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Total Synthesis of the All-Rare Sugar-Containing Pentasaccharide Repeating Unit of the O-Polysaccharide of *Plesiomonas shigelloides* Strain 302-73 (Serotype O1)

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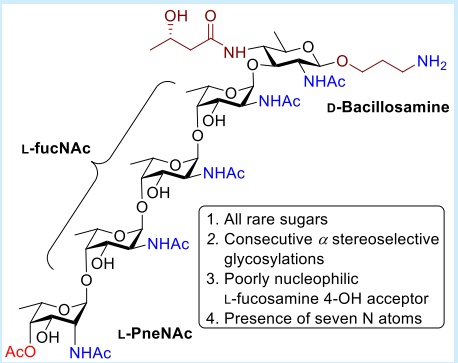
ABSTRACT: First total synthesis of the conjugation-ready pentasaccharide repeating unit of *Plesiomonas shigelloides* strain 302-73 (serotype O1) is reported. The complex target pentasaccharide is composed of all-rare amino sugars such as orthogonally functionalized D-bacillosamine, L-fucosamine, and L-pneumosamine linked through four consecutive α-linkages. The poor nucleophilicity of axial 4-OH of L-fucosamine and stereoselective glycosylations are the key challenges in the total synthesis, which was completed via a longest linear sequence of 27 steps in 3% overall yield.



Diarrhea is a leading cause of death in young children below age five. According to the WHO fact sheet, every year 525,000 children die due to diarrheal diseases.[1] *Plesiomonas shigelloides* is one of the significant causative agents of severe travelers' diarrhea worldwide with a high rate of morbidity and mortality.[2,3] Along with this, it also causes several other gastrointestinal infections like acute secretory gastroenteritis,[4] meningitis, bacteremia,[5] and invasive shigellosis-like diseases.[6] There are reports on the association of this pathogen with central nervous system disease, eye infections, and a variety of miscellaneous ailments.[7] The bacterial infection also leads to cholera-like illness,[8] pseudoappendicitis,[9] and even apoptotic cell death by entering in the human colon carcinoma Caco-2 cells.[10,11] With the gradual increase in antibiotic-resistant strains of *P. shigelloides* and due to the severity of the bacterium, effective treatments are urgently required. The development of vaccine therapy for the subtropical travelers is highly desirable.[2,7] The carbohydrate antigens expressed on the surfaces of these strains[12] are attractive synthetic targets for the development of a multicomponent glycoconjugate vaccine.[13]

Corsaro and co-workers isolated and characterized the O-chain of lipopolysaccharide (LPS) from *Plesiomonas shigelloides* strain 302-73 (serotype O1).[14] The polysaccharide was shown to be composed of an exclusively rare sugar-based pentasaccharide repeating unit (RU) as follows →3)-α-L-PneNAc4OAc(1→4)-α-L-FucNAc(1→4)-α-L-FucNAc(1→4)-α-L-FucNAc(1→3)-β-D-QuiNAc4NHb(1→. The three rare deoxy amino sugars L-pneumosamine, L-fucosamine, and 4-amino-D-quinosamine (also called as D-bacillosamine) are attached to a variety of functional groups at specific positions. The D-bacillosamine unit bears a 3*S*-hydroxybutyryl (Hb) amide linker at the C4 position, whereas the L-pneumosamine moiety has an OAc group at the C4 position. The presence of unusual sugars and the rare side chain which are virtually absent in host cells makes this pentasacccharide O-antigen a potential candidate for vaccine development.[15] The key challenges in the total synthesis of the pentasaccharide RU involves installation of four consecutive α-glycosidic linkages and synthesis of orthogonally protected rare sugar building blocks. Furthermore, the presence of seven nitrogen atoms dispensed over five sugar rings and the poor nucleophilicity of the 4-OH group of L-fucosamine makes the oligosaccharide assembly more challenging.[13,16] Our lab has developed an efficient protocol for the synthesis of rare D- and L-deoxyamino sugars via a one-pot regioselective S_N2 displacements of 2,4 bis-triflates derived from D-rhamnose[17,18] and L-rhamnose/L-fucose,[19] respectively. The methodology has been also applied by us[16−20] and others[21] for synthesizing a variety of bacterial O-glycans. Herein, we report the first total synthesis of the all-rare sugar containing conjugation-ready pentasaccharide RU **1**.

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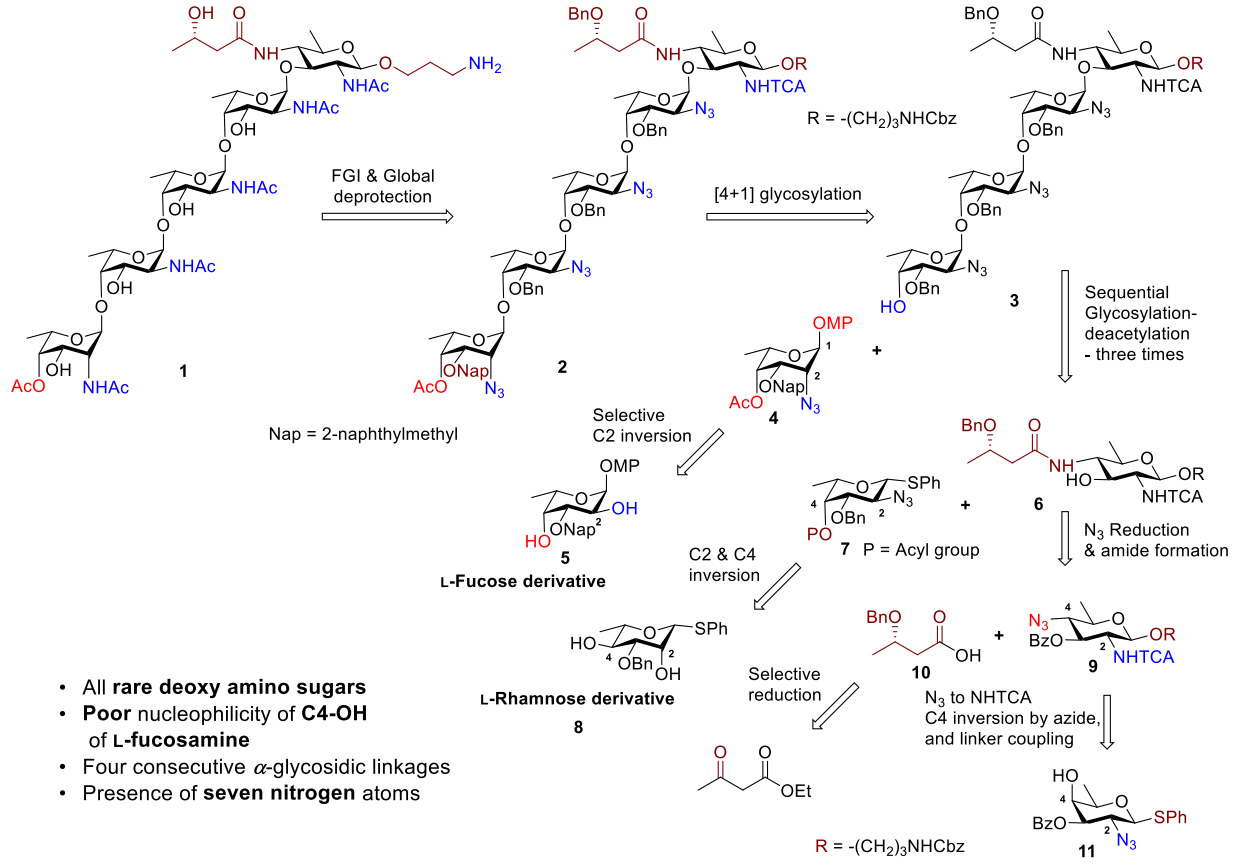
Scheme 1. Retrosynthetic Analysis



Retrosynthetically (Scheme 1), target molecule **1** can be synthesized by FGI and global deprotection of fully protected pentasaccharide **2**, which can be assembled by stereoselective glycosylation of L-pneumosamine donor derived from **4** and tetrasaccharide acceptor **3** in a [4 + 1] manner. Incidentally, the pneumosamine unit in the target molecule bears an OAc group at the C4 position. It was anticipated that the placement of 4-OAc group in L-pneumosamine donor **4** would assist α-stereoselectivity in glycosylation through anchimeric assistance,[22] especially in lieu of neighboring group participation from C2 functionality. Thus, a nonparticipating azide group could be used at the C2 position of L-pneumosamine building block **4**, which can be synthesized from L-fucose derivative **5** by a regioselective C2 triflation followed by azide inversion. The corresponding L-fucosyl thioglycoside gives O4 selectivity in controlled triflation and hence cannot be used here.[19] Compound **5** in turn can be obtained by a regioselective Nap protection of 3-OH of the corresponding L-fucosyl triol. The Nap group was placed at the O3 of L-pneumosamine, the connecting point of the RU, as a temporary protecting group owing to its selective removal from fully protected pentasaccharide **2** using DDQ[23] during chain elongation of the RU. The tetrasaccharide acceptor **3** can be assembled in a stepwise manner from the reducing end by the stereocontrolled installation of 1,2-*cis*-glycosidic linkages, first between 3-OH of orthogonally functionalized D-bacillosamine acceptor **6** and L-fucosamine donor **7**, followed by deacetylation and reiteration of glycosylation with donor **7** and deacetylation sequence, two times. Donor **7** was designed with a 4-*O*-acyl group as a temporary protecting group to provide anchimeric assistance in favor of α-stereoselective glycosylation[16] and later for the generation of a 4-OH acceptor in di-, tri-, and tetrasaccharide, respectively. L-Fucosamine donor **7** can be made from L-rhamnosyl 2,4-diol **8** via sequential S_N2 displacement of the corresponding L-rhamnosyl bis-triflate. The poor nucleophilicity of the L-fucosamine 4-OH acceptor was alleviated by placement of an electron-donating benzyl group at O3. The D-bacillosamine acceptor **6** could be synthesized by reduction of the C4-azide in compound **9** followed by coupling of the so-formed C4 amino group with the known[13] 3*S*-hydroxybutyryl acid derivative **10**. D-Bacillosamine derivative **9** can be synthesized from the known D-fucosamine derivative **11**[17,18] by conversion of C2-azide to NHTCA group followed by C4 inversion via azide displacement of C4-triflate and stereoselective coupling of thioglycoside donor with the linker acceptor 3-benzyloxycarbonylamino (NHCbz) propanol.

With this retrosynthetic plan, we began with the synthesis of the differentially functionalized D-bacillosamine acceptor **6**. Recently, Codée and co-workers have reported a synthesis of orthogonally protected D-bacillosamine derivatives via azidoselenation of D-fucal through a stepwise process.[24] For the synthesis of D-bacillosamine acceptor **6**, which bears three differentially protected amino groups, we started with the known D-fucosamine derivative **11**,[17,18] which could be readily prepared from D-rhamnose thioglycoside via our one-pot double-displacement methodology. As shown in Scheme 2a, compound **11** was subjected to azide reduction using Zn, AcOH conditions followed by selective protection of amine using trichloroacetyl chloride to obtain D-fucosamine derivative

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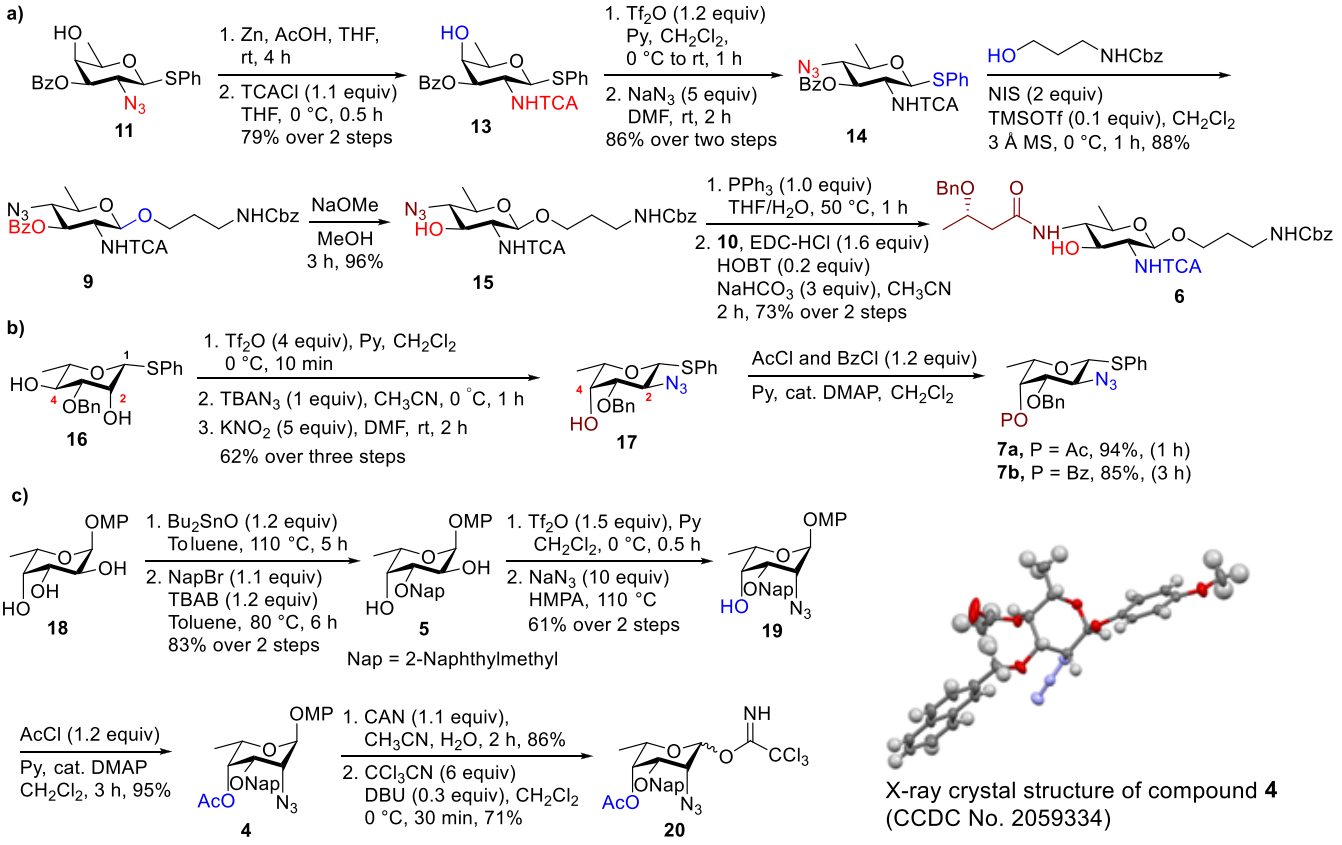
Scheme 2. Synthesis of Orthogonally Protected Rare Sugar Building Blocks



13 in 79% yield over two steps. In comparison, Staudinger conditions gave **13** in 54% yield. Subsequent triflation of 4-OH in **13** using triflic anhydride in pyridine and concomitant nucleophilic displacement of the formed C4-triflate with sodium azide afforded **14** in 86% yield over two steps. Glycosylation of thioglycoside donor **14** with Cbz protected amino propanol linker acceptor, at 0 °C under NIS/TMSOTf activation conditions furnished the desired β-linked glycoside **9** in 88% yield. The C3-OBz group in compound **9** was removed under Zemplén conditions to obtain alcohol **15** (96%). Using Staudinger reduction, the azide group was reduced to amine and subjected to coupling with acid **10** (EDC-HCl, HOBt, $NaHCO_3$) to give C4-amide acceptor **6** in 73% yield over two steps.

L-Fucosamine building blocks **7a** and **7b** were synthesized by a modification of our established protocol involving a highly regioselective one-pot S_N2 displacements of 3-OBz-protected L-rhamnosyl 2,4-bistriflates (Scheme 2b).[16,19] Previously, we had used the corresponding 3-OBz derivative as the substrate and the 4-OTf was either displaced by $TBANO_2$[19] or by intramolecular attack of C3-OBz group followed by water mediated ring opening of the so formed cyclic orthoester[16] to form 3-OBz and 4-OBz derivatives of L-fucosamine, respectively. Here, we explored 3-OBn derivative of L-rhamnose and found that it works well in the sequential one-pot S_N2 protocol using cheaply available KNO_2 as the nucleophile. Accordingly, the known L-rhamnosyl diol **16**[25] upon triflation was subjected to selective C-2 OTf displacement by azide using $TBAN_3$ (1 equiv) in CH_3CN at 0 °C followed by treatment with KNO_2 for C-4 OTf displacement to afford L-fucosamine compound **17** in 62% yield over three steps, after a single chromatographic purification. The C4-OH group of compound **17** was acylated by using AcCl or BzCl in pyridine, DMAP (cat.) conditions to furnish the L-fucosamine thioglycoside donors **7a** and **7b** in 94% and 85% yields, respectively.

Only a few methods are reported for the synthesis of rare amino L-pneumosamine derivatives in low yields.[26] Seeberger and co-workers tactically employed azidoselenation of L-fucal to generate a mixture of both L-fucosamine (52%) and L-pneumosamine (<25%).[27] We recently reported synthesis of 3-OBz derivative of L-pneumosamine from L-fucose via a regioselective C-2 triflation followed by azide inversion as a key step.[19] Synthesis of 3-O-Nap-protected L-pneumosamine building block **20** from the L-fucose derivative **18**[19] is shown in Scheme 2c. Triol **18** was regioselectively protected at the O3 position as a 2-naphthylmethyl (Nap) ether by using Bu_2SnO in toluene at 110 °C followed by treatment with 2-naphthylmethyl bromide and TBAB to furnish 2,4-diol **5** in 83% yield over two steps. Diol **5** upon regioselective triflation by using 1.5 equiv of Tf_2O and pyridine in CH_2Cl_2 solvent at 0 °C gave exclusively C2-OTf, which on treatment with NaN_3 (portionwise addition over 6 h) in HMPA at 110 °C afforded the desired L-pneumosamine compound **19** in 61% yield over two steps. Use of DMF in place of HMPA gave **19** in 52% yield. Compound **19** on acetylation using AcCl and pyridine gave fully protected L-pneumosamine derivative **4** (95%). The structure of compound **4** was further confirmed by X-ray single-crystal analysis (Scheme 2) which showed that **4** is present in $^1C_4$ conformation. Compound **4** was subjected to the cleavage of *p*-methoxyphenyl group using CAN/CH_3CN condition (86%), which on further treatment with CCl_3CN,

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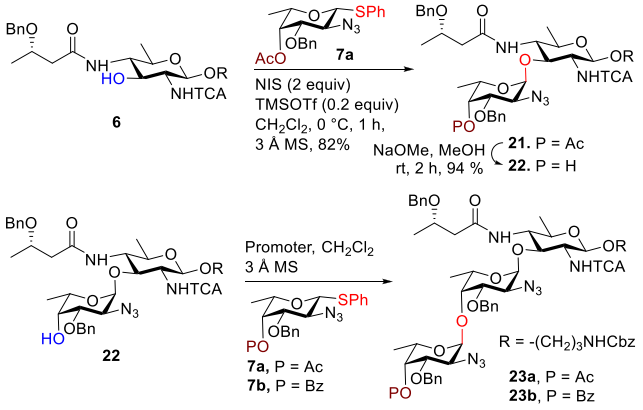
DBU in CH_2Cl_2 furnished L-pneumosamine imidate donor **20** in 71% yield.

After having all the rare sugar building blocks in hand, we went ahead for the glycosylation reactions (Table 1). L-

Table 1. Synthesis of Trisaccharide 23

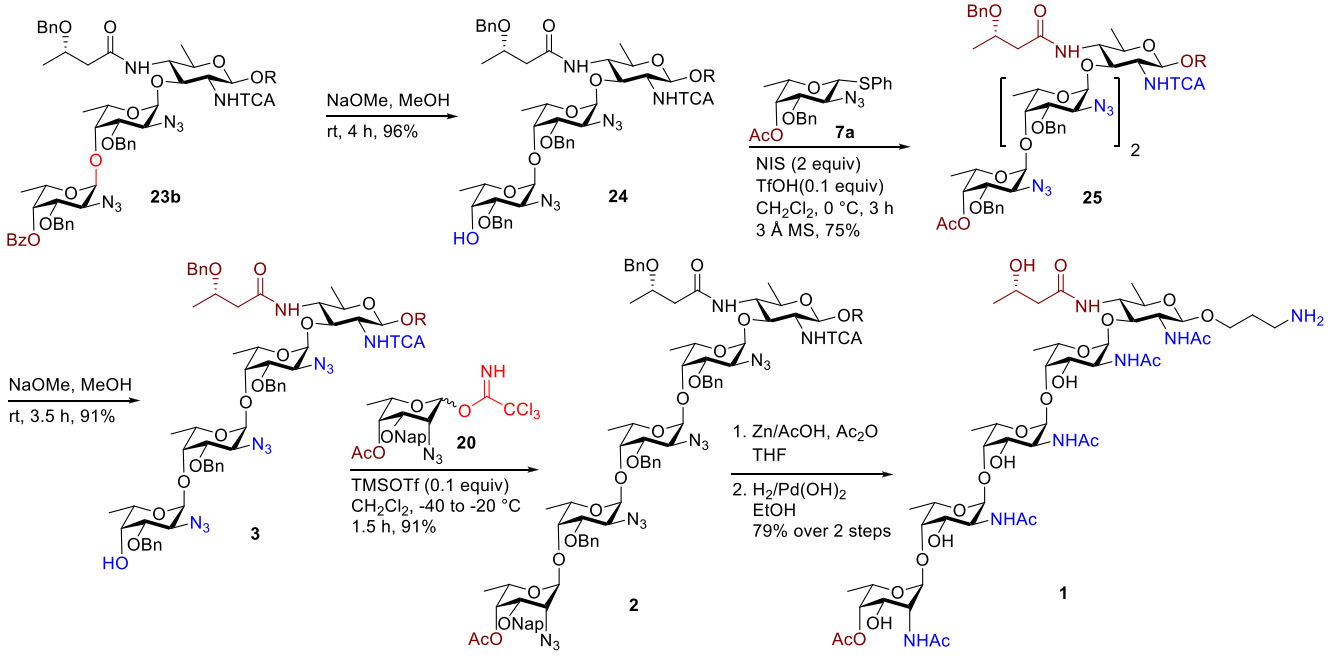


entry	donor, P =	promoter	temp (°C)	yield (%) (α/β ratio)
1	Ac	NIS, TMSOTf, CH_2Cl_2	0	51 (8.5:1.5)
2	Ac	NIS, TfOH, CH_2Cl_2	0	76 (9:1)
3	Ac	NIS, TfOH, CH_2Cl_2	−30	73 (9:1)
4	Ac	NIS, TfOH, CH_2Cl_2	−60	79 (9:1)
5	Bz	NIS, TfOH, CH_2Cl_2	0	72 (1:0)

Fucosamine thioglycoside donor **7a** on glycosylation using NIS and TMSOTf as a promoter in dry CH_2Cl_2 condition with acceptor **6** at 0 °C afforded α-linked disaccharide **21** in 82% yield, exclusively. The characteristic NMR signals (^{1}H NMR δ 4.88 (d, J = 3.3 Hz, 1H, H-1′), 4.83 (d, J = 8.2 Hz, 1H, H-1), ^{13}C NMR δ 99.1 (C-1) and 98.6 (C-1′) ppm) confirmed the formation of α-linked disaccharide **21**. Removal of the O4 acetyl group in disaccharide **21** by using NaOMe/methanol conditions furnished the disaccharide acceptor **22** (94%). The concomitant glycosylation of L-fucosamine donor **7a** with disaccharide acceptor **22** required tuning of the conditions for obtaining exclusive selectivity. The reaction conditions and results are summarized in Table 1. First, glycosylation of **7a** and **22** using NIS/TMSOTf conditions furnished trisaccharide **23a** in 51% yield with 8.5:1.5 α/β selectivity. To improve the yield, we changed the promoter from TMSOTf to TfOH. Under these conditions (Table 1, entry 2) we obtained trisaccharide **23a** in 76% yield and with marginally improved selectivity of α/β 9:1 (entry 2) at 0 °C. Further reducing the reaction temperature to −60 °C resulted in a slightly better yield of 79%; however, the selectivity remained the same (entry 4). Since it was not possible to separate the α/β isomers by column chromatography, it was necessary to get exclusive selectivity in this glycosylation. In order to increase the steric crowding to discourage the approach of the acceptor from bottom face,[16] we replaced the 4-OAc group in L-fucosamine donor **7a** with the 4-OBz group to construct **7b**. Gratifyingly, glycosylation of donor **7b** with disaccharide acceptor **22** using NIS/TfOH, CH_2Cl_2 condition furnished exclusively α-linked trisaccharide **23b** in 72% yield (entry 5).

Synthesis of target molecule **1** from trisaccharide **23b** is delineated in Scheme 3. Deprotection of the benzoate group in **23b** using NaOMe/methanol conditions furnished trisaccharide acceptor **24** in 96% yield. Glycosylation of thiofucoside donor **7a** under NIS/TfOH, 0 °C activation conditions with trisaccharide acceptor **24** afforded the desired α-linked tetrasaccharide **25**, exclusively, in 75% yield. Further deacetylation of compound **25** by using NaOMe/MeOH generated tetrasaccharide acceptor **3**, which upon subsequent glycosylation with L-pneumosamine imidate donor **20** using TMSOTf promoter over the temperature range of −40 °C to −20 °C afforded the fully protected pentasaccharide **2** in 91% yield as a single isomer. The α-stereochemistry of the newly formed glycosidic linkage was confirmed by measuring $^1J_{C-H}$

Scheme 3. Synthesis of Target Molecule 1



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coupling constant of the anomeric carbon of L- pneumosamine unit ($^{13}C\{^{1}H\}$ δ 100.6 (J = 172.5 Hz) ppm) (See SI for details). Finally, pentasaccharide **2** was treated with an excess amount of zinc powder in acetic acid and acetic anhydride for conversion of azide and NHTCA to NHAc followed by hydrogenolysis using H_2, 20 wt % $Pd(OH)_2/C$ in EtOH and subsequent purification using Sephadex G25 gel column to furnish target molecule **1** in 79% yield over two steps.

In conclusion, we have accomplished the first total synthesis of the linker attached pentasaccharide repeating unit **1** from *P. shigelloides* strain 302-73 (serotype O1). All densely functionalized rare amino sugars were synthesized expediently, and their stepwise glycosylation afforded pentasaccharide with excellent α-selectivity. The total synthesis of **1** was completed via the longest linear sequence of 27 steps in an overall yield of 3%. The target molecule with an aminopropyl linker at the reducing end will permit conjugation to a carrier protein for further immunological studies.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02239.

Experimental procedures, characterization data of synthetic compounds, and 1D and 2D NMR spectra (PDF)

Accession Codes

CCDC 2059334 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

†S.B. and B.K.G. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) *WHO fact sheets: diarrhoeal diseases*. https://www.who.int/news-room/fact-sheets/detail/diarrhoeaL-disease.

(2) Stock, I. *Plesiomonas shigelloides*: an emerging pathogen with unusual properties. *Rev. Med. Microbiol.* **2004**, *15*, 129−139.

(3) Brenden, R. A.; Miller, M. A.; Janda, J. M. Clinical disease spectrum and pathogenic factors associated with *Plesiomonas shigelloides* infections in humans. *Clin. Infect. Dis.* **1988**, *10*, 303−316.

(4) Mandal, B. K.; Whale, K.; Morson, B. C. Acute colitis due to *Plesiomonas shigelloides*. *BMJ.* **1982**, *285*, 1539−1540.

(5) Billiet, J.; Kuypers, S.; Van Lierde, S.; Verhaegen, J. *Plesiomonas shigelloides* meningitis and septicaemia in aneonate: report of a case and review of the literature. *J. Infect.* **1989**, *19*, 267−271.

(6) McNeeley, D.; Ivy, P.; Craft, J. C.; Cohen, I. *Plesiomonas*: biology of organism and diseases in children. *Pediatr. Infect. Dis.* **1984**, *3*, 176−181.

(7) Janda, J. M.; Abbott, S. L.; McIver, C. *Plesiomonas shigelloides* revisited. *Clin. Microbiol. Rev.* **2016**, *29*, 349−374.

(8) Tsukamoto, T.; Kinoshita, Y.; Shimada, T.; Sakazaki, R. Two epidemics of diarrhoeal disease possibly caused by *Plesiomonas shigelloides*. *J. Hyg.* **1978**, *80*, 275−280.

(9) Fischer, K.; Chakraborty, T.; Hof, H.; Kirchner, T.; Wamsler, O. Pseudoappendicitis caused by *Plesiomonas shigelloides*. *J. Clin. Microbiol.* **1988**, *26*, 2675−2677.

(10) Tsugawa, H.; Ono, T.; Murakami, H.; Okawa, Y. Invasive phenotype and apoptosis induction of *Plesiomonas shigelloides* P-1 strain to Caco-2 cells. *J. Appl. Microbiol.* **2005**, *99*, 1435−1443.

(11) Theodoropoulos, C.; Wong, T. H.; O'Brien, M.; Stenzel, D. *Plesiomonas shigelloides* enters polarized human intestinal Caco-2 Cells in an in vitro model system. *Infect. Immun.* **2001**, *69*, 2260−2269.

(12) Temitope, C. E.; Anthony, I. O. *Plesiomonas shigelloides* seventy years of systematics and taxonomy in perspective of the present-day diagnostic demands. *Res. J. Med. Sci.* **2017**, *11*, 103−113.

(13) Qin, C.; Schumann, B.; Zou, X.; Pereira, C. L.; Tian, G.; Hu, J.; Seeberger, P. H.; Yin, J. Total synthesis of a densely functionalized *Plesiomonas shigelloides* serotype 51 aminoglycoside trisaccharide antigen. *J. Am. Chem. Soc.* **2018**, *140*, 3120−3127.

(14) Pieretti, G.; Corsaro, M. M.; Lanzetta, R.; Parrilli, M.; Vilehes, S.; Merino, S.; Tomas, J. M. Structural studies of the O-chain poly saccharide from *Plesiomonas shigelloides* strain 302−73 (Serotype O1). *Eur. J. Org. Chem.* **2009**, 1365−1371.

(15) (a) Werz, D. B.; Ranzinger, R.; Herget, S.; Adibekian, A.; von der Lieth, C.-W.; Seeberger, P. H. Exploring the structural diversity of mammalian carbohydrates ("glycospace") by statistical databank analysis. *ACS Chem. Biol.* **2007**, *2*, 685−691. (b) Adibekian, A.; Stallforth, P.; Hecht, M.-L.; Werz, D. B.; Gagneux, P.; Seeberger, P. H. Comparative bioinformatics analysis of the mammalian and bacterial glycomes. *Chem. Sci.* **2011**, *2*, 337−344.

(16) Behera, A.; Rai, D.; Kulkarni, S. S. Total syntheses of conjugation-ready trisaccharide repeating units of *Pseudomonas aeruginosa* O11 and *Staphylococcus aureus* type 5 capsular poly-saccharide for vaccine development. *J. Am. Chem. Soc.* **2020**, *142*, 456−467.

(17) Emmadi, M.; Kulkarni, S. S. Synthesis of orthogonally protected bacterial, rare-sugar and D-glycosamine building blocks. *Nat. Protoc.* **2013**, *8*, 1870−1879.

(18) Emmadi, M.; Kulkarni, S. S. Expeditious synthesis of bacterial, rare sugar building blocks to access the prokaryotic glycome. *Org. Biomol. Chem.* **2013**, *11*, 3098−3102.

(19) Sanapala, S. R.; Kulkarni, S. S. Expedient route to access rare deoxy amino L-sugar building blocks for the assembly of bacterial glycoconjugates. *J. Am. Chem. Soc.* **2016**, *138*, 4938−4947.

(20) (a) Emmadi, M.; Kulkarni, S. S. Total synthesis of the bacillosamine containing α-L-serine linked trisaccharide of *Neisseria meningitides*. *Carbohydr. Res.* **2014**, *399*, 57−63. (b) Podilapu, A. R.; Kulkarni, S. S. First synthesis of *Bacillus cereus* Ch HF-PS Cell wall trisaccharide repeating unit. *Org. Lett.* **2014**, *16*, 4336−4339. (c) Podilapu, A. R.; Kulkarni, S. S. Total synthesis of repeating unit of *O*-Polysaccharide of *Providencia alcalifaciens* O22 via one-pot

glycosylation. *Org. Lett.* **2017**, *19*, 5466−5469. (d) Emmadi, M.; Kulkarni, S. S. Synthesis of rare deoxy amino sugar building blocks enabled the total synthesis of a polysaccharide repeating unit analogue from the LPS of *Psychrobacter cryohalolentis* K5T. *J. Org. Chem.* **2018**, *83*, 14323−14337. (e) Ghotekar, B. K.; Podilapu, A. R.; Kulkarni, S. S. Total synthesis of the lipid-anchor-attached core trisaccharides of lipoteichoic acids of *Streptococcus pneumoniae* and *Streptococcus oralis* Uo5. *Org. Lett.* **2020**, *22*, 537−541. (f) Pathan, E. K.; Ghosh, B.; Podilapu, A. R.; Kulkarni, S. S. Total synthesis of the repeating unit of Bacteroides fragilis Zwitterionic polysaccharide A1. *J. Org. Chem.* **2021**, *86*, 6090−6099.

(21) (a) Zhang, Q.; Gimeno, A.; Santana, D.; Wang, Z.; Valdés-Balbin, Y.; Rodríguez-Noda, L. M.; Hansen, T.; Kong, L.; Shen, M.; Overkleeft, H. S.; Vérez-Bencomo, V.; van der Marel, G. A.; Jiménez-Barbero, J.; Chiodo, F.; Codée, J. D. C. Synthetic, zwitterionic Sp1 oligosaccharides adopt a helical structure crucial for antibody interaction. *ACS Cent. Sci.* **2019**, *5*, 1407−1416. (b) Wang, P.; Huo, C.-X.; Lang, S.; Caution, K.; Nick, S. T.; Dubey, P.; Deora, R.; Huang, X. Chemical synthesis and immunological evaluation of a pentasaccharide bearing multiple rare sugars as a potential antipertussis vaccine. *Angew. Chem., Int. Ed.* **2020**, *59*, 6451−6458.

(22) Komarova, B. S.; Tsvetkov, Y. E.; Nifantiev, N. E. Design of α-selective glycopyranosyl donors relying on remote anchimeric assistance. *Chem. Rec.* **2016**, *16*, 488−506.

(23) (a) Xia, J.; Abbas, S. A.; Locke, R. D.; Piskorz, C. F.; Alderfer, J. L.; Matta, K. L. Use of 1,2-dichloro 4,5-dicyanoquinone (DDQ) for cleavage of the 2-naphthylmethyl (NAP) group. *Tetrahedron Lett.* **2000**, *41*, 169−173. (b) Liao, W.; Locke, R. D.; Matta, K. L. Selectin ligands: 2,3,4-tri-O-acetyl-6-O-(2-naphthyl)methyl (NAP) α-D-galactopyranosyl imidate as a novel glycosyl donor for the efficient total synthesis of branched mucin core 2-structure containing the NeuAcα2,3(SO_3Na-6)Galβ1,3GalNAcα sequence. *Chem. Commun.* **2000**, 369−370.

(24) van Mechelen, J.; Voorneveld, J.; Overkleeft, H. S.; Filippov, D. V.; van der Marel, G. A.; Codée, J. D. C. Synthesis of orthogonally protected and functionalized bacillosamines. *Org. Biomol. Chem.* **2020**, *18*, 2834−2837.

(25) Crich, D.; Picione, J. Direct synthesis of the β-L-rhamnopyranosides. *Org. Lett.* **2003**, *5*, 781−784.

(26) Panek, J. S.; Zhang, J. Diastereoeelectivity in the osmium tetraoxide promoted dihydroxylation of chiral (*E*)-crotylsilanes: asymmetric synthesis of silyl-functionalized γ-lactones. *J. Org. Chem.* **1993**, *58*, 294−296.

(27) Lisboa, M. P.; Khan, N.; Martin, C.; Xu, F.-F.; Reppe, K.; Geissner, A.; Govindan, S.; Witzenrath, M.; Pereira, C. L.; Seeberger, P. H. Semisynthetic glycoconjugate vaccine candidate against *Streptococcus pneumoniae* serotype 5. *Proc. Natl. Acad. Sci. U. S. A.* **2017**, *114*, 11063.

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