PROGRESS REPORT

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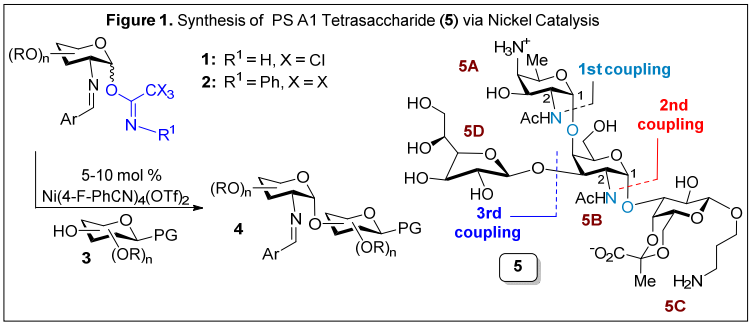
(A) ABSTRACT:

Although the use of vaccines to combat infectious diseases has greatly improved human health, they are poorly immunogenic and requires multiple doses for protection. As such, vaccines are co-administered with an adjuvant to enhance immunity. Numerous classes of vaccine adjuvants have been developed and showed the desired immune response over the past several decades. Unfortunately, only a few adjuvants are considered to be sufficiently potent and clinically liable for use in humans. In efforts to discover new vaccine adjuvants, zwitterionic polysaccharides (ZPSs), containing both negative and positive charge motifs in their repeating units, were found to activate $CD4^+$ T-cell-*dependent* immune responses and modulate host cytokine responses to bacterial infection. One of the best characterized ZPSs is zwitterionic polysaccharide PS A1, isolated from capsular *Bacteroides fragilis*. Studies showed that glycoconjugates, generated from conjugation of PS A1 to mucin antigen T_N, elicits high titer antibodies that are specific and selective for the T_N hapten. Despite the promise of PS A1 as a potential adjuvant, obtaining it from natural sources is a complicated process of extraction and purification that results in the production of minute, relatively impure quantities and could alter its structure. The objective of this project is to address this unmet challenge through the chemical synthesis of PS A1 tetrasaccharide **5** (Figure 1). A nickel-catalyzed selective coupling methods developed in our group are utilized to connect **5A** – **5D** leading to formation of **5**.

Figure 1. Synthesis of PS A1 Tetrasaccharide (**5**) via Nickel Catalysis



The first sugar unit was **5A** (Figure 1), which was prepared from glucosamine in 8 steps in gram scale. The second sugar **5B** was also prepared from glucosamine in 10 steps. Synthesis of **5C** started from D-galactose and 1,3-aminoalcohol linker. Galactofuranose **5D** was prepared from a known thiolglycoside donor. Next, the coupling of **5B** acceptor with **5A** donor utilizing our nickel catalyissi provided the desired disaccharide in good yield with excellent selectivity. The coupling of **5C** acceptor with the disaccharide intermediate mediated by the nickel catalyst provided the desired trisaccharide with excellent selectivity. Attempts to perform the coupling to generate the trisaccharide intermediate with donor **5D** to ultimately form PSA1 **5** and its analogs are underway and will be reported in due course.