Chemical Desymmetrization of Trehalose

Chemically Modifying Trehalose Mycolates

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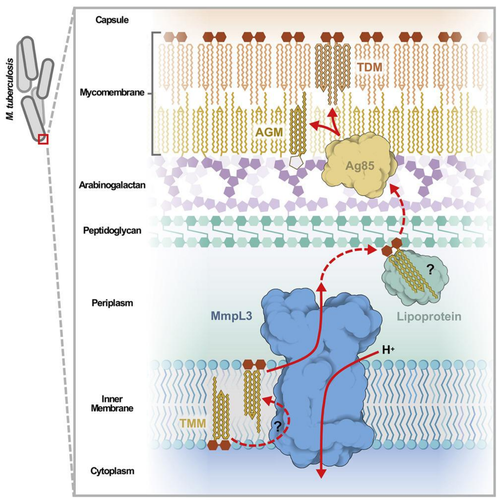
Introduction

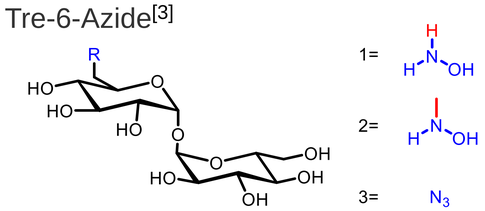
- Tuberculosis is caused by *Mycobacterium tuberculosis* (*Mtb*)
- Complex structure of the mycobacterial cell wall contributes to its virulence
- Mycobacterial membrane protein Large 3 (MmpL3) required for transport of trehalose monomycolates (TMMs) across cell membrane for cell wall synthesis[1]



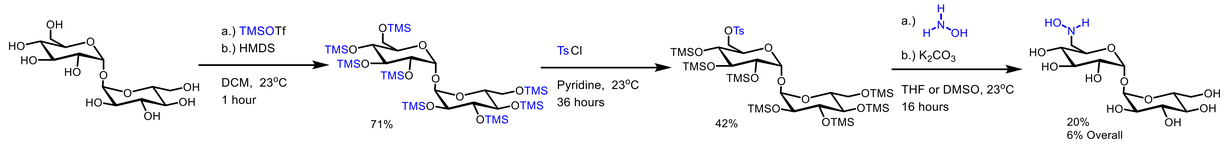
MmpL3 location within Mtb call wall[2]

Synthesis

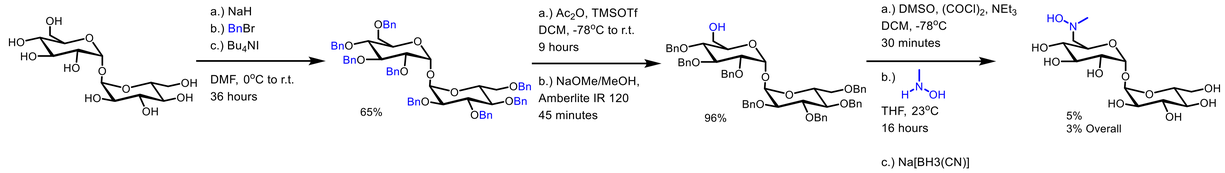
- Analogues of endogenous TMMs
- Tre-6-N-Hydroxylamine
- Tre-6-N-Methylhydroxylamine
- Tre-6-Azide[3]



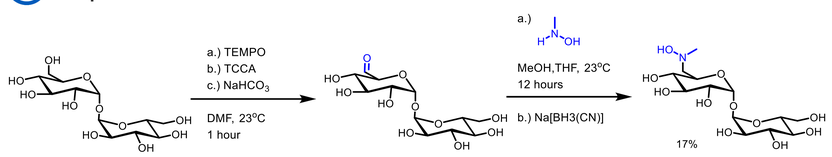
A Protected S_N2



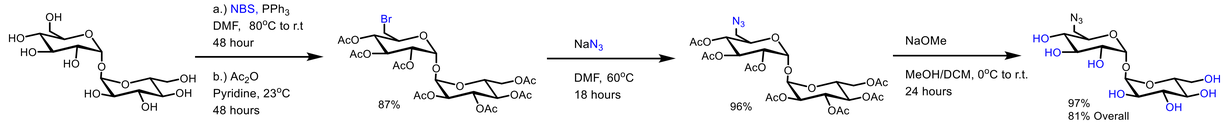
B Reductive Amination



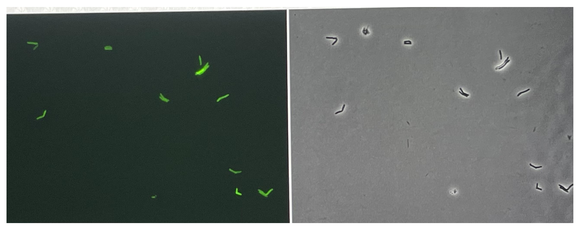
C Unprotected Reductive Amination



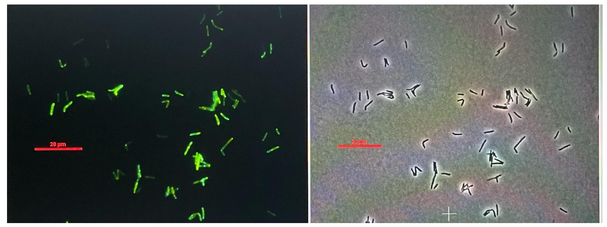
D Modified Appel



Metabolic Incorporation



6-NMeOHTre
(12.5 μM)



6-AzTre
(25 μM)

Conclusion

- Overcame selectivity issues in 6 and 6' positions
- Achieved protecting-group-free synthesis with NMeOH-Tre
- Observed improved overall yields
- Successful metabolic engineering
- Compounds were incorporated into *Mycobacterium smegmatis* and *Mycobacterium marinum* cell walls

Future Directions

- Drug assay development
- Glycolipid interactomics

Funding

- UTA Start-Up
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- UTA iEngage Fellowship

References

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2.Adams O, Deme JC, Parker JL, Fowler PW, Lea SM, Newstead S. 2021 Jul. Cryo-EM structure and resistance landscape of M. tuberculosis MmpL3: An emergent therapeutic target. Structure. doi:https://doi.org/10.1016/j.str.2021.06.013.

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