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A Synthetic Oligosaccharide Resembling *Francisella tularensis* Strain 15 *O*-Antigen Capsular Polysaccharide as a Lead for Tularemia Diagnostics and Therapeutics

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Abstract: *Francisella tularensis*, a category A bioterrorism agent, causes tularemia in many animal species. *F. tularensis* subspecies *tularensis* (type A) and *holarctica* (type B) are mainly responsible for human tularemia. The high mortality rate of 30–60 % caused by *F. tularensis* subspecies *tularensis* if left untreated and the aerosol dispersal renders this pathogen a dangerous bioagent. While a live attenuated vaccine strain (LVS) of *F. tularensis* type B does not provide sufficient protection against all forms of tularemia infections, a significant level of protection against *F. tularensis* has been observed for both passive and active immunization of mice with isolated *O*-antigen capsular polysaccharide. Well-defined, synthetic oligosaccharides offer an alternative approach towards the development of glycoconjugate vaccines. To identify diagnostics and therapeutics leads against tularemia, a collection of *F. tularensis* strain 15 *O*-antigen capsular polysaccharide epitopes were chemically synthesized. Glycan microarrays containing synthetic glycans were used to analyze the sera of tularemia-infected and non-infected animals and revealed the presence of IgG antibodies against the glycans. Two disaccharide (**13** and **18**), both bearing a unique formamido moiety, were identified as minimal glycan epitopes for antibody binding. These epitopes are the starting point for the development of diagnostics and therapeutics against tularemia.

Introduction

Francisella tularensis, the causative agent of tularemia (rabbit fever), is an aerobic, Gram-negative, facultative intracellular bacterium. As a zoonotic pathogen, it can affect a variety of animals and can be transmitted to humans in different ways with various clinical outcomes.[1–6] *F. tularensis* can be the result of infected insect bites (in Germany mainly ticks), inhalation, ingestion of contaminated food or water, or inoculation through a break in the skin.[2] This highly virulent pathogen requires approximately ten organisms to cause disease in humans.[2–4] The disease outcome depends on the virulence of the infecting organisms and the infection route, where pneumonic tularemia is the most severe form with a 30–60 % mortality rate if left untreated.[7] Classified as a category A bioterrorism agent by the Center for Disease Control and Prevention (CDC), *F. tularensis* can be easily aerosolized for high infectivity in humans.[3] The subspecies *tularensis* (type A) and *holarctica* (type B) mainly cause human tularemia, with type A being more severe and life-threatening, while type B is more prevalent.[8]

A live attenuated vaccine strain of type B *F. tularensis* strain has been developed clinically but it did not provide complete protection against all forms of the infections especially against pulmonary infection caused by inhalation. A new defined subunit vaccine comprised of *F. tularensis* cell surface *O*-antigen components such as lipopolysaccharide (LPS), or *O*-antigen capsular polysaccharide (CPS) was developed.[7] Mice vaccinated with *O*-antigen from mild acid hydrolysis of *F. tularensis* LPS, conjugated with bovine serum albumin (BSA), showed complete protection against intradermal challenge with highly virulent type B strain and partial protection against aerosol challenge with more severe type A strain.[6] A highly branched synthetic hexasaccharide resembling inner core of *F. tularensis* LPS, unlike the full length LPS, did not elicit an antigenic response in mice.[9] The *O*-antigen capsular polysaccharide is an alternative for the development of diagnostics and vaccines against tularemia.

Interestingly, both type A *tularensis* and type B *holarctica* subspecies share a common *O*-antigen capsular polysaccharide on their cell surfaces[7] containing a tetrasaccharide repeating unit (RU) (←2)-*β*-D-Quip4NFm-(1→4)-α-D-GalNAcAN-(1→4)-α-D-GalNAcAN-(1→3)-*β*-D-QuipNAc-

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(1→) with one or two repeats sufficient to provide protection against tularemia (Figure 1).[7,8,9–12]

Bacterial capsular polysaccharides are promising vaccine candidates against a number of pathogens given their presentation of unique glycans at the termini.[13–16] Nevertheless, the advancement of vaccines, diagnostics, or therapeutic tools necessitates a comprehensive structural understanding concerning the glycan motif that is recognized by protective antibodies.[8,17] Although oligosaccharide fragments from *F. tularensis* can be obtained by mild hydrolysis of LPS, their isolation is hazardous.[9] Therefore, the chemical synthesis of oligosaccharide fragments resembling *F. tularensis* strains is an attractive alternative. A linker, such as 5-aminopentanol, at the reducing end allows for conjugation to carrier proteins or to the surface or arrays. The *O*-antigen repeating unit of *F. tularensis* strain 15 CPS consists of two rare deoxy amino sugars, *N*-acetyl-D-quinovosamine (QuipNAc) and *N*-formyl-4-amino-D-quinovose (Quip4NFm), and two *N*-acetyl-D-galactosamine uronamides (GalNAcAN).[1,7,9–12] The presence of two different types of rare deoxy amino sugars, two oxidative centers in D-galactosamine derivatives, two consecutive 1,2-*cis* α-glycosidic linkages, and three different *N*-functional groups in the RU provides a multitude of synthetic challenges. Here, we report the first total synthesis of oligosaccharide fragments resembling *O*-antigen capsular polysaccharide of *F. tularensis* strain 15 and corresponding epitopes. Glycan microarrays were employed for screening sera samples from infected and non-infected animals for the identification of minimal epitopes of synthetic glycans as leads for the development of diagnostics and vaccines against tularemia.

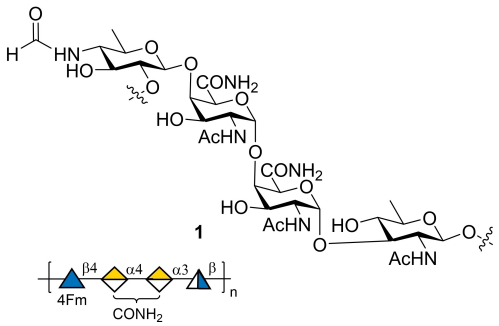


Figure 1. Repeating unit of the *O*-antigen capsular polysaccharide of *F. tularensis* strain 15.

Results and Discussion

Oligosaccharide Assembly

Glycans resembling *F. tularensis* strain 15 RU were chemically synthesized to identify epitopes. Retrosynthetic analysis of tetrasaccharide **2** bearing a 5-aminopentanol linker provides a framework for accessing various glycotopes for glycan microarray analysis (Figure 2). Target tetrasaccharide **2** can be obtained from fully protected tetrasaccharide **3** upon functional group interconversion (FGI) and global deprotection. Tetrasaccharide **3** contains a temporary protecting group on the D-galactosamines, enabling late-stage C-6 oxidation and subsequent modification. Moreover, the azido group on D-viosamine of **3** at the non-reducing end can be selectively reduced and functionalized forming the desired *N*-formamido group in the presence of *N*-trichloroacetyl (−NHTCA) groups. Protected tetrasaccharide **3** can be assembled via [3+1] glycosylation reaction between trisaccharide acceptor **4** and 4-azido-D-viosamine donor **5**. Trisaccharide acceptor **4** is assembled via sequential glycosylation between D-galactosamine donor **6** and linker

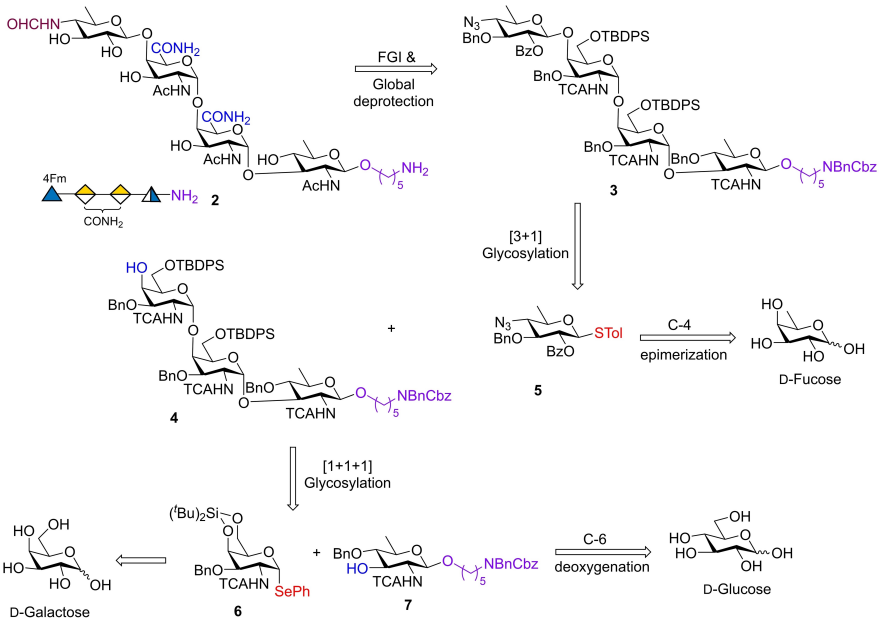


Figure 2. Retrosynthetic analysis of tetrasaccharide **2**.

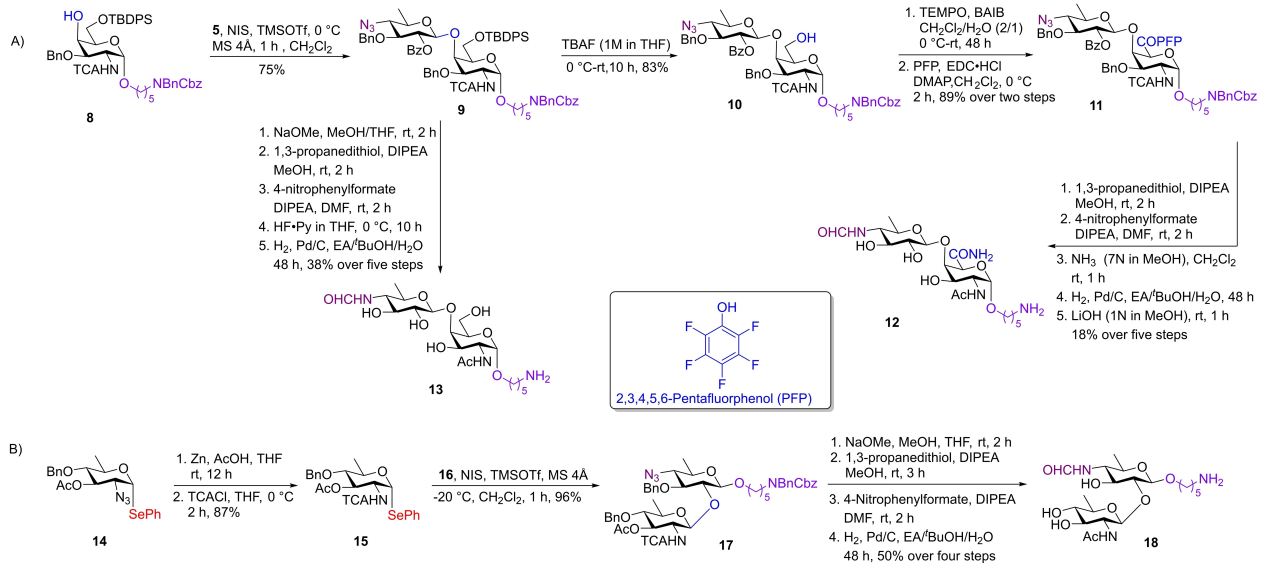
coupled D-quinovosamine 3-OH acceptor **7** followed by the hydrolysis of 4,6-di-*tert*-butylsilylidene group and regioselective protection of primary hydroxyl group with a *tert*-butyldiphenylsilyl (TBDPS). The 1,2-*cis*-glycosidic linkages on trisaccharide **4** can be formed by using a sterically hindering protecting group at the C-4 and C-6 positions on D-galactosamine. Monosaccharide building blocks **5**, **6**, and **7** can be synthesized from commercially-available sugars, such as D-fucose, D-galactose, and D-glucose (See the Supporting Information).

Based on the retrosynthetic analysis, the synthesis of 4-formamido containing disaccharide fragments and epitopes **12**, **13** and **18** are commenced (Scheme 1). First, D-galcatosamine acceptor **8** was glycosylated with D-viosamine donor **5** using NIS, TMSOTf as a promoter at 0 °C to obtain *β*-coupled disaccharide **9** in 75 % yield before treatment with TBAF (1 M in THF) to afford 6-OH disaccharide **10** in 83 % yield. Next, oxidation of disaccharide **10** was achieved by prolonged treatment (48 h) with catalytic amounts of TEMPO in the presence of BAIB in CH_2Cl_2/H_2O (2/1). The carboxylic compound was then further converted to its corresponding disaccharide pentafluorophenyl (PFP) ester **11** in 89 % yield over two steps. Later, the azido group at the C-4 center was selectively reduced to an amine by using 1,3-propanedithiol in DIPEA, MeOH[18] followed by reaction with 4-nitrophenylformate in DIPEA, DMF[19] at room temperature to afford the desired C-4 *N*-formamido disaccharide. Subsequently, pentafluorophenyl ester to amide conversion using ammonia (7 N solution in methanol) in CH_2Cl_2[20,21] followed by hydrogenolysis and finally LiOH treatment gave 4-formamido containing disaccharide uronamide **12** in 18 % yield over five steps (Scheme 1A).

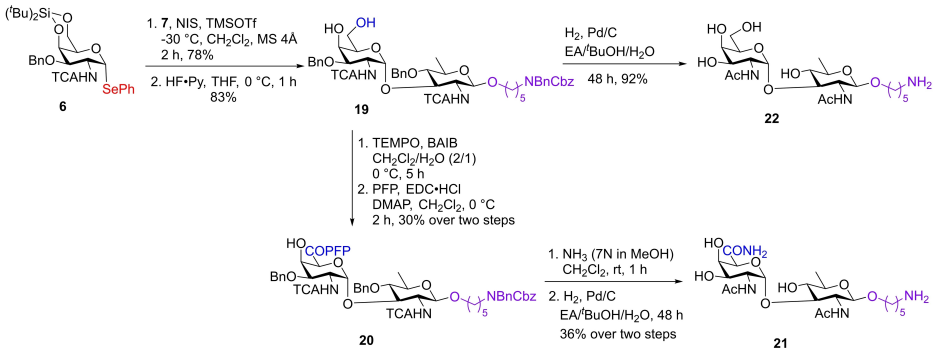
To access the non-oxidized disaccharide epitope **13**, we started from protected disaccharide **9** (Scheme 1A). Benzoyl ester cleavage under basic conditions was followed by reduction of the azide with 1,3-propanedithiol and selective *N*-formylation furnished the *N*-formamido glycan that upon removal of the TBDPS group with HF·Py followed by hydrogenolysis afforded disaccharide **13** in 38 % yield over five steps.

The synthesis of two rare sugars containing disaccharide glycotope **18** (Scheme 1B) started with known D-quinovosamine building block **14**[22] that was treated with zinc, acetic acid to obtain the corresponding amine that was treated with trichloroacetyl chloride (TCACl) to obtain desired D-quinovosamine donor **15** in 87 % yield over two steps. Glycosyl selenide **15** was reacted with D-viosamine acceptor **16** by using NIS, TMSOTf as a promoter at-20 °C to get complete *β*-linked disaccharide **17** in 96 % yield. Next, deacetylation under basic conditions, followed by azide reduction and regioselective *N*-formylation gave the formamido containing disaccharide before hydrogenolysis furnished the disaccharide **18** in 50 % yield over four steps.

The syntheses of reducing end disaccharide **21** and analog **22** (Scheme 2) commenced with the union of α-seleno-D-galactosamine donor **6** and D-quinovosamine acceptor **7** in the presence of NIS, TMSOTf at −30 °C to give α-glycosylated disaccharide in 78 % yield. The bulkier C-4,6 silylidene group in D-galactose or D-galactosamine results in highly α-stereoselective glycosylations even in the presence of participating C-2 neighboring groups.[23] The silylidene group on the disaccharide was then hydrolyzed by treatment with HF·Py to give diol disaccharide **19** in 83 % yield. For the oxidized reducing end disaccharide **21**, at first, the C-6 hydroxyl group of diol **19** was chemo-selectively oxidized by TEMPO in the presence of BAIB in CH_2Cl_2/H_2O (2/1) that was further converted to the PFP ester disaccharide **20** in 30 % yield over two steps. Next, the pentafluorophenyl ester was converted into the amide using NH_3 (7 N in MeOH) in CH_2Cl_2 followed by hydrogenolysis to provide disaccharide amide **21** in 36 % yield over two steps. To access disaccharide **22**, disaccharide diol **19** was subjected to hydrogenolysis to give deprotected disaccharide epitope **22** in 92 % yield.



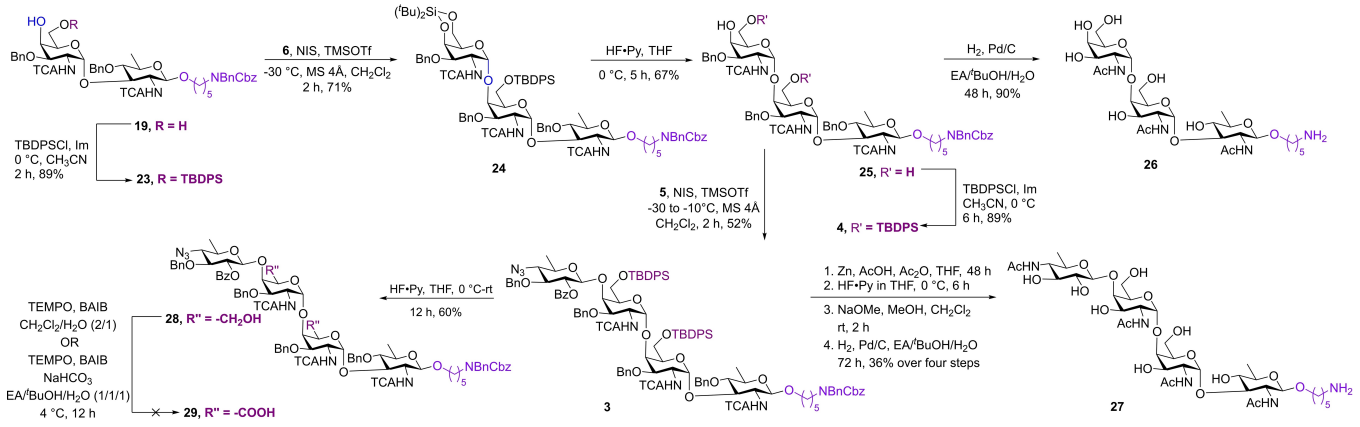
Scheme 1. A) Synthesis of *N*-formamido containing disaccharides **12** and **13**. B) Synthesis of rare sugars containing disaccharide **18**.



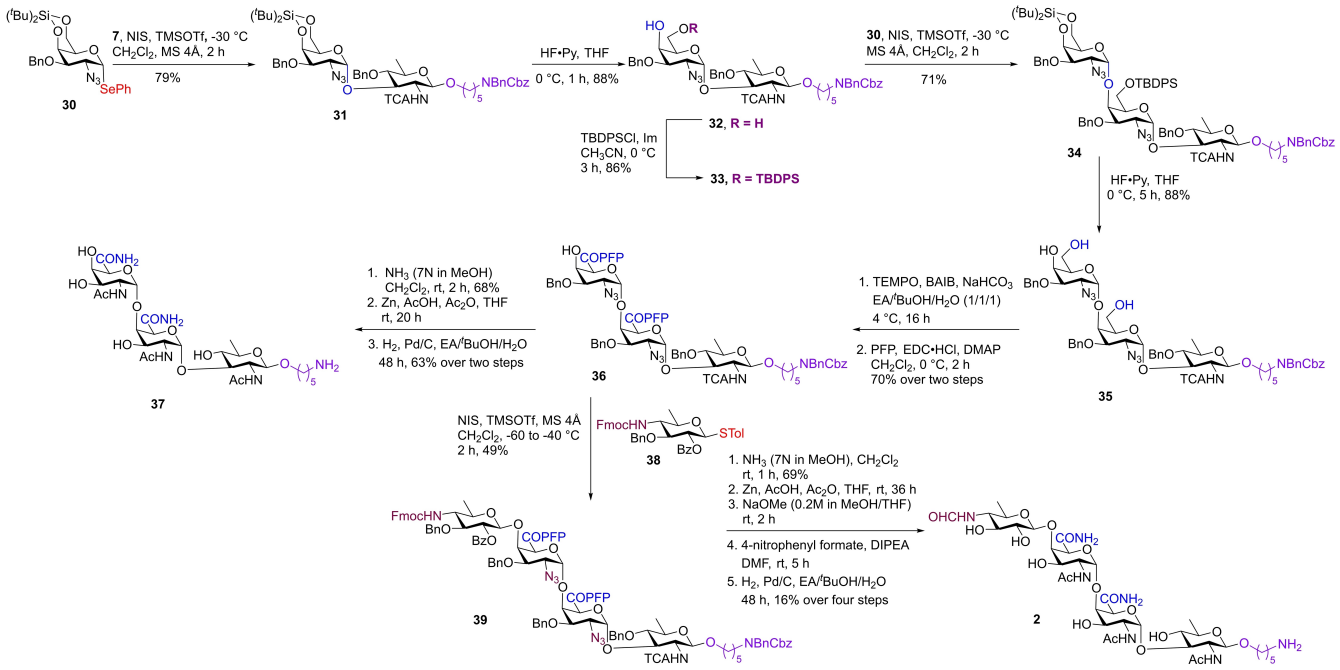
Scheme 2. Synthesis of disaccharides **21** and **22**.

Synthesis of trisaccharide epitope **26** and tetrasaccharide epitope **27** (Scheme 3) began with the selective protection of the C-6 hydroxyl group on disaccharide diol **19** with the bulky TBDPS group in the presence of imidazole in CH_3CN to obtain desired 4-OH disaccharide acceptor **23** in 89 % yield. Disaccharide acceptor **23** was glycosylated with donor **6** at −30 °C to get completely α-linked trisaccharide **24** in 71 % yield. Similarly, both the silylidene acetal and TBDPS group were cleaved using HF·Py at 0 °C to afford trisaccharide triol **25** in 67 % yield. Hydrogenolysis provided trisaccharide **26** in good yield (90 %). For the synthesis of tetrasaccharide epitope **27**, both primary hydroxyl groups in trisaccharide triol **25** were protected as TBDPS ethers to get C4-OH trisaccharide acceptor **4** in 89 % yield. Then, acceptor **4** was glycosylated with 4-azido D-viosamine donor **5** using NIS, TMSOTf at −30 to −10 °C to obtain *β*-linked tetrasaccharide **3** in 52 % yield. The moderate yield for this coupling is likely the result of the presence of bulky TBDPS groups as well as the lower nucleophilicity of the C-4 OH group. Next, both azide and NHTCA groups were converted to acetamide (NHAc) by zinc, acetic acid and acetic anhydride followed by silyl ether cleavage with HF·Py and subsequent benzoyl ester hydrolysis under basic conditions before hydrogenolysis afforded tetrasaccharide epitope **27** in 36 % yield over four steps.

With trisaccharide and tetrasaccharide epitopes **26** and **27** in hand, we undertook the synthesis of tetrasaccharide target **2**. TBDPS ether cleavage from protected tetrasaccharide **3** by HF·Py yielded 60 % of diol **28**. Double oxidation of diol **28** using TEMPO, BAIB in CH_2Cl_2/H_2O or $NaHCO_3$ in the presence of EA/^{t}BuOH/H_2O at 4 °C[24,25] resulted in decomposition of the starting material or glycosidic bond cleavage (Scheme 3). Similar results were observed for the oxidation of trisaccharide triol **25** as multiple NHTCA groups may result in glycosidic bond cleavage. The failed oxidation reactions on tetrasaccharide **28** and trisaccharide **25** prompted a modification of the synthetic strategy towards a pre-glycosylation-oxidation protocol (Scheme 4). D-Galactosamine donor **30**[25] was reacted with acceptor **7** at −30 °C to obtain α-linked disaccharide **31** in 79 % yield before treatment with HF·Py provided disaccharide diol **32**. The synthesis of trisaccharide triol **35** was performed in three steps. First, the C-6 hydroxyl group on disaccharide **32** was protected with a bulkier TBDPS group to obtain the corresponding 4-OH disaccharide acceptor **33** that was glycosylated with D-galactosamnine donor **30** using NIS, TMSOTf at −30 °C to obtain protected trisaccharide **34** before silyl ether cleavage with HF·Py provided triol **35** in 88 % yield. The double oxidation proceeded in good yield at this stage. Both primary hydroxyl groups in **35** were converted to the corresponding carboxylic acids using



Scheme 3. Synthesis of trisaccharide **26** and tetrasaccharide **27**.



Scheme 4. Synthesis of trisaccharide amide **37** and tetrasaccharide **2**.

catalytic amounts of TEMPO in the presence of BAIB, $NaHCO_3$ at 4 °C[24] in a heterogeneous solvent system of ethyl acetate, ^{t}BuOH and water. The dicarboxylic derivative was converted to the dipentafluorophenyl diester in the presence of EDC·HCl, and catalytic amounts of DMAP to afford trisaccharide diester **36** in 70 % yield. After the successful synthesis of trisaccharide ester **36**, our next aim was to obtain trisaccharide epitope **37** and target tetrasaccharide **2**. For the synthesis of diamide trisaccharide **37**, first both the pentafluorophenyl ester were converted to the amides using ammonia followed by conversion of the azide and NHTCA groups to NHAc using zinc, acetic acid and acetic anhydride and final hydrogenolysis reaction to obtain oxidized trisaccharide amide **37** in 63 % yield.

The synthesis of tetrasaccharide **2** started from the union of trisaccharide diester **36** and D-viosamine donor **38** at −60 to −40 °C in the presence of NIS and TMSOTf (0.5 equiv.) to furnish fully protected diester tetrasaccharide **39** in 49 %. Functional group interconversion and global deprotection of **39** mandated a judicious choice of deprotection reactions to avoid the formation of unwanted side products. Initially, base-labile PFP esters were converted to amides using ammonia to obtain diamide tetrasaccharide in 69 % yield followed by conversion of azido and NHTCA groups to acetamide upon treatment with zinc, acetic acid and acetic anhydride to furnish the corresponding *N*-acetyl tetrasaccharide. Fmoc and benzoate (Bz) groups were hydrolyzed under basic conditions to obtain C-4 amine. Regioselective *N*-formylation with 4-nitrophenylformate and DIPEA followed by hydrogenolysis gave desired target tetrasaccharide **2** in 16 % yield over four steps.

The synthetic glycans were immobilized in triplicates on glass slides to detect antibodies in serum samples derived from tularemia positive and negative animals (Figure 3 and Figure S1). The sera of tularemia positive pigs showed significantly higher IgG antibody binding to the monosaccharide **43**, the disaccharides **12**, **13**, **18**, **21** and trisaccharide **37** as well as tetrasaccharides **2** and **27** compared to tularemia negative pigs (Figure 3). Significant higher IgG antibody binding to monosaccharide **42**, disaccharides **12**, **13** and **18**, trisaccharide **26** and tetrasaccharide **2** were observed in sera of tularemia positive horses. Monosaccharide **43**, disaccharides **21**, **13** and **18** as well as trisaccharide **26** were recognized by antibodies in sera of tularemia positive cats and cheetahs. Tularemia positive dogs showed IgG antibody binding to the monosaccharide **43**, the disaccharides **13**, **12**, **18** and tetrasaccharide **2**, whereas the sera of tularemia negative rabbits showed IgG antibody binding of monosaccharides **40**, **41** and **42** (See Supporting Information, Figure S1). These experiments identified disaccharides **13** and **18** as leads for the development of diagnostic tools and therapeutics.

Conclusion

We describe the first total synthesis of glycans resembling *O*-antigens of capsular polysaccharides from *Francisella tularensis* strain 15. In order to define key immunogenic epitopes, total thirteen glycans were synthesized. Highly 1,2-*cis* α-stereoselective glycosylations were achieved by employing bulkier silylidene ethers. A variety of different oxidation protocols were explored for each glycan fragment. Milder conditions[19] were used for the installation of a formamido group on the 4,6-dideoxy-D-quinovosamine sugar unit than previously reported protocol.[26,27] A pre-

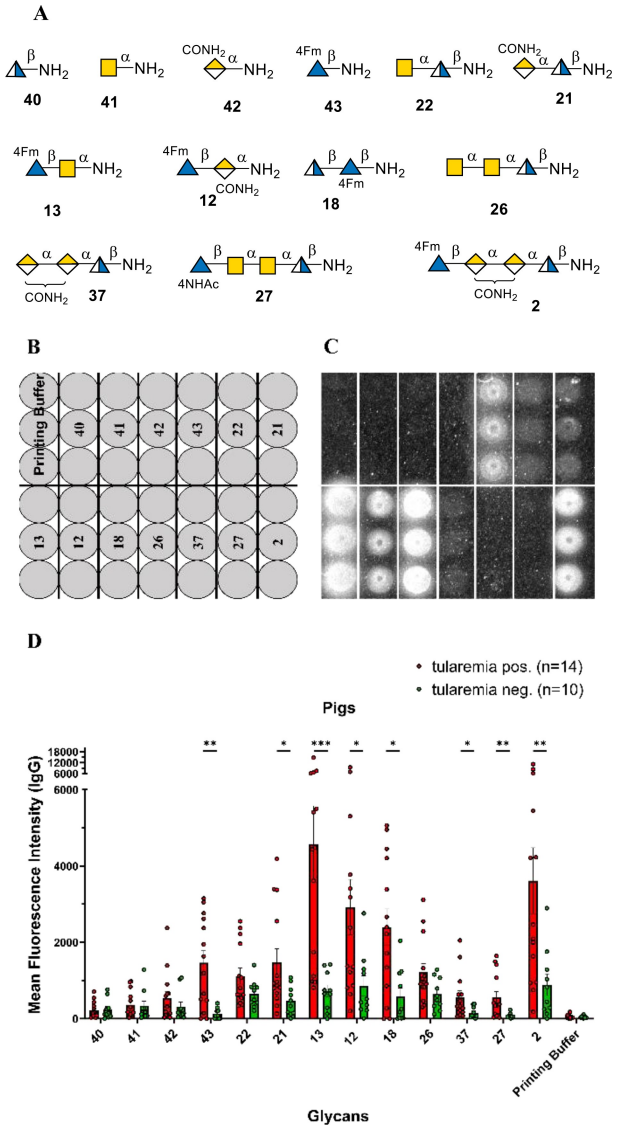


Figure 3. Structures of synthetic glycans (A) and glycan microarray analysis of *F. tularensis* related glycans (B–D). (B) Printing pattern of glycan microarray. (C) Exemplary binding pattern of pig serum to immobilized synthetic glycans. (D) Mean Fluorescence Intensity of IgG antibody binding to synthetic glycans. The sera are derived from tularemia positive (pos.; red) and negative (neg.; green) pigs. A serum dilution of 1 : 100 was used. Values represent mean ± SEM. Differences were tested for significance to tularemia negative animals using multiple Mann-Whitney test with (***) $p < 0.001$, (**) $p < 0.01$ and (*) $p < 0.05$.

glycosylation-oxidation protocol was developed to synthesize the densely nitrogen functionalized tetrasaccharide. The challenging assembly of tetrasaccharide **2** provides guidance for the synthesis of similar oligosaccharides. Glycan microarray results indicated that antibodies against disaccharide **13** and **18** can be detected in a significantly higher level in infected animals compared to non-infected animals suggesting the importance of *N*-formamido groups in identifying antibody recognition.[12] Antibodies against disaccharide **13** clearly showed that the D-galactosamine unit is more effective than the D-galacto uronamide. The minimal epitope required is a disaccharide unit. Glycans **13** and **18** are promising leads for diagnostics and therapeutics development against tularemia.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: *Francisella tularensis* · Rare-deoxy amino sugars · Total synthesis · Minimal epitope · Glycan-Immunology

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