Synthesis of Conjugation Ready Bacterial Trisaccharide Repeating Unit of *Staphylococcus aureus* Strain M

4th Synthesis in Drug Discovery and Development

P01

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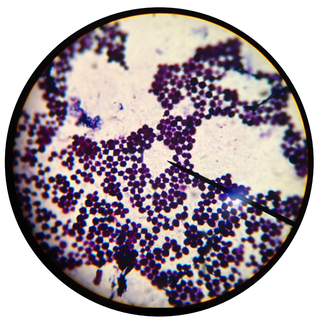
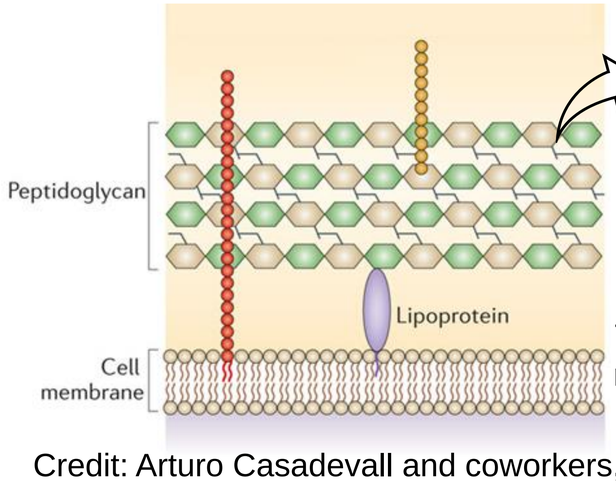
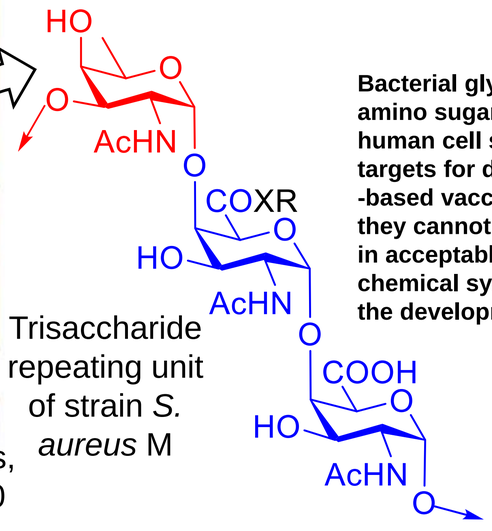


Microscopic Image of Gram-stained *S. aureus* (PC: Kaylee Dolloff/flickr)

- Colonizes ~30% of humans
- Mostly asymptomatic colonizer
- Opportunistic & devastating invasive pathogen
- Colonization and pathogenicity depends on strains/variants
- Strains can be identified by unique glycan sequences



Credit: Arturo Casadevall and coworkers, *Nat. Rev. Microbiol.,* 2015, **13**, 620–630

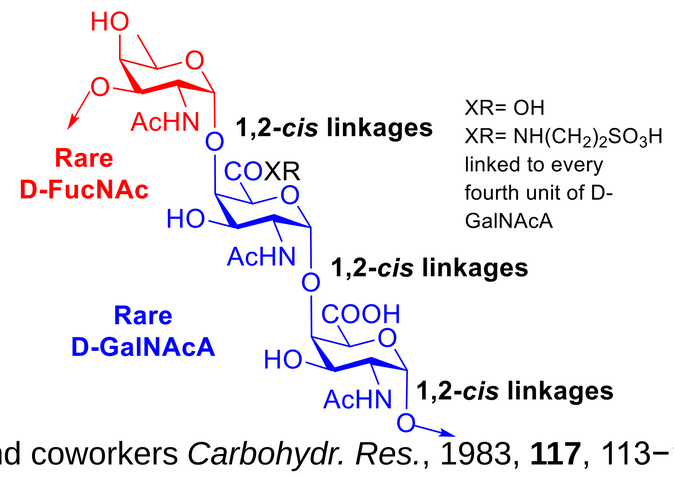


Trisaccharide repeating unit of strain *S. aureus* M

Bacterial glycoconjugates contains deoxy amino sugars that are not present on the human cell surface, making them good targets for drug discovery and carbohydrate -based vaccine development. Unfortunately, they cannot be isolated with sufficient purity in acceptable amounts, and therefore, chemical synthesis is a crucial step toward the development of these products.

Synthetic challenges in target molecule

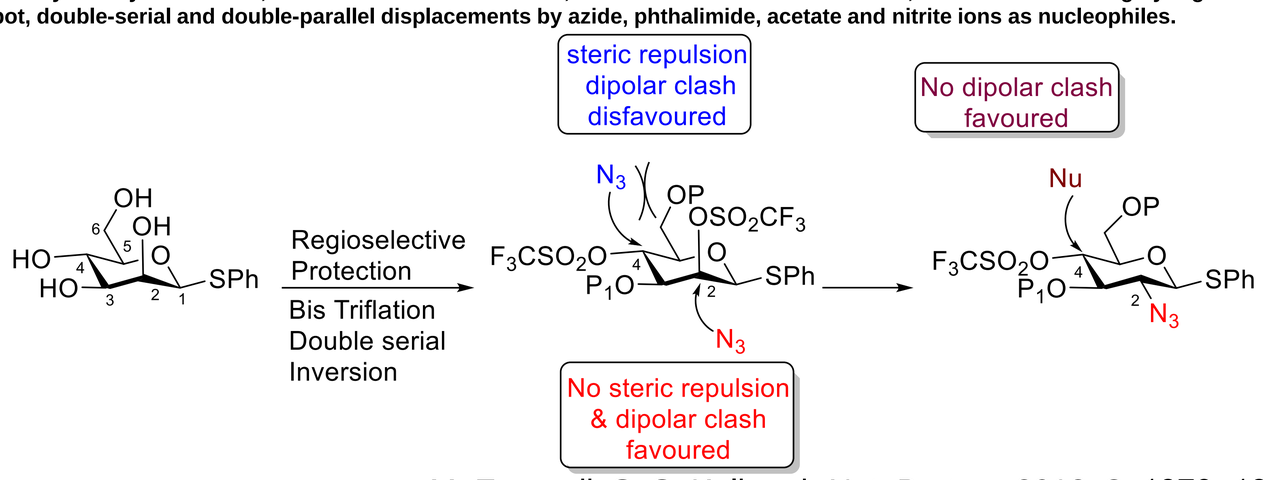
→4)-O-(2-acetamido-2-deoxy-α-D-galactopyranosyl uronic acid)-(1→4)-O-(2-acetamido-2-deoxy-α-D-galactopyranosyl uronic acid)-(1→3)-2-acetamido-2-deoxy-α-D-fucopyranosyl-(1→



J. H. Hash and coworkers *Carbohydr. Res.*, 1983, **117**, 113−123.

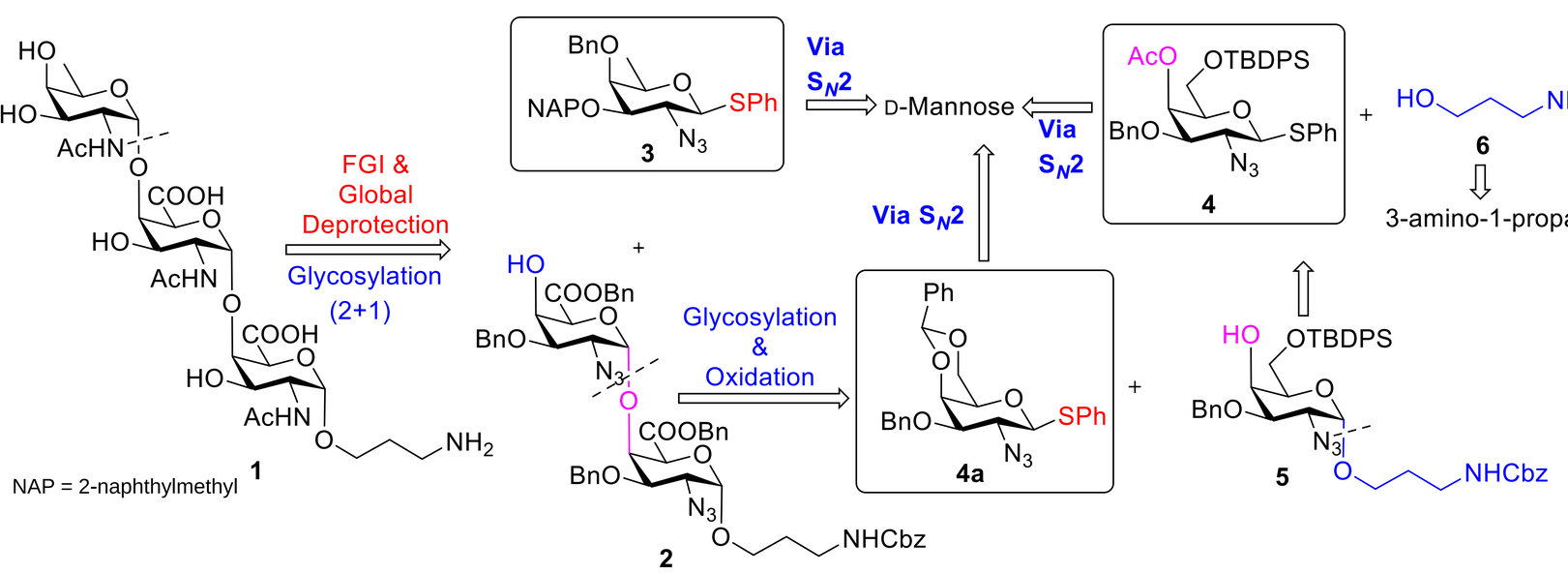
Lab methodology: Double serial/ parallel triflation inversion

Readily available β-D-thiophenylmannoside was first converted into the corresponding 2,4-diols via deoxygenation or silylation at C6, followed by O3 acylation. the 2,4-diols were converted into 2,4-bis-trifluoromethanesulfonates, which underwent highly regioselective, one-pot, double-serial and double-parallel displacements by azide, phthalimide, acetate and nitrite ions as nucleophiles.



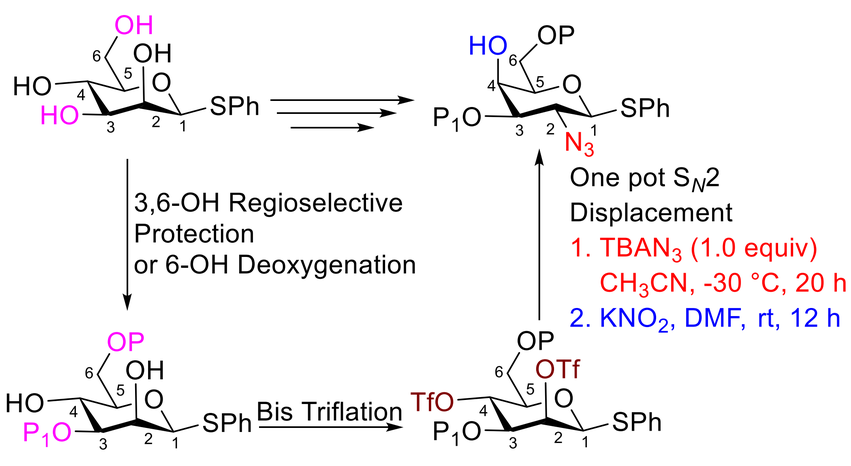
M. Emmadi, S. S. Kulkarni, *Nat. Protoc.*, 2013, **8**, 1870−1879.

Retrosynthetic strategy



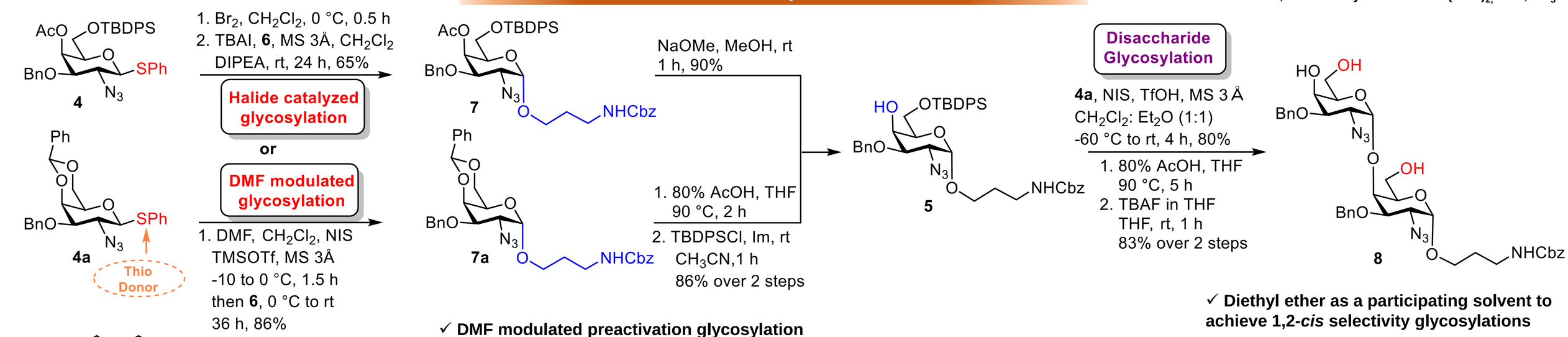
Compound **3:** Behera, A.; Rai, D.; Kulkarni, S. S. *J. Am. Chem. Soc.* **2020**, *142*, 456–467.

Synthesis of building blocks



6-OH protection= TBDPSCl, Imidazole, CH_3CN, rt
6-OH deoxygenation= i) TsCl, Pyridine, 0° C to rt
ii) LAH, THF, 85 °C
3-OH protection= i) Bu_2SnO, toluene, 110 °C
ii) BnBr/ NAPBr, TBAB
toluene, 90 °C/ 70 °C
2, 4-OH triflation= Tf_2O, Pyridine, 0 °C
6-OTBDPS removal= TBAF in THF
4, 6-OH benzylidene= $PhCH(OMe)_2$, CSA, CH_3CN

Forward synthesis



✓ **DMF modulated preactivation glycosylation 1,2-*cis*-selectivity in the case of linker**

✓ **Diethyl ether as a participating solvent to achieve 1,2-*cis* selectivity glycosylations**

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✓ **Longest linear sequence of 24 steps with an overall yield of 4.5%**

✓ **Target molecule has an aminopropyl linker attached to its reducing end allowing it to conjugate with carrier protein for further immunological evaluation.**

Ready for the protein conjugation

Trisaccharide RU of *S. aureus* Strain M

A. A. Shirsat, D. Rai, B. K. Ghotekar, S. S. Kulkarni, *Org. Lett.*, 2023, **25**, 2913−2917.

Acknowledgment

We thank all our lab mates. We would also like to thank department of chemistry and funding agencies-