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De Novo Asymmetric Synthesis of Anthrax Tetrasaccharide and Related Tetrasaccharide

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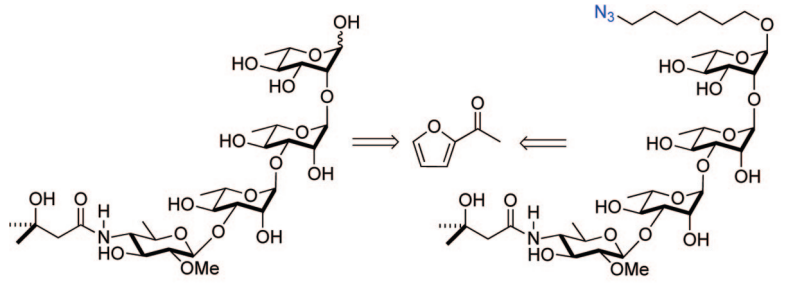

A de novo asymmetric approach to the natural product anthrax tetrasaccharide **1** and an analogue **2** with an anomeric hexyl azide group has been developed from acetylfuran. The construction of the tetrasaccharide was achieved by a traditional [3 + 1] glycosylation strategy. An iterative diastereoselective palladium-catalyzed glycosylation, Luche reduction, diastereoselective dihydroxylation, and regioselective acylation were employed for the assembly of the L-*rhamno*-trisaccharide building block. The anthrose building block also required a palladium-catalyzed azide allylation and a triflate inversion to set the *gluco*-stereochemistry in addition to Luche reduction and dihydroxylation.

Introduction

Bacillus anthracis, one of the most well-known members of the Bacillaceae family, is a Gram-positive, spore-forming bacterium which when inhaled causes anthrax, a fatal infectious disease in humans and other mammals.[1] Like most bacteria of *Bacillus* species, *B. anthracis* forms endospores. The mature spore exhibits high resistance to harsh chemicals, desiccation, extreme temperatures, radiation, and physical damage, which allows the spore to persist in soil for many years.[2] These same *Bacillus anthracis* properties make for the potential for its use as a biological weapon. Therefore, it is highly desirable to develop an effective and inexpensive vaccine as well as a method to detect this dangerous bacterium.

Anthrax tetrasaccharide **1** (Figure 1) was isolated from the surface of the exosporium glycoprotein BC1A of *B. anthracis* by Turnbough, who also elucidated its structure in 2004.[3] The structure of anthrax tetrasaccharide **1** consists of three L-rhamnose sugars and a D-sugar, called anthrose, which is unique to *B. anthracis* and not found in other spores *Bacillus* species. Because of its unique structure and the general resistance to evolutionary change of carbohydrates, the anthrax tetrasaccharide **1** has become a target for anthrax detection. Similarly, carrier protein conjugates of the anthrax tetrasaccharide are desired for anthrax vaccine development.[4] Since the first

(1) (a) Mock, M.; Fouet, A. *Annu. Rev. Microbiol.* **2001**, *55*, 647–671. (b) Sylvestre, P.; Couture-Tosi, E.; Mock, M. *Mol. Microbiol.* **2002**, *45*, 169–178.

(2) (a) Nicholson, W. L.; Munakata, N.; Horneck, G.; Melosh, H. J.; Setlow, P. *Microbiol. Mol. Biol. Rev.* **2000**, *64*, 548–572.

(3) Daubenspeck, J. M; Zeng, H.; Chen, P.; Dong, S.; Steichen, C. T; Krishna, N. R.; Pritchard, D. G.; Turnbough, C. L., Jr *J. Biol. Chem.* **2004**, *279*, 30945–30953.

(4) Tamborrini, M.; Werz, D. B.; Frey, J.; Pluschke, G.; Seeberger, P. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 6581–6582.

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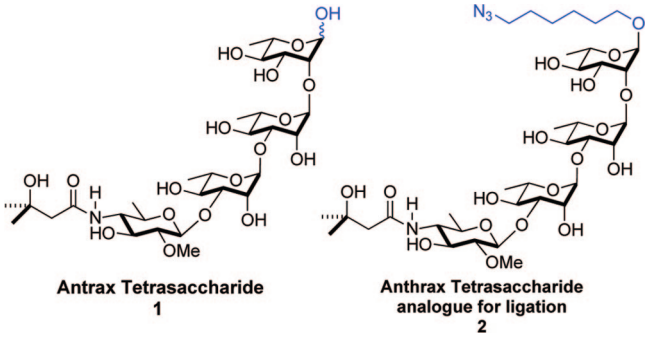
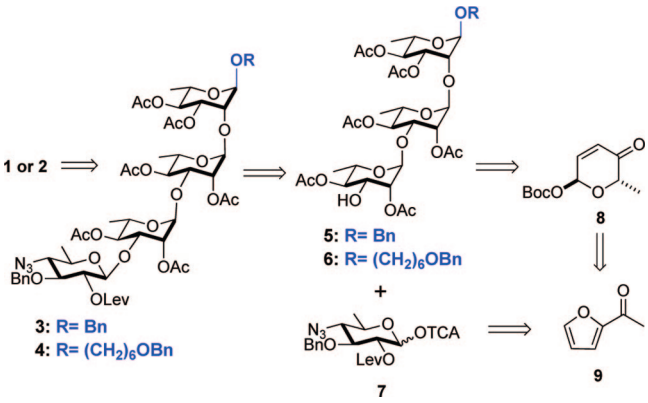


FIGURE 1. Anthrax tetrasaccharide **1** and analogue **2**.

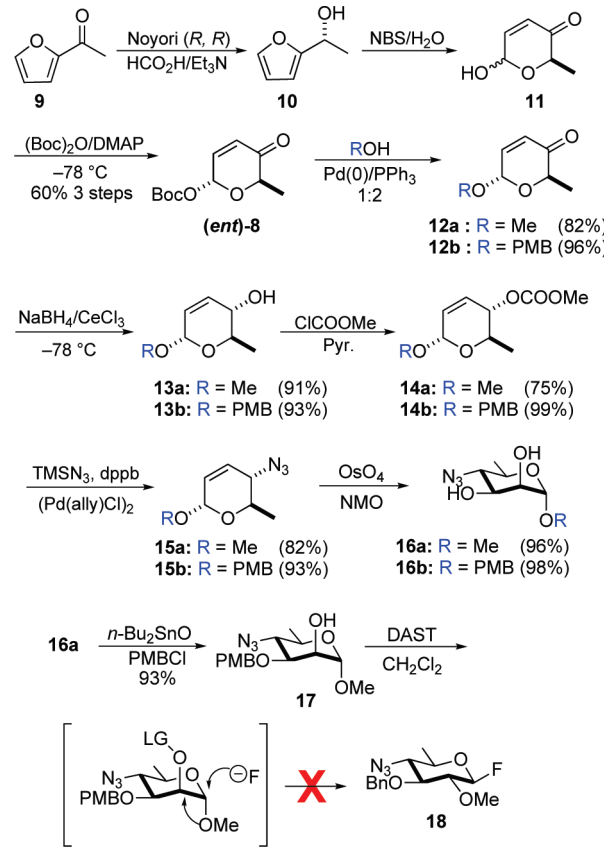
SCHEME 1. Retrosynthetic Analysis of Anthrax Tetrasaccharide 1 and Analogue 2



synthesis of an anthrax tetrasaccharide analogue by Seeberger,[5] several carbohydrate approaches to the anthrax tetrasaccharide and related tri- and pentasaccharides have been reported.[6] These routes featured the traditional carbohydrate approaches to draw their stereochemistry from the known rare D-fucose, D-galactose, or less common sugar L-rhamnose as a precursor. Previously, we have been investigating a de novo asymmetric methodology and its application to synthesize mono-, di-, and oligosaccharides via palladium-catalyzed reaction.[7] Herein, we describe the full account of our successful de novo asymmetric synthesis of anthrax tetrasaccharide **1** as well as the anthrax tetrasaccharide analogue **2**.[8] The terminal hexyl azide group of tetrasaccharide analogue **2** could serve as a point of attachment (e.g., carrier protein conjugation for vaccine development). This de novo asymmetric strategy features iterative use of palladium-catalyzed glycosylation and starts from commercially available and inexpensive acetylfuran.

Our de novo approach to anthrax tetrasaccharide and its analogue is outlined in Scheme 1. We envisioned the anthrax tetrasaccharides **1** or **2** could be prepared from tetrasaccharides **3** or **4** respectively, which in turn could be derived from the glycosylation of trisaccharides **5** or **6** with imidate **7**. The trisaccharides **5** and **6** could be assembled from pyranone **8** building block via iterative use of diasteroselective palladium-catalyzed glycosylation, Luche reduction, and Upjohn dihydroxylation. Eventually, the pyranone **8** and its enantiomer could be obtained from the achiral starting material acetylfuran **9** through asymmetric Noyori reduction and Achmatowicz oxidative ring expansion.

SCHEME 2. First-Generation Approach to Anthrose Monosaccharide Building Block 18



Results and Discussion

Our approach to the anthrose monosaccharide building block began with our efforts to introduce the D-stereochemistry of the anthrose sugar, which could be derived from the (*R*)-furyl alcohol **10**. Previously, we have shown that either the (*R*)- or (*S*)-furyl alcohol could be readily derived by an asymmetric Noyori reduction[9] of commercially available starting material acetylfuran **9** (Scheme 2). Noyori reduction of acetylfuran **9** produced the enantiomerically pure (>96% ee)[10] furfuryl alcohol **10**, which was subsequently exposed to oxidative rearrangement under typical Achmatowicz conditions (NBS/H_2O)[11] resulting in the formation of a ring-expanded hemiacetal **11**. The anomeric

(5) Werz, D. B.; Seeberger, P. H. *Angew. Chem., Int. Ed.* **2005**, *44*, 6315–6318.

(6) (a) Adamo, R.; Saksena, R.; Kovac., P. *Carbohydr. Res.* **2005**, *340*, 2579–2582. (b) Saksena, R.; Adamo, R.; Kovac, P. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 615–617. (c) Adamo, R.; Saksena, R.; Kovac, P. *Helv. Chim. Acta* **2006**, *89*, 1075–1089. (d) Mehta, A. S.; Saile, E.; Zhong, W.; Buskas, T.; Carlson, R.; Kannenberg, E.; Reed, Y.; Quinn, C. P.; Boons, G.-J. *Chem. Eur. J.* **2006**, *12*, 9136–9149. (e) Crich, D.; Vinogradova, O. *J. Org. Chem.* **2007**, *72*, 6513–6520. (f) Werz, D. B.; Adibekian, A.; Seeberger, P. H. *Eur. J. Org. Chem.* **2007**, 1976–1982.

(7) (a) Babu, R. S.; O'Doherty, G. A. *J. Am. Chem. Soc.* **2003**, *125*, 12406–12407. (b) Babu, R. S.; Zhou, M.; O'Doherty, G. A. *J. Am. Chem. Soc.* **2004**, *126*, 3428–3429.

(8) A portion of this work was originally communicated; see:(a) Guo, H.; O'Doherty, G. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 5206–5208.

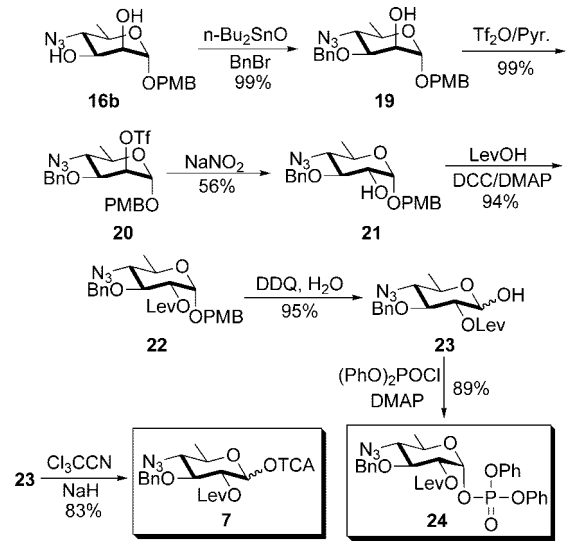
(9) (a) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521–2522. (b) Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40–73.

(10) The absolute stereochemistry and the level of enantioexcess of **10** and its enantiomer *ent*-**10** were determined by the method of Mosher; see: (a) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143–2147. (b) Yamaguchi, S.; Yasuhara, F.; Kabuto, K. T. *Tetrahedron* **1976**, *32*, 1363–1367. Similarly, the optical activity for these products was consistent with that reported in the literature; see: (d) Drueckhammer, D. G.; Barbas, C. F., III; Nozoki, K.; Wong, C.-H.; Wood, C. Y.; Ciufolini, M. A *J. Org. Chem.* **1993**, *58*, 4511–4512.

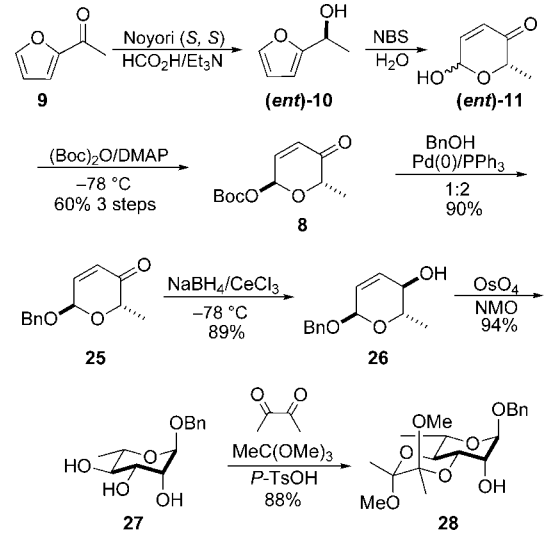
alcohol of hemiacetal **11** was converted to Boc-pyranone *ent*-**8** with a diastereoselectivity of 3:1 (α/β) by treatment with Boc_2O at −78 °C.[12] It is worth noting that this route provides Boc-pyranone *ent*-**8** in 60% overall yield (three steps) with only one chromatographic purification and this route is also reliable on scales as large as 100 g for both Boc-pyranone *ent*-**8** and its enantiomer **8**. Palladium-catalyzed glycosylation ($Pd(0)/PPh_3$, 1:2) of the pyranone *ent*-**8** with either methanol or *p*-methoxybenzyl alcohol afforded pyranones **12a** and **12b** as single diastereomers, both in excellent yields (82% and 96%, respectively). Diastereoselective Luche reduction ($NaBH_4/CeCl_3$)[13] of both **12a** and **12b** gave allylic alcohols **13a** and **13b**, which were treated with methyl chloroformate in the presence of a catalytic amount of DMAP to deliver allylic carbonates **14a** and **14b** in good yields for the two steps (68% and 92%, respectively). The methyl carbonates **14a** and **14b** underwent Pd-catalyzed azide allylation to regio- and stereoselectively generate allylic azide products **15a** and **15b** ($TMSN_3$, $(allyl\text{-}PdCl)_2$/DPPB, 82% and 93%, respectively).[14] Exposing the allylic azides **15a** and **15b** to the Upjohn conditions (OsO_4/NMO)[15] afforded the diols **16a** and **16b** with *manno*-stereochemistry in excellent yields (96% and 98%, respectively). Regioselective protection of the equatorial hydroxyl group of **16a** yielded PMB-ether **17** via a tin acetal intermediate (93%).[16] Finally, we attempted to prepare the anthrose monosaccharide precursor with an anomeric floride by employing the procedure developed by Nicolaou.[17] Unfortunately, we did not observe any sign of desired product **18**. Thus, we turned our attention to an alternative approach to prepare an anthrose monosaccharide building block (Scheme 3).

The alternative approach to anthrose monosaccharide building block started from *ent*-**8**. Tin-mediated selective protection of the equatorial hydroxyl group at the C-4 of **16b** afforded the benzyl ether **19** in excellent yield (99%). To install the *gluco*-stereochemistry of the anthrose precursor **21** from **19**, an inversion of the C-2 axial alcohol was required. Unfortunately, all efforts to directly convert **19** to **22** by a Mitsunobu inversion were unsuccessful. Instead, the free hydroxyl group of **19** was treated with triflic anhydride and pyridine to form triflate **20**, which was subsequently subjected to S_N2-type displacement ($NaNO_2$/DMF) to provide equatorial alcohol **21** in 56% yield.[6a,18] Esterification of the C-2 alcohol in **21** (LevOH/DCC/DMAP), followed by an oxidative PMB deprotection (DDQ/H_2O), resulted in anomeric alcohol **23** in good yield (85%, two steps).

SCHEME 3. Syntheses of Anthrose Monosaccharide Building Blocks 5 and 24



SCHEME 4. Enantioselective Synthesis of Monosaccharide Ley-spiroketal 28



Eventually, the two glycosyl donors imidate **7** and phosphate **24** were synthesized by treatment of the anomeric alcohol of **23** with trichloroacetonitrile (40% NaH) and diphenyl chlorophosphate (2 equiv of DMAP), respectively (**7**: 83%, **24**: 89%).

With the D-anthrose monosaccharide precursor in hand, we proceeded to the synthesis of L-*rhamno*-trisaccharide building block. The assembly of L-*rhamno*-monosaccharide moiety **28** (Scheme 4) also started from the inexpensive acetylfuran **9**. Noyori asymmetric reduction of acetylfuran followed by Achmatowicz oxidative rearrangement afforded hemiacetal *ent*-**11**, which was acylated with Boc_2O to provide Boc-pyranone **8** (60%, three steps). Exposure of the Boc-pyranone and benzyl alcohol to our palladium-catalyzed glycosylation conditions (0.25% Pd(0)/ 0.5% PPh_3) generated the benzyl pyranone **25** in excellent yield (90%) and with complete retention of stereochemistry. Diastereoselective reduction of the ketone **25** via Luche procedures ($NaBH_4/CeCl_3$) gave allylic alcohol **26** (89%) which was subsequently dihydroxylated using Upjohn conditions to form *rhamno*-stereochemistry triol **27** in excellent yield (94%). Selective protection of the C-3/C-4 diequatorial

(11) (a) Achmatowicz, O.; Bielski, R. *Carbohydr. Res.* **1977**, *55*, 165–176. For its recent use in carbohydrate synthesis, see:(b) Guo, H.; O'Doherty, G. A. *Org. Lett.* **2005**, *7*, 3921–3924.

(12) The relative stereochemistry and the level of diastereoselective induction were determined by analysis of the allylic coupling constants in the ^1H NMR spectra; see:(a) Babu, R. S.; Guppi, S. R.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 1605–1608. (b) Guppi, S. R.; O'Doherty, G. A. *J. Org. Chem.* **2007**, *72*, 4966–4969.

(13) (a) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226–2227. (b) Haukaas, M. H.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*, 401–404. (c) Abrams, J. N.; Babu, R. S.; Guo, H.; Le, D.; Le, J.; Osbourn, J. M.; O'Doherty, G. A. *J. Org. Chem.* **2008**, *73*, 1935–1940.

(14) (a) de Oliveira, R. N.; Cottier, L.; Sinou, D.; Srivastava, R. M. *Tetrahedron* **2005**, *61*, 8271–8281. (b) Guo, H.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 1609–1612. (c) Guo, H.; O'Doherty, G. A. *Tetrahedron* **2008**, *64*, 304–313.

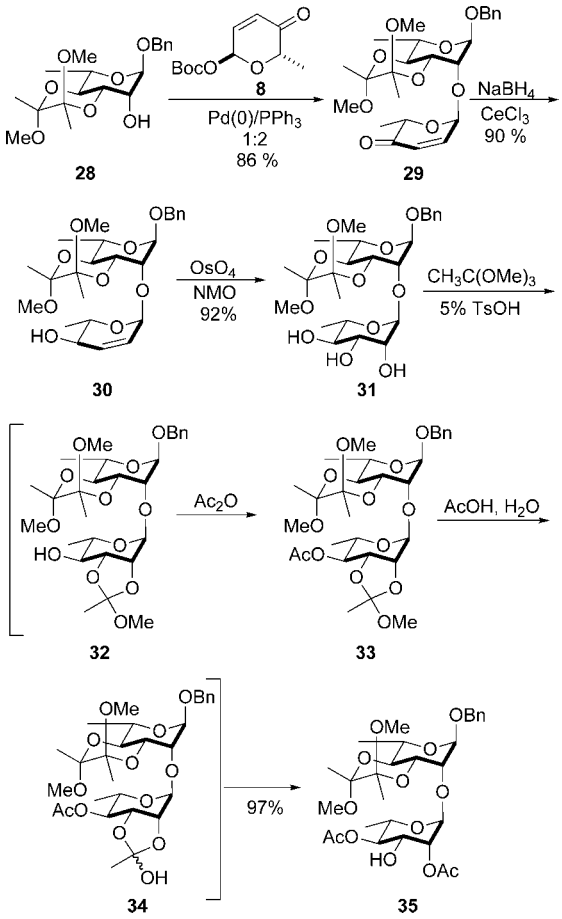
(15) (a) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *17*, 1973–1976. (b) Shan, M.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 5149–5152.

(16) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *17*, 1973−1976.

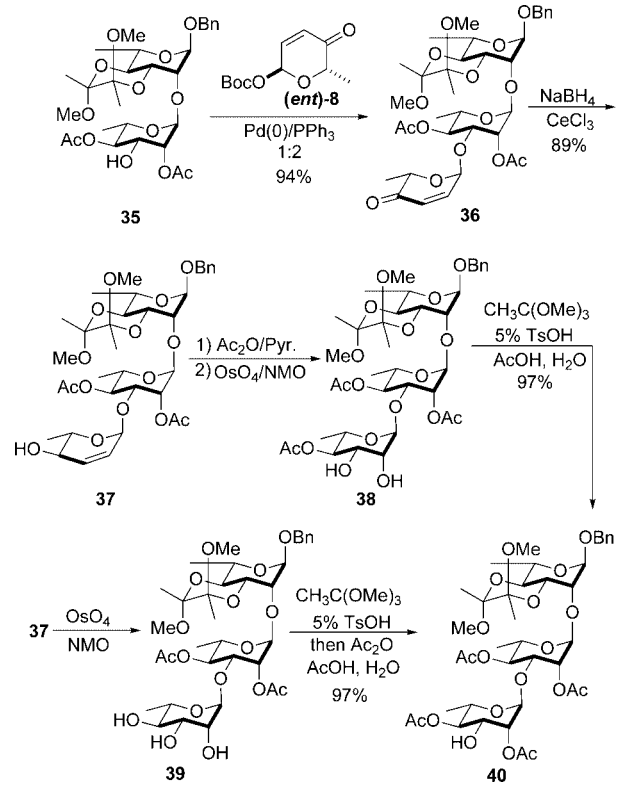
(17) Nicolaou, K. C.; Ladduwahetty, T.; Randall, J. L.; Chucholowski, A. *J. Am. Chem. Soc.* **1986**, *108*, 2466–2467.

(18) Wyn, D.; Jones, C.; Nash, R. J.; Bell, E. A.; Williams, J. M. *Tetrahedron Lett.* **1985**, *26*, 3125–3126.

SCHEME 5. Synthesis of Disaccharide 35 via Palladium-Catalyzed Glycosylation



SCHEME 6. Synthesis of Trisaccharide 40 via Palladium-Catalyzed Glycosylation



hydroxyl groups by the Ley-spiroketal procedure[19] furnished the Ley-spiroketal monosaccharide **28** in 88% yield.

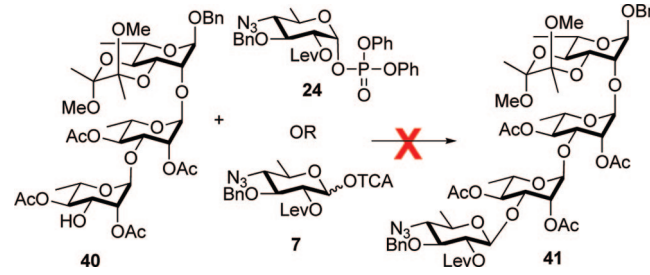
Encouraged by the successful synthesis of monosaccharide **28**, we next employed the same strategy for the synthesis of disaccharide **35** (Scheme 5). Monosaccharide **28** was glycosylated with Boc-pyranone **8** to yield the pyranone **29** as a single isomer in the presence of Pd(0) and PPh_3 (86%). Luche reduction of pyranone **29**, followed by diastereoselective dihydroxylation resulted in triol **31** in excellent overall yield (84%, two steps). The C-2/C-4 hydroxyl groups of triol **31** were protected as diacetate **35** via orthoester formation, acylation (**32** to **33**), and regioselective ring opening (**33** to **35**, via **34**) in excellent yield (97%). Specifically, the triol **31** was treated with trimethyl orthoacetate in the presence of catalytic amount of TsOH to selectively protect the C-2/C-3 *cis*-hydroxyl group to an orthoester **32**. The remaining free alcohol was converted to intermediate acetate **33** by treatment with Ac_2O. Regiospecific acidic hydrolysis of the five-membered ring orthoester **33** afforded diacetate **35** through intermediate **34**.[20]

Analogously, the tetraacetate trisaccharide **40** (Scheme 6) was prepared by a sequence of reactions involving palladium-catalyzed glycosylation, Luche reduction, Upjohn dihydroxylation, and regioselective acylation. Once again, palladium-catalyzed glycosylation of disaccharide **35** with Boc-pyranone **8** followed by Luche reduction provided allylic alcohol **37** in excellent yield (84%, two steps). The equatorial alcohol of **37** was protected with acetic anhydride to generate acetate which subsequently underwent Upjohn dihydroxylation to give diol **38** in excellent yield (93%, two steps). Finally, the trisaccharide **40** was furnished through orthoester formation and regiospecific hydrolysis of diol **38** by treatment with trimethyl orthoacetate and acetic acid (95%). The tetraacetate trisaccharide could also be synthesized by a two-step procedure. Upjohn dihydroxylation of allylic alcohol **37** followed by regioselective acylation yielded the trisaccharide **40** with excellent yield (91%).

To efficiently synthesize the tetrasaccharide **41** (Scheme 7), a traditional glycosylation approach was employed for the coupling of building blocks trisaccharide **40** and monosaccharide **7** or **24**. However, any attempt at glycosylation of trisaccharide **40** with either phosphate **24** or imidate **7** failed to form tetrasaccharide **41**; instead, the Ley-spiroketal protecting group was removed under these Lewis acidic conditions (e.g., 10% TMSOTf).

To prepare the more acid-stable glycosyl acceptor trisaccharide **5**, we decided to switch the Ley-spiroketal protecting group

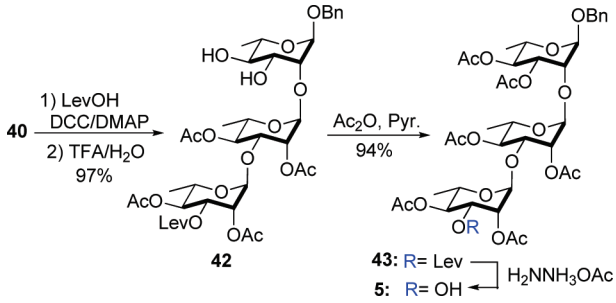
SCHEME 7. Attempted Synthesis of Tetrasaccharide 41 via Glycosylation



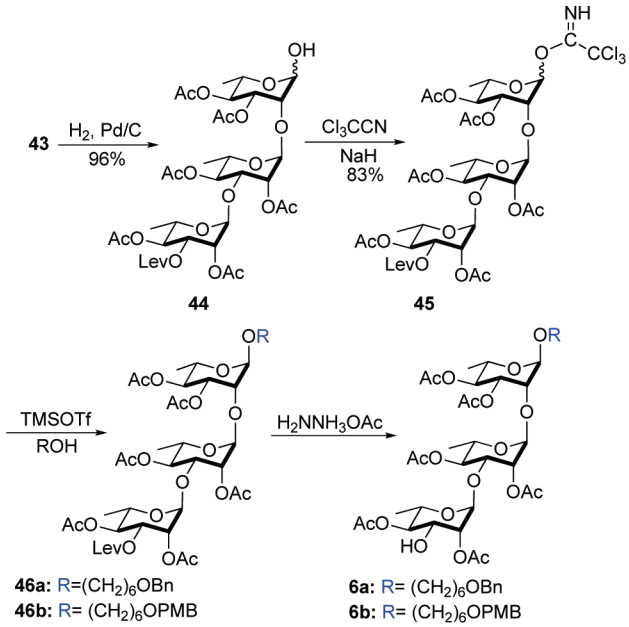
(19) (a) Ley, S. V.; Woods, M.; Zanotti-Gerosa, A. *Synthesis* **1992**, 52–54. (b) Ley, S. V.; Leslie, R.; Tiffin, P. D.; Woods, M. *Tetrahedron Lett.* **1992**, *33*, 4767–4770.

(20) (a) King, J. F.; Allbutt, A. D. *Can. J. Chem.* **1970**, *48*, 1754–1769. (b) Tsvetkov, Y. E.; Shashkov, A. S.; Knirel, Y. A.; Zahringer, U. *Carbohydr. Res.* **2001**, *335*, 221–243.

SCHEME 8. Synthesis of Trisaccharide 5



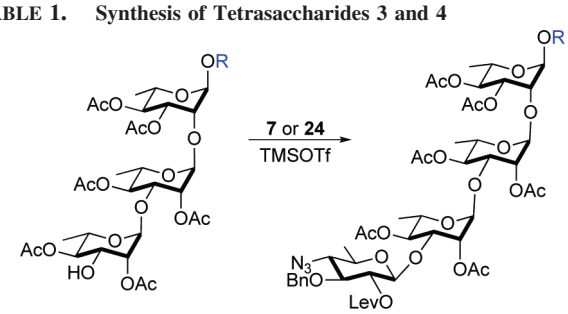
SCHEME 9. Synthesis of Trisaccharides 6a and 6b



to acetates. The equatorial alcohol of **40** (Scheme 8) was coupled with levulinic acid in presence of DCC and DMAP to produce the levulinate. Hydrolysis of the Ley-spiroketal (TFA/H_2O) provided the diol **42**, which was subsequently subjected to acylation with Ac_2O to afford hexaacetate **43**. Finally, removal of the levulinate protecting group by treatment with hydrazine acetate generated the free alcohol of trisaccharide **5** in excellent overall yield for four steps (91%). Having these acid stable protecting groups in **43** allowed for the synthesis of the trisaccharides **6a** and **6b** with the appropriate side chains for protein conjugation (Scheme 9). Hydrogenolysis of the benzyl ether of **43** formed the hemiacetal **44**, which was converted to imidate **45** at room temperature ($Cl_3CN/NaH_{(cat.)}$) in good yield (75%, two steps). Glycosylation of imidate **45** with 6-benzoxylhexanol or 6-(4-methoxybenzyloxy)hexanol by traditional glycosylation approach led to trisaccharides **46a** and **46b** in good yields (**46a**: 82%, **46b**: 86%, α/β = 10:1 for both reactions). Eventually, the acid stable trisaccharide **6a** and **6b** were synthesized by deprotection of the levulinate protecting group. Once again glycosylation of trisaccharides **5** and **6a** with either monosaccharides **24** or **7** delivered the corresponding tetrasaccharides **3** or **4** in excellent yields (82−90%) (Table 1). In both of these glycosylations, the C-2 levulinate groups in monosaccharides **5** and **6a** were used as an anchimeric direction groups to ensure β-selectivity.

Deprotection of levulinate protecting groups in **3** and **4** (Scheme 10), followed by an etherification with methyl iodide

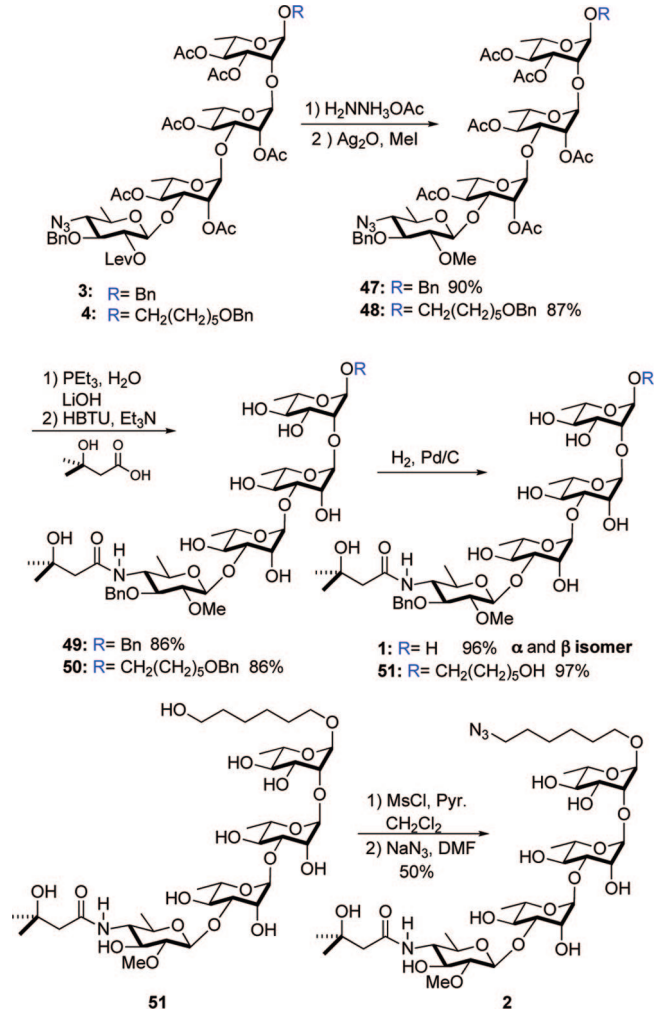
TABLE 1. Synthesis of Tetrasaccharides 3 and 4



acceptor	donor	product	yield (%)
5	**7**	**3**	90
6a	**7**	**4**	82
5	**24**	**3**	85

in the presence of Ag_2O, delivered the methyl ethers **47** and **48** in excellent yields (**47**: 90%, and **48**: 87%, two steps). It is worth mentioning that we found it was very difficult to prepare the methyl ether in the presence of all the acetate groups. After failing screening various solvents, bases, and methyl source for the methylation, we found the use of neat methyl iodide as solvent and Ag_2O as base were the optimal conditions.[5] A one-

SCHEME 10. Completion of Anthrax Tetrasaccharide (1) and Its Analogue (2)



pot condition has been employed to reduce the azides **47** and **48** to amines along with global deprotection of the acetate groups to generate the free alcohol ($PEt_3/LiOH/H_2O$). Selective peptide coupling of primary amine and 3-hydroxy-3-methylbutanioc acid (HBTU/Et_3N) afforded amides **49** and **50** in excellent yields (86% for both **49** and **50** in two steps). Removal of the benzyl groups in **49** and **50** under the hydrogenolysis conditions (H_2, Pd/C) provided the natural product anthrax tetrasaccharide **1** and 6-hydroxyhexyloxyl anthrax tetrasaccharide **51** in excellent yields (**1**: 96%, and **51**: 97%). Synthetic tetrasaccharide **1** had identical spectra data as the isolated natural material.[3] Finally, an anthrax tetrasaccharide analogue **2** was also achieved by a two-step procedure. Selective mesylation of primary alcohol **51**, followed by S_N2-type displacement with NaN_3 produced the 6-azidohexyloxyl anthrax tetrasaccharide **2** (50%), which should be ready for conjugation to carrier protein and anthrax detector/vaccine development.

Conclusions

In conclusion, a highly enantio- and diastereocontrolled approach to natural product anthrax tetrasaccharide **1** as well as its analogue **2** has been developed in a convergent [3 + 1] manner, where both the mono- and trisaccharide fragments were assembled from achiral starting materials by use of asymmetric catalysis. This de novo asymmetric route illustrates the utilities of Noyori reduction, palladium-catalyzed glycosylation, palladium-catalyzed azide allylation, diastereoselective dihydroxylation, Luche reduction, and selective acylation. The anthrax tetrasaccharide **1** was achieved in 25 steps and 13% overall yield from achiral starting material acetylfuran **9**, which has comparable efficiency to previous carbohydrate approaches. Further application of this approach to the synthesis of various analogues and biological activity testing is ongoing.

Experimental Section[21]

(2*R*,3*S*,6*S*)-3,6-Dihydro-6-methoxy-2-methyl-2*H*-pyran-3-ol (13a). A solution of pyranone **12a** (3.6 g, 25.4 mmol) in dry CH_2Cl_2 (25.4 mL) and 0.4 M $CeCl_3$/MeOH (25.4 mL) was cooled to −78 °C. $NaBH_4$ (985 mg, 25.4 mmol) was added, and the reaction mixture was stirred for 4 h at −78 °C. The resulting solution was diluted with Et_2O (300 mL) and was quenched with 150 mL of saturated $NaHCO_3$, extracted (3 × 300 mL) with Et_2O, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using silica gel chromatography eluting with 20% EtOAc/hexane to give 3.32 g (23.1 mmol, 91%) of allylic alcohol **13a** as a colorless oil: $R_f = 0.26$ (30% EtOAc/hexane); $[\alpha]^{25}_D = +104$ ($c = 1.5$, CH_2Cl_2); IR (thin film, cm^{-1}) 3396, 2975, 2934, 2894, 1449, 1399, 1040, 960; ^1H NMR (600 MHz, $CDCl_3$) δ 5.92 (d, $J = 10.2$ Hz, 1H), 5.73 (ddd, $J = 10.2$, 3.0, 1.8 Hz, 1H), 4.81 (d, $J = 1.8$ Hz, 1H), 3.79 (dd, $J = 9.0$, 6.6 Hz, 1H), 3.67 (m, 1H), 3.42 (s, 3H), 1.92 (d, $J = 1.8$ Hz, 1H, OH), 1.32 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (150.8 MHz, $CDCl_3$) δ 140.0, 126.0, 95.3, 69.4, 67.9, 55.5, 17.9.

(2*R*,3*S*,6*S*)-6-(4-Methoxy)-3,6-dihydro-2-(methyl)-2*H*-pyran-3-yl Methyl Carbonate (14a). To a stirring solution of allylic alcohol **13a** (2.6 g, 17.8 mmol), pyridine (17.8 mL), and DMAP (769 mg, 6.3 mmol) in dry CH_2Cl_2 (173 mL), was dropwise added methyl chloroformate (5.03 mL, 71.2 mmol) at 0 °C. After the reaction proceeded for 1 h at 0 °C, water (100 mL) was added, and the resulting mixture was extracted with CH_2Cl_2 (3 × 200 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 5% EtOAc/hexane to give 2.70 g (13.35 mmol, 75%) of carbonate **14a** as a colorless oil: R_f (30% EtOAc/hexane) = 0.67; $[\alpha]^{25}_D = +178$ ($c = 1.1$, CH_2Cl_2); IR (thin film, cm^{-1}) 2981, 2959, 2900, 1746, 1442, 1253, 1052, 1024, 962; ^1H NMR (600 MHz, $CDCl_3$) δ 5.90 (d, $J = 10.2$ Hz, 1H), 5.80 (ddd, $J = 10.2$, 3.0, 1.8 Hz, 1H), 4.84 (ddd, $J = 9.6$, 3.0, 1.8 Hz, 1H), 4.82 (d, $J = 1.8$ Hz, 1H), 3.92 (dq, $J = 9.0$, 6.6, 1H), 3.77 (s, 3H), 3.40 (s, 3H), 1.25 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.4, 129.2, 128.0, 95.4, 74.6, 64.6, 55.8, 55.0, 17.9; CIHRMS calcd for $[C_9H_{14}O_5Na^+]$ 225.0739, found 225.0738.

(2*R*,3*S*,6*S*)-3-Azido-3,6-dihydro-6-methoxy-2-methyl-2*H*pyran (15a). To a stirring solution of carbonate **14a** (1.3 g, 6.4 mmol), allylpalladium chloride dimer (25 mg, 1.0 mmol %), and 1,4-bis(diphenylphosphino)butane (110 mg, 4.0 mmol %) in dry THF (6.4 mL) was added $TMSN_3$ (1.27 mL, 9.6 mmol) under argon atmosphere. The reaction mixture was stirred at room temperature for 0.5 h, solvent was evaporated under reduced pressure, and the product was purified using silica gel flash chromatography eluting with 3% EtOAc/hexane to give 886 mg (5.25 mmol, 82%) of allylic azide **15a** as colorless oil: R_f (20% EtOAc/hexane) = 0.70; $[\alpha]^{25}_D = +186$ ($c = 0.5$, CH_2Cl_2); IR (thin film, cm^{-1}) 2979, 2934, 2898, 2094, 1398, 1189, 1049, 963; ^1H NMR (600 MHz, $CDCl_3$) δ 5.96 (d, $J = 10.2$ Hz, 1H), 5.89 (ddd, $J = 10.2$, 3.0, 1.8 Hz, 1H), 4.84 (d, $J = 1.2$ Hz, 1H), 3.80 (dq, $J = 9.6$, 6.6, 1H), 3.54 (dd, $J = 9.6$, 1.8 Hz, 1H), 3.43 (s, 3H), 1.35 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (150.8 MHz, $CDCl_3$) δ 128.7, 128.5, 95.3, 65.9, 60.3, 55.8, 18.6; CIHRMS calcd for $[C_7H_{11}N_3O_2Na^+]$ 192.0743, found 192.0749.

(2*S*,3*R*,4*S*,5*S*)-5-Azidotetrahydro-2-methoxy-6-methyl-2*H*-pyran-3,4-diol (16a). To a 2-methyl-2-propanol/acetone (22.8 mL, 1:1 (v/v)) solution of allylic azide **15a** (1.92 g, 11.4 mmol) at 0 °C was added a solution of *N*-methylmorpholine *N*-oxide/water (50% w/v, 11.4 mL). Crystalline OsO_4 (29 mg, 1 mol %) was added, and the reaction was allowed to stir for 18 h. The reaction mixture was quenched with 50 mL of saturated $Na_2S_2O_3$ solution, extracted with EtOAc (3 × 200 mL), dried (Na_2SO_4), concentrated under reduced pressure, and then purified using silica gel flash chromatography eluting with 50% EtOAc/hexane to afford diol **16a** (2.13 g, 10.9 mmol, 96%): $R_f = 0.20$ (50% EtOAc/hexane); mp = 83−85 °C; $[\alpha]^{25}_D = +114$ ($c = 1.0$, CH_2Cl_2); IR (thin film, cm^{-1}) 3387, 2978, 2937, 2837, 2109, 1613, 1385, 1131, 1061, 95, 967; ^1H NMR (600 MHz, $CDCl_3$) δ 4.66 (d, $J = 1.2$ Hz, 1H), 3.88 (dd, $J = 3.6$, 1.2 Hz, 1H), 3.81 (dd, $J = 9.6$, 3.6 Hz, 1H), 3.74 (s, 1H), 3.72 (s, 1H), 3.54 (dq, $J = 9.6$, 6.6, 1H), 3.32 (s, 3H), 3.29 (dd, $J = 9.6$, 9.6 Hz, 1H), 1.33 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 100.7, 70.4, 70.1, 66.7, 65.6, 55.0, 18.3; CIHRMS calcd for $[C_7H_{13}N_3O_4Na^+]$ 226.0804, found 226.0803.

(2*S*,3*R*,4*S*,5*R*)-4-(4-Methoxybenzyloxy)-5-azidotetrahydro-2-methoxy-6-methyl-2*H*-pyran-3-ol (17). A stirring mixture of diol **16a** (363 mg, 1.79 mmol) and *n*-Bu_2SnO (459 mg, 1.84 mmol) in toluene (26 mL) was refluxed for 3 h. After the mixture was cooled to room temperature, CsF (330 mg), tetrabutylammonium iodide (726 mg, 1.97 mmol), and PMBBr (0.22 mL, 1.87 mmol) were added, and the mixture was refluxed for 2 h. The solution was cooled to room temperature. The reaction mixture was diluted in 100 mL of saturated $NaHCO_3$ solution and then extracted with ethyl ether (3 × 100) and dried (Na_2SO_4). The extraction was concentrated under reduced pressure and then purified using silica gel chromatography eluting with 25% EtOAc/hexane to give PMB-ether **17** (538 mg, 1.66 mmol, 93%) as a colorless oil: $R_f = 0.32$ (40% EtOAc/hexane); $[\alpha]^{25}_D = +123$ ($c = 1.8$, CH_2Cl_2); IR (thin film, cm^{-1}) 3457, 2935, 2836, 2110, 1612, 1513, 1246, 1063, 995, 818; ^1H NMR (600 MHz, $CDCl_3$) δ 7.31 (d, $J = 8.4$ Hz, 2H), 6.90 (d, $J = 8.4$ Hz, 2H), 4.68 (d, $J = 1.2$ Hz, 1H), 4.62 (d, $J = 11.4$ Hz, 1H), 4.58 (d, $J = 11.4$ Hz, 1H), 3.93 (dd, $J = 3.6$, 1.2 Hz, 1H), 3.80 (s, 3H), 3.68 (dd, $J = 9.6$, 3.6 Hz, 1H), 3.49 (dq, $J = 9.6$, 6.6 Hz, 1H), 3.38 (dd, $J = 9.6$, 9.6 Hz, 1H), 3.33 (s, 3H), 2.59

(21) Presented in this Experimental Section are the experimental procedures and spectral data for the new compounds required for the synthesis of the anthrax tetrasaccharide and its analogue. Complete experimental procedures and spectral data for all compounds are presented in the Supporting Information.

(s, 1H, OH), 1.32 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.6, 129.8, 128.6, 114.0, 100.2, 78.0, 71.6, 67.2, 66.5, 63.9, 55.3, 55.0, 18.3; CIHRMS calcd for [$C_{15}H_{21}N_3O_5Na^+$] 346.1373, found 346.1379.

(3*S*,4*S*,5*S*)-2-((3*S*,4*S*,5*S*)-2-((3*S*,4*S*,5*S*)-2-hydroxytetrahydro-4,5-diacetoxy-6-methyl-2*H*-pyran-3-yloxy)tetrahydro-3,5-diacetoxy-6-methyl-2*H*-pyran-4-yloxy)-3,5-diacetoxytetrahydro-6-methyl-2*H*-pyran-4-yl 4-Oxopentanoate (44). To a solution of Bn-ether **43** (1.53 g, 1.7 mmol) in 5 mL of MeOH was added 10% Pd/C (100 mg). The reaction suspension was stirred under a hydrogen balloon for 24 h, filtered by passing through a Celite pad, and concentrated under reduced pressure and in vacuo to give 1.26 g of anomeric alcohol **44** (1.56 mmol, 92%) as a white foam: mp 78−84 °C; $R_f = 0.51$ (80% EtOAc/hexane); $[\alpha]^{25}_D = -19$ ($c = 1.0$, CH_2Cl_2); IR (thin film, cm^{-1}) 3446, 2940, 2983, 1745, 1371, 1222, 1038, 914; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.28 (dd, $J = 9.6$, 3.6 Hz, 1H), 5.21 (dd, $J = 3.6$, 1.8 Hz, 1H), 5.16 (d, $J = 1.8$ Hz, 1H), 5.15 (dd, $J = 9.6$, 3.0 Hz, 1H), 5.08 (dd, $J = 9.6$, 9.6 Hz, 1H), 5.05 (dd, $J = 3.6$, 1.8 Hz, 1H), 5.04 (dd, $J = 9.6$, 9.6 Hz, 1H), 5.02 (dd, $J = 9.6$, 9.6 Hz, 1H), 4.93 (d, $J = 1.8$ Hz, 1H), 4.80 (d, $J = 1.8$ Hz, 1H), 4.14 (dd, $J = 9.6$, 3.0 Hz, 1H), 4.06 (dq, $J = 9.6$, 6.6 Hz, 1H), 4.02 (dd, $J = 3.6$, 1.8 Hz, 1H), 3.89 (dq, $J = 9.0$, 6.6 Hz, 1H), 3.85 (dq, $J = 9.6$, 6.6 Hz, 1H), 3.06 (br., 1H, OH), 2.72 (ddd, $J = 18.6$, 8.4, 5.4 Hz, 1H), 2.61 (ddd, $J = 18.6$, 6.6, 5.4 Hz, 1H), 2.51 (ddd, $J = 18.6$, 8.4, 5.4 Hz, 1H), 2.43 (ddd, $J = 18.6$, 6.6, 5.4 Hz, 1H), 2.15 (s, 3H), 2.13 (s, 3H), 2.11 (s, 3H), 2.08 (s, 3H), 2.07 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H), 1.21 (d, $J = 6.6$ Hz, 3H), 1.20 (d, $J = 6.6$ Hz, 3H), 1.15 (d, $J = 6.6$ Hz, 3H);^{13}C NMR (150.8 MHz, $CDCl_3$) δ 206.2, 171.3, 170.5, 170.4, 170.3, 170.2 (2 C), 169.8, 99.4, 98.7, 93.3, 77.4, 74.3, 72.1, 71.4, 71.3, 70.7, 70.3, 70.1, 68.9, 67.5, 67.3, 66.4, 37.7, 29.7, 27.9, 21.0, 20.9 (2 C), 20.8 (2 C), 20.7, 17.6, 17.4, 17.2; CIHRMS calcd for [$C_{35}H_{50}O_{21}Na^+$]: 829.2737, found 829.2743.

(3S,4S,5*S*)-2-((3S,4S,5*S*)-2-((3S,4S,5*S*)-2-(2,2,2-trichloroacetoyloxy)-tetrahydro-4,5-diacetoxy-6-methyl-2H-pyran-3-yloxy)-tetrahydro-3,5-diacetoxy-6-methyl-2H-pyran-4-yloxy)-3,5-diacetoxy-tetrahydro-6-methyl-2H-pyran-4-yl 4-oxopentanoate (45). To a CH_2Cl_2 (7 mL) solution of alcohol **44** (1.06 g, 1.31 mmol) and trichloroacetonitrile (7.4 mL) was added catalytic amount NaH (15 mg) at 0 °C. The reaction mixture was stirred for 1.5 h at 0 °C, The solvent was removed under reduced pressure, and purified using silica gel flash chromatography eluting with pure ether to give imidate **45** (996 mg, 1.06 mmol, 81%) as colorless oil: $R_f = 0.70$ (80% EtOAc/hexane); major product: IR (thin film, cm^{-1}) 2983, 2939, 1744, 1370, 1221, 1044, 915; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.67 (s, 1H), 5.27 (dd, $J = 9.6$, 3.6 Hz, 1H), 5.22 (dd, $J = 3.6$, 1.8 Hz, 1H), 5.17 (dd, $J = 9.6$, 3.0 Hz, 1H), 5.13 (dd, $J = 9.6$, 9.6 Hz, 1H), 5.11 (dd, $J = 9.6$, 9.6 Hz, 1H), 5.07 (dd, $J = 3.6$, 1.8 Hz, 1H), 5.06 (d, $J = 1.8$ Hz, 1H), 5.06 (dd, $J = 9.6$, 9.6 Hz, 1H), 4.94 (d, $J = 1.8$ Hz, 1H), 4.84 (d, $J = 1.8$ Hz, 1H), 4.22 (dd, $J = 3.6$, 1.8 Hz, 1H), 4.13 (dd, $J = 9.6$, 3.0 Hz, 1H), 4.05 (dq, $J = 9.0$, 6.6 Hz, 1H), 3.90 (dq, $J = 9.6$, 6.6 Hz, 2H), 2.74 (ddd, $J = 18.6$, 8.4, 5.4 Hz, 1H), 2.62 (ddd, $J = 18.6$, 6.6, 5.4 Hz, 1H), 2.51 (ddd, $J = 18.6$, 8.4, 5.4 Hz, 1H), 2.43 (ddd, $J = 18.6$, 6.6, 5.4 Hz, 1H), 2.17 (s, 3H), 2.15 (s, 3H), 2.14 (s, 3H), 2.13 (s, 3H), 2.08 (s, 6H), 2.05 (s, 3H), 1.26 (d, $J = 6.6$ Hz, 3H), 1.20 (d, $J = 6.6$ Hz, 3H), 1.18 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 206.1, 171.3, 170.4, 170.3, 170.2, 170.1, 169.6, 160.3, 99.5, 98.8, 96.1, 74.8, 74.4, 72.0, 71.2, 70.7, 70.6, 70.2, 70.1, 69.4, 68.9, 67.8, 67.4, 65.9, 37.7, 29.8, 27.9, 21.0 (2 C), 20.9, 20.8 (2 C), 20.7, 17.6, 17.3, 17.2; CIHRMS calcd for [$C_{36}H_{50}Cl_3NO_{21}Na^+$]: 960.1839, found 960.1830.

(3*S*,4*S*,5*S*)-2-((3*S*,4*S*,5*S*)-2-((3*S*,4*S*,5*S*)-2-(6-(benzyloxy)hexyloxy)-tetrahydro-4,5-diacetoxy-6-methyl-2H-pyran-3-yloxy)-tetrahydro-3,5-diacetoxy-6-methyl-2H-pyran-4-yloxy)-3,5-diacetoxy-tetrahydro-6-methyl-2H-pyran-4-yl 4-oxopentanoate (46a). To a solution of trisaccharide imidate **45** (815 mg, 0.868 mmol) and 6-benzyloxy-hexanol (361 mg, 1.74 mmol) in 2.2 mL CH_2Cl_2 with molecular sieve at 0 °C was added TMSOTf (38 mg, 0.174 mmol). The reaction was stirred at 0 °C for 0.5 h, quenched with saturated $NaHCO_3$ solution (10 mL), extracted with Et_2O (3 × 50 mL), dried (Na_2SO_4), concentrated under reduced pressure and purified by passing a pad of silica gel eluting with 70% EtOAc/hexane to give 709 mg (0.712 mmol, 82%) trisaccharide **46a** as white foam, mp: 57−64 °C; $R_f = 0.59$ (70% EtOAc/hexane); $[\alpha]^{25}_D = -35$ ($c = 1.0$, CH_2Cl_2); IR (thin film, cm^{-1}) 2983, 2937, 2861, 1743, 1370, 1220, 984; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25−7.34 (m, 5H), 5.21 (dd, $J = 3.6$, 1.8 Hz, 1H), 5.19 (dd, $J = 9.6$, 3.6 Hz, 1H), 5.17 (dd, $J = 9.6$, 3.6 Hz, 1H), 5.09 (dd, $J = 9.6$, 9.6 Hz, 1H), 5.06 (dd, $J = 9.6$, 9.6 Hz, 1H), 5.05 (dd, $J = 3.0$, 1.8 Hz, 1H), 5.00 (dd, $J = 9.6$, 9.6 Hz, 1H), 4.93 (d, $J = 1.8$ Hz, 1H), 4.79 (d, $J = 1.8$ Hz, 1H), 4.70 (d, $J = 1.8$ Hz, 1H), 4.49 (s, 2H), 4.14 (dd, $J = 9.6$, 3.6 Hz, 1H), 3.96 (dd, $J = 3.0$, 1.8 Hz, 1H), 3.89 (dq, $J = 9.6$, 6.6 Hz, 1H), 3.86 (dq, $J = 9.6$, 6.6 Hz, 1H), 3.80 (dq, $J = 9.6$, 6.6 Hz, 1H), 3.63 (dt, $J = 9.6$, 6.6 Hz, 1H), 3.45 (t, $J = 6.6$ Hz, 2H), 3.38 (dt, $J = 9.6$, 6.6 Hz, 1H), 2.73 (ddd, $J = 18.0$, 7.2, 7.2 Hz, 1H), 2.62 (ddd, $J = 18.0$, 7.2, 7.2 Hz, 1H), 2.52 (ddd, $J = 18.0$, 6.6, 6.6 Hz, 1H), 2.43 (dd, $J = 18.0$, 7.2, 6.6 Hz, 1H), 2.17 (s, 3H), 2.15 (s, 3H), 2.13 (s, 3H), 2.12 (s, 3H), 2.08 (s, 3H), 2.07 (s, 3H), 2.02 (s, 3H), 1.60 (m, 4H), 1.37 (m, 4H), 1.22 (d, $J = 6.6$ Hz, 3H), 1.20 (d, $J = 6.6$ Hz, 3H), 1.17 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 206.1, 171.3, 170.5, 170.3 (2 C), 170.2, 170.1, 169.8, 137.8, 128.4, 127.7, 127.6, 99.5, 99.7, 98.6, 77.4, 74.3, 73.0, 72.2, 71.5, 71.3, 70.8, 70.7, 70.4, 70.1, 68.9, 68.0, 67.4, 67.3, 66.3, 37.7, 29.8, 29.7, 29.4, 27.9, 26.1 26.0, 21.1, 21.0, 20.9, 20.86, 20.8 (2 C), 17.6, 17.5, 17.2; CIHRMS calcd for [$C_{48}H_{68}O_{22}Na^+$]: 1019.4100, found 1019.4101.

(3*S*,4*S*,5*S*)-2-((3*S*,4*S*,5*S*)-2-((3*S*,4*S*,5*S*)-2-(6-(4-methoxybenzyloxy)-hexyloxy)-tetrahydro-4, 5-diacetoxy-6-methyl-2H-pyran-3-yloxy)-tetrahydro-3, 5-diacetoxy-6-methyl-2H-pyran-4-yloxy)-3, 5-diacetoxy-tetrahydro-6-methyl-2H-pyran-4-yl 4-oxopentanoate (46b). To a solution of trisaccharide imidate **45** (600 mg, 0.639 mmol) and 6-(4-methoxybenzyloxy)hexan-1-ol (305 mg, 1.28 mmol) in 2.0 mL CH_2Cl_2 with molecular sieve at 0 °C was added TMSOTf (28 mg, 0.174 mmol). The reaction was stirred at 0 °C for 0.5 h, quenched with saturated $NaHCO_3$ solution (10 mL), extracted with Et_2O (3 × 50 mL), dried (Na_2SO_4), concentrated under reduced pressure and purified by passing a pad of silica gel eluting with 70% EtOAc/hexane to give 564 mg (0.55 mmol, 86%) trisaccharide **46b**; $R_f = 0.57$ (80% EtOAc/hexane); $[\alpha]^{25}_D = -29$ ($c = 0.9$, CH_2Cl_2); IR (thin film, cm^{-1}) 2984, 2938, 2858, 1746, 1370, 1222, 985; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.24 (d, $J = 8.4$ Hz, 2H), 6.87 (d, $J = 8.4$ Hz, 2H), 5.22 (dd, $J = 3.6$, 1.8 Hz, 1H), 5.19 (dd, $J = 9.6$, 3.6 Hz, 1H), 5.16 (dd, $J = 9.6$, 3.6 Hz, 1H), 5.09 (dd, $J = 9.6$, 9.6 Hz, 1H), 5.06 (dd, $J = 9.6$, 9.6 Hz, 1H), 5.05 (dd, $J = 3.0$, 1.8 Hz, 1H), 5.00 (dd, $J = 9.6$, 9.6 Hz, 1H), 4.94 (d, $J = 1.8$ Hz, 1H), 4.79 (d, $J = 1.8$ Hz, 1H), 4.69 (d, $J = 1.8$ Hz, 1H), 4.42 (s, 2H), 4.14 (dd, $J = 9.6$, 3.6 Hz, 1H), 3.96 (dd, $J = 3.0$, 1.8 Hz, 1H), 3.90 (dq, $J = 9.6$, 6.6 Hz, 1H), 3.86 (dq, $J = 9.6$, 6.6 Hz, 1H), 3.80 (dq, $J = 9.6$, 6.6 Hz, 1H), 3.79 (s, 3H), 3.63 (dt, $J = 9.6$, 6.6 Hz, 1H), 3.64 (dt, $J = 9.6$, 6.6 Hz, 1H), 3.45 (t, $J = 6.6$ Hz, 2H), 3.39 (dt, $J = 9.6$, 6.6 Hz, 1H), 2.72 (ddd, $J = 18.0$, 7.2, 7.2 Hz, 1H), 2.62 (ddd, $J = 18.0$, 7.2, 7.2 Hz, 1H), 2.52 (ddd, $J = 18.0$, 6.6, 6.6 Hz, 1H), 2.43 (ddd, $J = 18.0$, 7.2, 6.6 Hz, 1H), 2.17 (s, 3H), 2.15 (s, 3H), 2.13 (s, 3H), 2.12 (s, 3H), 2.08 (s, 3H), 2.07 (s, 3H), 2.02 (s, 3H), 1.60 (m, 4H), 1.37 (m, 4H), 1.22 (d, $J = 6.6$ Hz, 3H), 1.20 (d, $J = 6.6$ Hz, 3H), 1.17 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 206.1, 171.3, 170.5, 170.3 (2 C), 170.2, 170.1, 169.8, 159.2, 130.9, 129.3, 113.9, 99.5, 98.7, 98.6, 77.3, 74.3, 72.6, 72.2, 71.5, 71.3, 70.8, 70.7, 70.1(2 C), 68.9, 68.1, 67.4, 67.3, 66.3, 55.4, 37.8, 31.0, 29.8, 29.7, 29.4, 27.9, 26.1 26.0, 21.1, 21.0, 20.9, 20.8 (2 C), 17.6, 17.5, 17.2; CIHRMS calcd for [$C_{49}H_{70}O_{23}Na^+$]: 1049.4200, found 1049.4206.

(3*S*,4*S*,5*R*)-2-((3*S*,4*S*,5*S*)-2-((3*S*,4*S*,5*S*)-2-(6-(benzyloxy)hexyloxy)-tetrahydro-4,5-diacetoxy-6-methyl-2H-pyran-3-yloxy)-tetrahydro-3,5-diacetoxy-6-methyl-2H-pyran-4-yloxy)-tetrahydro-4-hydroxy-6-methyl-2H-pyran-3, 5-yl diacetate (6a). To a solution of levulinoyl ester **46a** (560 mg, 0.56 mmol) in CH_2Cl_2 (11.2 mL) was added a solution of hydrazinium acetate (1.5 M, 0.40 mL) in methanol.

The reaction was stirred for 2 h, quenched with saturated $NaHCO_3$ solution (50 mL), extracted with Et_2O (3 × 150 mL), dried (Na_2SO_4), concentrated under reduced pressure and purified using silica gel flash chromatography eluting with pure ether to give 476 mg (0.53 mmol, 94%) alcohol **6a** as white foam, mp: 56−59 °C; R_f = 0.45 (50% EtOAc/hexane); $[\alpha]^{25}_D = -33$ (c = 0.62, CH_2Cl_2); IR (thin film, cm^{-1}) 2981, 2938, 2110, 1742, 1368, 1220, 1037, 912; ^1H NMR (600 MHz, $CDCl_3$) δ 7.22−7.31 (m, 5H), 5.17 (dd, J = 9.6, 3.6 Hz, 1H), 5.15 (dd, J = 3.6, 1.8 Hz, 1H), 5.05 (dd, J = 9.6, 9.6 Hz, 1H), 4.98 (dd, J = 9.6, 9.6 Hz, 1H), 4.95 (d, J = 1.8 Hz, 1H), 4.87 (dd, J = 3.6, 1.8 Hz, 1H), 4.81 (dd, J = 9.6, 9.6 Hz, 1H), 4.75 (d, J = 1.8 Hz, 1H), 4.67 (d, J = 1.8 Hz, 1H), 4.47 (s, 2H), 4.11 (dd, J = 9.6, 3.6 Hz, 1H), 3.94 (dd, J = 3.6, 1.8 Hz, 1H), 3.85 (dd, J = 9.6, 3.6 Hz, 1H), 3.84 (dq, J = 9.6, 6.6 Hz, 1H), 3.78 (dq, J = 9.6, 6.6 Hz, 2H), 3.62 (dt, J = 9.6, 6.6 Hz, 1H), 3.43 (d, J = 6.6 Hz, 2H), 3.37 (dt, J = 9.6, 6.6 Hz, 1H), 2.36 (d, J = 9.0 Hz, 1H, OH), 2.12 (s, 6H), 2.11 (s, 3H), 2.09 (s, 3H), 2.03 (s, 3H), 1.99 (s, 3H), 1.58 (m, 4H), 1.35 (m, 4H), 1.20 (d, J = 6.6 Hz, 3H), 1.17 (d, J = 6.6 Hz, 3H), 1.14 (d, J = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.5, 170.3 (3 C), 170.1, 169.6, 138.7, 128.3, 127.6, 127.4, 99.4, 99.8, 98.5, 77.2, 74.4, 73.9, 72.8(2 C), 72.2, 71.5, 71.4, 70.7, 70.3, 68.1, 67.9, 67.4, 66.8, 66.2, 29.6, 29.3, 26.0, 25.9, 21.0, 20.9 (2 C), 20.7 (2 C), 20.6, 17.5, 17.3, 17.0; CIHRMS calcd for $[C_{43}H_{62}O_{20}Na^+]$: 921.3732, found 921.3734.

(3*S*,4*S*,5*R*)-2-((3*S*,4*S*,5*S*)-2-((3*S*,4*S*,5*S*)-2-(6-(4-methoxybenzyloxy)-hexyloxy)-tetrahydro-4, 5-diacetoxy-6-methyl-2H-pyran-3-yloxy)-tetrahydro-3,5-diacetoxy-6-methyl-2H-pyran-4-yloxy)-tetrahydro-4-hydroxy-6-methyl-2H-pyran-3, 5-yl diacetate (6b). To a solution of levulinoyl ester **46b** (706 mg, 0.688 mmol) in CH_2Cl_2 (13.8 mL) was added a solution of hydrazinium acetate (1.5 M, 9.2 mL) in methanol. The reaction was stirred for 2 h, quenched with saturated $NaHCO_3$ solution (60 mL), extracted with Et_2O (3 × 120 mL), dried (Na_2SO_4), concentrated under reduced pressure and purified using silica gel flash chromatography eluting with pure ether to give 620 mg (0.66 mmol, 96%) alcohol **6b** as a white foam, mp: 68−72 °C; R_f = 0.47 (50% EtOAc/hexane); $[\alpha]^{25}_D = -32$ (c = 1.0, CH_2Cl_2); IR (thin film, cm^{-1}) 2978, 2939, 1743, 1374, 1226, 1040, 986; ^1H NMR (600 MHz, $CDCl_3$) δ 7.25 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.4 Hz, 2H), 5.20 (dd, J = 9.6, 3.6 Hz, 1H), 5.17 (dd, J = 3.6, 1.8 Hz, 1H), 5.08 (dd, J = 9.6, 9.6 Hz, 1H), 5.00 (dd, J = 9.6, 9.6 Hz, 1H), 4.97 (d, J = 1.8 Hz, 1H), 4.89 (dd, J = 3.0, 1.8 Hz, 1H), 5.83 (dd, J = 9.6, 9.6 Hz, 1H), 4.77 (d, J = 1.8 Hz, 1H), 4.69 (d, J = 1.8 Hz, 1H), 4.42 (s, 2H), 4.14 (dd, J = 9.6, 3.6 Hz, 1H), 3.96 (dd, J = 3.0, 1.8 Hz, 1H), 3.87 (dd, J = 9.6, 3.6 Hz, 1H), 3.86 (dq, J = 9.6, 6.6 Hz, 1H), 3.70 (dq, J = 9.6, 6.6 Hz, 2H), 3.79 (s, 3H), 3.62 (dt, J = 9.6, 6.6 Hz, 1H), 3.43 (t, J = 6.6 Hz, 2H), 3.39 (dt, J = 9.6, 6.6 Hz, 1H), 2.15 (s, 6H), 2.13 (s, 3H), 2.12 (s, 3H), 2.06 (s, 3H), 2.02 (s, 3H), 1.58 (m, 4H), 1.35 (m, 4H), 1.22 (d, J = 6.6 Hz, 3H), 1.20 (d, J = 6.6 Hz, 3H), 1.16 (d, J = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.7, 170.4 (2 C), 170.3, 170.2, 169.7, 159.2, 130.8, 129.3, 113.8, 99.5, 98.8, 98.5, 77.2, 74.5, 74.0, 72.9, 72.6, 72.3, 71.6, 71.5, 70.8, 70.1, 68.3, 68.0, 67.5, 66.8, 66.2, 55.3, 29.7, 29.4, 26.1, 26.0, 21.1, 20.0 (2 C), 20.8 (2 C), 20.7, 17.6, 17.4, 17.1; CIHRMS calcd for $[C_{44}H_{64}O_{21}Na^+]$: 951.3838, found 951.3837.

(2*S*,3*S*,4*S*,5*R*)-2-((2*S*,4*S*,5*S*)-2-((2*S*,4*S*,5*S*)-2-((2*R*,4*S*,5*S*)-2-(6-(benzyloxy)hexyloxy)-tetrahydro-4, 5-diacetoxy-6-methyl-2H-pyran-3-yloxy)-tetrahydro-3,5-diacetoxy-6-methyl-2H-pyran-4-yloxy)-tetrahydro-3,5-diacetoxy-6-methyl-2H-pyran-4-yloxy)-5-azido-4-(benzyloxy)-tetrahydro-6-methyl-2H-pyran-3-yl 4-oxopentanoate (4). To a solution of trisaccharide **6a** (898 mg, 1 mmol) and imidate **7** (782 mg, 1.5 mmol) in 2 mL CH_2Cl_2 with molecular sieve at 0 °C was added TMSOTf (66 mg, 0.168 mmol). The reaction was stirred at 0 °C for 0.5 h, quenched with saturated $NaHCO_3$ solution (10 mL), extracted with Et_2O (3 × 100 mL), dried (Na_2SO_4), concentrated under reduced pressure and purified by passing through a pad of silica gel eluting with 50% EtOAc/hexane to give 1.03 g (0.82 mmol, 82%) tetrasaccharide **4** as a white foam, mp: 62−65 °C; R_f = 0.43 (50% EtOAc/hexane); $[\alpha]^{25}_D = -6$ (c = 0.8, CH_2Cl_2); IR (thin film, cm^{-1}) 2981, 2938, 2860, 2110, 1742, 1368, 1220, 1037, 912; ^1H NMR (600 MHz, $CDCl_3$) δ 7.25−7.35 (m, 10H), 5.20 (dd, J = 9.6, 3.6 Hz, 1H), 5.18 (dd, J = 3.6, 1.8 Hz, 1H), 5.06 (dd, J = 9.6, 9.6 Hz, 1H), 4.99 (dd, J = 9.6, 9.6 Hz, 1H), 4.98 (dd, J = 9.6, 9.6 Hz, 1H), 4.97 (d, J = 1.8 Hz, 1H), 4.89 (dd, J = 3.6, 1.8 Hz, 1H), 4.88 (dd, J = 9.6, 9.6 Hz, 1H), 4.78 (d, J = 1.8 Hz, 1H), 4.77 (d, J = 11.4 Hz, 1H), 4.72 (d, J = 11.4, Hz, 1H), 4.69 (d, J = 1.8 Hz, 1H), 4.49 (s, 2H), 4.40 (d, J = 7.8 Hz, 1H), 4.10 (dd, J = 9.6, 3.0 Hz, 1H), 3.96 (dd, J = 3.0, 1.8 Hz, 1H), 3.88 (dd, J = 9.6, 3.6 Hz, 1H), 3.86 (dq, J = 9.6, 6.6 Hz, 1H), 3.79 (dq, J = 9.6, 6.6 Hz, 1H), 3.73 (dq, J = 9.6, 6.6 Hz, 1H), 3.64 (dt, J = 9.6, 6.6 Hz, 1H), 3.46 (t, J = 6.6 Hz, 2H), 3.45 (dd, J = 9.6, 9.6 Hz, 1H), 3.39 (dt, J = 9.6, 6.6 Hz, 1H), 3.23 (dq, J = 9.6, 6.6 Hz, 1H), 3.16 (dd, J = 9.6, 7.8 Hz, 1H), 2.76 (ddd, J = 18.0, 7.2, 7.2 Hz, 1H), 2.66 (ddd, J = 18.0, 7.2, 7.2 Hz, 1H), 2.50 (t, J = 7.2 Hz, 2H), 2.14 (s, 6H), 2.13 (s, 3H), 2.09 (s, 3H), 2.07 (s, 3H), 2.05 (s, 3H), 2.02 (s, 3H), 1.59−1.64 (m, 4H), 1.31−1.42 (m, 4H), 1.36 (d, J = 6.6 Hz, 3H), 1.20 (d, J = 6.6 Hz, 3H), 1.17 (d, J = 6.6 Hz, 3H), 1.16 (d, J = 6.6 Hz, 3H); ^{13}C NMR (150.8 MHz, $CDCl_3$) δ 206.3, 170.3, 170.4 (2 C), 170.3, 170.1, 169.8, 169.7, 138.7, 137.6, 128.4 (2 C), 128.2, 127.9, 127.7, 127.5, 100.8. 99.4, 99.3, 98.5, 81.1, 77.2, 74.7 (2 C), 73.7, 73.4, 72.9, 72.6, 72.2, 71.8, 71.7, 71.5, 70.9, 70.8, 70.4, 68.0, 67.6, 67.3, 67.2, 66.2, 38.0, 29.8, 29.7, 29.4, 27.7, 26.1, 26.0, 21.1, 21.0 (2 C), 20.8 (2C), 20.7, 18.2, 17.6, 17.4, 17.1; CIHRMS calcd for $[C_{61}H_{83}N_3O_{25}Na^+]$: 1280.5213, found 1280.5210.

(2*S*,3*S*,4*S*,5*R*)-2-((2*S*,4*S*,5*S*)-2-((2*S*,4*S*,5*S*)-2-((2*R*,4*S*,5*S*)-2-(6-(Benzyloxy)hexyloxy)tetrahydro-4,5-diacetoxy-6-methyl-2*H*-pyran-3-yloxy)tetrahydro-3,5-diacetoxy-6-methyl-2*H*-pyran-4-yloxy)tetrahydro-3,5-diacetoxy-6-methyl-2*H*-pyran-4-yloxy)-5-azido-4-(benzyloxy)tetrahydro-6-methyl-2*H*-pyran-3-ol (48a). To a solution of levulinoyl ester **4** (600 mg, 0.477 mmol) in CH_2Cl_2 (9.5 mL) was added a solution of hydrazinium acetate (1.5 M, 0.36 mL) in methanol. The reaction was stirred for 2 h, quenched with saturated $NaHCO_3$ solution (50 mL), extracted with Et_2O (3 × 100 mL), dried (Na_2SO_4), concentrated under reduced pressure, and purified using silica gel flash chromatography eluting with 60% EtOAc/hexane to give 363 mg (0.45 mmol, 95%) of alcohol **48a** as a white foam: mp 64−67 °C; R_f = 0.60 (50% EtOAc/hexane); $[\alpha]^{25}_D = -10$ (c = 1.0, CH_2Cl_2); IR (thin film, cm^{-1}) 2983, 2938, 2894, 2110, 1742, 1372, 1223, 1039, 912; ^1H NMR (600 MHz, $CDCl_3$) δ 7.25−7.40 (m, 10H), 5.21 (dd, J = 9.6, 3.6 Hz, 1H), 5.19 (dd, J = 3.6, 1.8 Hz, 1H), 5.07 (dd, J = 9.6, 9.6 Hz, 1H), 5.03 (dd, J = 9.6, 9.6 Hz, 1H), 5.00 (dd, J = 9.6, 9.6 Hz, 1H), 4.98 (dd, J = 3.6, 1.8 Hz, 1H), 4.94 (d, J = 11.4 Hz, 1H), 4.93 (d, J = 1.2 Hz, 1H), 4.79 (d, J = 11.4 Hz, 1H), 4.78 (d, J = 1.2, Hz, 1H), 4.70 (d, J = 1.8 Hz, 1H), 4.50 (s, 2H), 4.21 (d, J = 7.8 Hz, 1H), 4.10 (dd, J = 9.6, 3.0 Hz, 1H), 3.96 (dd, J = 3.0, 1.8 Hz, 1H), 3.89 (dd, J = 9.6, 3.6 Hz, 1H), 3.87 (dq, J = 9.6, 6.6 Hz, 1H), 3.80 (dq, J = 9.6, 6.6 Hz, 1H), 3.79 (dq, J = 9.6, 6.6 Hz, 1H), 3.64 (dt, J = 9.6, 6.6 Hz, 1H), 3.47 (t, J = 6.6 Hz, 2H), 3.45 (dd, J = 9.6, 9.6 Hz, 1H), 3.36 (dq, J = 9.6, 6.6 Hz, 1H), 3.31 (dd, J = 9.6, 9.6 Hz, 1H), 3.21 (dt, J = 9.6, 6.6 Hz, 1H), 3.07 (dd, J = 9.6, 7.8 Hz, 1H), 2.15 (s, 3H), 2.13 (s, 3H), 2.11 (s, 3H), 2.10 (s, 3H), 2.06 (s, 3H), 2.02 (s, 3H), 1.56−1.64 (m, 4H), 1.33−1.42 (m, 4H), 1.32 (d, J = 6.6 Hz, 3H), 1.20 (d, J = 6.6 Hz, 3H), 1.19 (d, J = 6.6 Hz, 3H), 1.17 (d, J = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.9, 170.5, 170.4, 170.3, 170.2, 169.8, 138.7, 138.1, 128.5, 128.4, 128.3, 127.9, 127.7, 127.6, 104.0. 99.4, 99.2, 98.5, 82.2, 77.3, 75.4, 75.0, 74.9, 74.7, 72.9, 72.6, 72.4, 72.2, 71.7, 71.5, 70.9, 70.8, 70.4, 68.0, 67.3, 67.1, 67.0, 66.2, 29.7, 29.4, 26.1, 26.0, 21.2, 21.1 (2 C), 20.8 (2 C), 20.7, 18.3, 17.6, 17.5, 17.1; CIHRMS calcd for $[C_{56}H_{77}N_3O_{23}Na^+]$ 1182.4846, found 1182.4845.

(2*S*,4*S*,5*S*)-4-((2*S*,3*S*,4*S*,5*R*)-5-Azido-4-(6-(benzyloxy)hexyloxy)-tetrahydro-3-methoxy-6-methyl-2*H*-pyran-2-yloxy)-2-((2*S*,4*S*,5*S*)-2-((2*R*,4*S*,5*S*)-2-benzyloxy-4,5-diacetoxytetrahydro-6-methyl-2*H*-pyran-3-yloxy)-3,5-diacetoxytetrahydro-6-methyl-2*H*-pyran-4-

yloxy)tetrahydro-6-methyl-2*H*-pyran-3,5-yl Diacetate (48). To a mixture of alcohol **48a** (625 mg, 0.54 mmol) and silver(I) oxide (2.5 g, 10.9 mmol) was added 3 mL of CH_3I. The reaction suspension was stirred at 55 °C for 3 days. The reaction mixture was then passed through a Celite pad with 200 mL of Et_2O, concentrated under reduced pressure, and purified using silica gel flash chromatography eluting with 50% EtOAc/hexane to give 582 mg (0.50 mmol, 92%) of methyl ether **48** as a white foam: mp 61−64 °C; R_f = 0.62 (50% EtOAc/hexane); $[\alpha]^{25}_D$ = −11 (c = 2.0, CH_2Cl_2); IR (thin film, cm^{-1}) 2979, 2934, 2857, 2110, 1745, 1370, 1223, 1092, 1041; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25−7.39 (m, 10H), 5.23 (dd, J = 9.6, 3.6 Hz, 1H), 5.18 (dd, J = 3.6, 1.8 Hz, 1H), 5.12 (dd, J = 9.6, 9.6 Hz, 1H), 5.07 (dd, J = 9.6, 9.6 Hz, 1H), 5.01 (dd, J = 3.6, 1.8 Hz, 1H), 5.00 (dd, J = 9.6, 9.6 Hz, 1H), 4.93 (d, J = 1.2, Hz, 1H), 4.86 (d, J = 11.4 Hz, 1H), 4.78 (d, J = 1.8 Hz, 1H), 4.77 (d, J = 11.4 Hz, 1H), 4.70 (d, J = 1.8 Hz, 1H), 4.49 (s, 2H), 4.30 (d, J = 7.8 Hz, 1H), 4.12 (dd, J = 9.6, 3.0 Hz, 1H), 3.96 (dd, J = 3.0, 1.8 Hz, 1H), 3.89 (dd, J = 9.6, 3.6 Hz, 1H), 3.87 (dq, J = 9.6, 6.6 Hz, 1H), 3.80 (dq, J = 9.6, 6.6 Hz, 1H), 3.75 (dq, J = 9.6, 6.6 Hz, 1H), 3.65 (dt, J = 9.6, 6.6 Hz, 1H), 3.47 (t, J = 6.6 Hz, 2H), 3.46 (s, 3H), 3.40 (dt, J = 9.6, 6.6 Hz, 1H), 3.31 (dd, J = 9.6, 9.6 Hz, 1H), 3.16 (dq, J = 9.6, 6.6 Hz, 1H), 3.04 (dd, J = 9.6, 9.6 Hz, 1H), 3.02 (dd, J = 9.6, 7.8 Hz, 1H), 2.16 (s, 3H), 2.14 (s, 3H), 2.10 (s, 6H), 2.06 (s, 3H), 2.02 (s, 3H), 1.56−1.67 (m, 4H), 1.30−1.42 (m, 4H), 1.29 (d, J = 6.6 Hz, 3H), 1.20 (d, J = 6.6 Hz, 3H), 1.19 (d, J = 6.6 Hz, 3H), 1.17 (d, J = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.5, 170.4, 170.3, 170.2, 170.1, 169.7, 138.7, 138.0, 128.5, 128.4, 128.3, 127.9, 127.7, 127.6, 104.2. 99.4, 99.2, 98.5, 84.0, 82.8, 77.3, 75.4, 75.2, 74.7, 72.9, 72.3 (2 C), 72.2, 71.7, 71.5, 70.8, 70.5, 70.4, 68.0, 67.4 (2 C), 67.3, 66.3, 60.7, 29.7, 29.4, 26.1, 26.0, 21.1 (3 C), 20.8 (3 C), 18.3, 17.6, 17.5, 17.2; CIHRMS calcd for [$C_{57}H_{79}N_3O_{23}Na^+$] 1196.5002, found 1196.5001.

(3*R*,4*S*,6*R*)-5-((2*S*,4*S*,5*S*)-4-((2*S*,4*R*,5*S*)-4-((2*S*,3*S*,4*S*,5*R*)-5-Amino-4-(6-(benzyloxy)hexyloxy)tetrahydro-3-methoxy-6-methyl-2*H*-pyran-2-yloxy)tetrahydro-3,5-dihydroxy-6-methyl-2*H*-pyran-2-yloxy)tetrahydro-3,5-dihydroxy-6-methyl-2*H*-pyran-2-yloxy)-6-(benzyloxy)tetrahydro-2-methyl-2*H*-pyran-3,4-diol (50a). To a stirring solution of acetate **48** (608 mg, 0.52 mmol) in 5.2 mL of MeOH/THF/H_2O (10/10/1) was added PEt_3 (184 mg, 1.56 mmol) for 10 min, and then LiOH (151 mg, 6.24 mmol) was added. The reaction was stirred for 2 h, evaporated solvent under reduced pressure, and purified using silica gel flash chromatography eluting with 20% MeOH/CH_2Cl_2. The resulted product was applied to ion-exchange chromatography (Dowex 1× 8, 200 mesh, H^+ form) eluting with water. Removal of water in vacuo gave 432 mg (0.48 mmol, 93%) of alcohol **50a** as a white powder: mp 148−150 °C; R_f = 0.44 (20% methanol/EtOAc); $[\alpha]^{25}_D$ = −67 (c = 1.0, MeOH); IR (thin film, cm^{-1}) 3381, 2967, 2934, 2855, 1454, 1363, 1123, 1063, 986; ^{1}H NMR (600 MHz, CD_3OD) δ 7.22−7.44 (m, 10H), 5.04 (d, J = 1.2 Hz, 1H), 4.96 (d, J = 11.4 Hz, 1H), 4.90 (d, J = 1.2 Hz, 1H), 4.81 (d, J = 11.4 Hz, 1H), 4.75 (d, J = 1.2 Hz, 1H), 4.72 (d, J = 7.8 Hz, 1H), 4.46 (s, 2H), 4.16 (dd, J = 3.0, 1.8 Hz, 1H), 4.05 (dd, J = 3.0, 1.8 Hz, 1H), 3.92 (dd, J = 9.6, 3.0 Hz, 1H), 3.81 (dq, J = 9.6, 6.6 Hz, 1H), 3.78 (dd, J = 9.6, 3.0 Hz, 1H), 3.77 (dd, J = 3.0, 1.8 Hz, 1H), 3.74 (dd, J = 9.6, 3.0 Hz, 1H), 3.72 (dq, J = 9.6, 6.6 Hz, 1H), 3.65 (dq, J = 9.6, 6.6 Hz, 1H), 3.62 (dq, J = 9.6, 6.6 Hz, 1H), 3.57(s, 3H), 3.55 (dt, J = 9.6, 6.6 Hz, 1H), 3.54 (dd, J = 9.6, 9.6 Hz, 1H), 3.53 (dq, J = 9.6, 6.6 Hz, 1H), 3.50 (dd, J = 9.6, 9.6 Hz, 1H), 3.46 (t, J = 6.6 Hz, 2H), 3.37 (dt, J = 9.6, 6.6 Hz, 1H), 3.34 (dd, J = 9.6, 9.6 Hz, 1H), 3.24 (dd, J = 9.6, 7.8 Hz, 1H), 2.90 (dd, J = 9.6, 9.6 Hz, 1H), 1.59 (m, 4H), 1.37 (m, 4H), 1.34 (d, J = 6.6 Hz, 3H), 1.28 (d, J = 6.6 Hz, 3H), 1.23 (d, J = 6.6 Hz, 6H); ^{13}C NMR (150 MHz, CD_3OD) δ 140.0, 139.6, 129.5, 129.4, 129.2, 129.0, 128.9, 128.7, 105.7, 104.0, 103.6, 100.4, 85.8, 81.7, 80.2, 80.0, 79.2, 75.6, 74.5, 74.0, 73.4, 73.1, 72.3, 71.9 (2 C), 71.4, 70.7, 70.5, 70.0, 69.5, 68.7, 60.9, 58.0, 30.8, 30.6, 27.2, 27.1, 18.3, 18.2, 18.1, 18.0; CIHRMS calcd for [$C_{45}H_{69}NO_{17}Na^+$] 918.4458, found 918.4463.

***N*-((3*R*,5*S*,6*S*)-6-((2*S*,3*S*,4*S*,5*S*)-2-((2*S*,3*S*,4*S*,5*S*)-2-((2*R*,3*S*,4*S*,5*S*)-2-(6-(Benzyloxy)hexyloxy)-4,5-dihydroxytetrahydro-6-methyl-2*H*-pyran-3-yloxy)-3,5-dihydroxytetrahydro-6-methyl-2*H*-pyran-4-yloxy)-3,5-dihydroxytetrahydro-6-methyl-2*H*-pyran-4-yloxy)-4-(benzyloxy)tetrahydro-5-methoxy-2-methyl-2*H*-pyran-3-yl)-3-hydroxy-3-methylbutanamide (50).** To a solution of amine **50a** (504 mg, 0.56 mmol) in 1.12 mL of THF and Et_3N (177 μL, 1.12 mmol) were added HBTU (205 mg, 0.62 mmol) and 3-hydroxy-3-methylbutanoic acid (73 mg, 0.62 mmol). The reaction mixture was stirred for 10 h, solvent was evaporated under reduced pressure, and the product was purified using silica gel flash chromatography eluting with 35% MeOH/ EtOAc to give 513 mg (0.52 mmol, 92%) amide **50** as white powder: mp 112−116 °C; R_f = 0.63 (20% methanol/EtOAc); $[\alpha]^{25}_D$ = −55 (c = 1.0, MeOH); IR (thin film, cm^{-1}) 3411, 2974, 2934, 2866, 1639, 1454, 1123, 1042, 843; ^{1}H NMR (600 MHz, CD_3OD) δ 7.23−7.37 (m, 10H), 5.07 (d, J = 1.8 Hz, 1H), 4.92 (d, J = 1.8 Hz, 1H), 4.83 (d, J = 11.4 Hz, 1H), 4.78 (d, J = 1.8 Hz, 1H), 4.67 (d, J = 7.8 Hz, 1H), 4.66 (d, J = 11.4 Hz, 1H), 4.48 (s, 2H), 4.19 (dd, J = 3.0, 1.8 Hz, 1H), 4.07 (dd, J = 3.0, 1.8 Hz, 1H), 3.92 (dd, J = 9.6, 3.0 Hz, 1H), 3.85 (dq, J = 9.6, 6.0 Hz, 1H), 3.81 (dd, J = 9.6, 3.0 Hz, 1H), 3.79 (dd, J = 3.0, 1.8, Hz, 1H), 3.76 (dd, J = 9.6, 3.0 Hz, 1H), 3.74 (dq, J = 9.6, 6.0 Hz, 1H), 3.72 (dd, J = 9.6, 9.6 Hz, 1H), 3.65 (dq, J = 9.6, 6.0 Hz, 1H), 3.64 (s, 3H), 3.58 (dd, J = 9.6, 9.6 Hz, 1H), 3.54 (dt, J = 9.6, 6.0 Hz, 1H), 3.52 (dd, J = 9.6, 9.6 Hz, 1H), 3.49 (dq, J = 9.6, 6.0 Hz, 1H), 3.48 (t, J = 6.0 Hz, 2H), 3.42−3.49 (m, 1H), 3.40 (dt, J = 9.6, 6.0 Hz, 1H), 3.36 (dd, J = 9.6, 9.6 Hz, 1H), 3.19 (dd, J = 9.6, 7.8 Hz, 1H), 2.29 (s, 2H), 1.59 (m, 4H), 1.39 (m, 4H), 1.30 (d, J = 6.0 Hz, 3H), 1.25 (d, J = 6.6 Hz, 3H), 1.24 (d, J = 6.6 Hz, 3H), 1.23 (s, 3H), 1.22 (s, 3H), 1.21 (d, J = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, CD_3OD) δ 174.4, 140.2, 140.0, 129.5, 129.4, 129.0, 128.8, 128.7, 128.6, 105.6, 104.0, 103.6, 100.4, 85.9, 83.0, 81.9, 80.3, 79.2, 75.7, 74.5, 74.0, 73.4, 73.2, 72.3, 72.1, 71.9, 71.8, 71.4, 70.7, 70.6, 70.3, 70.0, 68.7, 67.0, 61.1, 57.1, 30.8, 30.6, 29.8, 29.6, 27.2, 27.1, 18.6, 18.3, 18.1, 18.0; CIHRMS calcd for [$C_{50}H_{77}NO_{19}Na^+$] 1018.4987, found 1018.4988.

***N*-((3*R*,5*S*,6*S*)-6-((2*S*,3*S*,4*S*,5*S*)-2-((2*S*,3*S*,4*S*,5*S*)-2-((2*R*,3*S*,4*S*,5*S*)-2-(6-Hydroxyhexyloxy)-4,5-dihydroxy-tetrahydro-6-methyl-2*H*-pyran-3-yloxy)-3,5-dihydroxytetrahydro-6-methyl-2*H*-pyran-4-yloxy)-3,5-dihydroxytetrahydro-6-methyl-2*H*-pyran-4-yloxy)-4-hydroxytetrahydro-5-methoxy-2-methyl-2*H*-pyran-3-yl)-3-hydroxy-3-methylbutanamide (51).** To a solution of Bn-ether **50** (350 mg, 0.35 mmol) in 3.5 mL of MeOH was added 10% Pd/C (100 mg). The reaction suspension was stirred under a hydrogen balloon for 24 h, filtered by passing through a Celite pad, and concentrated under reduced pressure and vacuo to give 277 mg of alcohol **51** (0. 34 mmol, 97%) as a white powder: mp 101−105 °C; R_f = 0.40 (30% methanol/EtOAc); $[\alpha]^{25}_D$ = −62 (c = 1.6, MeOH); IR (thin film, cm^{-1}) 3366, 2972, 2935, 2876, 1639, 1385, 1123, 1041, 987; ^{1}H NMR (600 MHz, CD_3OD) δ 5.13 (d, J = 1.8 Hz, 1H), 4.98 (d, J = 1.8 Hz, 1H), 4.85 (d, J = 1.8 Hz, 1H), 4.69 (d, J = 7.8 Hz, 1H), 4.26 (dd, J = 3.0, 1.8 Hz, 1H), 4.13 (dd, J = 3.0, 1.8 Hz, 1H), 3.99 (dd, J = 9.6, 3.0 Hz, 1H), 3.91 (dq, J = 9.6, 6.0 Hz, 1H), 3.87 (dd, J = 9.6, 3.0 Hz, 1H), 3.86 (dd, J = 3.0, 1.8, Hz, 1H), 3.82 (dd, J = 9.6, 3.0 Hz, 1H), 3.80 (dq, J = 9.6, 6.0 Hz, 1H), 3.74 (dq, J = 9.6, 6.0 Hz, 1H), 3.73 (s, 3H), 3.67 (dd, J = 9.6, 9.6 Hz, 1H), 3.64 (dd, J = 9.6, 9.6 Hz, 1H), 3.63 (dt, J = 9.6, 6.0 Hz, 1H), 3.62 (t, J = 6.0 Hz, 2H), 3.59 (dd, J = 9.6, 9.6 Hz, 1H), 3.50 (dq, J = 9.6, 6.0 Hz, 1H), 3.49 (dd, J = 9.6, 9.6 Hz, 1H), 3.48 (dd, J = 9.6, 9.6 Hz, 1H), 3.43 (dd, J = 9.6, 9.6 Hz, 1H), 3.09 (dd, J = 9.6, 7.8 Hz, 1H), 2.45 (m, 2H), 1.67 (m, 2H), 1.62 (m, 2H), 1.48 (m, 4H), 1.37 (d, J = 6.0 Hz, 3H), 1.36 (s, 3H), 1.35 (s, 3H), 1.32 (d, J = 6.6 Hz, 3H), 1.31 (d, J = 6.6 Hz, 3H), 1.28 (d, J = 6.6 Hz, 3H); ^{13}C NMR (67.5 MHz, CD_3OD) δ 174.7, 105.5, 104.0, 103.6, 100.4, 85.7, 81.9, 80.3, 79.2, 75.1, 74.5, 73.4, 73.1, 72.3, 71.9, 71.8, 71.1, 70.8, 70.7, 70.3, 70.0, 68.7, 68.1, 63.0,

61.3, 58.1, 33.7, 30.7, 29.8, 29.7, 27.3, 26.8, 18.6, 18.3, 18.1, 18.0; CIHRMS calcd for [$C_{36}H_{65}NO_{19}Na^+$] 838.4048, found 838.4045.

***N*-((3*R*,5*S*,6*S*)-6-((2*S*,3*S*,4*S*,5*S*)-2-((2*S*,3*S*,4*S*,5*S*)-2-((2*R*,3*S*,4*S*,5*S*)-2-(6-Methanesulfonoylhexyloxy)-4,5-dihydroxytetrahydro-6-methyl-2*H*-pyran-3-yloxy)-3,5-dihydroxytetrahydro-6-methyl-2*H*-pyran-4-yloxy)-3,5-dihydroxytetrahydro-6-methyl-2*H*-pyran-4-yloxy)-4-hydroxytetrahydro-5-methoxy-2-methyl-2*H*-pyran-3-yl)-3-hydroxy-3-methylbutanamide (2a).** To a solution of primary alcohol **51** (200 mg, 0.245 mmol) in 1.2 mL of CH_2Cl_2 and 1.2 mL of pyridine was added a 0.45 M CH_2Cl_2 solution of MsCl 62 μL at 0 °C. After 0.5 h, another 62 μL of MsCl solution was added again. The reaction mixture was stirred for 3 h at 0 °C, evaporated solvent under reduced pressure, and purified using silica gel flash chromatography eluting with 30% MeOH/CH_2Cl_2 to give 127 mg (0.142 mmol, 58%) mesylate **2a** as a white powder: mp 128−131 °C; R_f = 0.49 (30% methanol/EtOAc); $[\alpha]^{25}_D$ = −67 (c = 0.9, MeOH); IR (thin film, cm^{-1}) 3407, 2967, 2933, 2860, 1641, 1456, 1349, 1172, 1070, 982; ^{1}H NMR (600 MHz, CD_3OD and $CDCl_3$) δ 5.34 (d, J = 1.8 Hz, 1H), 5.19 (d, J = 1.8 Hz, 1H), 5.06 (d, J = 1.8 Hz, 1H), 4.95 (d, J = 7.8 Hz, 1H), 4.52 (t, J = 6.6 Hz, 1H), 4.45 (dd, J = 3.0, 1.8 Hz, 1H), 4.32 (dd, J = 3.0, 1.8 Hz, 1H), 4.18 (dd, J = 9.6, 3.0 Hz, 1H), 4.12 (dq, J = 9.6, 6.0 Hz, 1H), 4.10 (dd, J = 3.0, 1.8, Hz, 1H), 4.07 (dd, J = 9.6, 3.0 Hz, 1H), 4.04 (dd, J = 9.6, 3.0 Hz, 1H), 4.03 (dq, J = 9.6, 6.0 Hz, 1H), 3.95 (s, 3H), 3.94 (dq, J = 9.6, 6.0 Hz, 1H), 3.89 (dd, J = 9.6, 3.0 Hz, 1H), 3.88 (dd, J = 9.6, 9.6 Hz, 1H), 3.80 (dt, J = 9.6, 6.6 Hz, 1H), 3.79 (dd, J = 9.6, 9.6 Hz, 1H), 3.71 (dd, J = 9.6, 9.6 Hz, 1H), 3.70 (dq, J = 9.6, 6.0 Hz, 1H), 3.68 (dt, J = 9.6, 6.6 Hz, 1H), 3.65 (dd, J = 9.6, 9.6 Hz, 1H), 3.64 (dd, J = 9.6, 9.6 Hz, 1H), 3.34 (dd, J = 9.6, 7.8 Hz, 1H), 3.33 (s, 3H), 2.66 (m, 2H), 2.05 (m, 2H), 1.89 (m, 2H), 1.72 (m, 4H), 1.58 (d, J = 6.0 Hz, 3H), 1.57 (s, 3H), 1.56 (s, 3H), 1.56 (d, J = 6.6 Hz, 3H), 1.55 (d, J = 6.6 Hz, 3H), 1.51 (d, J = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, CD_3OD and $CDCl_3$) δ 174.4, 104.5, 103.4, 102.8, 99.7, 85.0, 82.0, 79.8, 79.1, 74.7, 73.8, 72.6, 72.5, 71.7, 71.2, 71.1, 70.9, 70.4, 70.0, 69.5, 69.3, 68.1, 61.2, 57.5, 37.5, 30.3, 30.0, 29.9, 29.8, 29.7, 29.3, 26.4, 26.0, 18.4, 18.0, 17.9, 17.8; CIHRMS calcd for [$C_{37}H_{67}NO_{21}SNa^+$] 916.3818, found 916.3824.

***N*-((3*R*,5*S*,6*S*)-6-((2*S*,3*S*,4*S*,5*S*)-2-((2*S*,3*S*,4*S*,5*S*)-2-((2*R*,3*S*,4*S*,5*S*)-2-(6-Azidohexyloxy)-4, 5-dihydroxytetrahydro-6-methyl-2*H*-pyran-3-yloxy)-3,5-dihydroxytetrahydro-6-methyl-2*H*-pyran-4-yloxy)-3,5-dihydroxytetrahydro-6-methyl-2*H*-pyran-4-yloxy)-4-hydroxytetrahydro-5-methoxy-2-methyl-2*H*-pyran-3-yl)-3-hydroxy-3-methylbutanamide (2).** To a solution of mesylate **2a** (134 mg, 0.15 mmol) in 2 mL of DMF was added NaN_3 (292 mg, 4.5 mmol). The reaction mixture was stirred at 60 °C for 15 h, and the solvent DMF was distilled under vacuo at 60 °C. The residue was purified using silica gel flash chromatography eluting with 30% MeOH/EtOAc to give azide anthrax tetrasaccharide **2** (110 mg, 0.13 mmol, 87%) as a white powder: mp 132−134 °C; R_f = 0.58 (30% methanol/EtOAc); $[\alpha]^{25}_D$ = −70 (c = 1.0, MeOH); IR (thin film, cm^{-1}) 3372, 2975, 2935, 2097, 1641, 1452, 1124, 1066; ^{1}H NMR (600 MHz, CD_3OD) δ 5.14 (d, J = 1.8 Hz, 1H), 4.99 (d, J = 1.8 Hz, 1H), 4.89 (d, J = 1.8 Hz, 1H), 4.71 (d, J = 7.8 Hz, 1H), 4.26 (dd, J = 3.0, 1.8 Hz, 1H), 4.14 (dd, J = 3.0, 1.8 Hz, 1H), 3.99 (dd, J = 9.6, 3.0 Hz, 1H), 3.92 (dq, J = 9.6, 6.0 Hz, 1H), 3.87 (dd, J = 9.6, 3.0 Hz, 1H), 3.86 (dd, J = 3.0, 1.8 Hz, 1H), 3.82 (dd, J = 9.6, 3.0 Hz, 1H), 3.81 (dq, J = 9.6, 6.0 Hz, 1H), 3.76 (dq, J = 9.6, 6.0 Hz, 1H), 3.74 (s, 3H), 3.68 (dd, J = 9.6, 9.6 Hz, 1H), 3.65 (dd, J = 9.6, 9.6 Hz, 1H), 3.62 (dt, J = 9.6, 6.0 Hz, 1H), 3.59 (dd, J = 9.6, 9.6 Hz, 1H), 3.52 (dd, J = 9.6, 9.6 Hz, 1H), 3.51 (dq, J = 9.6, 6.0 Hz, 1H), 3.50 (dt, J = 9.6, 6.6 Hz, 1H), 3.45 (dd, J = 9.6, 9.6 Hz, 1H), 3.37 (t, J = 7.2 Hz, 2H), 3.10 (dd, J = 9.6, 7.8 Hz, 1H), 2.46 (m, 2H), 1.69 (m, 4H), 1.50 (m, 4H), 1.38 (d, J = 6.0 Hz, 3H), 1.37 (s, 3H), 1.36 (s, 3H), 1.33 (d, J = 6.6 Hz, 3H), 1.32 (d, J = 6.6 Hz, 3H), 1.29 (d, J = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.7, 105.5, 104.0, 103.6, 100.4, 85.7, 82.0, 80.3, 79.2, 75.1, 74.5, 73.4, 73.2, 72.4, 72.3, 71.9, 71.8, 70.8, 70.7, 70.3, 70.0, 68.6, 61.3, 58.2, 52.5, 49.7, 30.6, 30.0, 29.8, 29.7, 27.7, 27.0, 18.6, 18.3, 18.1, 18.0; CIHRMS calcd for [$C_{36}H_{64}N_4O_{18}Na^+$] 863.4108, found 863.4113.

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Supporting Information Available: Complete experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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