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Automated Glycan Assembly of Mycobacterial Hexaarabinofuranoside and Docosasaccharide Arabinan (Araf_{23}) Motifs found on *Mycobacterium tuberculosis*

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Abstract: *Mycobacteria* are covered in a thick layer of different polysaccharides that helps to avert the innate immune response. Lipoarabinomannan (LAM) and arabinogalactan (AG) are ubiquitously contained in these envelopes, and rapid access to defined oligo- and polysaccharides is essential to elucidate their structural and biological roles. Arabinofuranose (Ara*f*) residues in LAM and AG are connected either via α-1,2-*trans* linkages that are synthetically straightforward to install or the more challenging β-(1,2-*cis*) linkages. Herein, it was demonstrated that automated glycan assembly (AGA) can be used to quickly prepare 1,2-*cis*-β-Ara*f* as illustrated by the assembly of a highly branched arabinan hexasaccharide and a docosasaccharide arabinan (Araf_{23}) motif.

Introduction

Mycobacterium tuberculosis (*M.tb*), the etiological agent of tuberculosis (TB) uses diverse strategies to survive the host immune surveillance, resulting in latent tuberculosis.[1] Lipoarabinomannan (LAM) and arabinogalactan (AG) are two major structural components of the mycobacterial cell wall that both contain arabinan albeit with slight differences in their core motifs.[2]

The synthesis of structurally defined oligosaccharides has focused more on the assembly of polypyranosides than polyfuranosides. Numerous syntheses of *M.tb* lipopolysaccharide cell wall components[3] have enabled the elucidation of substrate specificities in biological settings.[4] The stereocontrolled β-arabinofuranosylation is challenging because 1,2-*cis* glycosidic linkages[5] cannot rely simply on anchimeric assistance to exercise stereocontrol. The simultaneous installation of two1,2-cis-β-arabinofuranosyl residues on two nucleophiles in the same molecule[6] was key to the first total synthesis of an arabinan dodecasaccharide via a convergent fragment approach.[7] Later, stereoselective β-arabinofuranosylation via intramolecular aglycon delivery (IAD)[8] also gave rise to an arabinan docosaccharide. A tridecasaccharide[9] and heneicosasaccharyl Man-LAM were prepared using orthogonally protected alkynyl glycosyl carbonates as glycosylating agents that are activated by [Au]/[Ag] catalysis.[10] This approach was extended in a "cassette approach" to the convergent synthesis of heneicosafuranosyl arabinogalactan (HAG).[11] A highly convergent iterative one-pot glycosylation strategy utilizing 3,5-O-tetraisopropyldisiloxanylidene[12] protected thioglycosides empowered the total synthesis of 92-mer mycobacterial arabinogalactan.[13] Recently, a solution-phase synthesizer was employed in the one-pot block coupling of oligo- and polysaccharide fragments to construct glycans as large as a linear 1080-mer.[14] To date, hyper branched arabinan motifs have not been prepared in automated fashion. Automated glycan assembly (AGA),[15] based on the solid phase synthesis paradigm, has proven fast and reliable in preparing a host of pyranose[16] and furanose[17] polysaccharides. To illustrate the power of AGA, we here disclose the stereoselective syntheses of highly branched arabinan hexasaccharide **1** and docosasaccharide arabinan (Araf_{23}) **2** as examples for challenging 1,2-*cis*-β-Ara*f* containing oligosaccharide motifs (Figure 1).

Results and Discussion

The target oligosaccharides **1** and **2** can be prepared using AGA employing the building blocks **4**, **5**, **6** and **7** that carry judiciously selected orthogonal protecting groups (Figure 1). The syntheses of thioglycoside building blocks **4**, **5** and **7** commenced from thioglycoside **8**.[18] Selective protection of the primary hydroxyl as corresponding trityl ether, followed by benzoylation furnished the thioglycoside and subsequent acid-mediated removal of the trityl group provided **9**. Fmoc carbonylation of the hydroxyl in compound **9** afforded the desired thioglycoside building block **4** in excellent yield. Using di-*tert*-butylsilylbis(trifluoromethanesulfonate) and 2,6-

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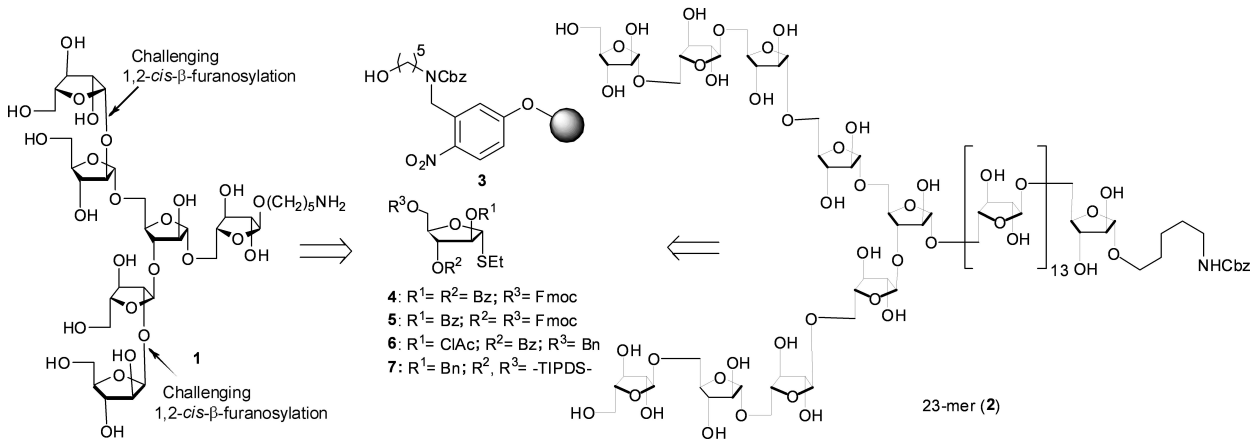


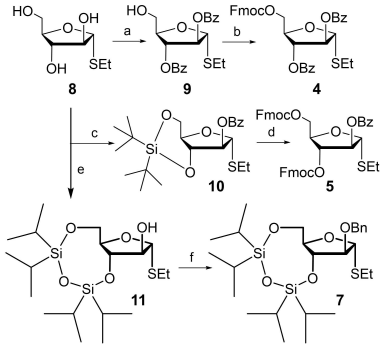
Figure 1. Retrosynthetic analysis of arabinan hexasaccharide **1** and docosasaccharide arabinan (Araf_{23}) **2**.

lutidine, thiofuranoside **8** was converted to the silyl acetal, which was further converted to fully protected compound **10** by benzoylation. Selective removal of the silyl acetal protection by treatment with HF·Py gave access to the diol, which upon Fmoc protection resulted in building block **5**. In order to install the challenging 1,2-cis-β-arabinofuranosyl linkages at the non-reducing end of **1**, we chose conformationally locked 3,5-*O*-tetraisopropyldisiloxanylidene protected thiofuranoside **7**.[12] Access to building block **7** required 3,5-O-cyclic protection of thiofuranoside **8** using 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane to generate the corresponding 3,5-*O*-tetraisopropyldisiloxanylidene **11**, followed by benzylation (Scheme 1).

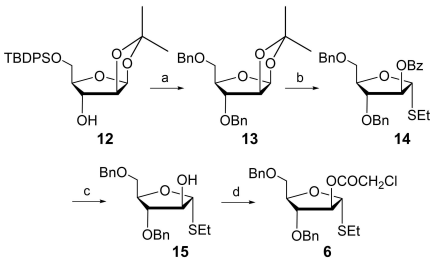
For the synthesis of building block **6**, arabinofuranose **12**[19] was treated with TBAF and the resulting diol was further converted to fully protected **13**. Corresponding thiofuranoside **14** was prepared from **13** by aqueous acetic acid-mediated hydrolysis of acetonide protection, benzoylation, and subsequent coupling of an anomeric mixture of benzoyl furanoside with ethanethiol in the presence of $BF_3{\cdot}OEt_2$. Methanolysis under Zemplen conditions was followed by a reaction with chloroacetyl chloride in the presence of DMAP and pyridine furnished thiofuranoside **6** (Scheme 2).

With thiofuranoside building blocks **4**, **5**, **6** and **7** in hand, polystyrene resin containing the photocleavable aminopentanol linker **3** was placed in the reaction vessel of the automated synthesizer to prepare branched arabinan hexasaccharide **1**. Initially, branched arabinan tetramer **16** was prepared with representative building blocks using a four-step AGA process consisting of acidic wash, glycosylation, capping to mask unreacted nucleophiles, and removal of the temporary protecting group. Analysis of the automated synthesis products using analytical HPLC and MALDI-TOF (Figure S1) revealed that the automated process delivered the target tetramer **16** (Scheme 3). Arabinan tetramer **16**, was subjected to selective removal of the chloroacetate groups in the presence of the benzoate esters using thiourea on the automated synthesizer to deliver diol **17** (Scheme 3).

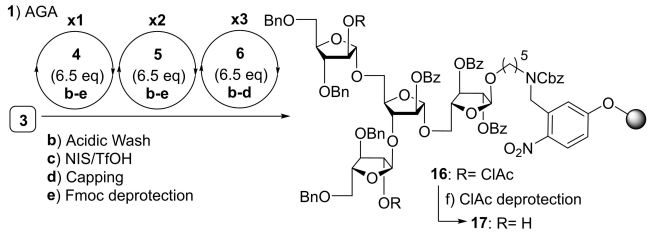
Having established an efficient automated synthesis of tetramer **17**, the stage was set for 1,2-*cis*-β-arabinofuranosylations in a single step. In addition to the type of arabinofuranosyl building block, the temperature is crucial in maintaining the selectivity of arabinofuranosylations.[6] AGA of tetramer **17** using conformationally constrained thiofuranoside **7** at −75 °C afforded the desired hexasaccharide **18** (Scheme 4).



Scheme 1. Synthesis of building blocks **4**, **5** and **7**. Reagents and conditions: (a) (i) TrCl, Py., then PhCOCl, pyridine; (ii) *p*-TSA, MeOH, 72% (two steps); (b) FmocCl, pyridine, CH_2Cl_2, 93%; (c) (i) *t*-$Bu_2Si(OTf)_2$, 2,6-lutidine; (ii) PhCOCl, pyridine, 68% (2 steps); (d) (i) HF/pyridine, THF; (ii) FmocCl, pyridine, 50% (2 steps); (e) TIPDSCl, pyridine, 86%; (f) BnBr, NaH (60%), DMF, 90%.



Scheme 2. Synthesis of building block **6**. [a]Reagents and conditions: (a) (i) 1M TBAF, THF; (ii) BnBr, NaH (60%), DMF, 97%. (two steps); (b) (i) AcOH/H_2O, 50 °C; (ii) PhCOCl, pyridine, 65% (two steps); (iii) EtSH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 72%; (c) NaOMe, MeOH/CH_2Cl_2, 97%; (d) $ClCH_2COCl$, pyridine, 4-DMAP, 83%.



Scheme 3. Synthesis of α-D-(1→5),α-D-(1→3)-linked branched arabinan tetramer **16** using building blocks **4**, **5** and **6**.

Analysis of the HPLC trace of crude **18** (Figure S3), made us wonder whether the tethered 1,1,3,3-tetraisopropyldisiloxanes in **18** render the compounds so non-polar that they elute together. Skeptical about the stereoselective outcomes of the β-arabinofuranosylations at low temperatures, we cleaved the TIPDS protection in **18** on resin using TASF as a mild anhydrous fluoride source, followed by benzoylation to furnish fully protected arabinan hexamer **19** (Scheme 4). Then, the arabinan hexamer **19** was released from the polymer support by UV irradiation using a continuous flow device. After functional group interconversions, the HPLC trace showed protected arabinan hexamer **19** as the major product along with compounds containing α-arabinofuranosyl linkages.

The desired product was purified by preparative HPLC and the structural integrity of protected highly branched arabinan hexasaccharide **19** was confirmed by ^{1}H, ^{13}C NMR, as well as MALDI mass spectrometry. The stereoselective generation of β-arabinofuranosyl linkages by automated glycan assembly was determined by NMR spectroscopy.[20] Six signals in the anomeric region of the ^{13}C NMR of compound **19**, indicate two distinct upfield shifted peaks (101.0 and 100.7 ppm) that correspond to β-arabinofuranosyl residues. Chemical shift correlation and structural elucidation **19** was in good agreement with literature reports.[6] Fully protected hexasaccharide **19** was treated with sodium methoxide to cleave all benzoate ester groups, followed by $Pd(OH)_2$/C-catalyzed hydrogenolysis in the presence of hydrogen furnished highly branched arabinan hexasaccharide **1** (2 mg).

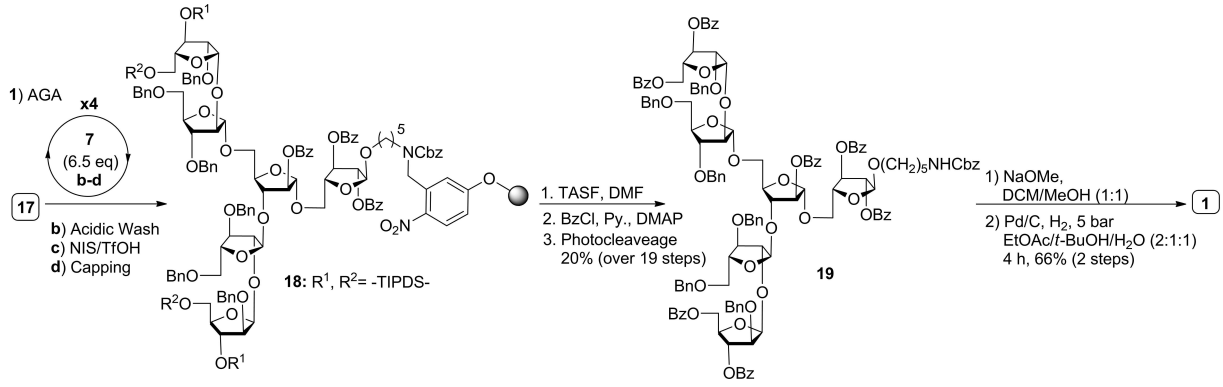
With an AGA process to prepare arabinan hexasaccharide **1** in hand, we challenged the limits of oligofuranoside assembly to make the framework of the target docosasaccharide arabinan (Araf_{23}) motif **20** utilizing building blocks **4** and **5**. Initially, linear Araf_8 was assembled using building block **4** with polystyrene Merrifield resin equipped with photocleavable linker **3** at the reducing-end terminus. Then, Araf_8 acceptor immobilized on the resin was subjected to nine iterative AGA cycles, afforded Araf_{17} by incorporating building blocks **4** and **5**. Thioglycoside **4** was added simultaneously onto the reactive sites to form α-D-(1→5), α-D-(1→3)-linked Araf_{17} that was characterized (Figure S5). Subsequent formation of docosasaccharide arabinan (Araf_{23}) **20** was achieved upon reacting α-D-(1→5), α-D-(1→3)-linked Araf_{17} with thioglycoside **4** and **5**. Following AGA, the resin was subjected to UV irradiation using a continuous flow device[21] to cleave the protected α-D-(1→5), α-D-(1→3)-linked docosasaccharide arabinan (Araf_{23}) motif **20** from the resin. Purification by normal phase HPLC revealed Araf_{23} **20** (13 %) and the structure was characterized thoroughly. Methanolysis of fully protected Araf_{23} (**20**) under Zemplen conditions furnished Araf_{23} **2** (42 %) (Scheme 5).

Conclusion

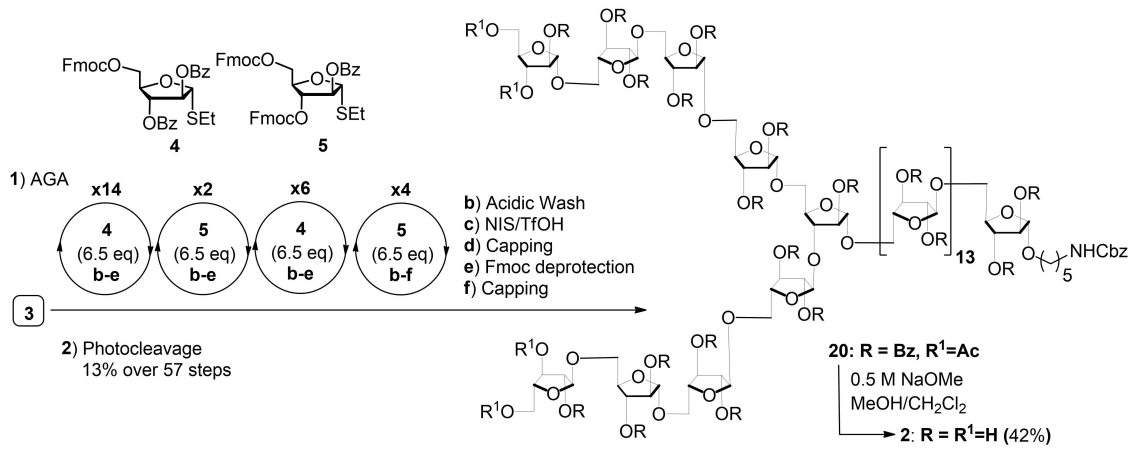
We disclosed the first automated glycan assembly of a hexaarabinofuranoside containing 1,2-*cis*-β-Ara*f* residues, as well as the docosasaccharide arabinan (Araf_{23}) motif. Key to a robust AGA process are protected orthogonal thiofuranoside building blocks that will be helpful for the synthesis of other arabinose containing glycans found in the envelope of *Mycobacterium tuberculosis.*

Experimental Section

Automated Synthesis: Solvents used for dissolving building blocks and preparing the activator, TMSOTf and capping solutions were taken from an anhydrous solvent system (jcmeyer-solvent systems). Other solvents used were HPLC grade. The building blocks were co-evaporated three times with toluene and dried 2 h under high vacuum before use. Activator, deprotection, acidic wash, capping



Scheme 4. Synthesis of α-D-(1→5),α-D-(1→3),β-D-(1→2)-linked highly branched arabinan hexamer **1**.



Scheme 5. Synthesis of α-D-(1→5),α-D-(1→3)-linked docosasaccharide arabinan (Araf_{23}) motif **2**.

and building block solutions were freshly prepared and kept under argon during the automation run. All yields of products obtained by AGA were calculated based on resin loading. Resin loading was determined by performing one glycosylation (Module C) with ten equivalents of building block followed by DBU promoted Fmoc-cleavage and determination of dibenzofulvene production by measuring its UV absorbance. Automated syntheses were performed on a home-built synthesizer developed at the Max Planck Institute of Colloids and Interfaces.[22] Merrifield resin LL (100–200 mesh, NovabiochemTM) was modified and used as solid support.[23]

Preparation of Stock Solutions[24]

Building block: building block was dissolved in 1 mL dichloromethane (DCM).

Activator solution: Recrystallized NIS (1.56 g) was dissolved in 60 mL of a 2:1 mixture of anhydrous CH_2Cl_2 and anhydrous dioxane. Then triflic acid (67 μL) was added. The solution was kept at 0 °C for the duration of the automation run.

Fmoc deprotection solution: A solution of 20% piperidine in dimethylformamide (DMF) (v/v) was prepared; or A solution of 5% DBU in dichloromethane (CH_2Cl_2) (v/v) was prepared.

TMSOTf solution: Trimethylsilyltrifluoromethanesulfonate (TMSOTf) (0.9 mL) was added to DCM (80 mL).

Capping solution: A solution of 10% acetic anhydride (Ac_2O) and 2% methanesulfunic acid (MsOH) in anhydrous CH_2Cl_2 (v/v) was prepared.

ClOAc deprotection solution: A solution of 2.5 g of thiourea in a mixture of 2-methoxyethanol (50 mL) and pyridine (5 mL) was prepared.

Modules for Automated Synthesis

Module A: Resin Preparation for Synthesis (20 min): All automated syntheses were performed on 140 μmol scale (40 mg). Resin was placed in the reaction vessel and swollen in DCM for 20 min at room temperature prior to synthesis. During this time, all reagent lines required for the synthesis were washed and primed. Before the first glycosylation, the resin was washed with the DMF, tetrahydrofuran (THF), and CH_2Cl_2 (three times each with 2 mL for 25 s). This step is conducted as the first step for every synthesis.

Module B: Acidic Wash with TMSOTf Solution (20 min): The resin was swollen in CH_2Cl_2 (2 mL) and the temperature of the reaction vessel was adjusted to −20 °C. Upon reaching the temperature, TMSOTf solution (1 mL) was added drop wise to the reaction vessel. After bubbling for argon 3 min, the acidic solution was drained and the resin was washed with 2 mL CH_2Cl_2 for 25 s.

Module C: Thioglycoside Glycosylation (20–60 min): The building block solution (0.095–0.123 mmol (5–6.5 equivalents) of BB in 1 mL of CH_2Cl_2 per glycosylation) was delivered to the reaction vessel. After the set temperature (−20 °C) was reached, the reaction was started by drop wise addition of the activator solution (1.0 mL, excess). The glycosylation was performed by increasing the temperature to 0 °C for 20–60 min (depending on oligosaccharide length). After completion of the reaction, the solution is drained and the resin was washed with CH_2Cl_2, CH_2Cl_2:dioxane (1:2, 3 mL for 20 s) and CH_2Cl_2 (twice, each with 2 mL for 25 s). The temperature of the reaction vessel is increased to 25 °C for the next module.

Module D: Capping (30 min): The resin was washed with DMF (twice with 2 mL for 25 s) and the temperature of the reaction vessel was adjusted to 25 °C. Pyridine solution (2 mL, 10% in DMF) was delivered into the reaction vessel. After 1 min, the reaction solution was drained and the resin washed with CH_2Cl_2 (three times with 3 mL for 25 s). The capping solution (4 mL) was delivered into the reaction vessel. After 20 min, the reaction solution was drained and the resin washed with CH_2Cl_2 (three times with 3 mL for 25 s).

Module E: Fmoc Deprotection (14 min): The resin was washed with DMF (three times with 2 mL for 25 s) and the temperature of the reaction vessel was adjusted to 25 °C. Fmoc deprotection solution (2 mL) was delivered into the reaction vessel. After 5 min, the reaction solution was drained and the resin washed with DMF (three times with 3 mL for 25 s) and CH_2Cl_2 (five times each with 2 mL for 25 s). The temperature of the reaction vessel is decreased to −20 °C for the next module.

Module F: ClOAc Deprotection: The resin is first washed with CH_2Cl_2 (3×2 mL for 15 s) then ClOAc deprotection Solution (2 mL) was delivered to the reaction vessel. The temperature of the reaction vessel is then adjusted to and maintained at 90 °C by microwave irradiation (max power = 180 W). After 22 min, the reaction solution is drained from the reaction vessel. The resin is washed with DMF (3×2 mL for 15 s). Then fresh ClOAc deprotection Solution 2 (2 mL)

is delivered and the process is repeated twice more. Then, the resin is washed with DMF (3×3 mL for 15 s) and CH_2Cl_2 (5×3 mL for 15 s). After this module the resin is ready for the next glycosylation cycle.

Post-Synthesizer Manipulations

Cleavage from Solid Support: After automated synthesis, the oligosaccharides were cleaved from the solid support using a continuous-flow photo reactor as described previously.[21,16a,25]

Purification: Solvent was evaporated in vacuo and the crude products were dissolved in a 1:1 mixture of hexane and ethyl acetate and analyzed using analytical HPLC (DAD1F, 280 nm). Pure compounds were afforded by preparative HPLC (Agilent 1200 Series spectrometer).

Method A: (YMC-Diol-300 column, 150×4.6 mm) flow rate of 1.0 mL/min with Hex-20% EtOAc as eluents [isocratic 20% EtOAc (5 min), linear gradient to 60% EtOAc (5 min), linear gradient to 60% EtOAc (30 min), linear gradient to 100% EtOAc (5 min)].

Method B: (Luna® 5 μm Silica column, 250×4.6 mm) flow rate of 1.0 mL/min with Hex-20% EtOAc as eluents [isocratic 20% EtOAc (5 min), linear gradient to 60% EtOAc (5 min), linear gradient to 60% EtOAc (30 min), linear gradient to 100% EtOAc (5 min)].

Method C: (Hypercarb, 150×10 mm) flow rate of 4.0 mL/min with water (0.1% formic acid) as eluents [isocratic (5 min), linear gradient to 10% ACN (30 min), linear gradient to 100% ACN (5 min)].

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: automated glycan assembly · glycosylation · *Mycobacterium tuberculosis* · oligoarabinofuranosides · solid-phase synthesis

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