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Towards a Shortened Synthesis of Lipid II and its Analogues

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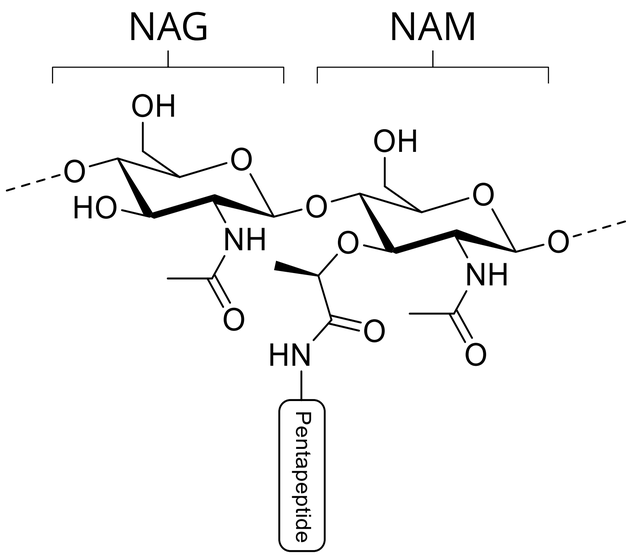
1. Introduction

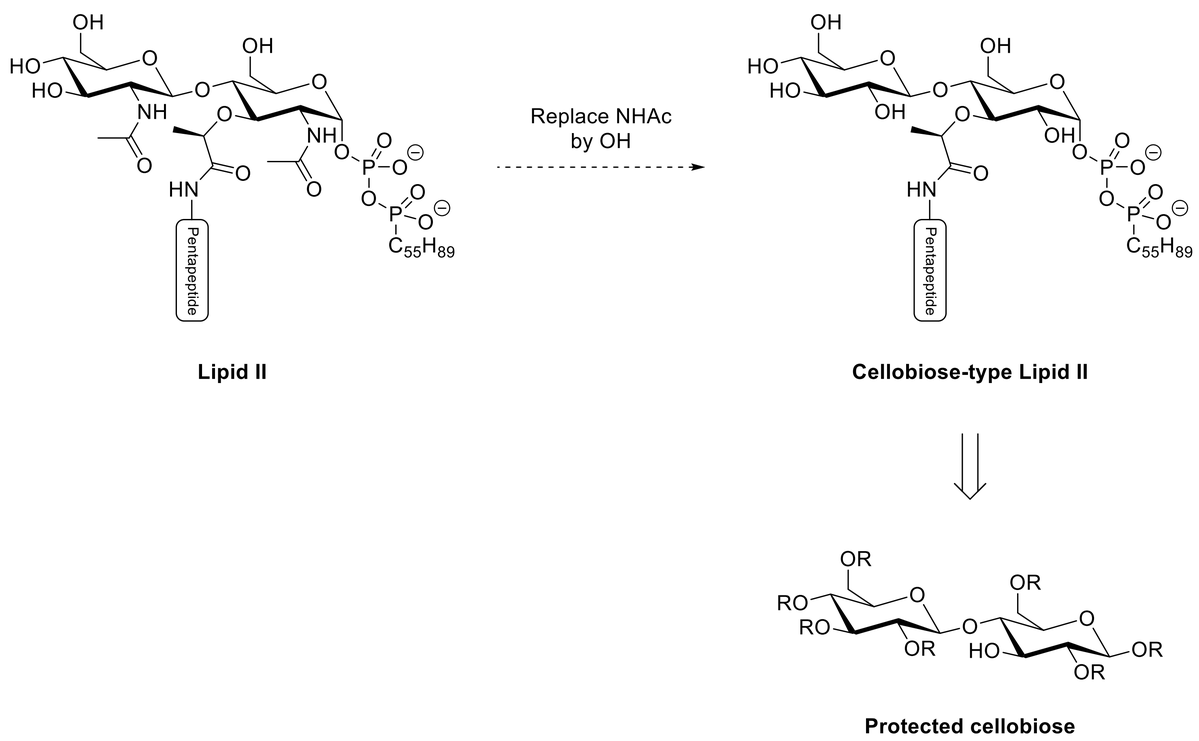
- Due to rising antimicrobial resistance, existing antibiotic drugs are losing their effectiveness. Antibiotic drugs with new modes of action are urgently needed.
- The bacterial cell wall is a common and easily accessible target for antibiotic drugs. It is made of peptidoglycan, which consists of alternating NAG-NAM units linked to a pentapeptide.
- Peptidoglycan glycosyltransferases (PGTs) are enzymes involved in the elongation of peptidoglycan chains by appending Lipid II, the monomeric precursor to peptidoglycan.
- PGTs are relatively poorly studied, and currently no commercially available drug targets them.
- The difficulty in studying PGTs is in part due to the laborious synthesis of Lipid II, which involves many rounds of protection and deprotection, resulting in very low overall yields.



Structure of the repeating unit of peptidoglycan

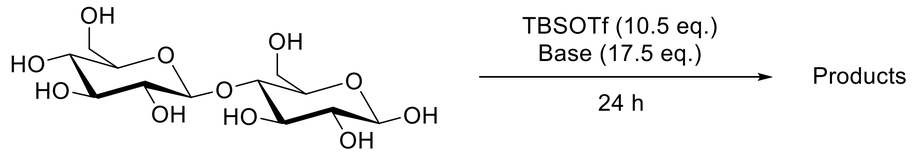
2. Methodology

- We propose a shortened synthesis starting from the unfunctionalized disaccharide and using only one protecting group: the *tert*-butyldimethylsilyl (TBS) group.
- Due to the high cost of chitobiose (the disaccharide core of Lipid II), we used cellobiose as the starting material and a model compound.
- The silylation of cellobiose was investigated to see if the appropriately-substituted cellobiose can be obtained directly.
- Reactions were performed using TBS triflate (TBSOTf), a highly reactive silylating agent.
- Conditions varied: Solvent, base, temperature



Proposed strategy for a shortened synthesis of Lipid II and its analogues (R = protecting group)

3. Results & Discussion



Reaction	Solvent	Base	Temperature
1	DCM	2,6-lutidine	0 °C → rt
2	DCM	2,6-lutidine	0 °C
3*	DCM	2,6-lutidine	rt
4	DMF	2,6-lutidine	0 °C → rt
5	DMF	2,6-lutidine	rt → 40 °C
6	DMF	Imidazole	rt
7	DMF	Imidazole	rt → 40 °C

*TBSOTf added portionwise at 30 min intervals, 1.1 eq. per portion

- **Solvent:** Reactions in DCM generally afforded the fully-silylated cellobiose. Reactions proceeded better in DMF.
- **Base:** Reactions with imidazole yield the hexa-silylated cellobiose as the most substituted product. Using 2,6-lutidine gives products with greater substitution.
- **Temperature:** Mild heating speeds up the sluggish reaction.
- Unfortunately, difficulties with the purification meant that the possible desired product could not be isolated and characterised in time.

4. Future Directions

- Further reaction optimization to increase yield
- Improve the purification method
- Determine the structure of the possible desired product