The First Diastereoselective Total Synthesis of 6-L-glycero-α-D-ido-Heptopyranose Related to Campylobacter jejuni HS:3

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Abstract:

Diarrheal diseases remain a major global public health concern, with Campylobacter jejuni recognized as a leading bacterial cause of gastroenteritis worldwide[1]. Certain C. jejuni serotypes are also strongly associated with post-infectious complications, most notably Guillain–Barré syndrome (GBS)[2]. The capsular polysaccharide (CPS) of C. jejuni HS:3 features an unusual, α(1→4)-linked repeating disaccharide composed of 6-L-glycero-α-D-ido-heptopyranose and α-D-galactose, which bears a non-stoichiometric O-2 methyl phosphoramidate substituent on the heptose residue (Figure 1)[3,4]. Here, we report an efficient and highly diastereoselective approach to synthesize the unique allyl 6-L-glycero-α-D-ido-heptopyranoside (1, Figure 1) from D-galactose to serve as a vaccine candidate for immunological studies.

Two key stereochemical challenges were successfully addressed during the development of this synthetic route toward the rare heptose antigen. The first challenge involved establishing a diastereoselective methodology to construct the 6-L-glycero-D-galacto-heptose framework, which required precise control over the stereochemical outcome during the seven-carbon backbone elongation and its subsequent separation from the 6-D-glycero-D-galacto-heptose epimer. The second challenge required converting the 6-L-glycero-D-galacto-heptose configuration into the desired 6-L-glycero-D-ido-heptose configuration. To achieve this, a double-inversion strategy at C-2 and C-3 was developed to efficiently transform the 6-L-glycero-D-galacto-configured precursor into a 2,3-epoxy 6-L-glycero-D-talo-heptopyranosyl intermediate. Subsequent one-pot, highly regio- and stereoselective nucleophilic ring-opening of this 2,3-epoxide successfully afforded the targeted core.

The conformational flexibility of the resulting 6-L-glycero-D-ido-heptopyranoside adds further synthetic and analytical complexity. Despite the potential for the targeted monosaccharide to undergo ring flipping between the $^{4}C_{1}$, $^{1}C_{4}$, and $^{O}S_{2}$ conformations, our NMR studies confirmed that the $^{4}C_{1}$ conformer predominates in solution. This preference is likely stabilized by favorable intramolecular hydrogen bonding networks between the OH-2/OH-4 and OH-3/O-1 pairs. Ultimately, this work successfully addressed a key synthetic challenge associated with the core structure of Campylobacter jejuni HS:3.

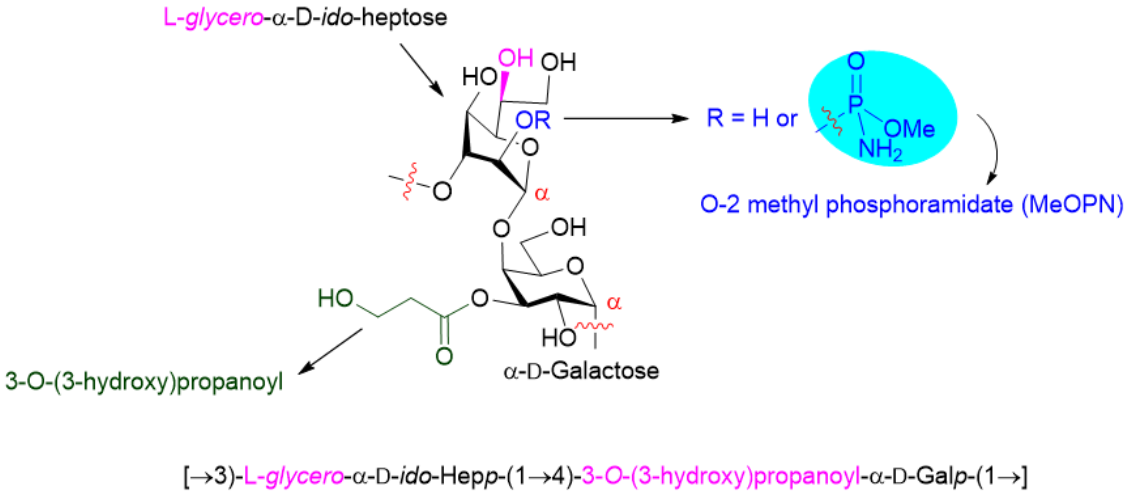

Fig. 1. Chemical structures of repeating disaccharides related to capsular polysaccharides of C. jejuni HS:3