.4, 127.4, 128.0, 128.1, 128.7, 129.1, 131.4, 134.2, 138.1.

*Phenyl 3,4-di-O-benzyl-1-thio-α-L-rhamnopyranoside (**4**)*[13]

A suspension of compound **13** (0.5 g, 1.44 mmol) and Bu_2SnO (430.6 mg, 1.73 mmol) in dry toluene (10 mL) was refluxed in Dean-Stark apparatus for 5 h. Then, BnBr (0.26 mL, 2.16 mmol) and tetrabutylammonium bromide (232.1 mg, 0.72 mmol) were added to the resulting clear solution. It was kept on stirring at 80 °C until completion of the reaction (indicated by TLC). Excess toluene was removed under vacuum, and the resulting crude product was directly used for column chromatography on silica gel. Column elution by PE/EtOAc, 3:1 furnished pure compound **4** as colorless syrup (0.57 g, 90%). $[\alpha]_D^{25}$ -181.5 (*c* 1.5, $CHCl_3$); lit[13a] $[\alpha]_D^{25}$ -196.1 (*c* 1.2, $CHCl_3$); ^{1}H (300 MHz, $CDCl_3$): δ 1.23 (s, 3H, *J* = 6.0 Hz, C*H*$_3$), 2.61 (s, 1H), 3.45 (t, 1H, *J* = 9.3 Hz), 3.78 (dd, 1H, *J* = 3.3, 10.0 Hz), 4.12 (m, 1H), 4.16 (s, 1H), 4.57 (d, 1H, *J* = 11.1 Hz), 4.64 (s, 2H), 4.81 (d, 1H, *J* = 10.8 Hz), 5.44 (s, 1H), 7.14-7.37 (m, 15H, ArH).

*Phenyl 2-O-benzoyl-3,4-di-O-benzyl-1-thio-α-L-rhamnopyranoside (**5a**)*[13a]

To a solution of compound **4** (524 mg, 1.2 mmol) and dry pyridine, BzCl (0.21 mL, 1.8 mmol) was added. It was kept on stirring at ambient temperature until completion of the reaction (indicated by TLC). Excess pyridine was removed under vacuum, and was washed with brine solution. The organic layer was dried over anhydrous Na_2SO_4 and concentrated to afford the benzoylated product. Column elution by PE/EtOAc, 4:1 furnished pure compound **5a** as white foam (616 mg, 95%). ^{1}H (500 MHz, $CDCl_3$): δ 1.41 (d, *J* = 6.0 Hz, 3H), 3.65 (t, *J* = 9.0 Hz, 1H), 4.05 (dd, *J* = 2.5, 9.0 Hz, 1H), 4.32 (m, 1H), 4.62 (d, *J* = 11.5 Hz, 1H), 4.68 (d, *J* = 11.0 Hz, 1H), 4.81 (d, *J* = 11.5 Hz, 1H), 4.96 (d, *J* = 11.0 Hz, 1H), 5.57 (s, 1H, PhC*H*), 5.86 (d, *J* = 1.5 Hz, 1H, H-1), 7.28-7.38 (m, 13H, ArH), 7.47-7.50 (m, 4H, ArH), 7.59-7.62 (m, 1H, ArH), 8.08-8.10 (d, *J* = 7.5 Hz, 2H, ArH). ^{13}C (125 MHz, $CDCl_3$): δ 18.1, 69.2, 71.1, 71.7, 75.5, 78.5, 80.2, 86.2, 127.7, 127.8, 128.1, 128.2, 128.4, 128.5, 129.1, 129.9, 131.8, 133.3, 134.0, 137.7, 138.3, 165.7.

*Phenyl 3,4-Di-O-benzyl-2-O-(2-naphthylmethyl)-1-thio-α-L-rhamnopyranoside (**5b**)*[13b]

To a solution of compound **4** (100 mg, 0.23 mmol) and dry DMF, 60 % oil suspension of NaH (9 mg, 0.35 mmol) and NapBr (77.4 mg, 0.35 mmol) was added. It was kept on stirring at ambient temperature until completion of the reaction (indicated by TLC). Excess NaH was quenched with MeOH, DMF was removed under vacuum, and was washed with brine solution. The organic layer was dried over anhydrous Na_2SO_4 and concentrated to afford the napthylmethylated product. Column elution by PE/EtOAc, 5:1 furnished pure compound **5b** as white solid (121.5 mg, 92%). ^{1}H (300 MHz, $CDCl_3$): δ 1.43 (d, *J* = 6.3 Hz, 3H), 3.79 (t, *J* = 9.4 Hz, 1H), 3.92 (dd, *J* = 9.4, 3.1 Hz, 1H), 4.09 (dd, *J* = 3.0, 1.7 Hz, 1H), 4.18 - 4.26 (m, 1H), 4.65 (d, *J* = 11.7 Hz, 1H), 4.69 (d, *J* = 11.7 Hz, 1H), 4.73 (d, *J* = 10.8 Hz, 1H), 4.86 (d, *J* = 12.5 Hz, 1H), 4.93 (d, *J* = 12.6 Hz, 1H), 5.05 (d, *J* = 10.8 Hz, 1H), 5.56 (d, *J* = 1.5 Hz, 1H), 7.23 - 7.30 (m, 3H), 7.31 - 7.44 (m, 12H), 7.50 - 7.59 (m, 3H), 7.77 - 7.90 (m, 4H). ^{13}C (75 MHz, $CDCl_3$) δ: 18.0, 69.5, 72.3, 72.4, 75.6, 76.6, 80.1, 80.6, 86.0, 126.05, 126.14, 126.2, 127.0, 127.3, 127.8, 127.9, 128.0, 128.1, 128.3, 128.5, 129.1, 133.1, 133.3, 134.7, 135.4, 138.3, 138.6.

*3-(N-benzyloxycarbonyl) propyl 3,4,6-tri-O-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (**18**)*[15, 16]

To a mixture of **17** (150.0 mg, 0.285 mmol) and 3-(*N*-benzyloxycarbonyl) propanol (50.0 mg, 0.238 mmol) in dry

CH_2Cl_2 (5 mL), flame activated molecular sieves (4Å) were added. It was stirred at room temperature under argon atmosphere. After 40 min the mixture was cooled to -5ºC and TCCA (55.3 mg, 0.238 mmol) was added to it. Then TMSOTf (12.9 µL, 0.071 mmol) was added via a micro-syringe. After the acceptor was consumed completely (checked by TLC) the reaction was quenched by Et_3N (130.0 µL). The reaction mixture was filtered off through Celite bed. The filtrate was diluted with CH_2Cl_2 and washed subsequently with saturated $NaHCO_3$ solution and water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated to afford the glycosylated product. The crude product was purified by column chromatography on silica gel (60-120 mesh) (PE:EtOAc 4:1) to afford **8** (128.7 mg) in 86% as white foam. $[\alpha]^{25}_D$ + 10.9 (*c* 1.0, $CHCl_3$); lit.[15, 16] $[\alpha]_D$ +18.1 (*c* 1.1, $CHCl_3$). ^1H (300 MHz, $CDCl_3$): δ 1.68-1.70 (m, 2H), 1.85 (s, 3H, COCH_3), 2.03 (s, 3H, COCH_3), 2.07 (s, 3H, COCH_3), 3.04-3.16 (m, 2H), 3.55 (m, 1H), 3.82-3.89 (m, 2H), 4.19 (dd, *J* = 2.1, 12.2 Hz, 1H), 4.22-4.34 (m, 2H), 4.95 (m, 1H), 5.01 (s, 2H), 5.16 (t, *J* = 9.6 Hz, 1H), 5.38 (d, *J* = 8.5 Hz, 1H), 5.75 (dd, *J* = 9.1, 10.7 Hz, 1H), 7.30-7.35 (m, 5H, ArH), 7.70-7.73 (m, 2H, ArH), 7.81-7.83 (m, 2H, ArH). The spectral data were consistent with those in the literature.[15]

*3-(N-benzyloxycarbonyl) propyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (**19**)*

A suspension of compound **18** (1 g, 2.08 mmol) in 0.1 M NaOMe in dry MeOH (10 mL) was stirred for 45 min at room temperature. After completion of the reaction (indicated by TLC), Dowex 50(H^+) resin was poured into the clear solution, and it was swirled occasionally. After 30 min the resin was filtered, and the bed was washed with distilled MeOH (3×5 mL). The combined filtrate was evaporated to dryness to furnish the title compound **19** in quantitative yield. It was dried thoroughly and directly used without characterization for the next step.

*3-(N-benzyloxycarbonyl) propyl-4,6-O-benzylidene-2-deoxy-2-phthalimido-β-D-glucopyranoside (**6**)*

To a suspension of **19** (0.5 g, 1.41 mmol) and benzaldehyde dimethylacetal (0.32 mL, 2.12 mmol) in dry CH_3CN (25 ml), anhydrous $FeCl_3$ (68.6 mg, 0.42 mmol) was added, and it was stirred at ambient temperature. After completion of the reaction (indicated by TLC) solvent was evaporated under reduced pressure. The solid mass was dissolved in CH_2Cl_2 and washed subsequently with saturated $NaHCO_3$ solution (200 mL) and water (200 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated under vacuum to furnish the crude product. It was purified by column chromatography on silica gel (eluent: PE/EtOAc, 1:1) to give pure title compound **5** as white foam (0.5 g mg, 81%). $[\alpha]^{25}_D$ -39.8 (*c* 1.48, $CHCl_3$). ^1H (300 MHz, $CDCl_3$): δ 1.69 (m, 1H), 2.54 (m, 1H), 3.09-3.13 (m, 1H), 3.49-3.68 (m, 3H), 3.77-3.90 (m, 2H), 4.24 (dd, *J* = 8.4, 10.4 Hz, 1H), 4.38 (m, 1H), 4.62 (m, 1H), 4.90 (bs, 1H), 5.02 (s, 1H), 5.27 (d, 1H, *J* = 8.6 Hz), 5.30 (s, 1H), 5.55 (s, 1H, PhC*H*), 7.29-7.39 (m, 8H, ArH), 7.48-7.51 (m, 2H, ArH), 7.69-7.72 (m, 2H), 7.81-7.84 (m, 2H). ^{13}C (75 MHz, $CDCl_3$): δ 29.5, 29.8, 38.1, HRMS *m/z* for ($C_{64}H_{70}N_2O_{20}Na^+$) calcd: 1209.4420, found: 1209.4421.

*3-(N-benzyloxycarbonyl) propyl 2-O-benzoyl-3,4-di-O-benzyl-α-L-rhamnopyranosyl-(1→3)-4,6-O-benzylidene-2-deoxy-2-acetamido-β-D-glucopyranoside (**20**)*

To a solution of **5a** (160 mg, 0.30 mmol) and **6** (145 mg, 0.25 mmol) in dry CH_2Cl_2 (12 mL) activated molecular sieves (4Å) were added, and the reaction was kept on stirring under argon atmosphere for 45 min. After that NIS (67 mg, 0.30 mmol) and TMSOTf (16 µL, 0.08 mmol) (*via* a micro syringe) were then added to the reaction vessel keeping the temperature at -5 °C. After the addition, reaction temperature was raised gradually to room temperature. The reaction was completed after 15 min (indicated by TLC). Reaction mass was then filtered through Celite bed, and the bed was washed with CH_2Cl_2 (3×5 mL). The combined filtrate was washed subsequently with saturated aqueous $NaHCO_3$ (1x100 mL), saturated aqueous $Na_2S_2O_3$ (1x100 mL) and water (2x50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated to furnish a syrupy compound. The crude product was purified by column chromatography (eluent: PE/EtOAc, 2:1) to afford the disaccharide **20** as white foam (230 mg, 92 %). ^1H NMR (500 MHz, $CDCl_3$): δ 0.80 (d, *J* = 6.0 Hz, 3H), 1.67 (m, 2H), 3.08-3.12 (m,2H). 3.35 (t, *J* = 9.5 Hz, 1H), 3.53 (m, 2H), 3.65-3.68 (m, 2H), 3.81 (t, *J* = 10.0 Hz, 1H), 3.83-3.86 (m, 2H), 3.93 (m, 1H), 4.31 (dd, *J* = 8.5, 10.0 Hz, 1H), 4.38 (m, 1H), 4.44 (d, *J* = 11.5 Hz, 1H), 4.52 (d, *J* = 11.0 Hz, 1H), 4.56 (d, *J* = 11.5 Hz, 1H), 4.61-4.65 (m, 2H), 4.81 (d, *J* = 11.0 Hz, 1H), 4.88 (brs,1H), 5.04-5.07 (m,3H), 5.25 (d, *J* = 8.5 Hz, 1H), 5.54 (s, 1H,PhC*H*), 7.22 (brs, 8H, ArH), 7.28-7.38 (m, 12H, ArH), 7.47-7.51 (m, 3H, ArH), 7.66-7.71 (m, 3H, ArH), 7.86 (bs, 2H, ArH). HRMS *m/z* for ($C_{59}H_{58}N_2O_{14}Na^+$) calcd: 1041.3786, found: 1041.3785.

*3-(N-benzyloxycarbonyl) propyl 3,4-di-O-benzyl-2-O-(2-naphthylmethyl)-α-L-rhamnopyranosyl-(1→3)-4,6-O-benzylidene-2-deoxy-2-acetamido-β-D-glucopyranoside (**21**)*

To a solution of **5b** (88 mg, 0.15 mmol) and **6** (75 mg, 0.13mmol) in dry CH_2Cl_2 (8 mL) activated molecular sieves (4Å) were added, and the reaction was kept on stirring under argon atmosphere for 45 min. After that NIS (34 mg, 0.15 mmol) and TMSOTf (8.3 µL, 0.05 mmol) (*via* a micro syringe) were then added to the reaction vessel keeping the temperature at -5 °C. After the addition, reaction temperature was raised gradually to room temperature. The reaction was completed after 15 min (indicated by TLC). Reaction mass was then filtered through Celite bed, and the bed was washed with CH_2Cl_2 (3×5 mL). The combined filtrate was washed subsequently with saturated aqueous $NaHCO_3$ (1x50 mL), saturated aqueous $Na_2S_2O_3$ (1x50 mL) and water (2x50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated to furnish a syrupy compound. The crude product was purified by column chromatography (eluent: PE/EtOAc, 4:1) to afford the disaccharide **21** as syrup (119.5 mg, 89%). ^1H NMR (400 MHz, $CDCl_3$): δ 0.87 (d, *J* = 6.0 Hz, 3H), 1.69 (m, 1H), 3.10-3.14 (m, 2H), 3.42-3.56 (m, 3H), 3.64-3.69 (m, 2H), 3.76-3.93 (m, 4H), 4.20 (s, 2H), 4.29 (t, *J* = 9.5 Hz, 1H), 4.40 (d, *J* = 11.0 Hz, 2H), 4.50 (d, *J* = 10.8 Hz, 1H), 4.52 (d, *J* = 9.2 Hz, 1H), 4.64 (t, *J* = 9.2 Hz, 1H), 4.75 (s, 1H), 4.83 (d, *J* = 10.8 Hz, 1H), 4.91 (bs, 1H), 5.03 (s, 2H), 5.29 (d, *J* = 8.4 Hz, 1H), 5.54 (s, 1H, PhC*H*), 7.06 (d, *J* = 8.4 Hz, 1H, ArH), 7.24-7.36 (m, 18H, ArH), 7.43-7.78 (m, 12H, ArH), 8.67 (bs, 1H, N*H*). ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.5, 29.6, 29.8, 38.1, 56.7, 66.6, 66.7, 67.6, 68.5, 68.8, 72.0, 72.6, 74.5, 75.1, 76.3, 77.4, 79.7, 80.4, 80.8, 98.6, 98.9, 102.0, 123.7, 125.4, 125.88, 125.92, 126.1, 126.5, 127.3, 127.49, 127.54, 127.6, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3,

128.36, 128.38, 128.6, 129.2, 131.3, 133.0, 133.3, 134.6, 135.5, 136.8, 137.1, 138.7, 138.9, 156.4. HRMS *m/z* for ($C_{63}H_{62}N_2O_{13}Na^+$) calcd: 1077.4150, found: 1077.4152.

*3-(N-benzyloxycarbonyl) propyl 3,4-di-O-benzyl-α-L-rhamnopyranosyl-(1→3)-4,6-O-benzylidene-2-deoxy-2-acetamido-β-D-glucopyranoside (**22**)*

To a solution of **22** (64 mg, 0.06mmol) in CH_2Cl_2/H_2O (5 mL, 19:1) DDQ (17 mg, 0.08 mmol) was added, and the reaction was kept on stirring under ambient temperature for 2 hr. After that the reaction mass was washed with water (2x100 mL) and the organic layer was dried over anhydrous Na_2SO_4 and concentrated to furnish a syrupy compound. The crude product was purified by column chromatography (eluent: PE/EtOAc, 2:1) to afford the disaccharide acceptor **22** as syrup (48 mg, 87%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.70 (d, *J* = 6.3 Hz, 3H), 1.59 (m, 1H), 2.94-3.05 (m, 2H), 3.15 (t, *J* = 9.0 Hz, 1H), 3.43 (m, 1H), 3.47-3.74 (m, 5H), 3.75-3.89 (m, 3H), 4.18 (dd, *J* = 8.7, 10.2 Hz, 1H), 4.31 (dd, *J* = 5.6, 13.6 Hz, 1H), 4.39-4.46 (m, 3H), 4.49-4.55 (m, 3H), 4.58-4.67 (m, 2H), 4.76 (d, *J* = 8.0 Hz, 1H), 4.80 (bs, 1H), 4.95 (bs, 2H), 5.18 (d, *J* = 8.7 Hz, 1H), 5.44 (s, 1H, PhC*H*), 7.12-7.30 (m, 18H, ArH), 7.41-7.44 (m, 2H, ArH), 7.63-7.66 (m, 2H, ArH), 7.75-7.78 (m, 2H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.4, 29.8, 38.1, 56.8, 66.6, 67.6, 67.8, 68.7, 68.8, 72.0, 74.3, 75.2, 77.3, 79.8, 80.0, 80.9, 98.9, 99.6, 102.1, 123.9, 126.6, 127.7, 127.9, 128.0, 128.2, 128.3, 128.4, 128.60, 128.62, 129.2, 131.4, 134.7, 137.1, 138.0, 138.6, 156.4. HRMS *m/z* for ($C_{52}H_{54}N_2O_{13}Na^+$) calcd: 937.3524, found: 937.3523.

*Stepwise synthesis of 3-(N-benzyloxycarbonyl) propyl 2,3,4-tri-O-acetyl-α-L-rhamnopyranosyl-(1→2)-3,4-di-O-benzyl-α-L-rhamnopyranosyl-(1→3)-4,6-O-benzylidene-2-deoxy-2-acetamido-β-D-glucopyranoside (**2**)*

To a solution of **3** (22 mg, 0.05 mmol) and **22** (40 mg, 0.04mmol) in dry CH_2Cl_2 (5 mL) activated molecular sieves (4Å) were added, and the reaction was kept on stirring under argon atmosphere for 45 min. Then the reaction vessel was placed in a -15 °C cold bath, and NIS (11.0 mg, 0.05mmol) and TMSOTf (4 µL, 0.02 mmol) (*via* a micro syringe) were then added to it. After 10 min complete consumption of both the starting materials was observed. The reaction mass was then filtered through Celite bed, and the bed was washed with CH_2Cl_2 (3×5 mL). The combined filtrate was washed subsequently with saturated aqueous $NaHCO_3$ (1x50 mL), saturated aqueous $Na_2S_2O_3$ (1x50 mL) and water (2x50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated to furnish a syrupy compound. The crude product was purified by flash column chromatography (eluent: PE/EtOAc, 1:1) to afford the desired fully protected trisaccharide **2** as white foam (40.5 mg, 78%).

*One-pot sequential synthesis of 3-(N-benzyloxycarbonyl) propyl 2,3,4-tri-O-acetyl-α-L-rhamnopyranosyl-(1→2)-3,4-di-O-benzyl-α-L-rhamnopyranosyl-(1→3)-4,6-O-benzylidene-2-deoxy-2-acetamido-β-D-glucopyranoside (**2**)*

To a solution of **3** (50.0 mg, 0.11 mmol) and **4** (43.6 mg, 0.10 mmol) in dry CH_2Cl_2 (8 mL) activated molecular sieves (4Å) were added, and the reaction was kept on stirring under argon atmosphere for 45 min. Then the reaction vessel was placed in a -30 °C cold bath, and TMSOTf (5.4 µL, 0.03 mmol) was added to it via a micro syringe. After 10 min complete consumption of both the starting materials was observed. Acceptor **6** (53.0 mg, 0.09 mmol) and NIS (30.0 mg, 0.13 mmol) were then added to the same vessel. After the addition, reaction temperature was raised gradually to room temperature. The second step of the reaction was completed after 30 min (indicated by TLC). The reaction mass was then filtered through Celite bed, and the bed was washed with CH_2Cl_2 (3×5 mL). The combined filtrate was washed subsequently with saturated aqueous $NaHCO_3$ (2x50 mL) and water (2x50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated to furnish a syrupy compound. The crude product was purified by flash column chromatography (eluent: PE/EtOAc, 1:1) to afford the desired fully protected trisaccharide **2** as white foam (86.0 mg, 81%). $[\alpha]^{25}_D$ -34.2 (*c* 1.30, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.72-0.76 (2d, *J* = 6.5 Hz, 6H, 2×C*H*$_3$), 1.55 (m, 1H, C*H*$_2$), 1.85 (s, 3H, COC*H*$_3$), 1.91 (s, 3H, COC*H*$_3$), 1.95 (s, 3H, COC*H*$_3$), 2.98-3.03 (m, 2H, NC*H*$_2$), 3.20-3.24 (apparent t, 1H, *J* = 9.5 Hz, H-4'), 3.34 (br s, 1H, H-5'), 3.43 (m, 1H, C*H*$_2$), 3.51-3.60 (m, 3H, H-4, H-6a, PhC*H*$_2$), 3.65-3.79 (m, 4H, H-5, H-2', H-3', C*H*$_2$), 3.87 (s, 1H, H-1'), 4.15 (apparent t, *J* = 9.0, 10.0 Hz, 1H, H-2), 4.30 (dd, *J* = 4.5, 10.5 Hz, 1H, H-6), 4.35 (d, *J* = 12.0 Hz, 1H, PhC*H*$_2$), 4.42-4.48 (m, 3H, H-3, H-5", PhC*H*$_2$), 4.56 (br s, 1H, H-1"), 4.69-4.73 (m, 2H, H-4", PhC*H*$_2$), 4.77 (m, 1H, H-2"), 4.95 (br s, 2H, PhC*H*$_2$), 5.02-5.03 (m, 2H, H-3', PhC*H*$_2$), 5.17 (d, *J* = 8.5 Hz, 1H, H-1), 5.44 (s, 1H, PhC*H*), 7.19-7.36 (m, 18H, ArH), 7.47-7.51 (m, 2H, ArH), 7.69-7.80 (m, 2H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.1 (*C*H$_3$), 17.3 (*C*H$_3$), 20.7 (CO*C*H$_3$), 20.79 (CO*C*H$_3$), 20.84 (CO*C*H$_3$), 29.5, 38.0, 56.6 (C-2), 66.4 (C-4), 66.6 (Ph*C*H$_2$, C-6a), 68.3 (O*C*H$_2$), 68.7 (C-5), 68.8 (C-2', C-6, Ph*C*H$_2$), 69.8 (C-3"), 71.0 (C-4"), 71.9 (2×Ph*C*H$_2$), 75.2 (2×Ph*C*H$_2$), 75.5 (C-2", C-5", C-3), 78.1 (C-5'), 79.0 (C-3'), 79.9 (C-4'), 80.7 (C-4), 98.7 (C-1), 99.6 (C-1'), 99.7 (C-1"), 102.0 (Ph*C*H), 126.4, 127.4, 127.47, 127.54, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 129.1, 131.4. 134.2, 137.0, 138.5, 138.7, 156.3, 169.4, 169.8, 170.1; HRMS *m/z* for ($C_{64}H_{70}N_2O_{20}Na^+$) calcd: 1209.4420, found: 1209.4421. NMR spectra of the compound **2** obtained by both protocol was identical.

*3-(N-benzyloxycarbonyl) propyl α-L-rhamnopyranosyl-(1→2)-α-L-rhamnopyranosyl-(1→3)-2-deoxy-2-acetamido-β-D-glucopyranoside (**1**)*

Protected trisaccharide **2** (60 mg, 0.034 mmol) was refluxed in butanol (6 mL) and ethelene diamine (1.5 mL) for 8 h and then excess solvent was removed under reduced pressure. Residual water was co-evaporated with toluene (2 x 5 mL) and the resulting compound was treated with dry pyridine (5 mL) and Ac_2O (2 mL) for 12 h at room temperature. After complete conversion excess solvent was removed under vacuum. The crude mass was column filtered (PE/EtOAc, 3:2) and the pure product was dissolved in MeOH (7 mL) and NaOMe (1 M in MeOH, 0.5 mL) was added. The mixture was stirred for 10 h and then reaction was quenched with Dowex-50W cation exchange resin (H^+). The resin was filtered off and then washed with MeOH (4 x 5 mL). The combined filtrate and washings was evaporated under reduced pressure. The resulting mass and 10% Pd-C (70 mg) was taken in AcOH (1 mL), MeOH (3 mL), H_2O (1 mL) and kept on stirring under H_2 atmosphere for 24 h. The catalyst was filtered through Celite bed, and the bed was washed with MeOH (3 x 5 mL). The combined filtrate and washings was concentrated under reduced pressure. It was passed through a 0.45µm Millipore

membrane, and lyophilized to afford **1** as white foam (30.0 mg, 90 %); ^{1}H NMR (500 MHz, D_2O): δ 1.25-1.30 (2d, 6H, *J* = 6.0 Hz, 2×C*H*$_3$), 1.87-1.90 (m, 2H), 2.10 (s, 3H, COC*H*$_3$), 2.93-2.99 (m, 2H), 3.43-3.54 (m, 4H), 3.59 (apparent t, *J* = 8.0, 9.5 Hz, 1H), 3.71-3.86 (m, 7H), 3.94-4.05 (m, 4H), 4.58 (d, *J* = 8.5 Hz, 1H), 4.85 (s, 1H), 5.07 (s, 1H). ^{13}C (75 MHz, D_2O): δ 16.5, 16.9, 22.5, 23.1, 26.8, 37.5, 55.6, 60.7, 67.7, 68.6, 68.9, 69.1, 69.8, 70.1, 72.1, 75.9, 80.4, 81.4, 99.7, 100.5, 102.7, 174.6.. HRMS (ESI-TOF) Calcd for $C_{23}H_{42}N_2O_{14}Na$ [M + Na]+ 593.2534, found 593.2531.

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Synthetic Routes Toward the Trisaccharide Related to the Lipopolysaccharide of *Burkholderia sp.* HKI-402 (B4)

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Stepwise and one-pot sequential synthesis of the trisaccharide using trichloroacetimidate and thioglycosyl donors along with 3-(*N*-benzyloxycarbonyl) propyl glycoside acceptor.