Total Chemical Synthesis of a Glycoprotein by Native Chemical Ligation

Significance: The authors have developed a new approach for the synthesis of unprotected thioesters by using Fmoc-based solid-phase peptide synthesis and have demonstrated its utility in the total synthesis of a glycosylated protein, the antimi-
crobial O-linked glycoprotein diptericin, by the na-
tive chemical ligation method. This method utilizes
an alkanesulfonamide ‘safety-catch’ linker, which
circumvented the problems associated with the in-
compatibility of glycosidic linkages with Boc chem-
istry and of thioesters with Fmoc chemistry.

Comment: The C-terminal residue of the peptide
is attached to the resin through an acid- and base-
stable N-acyl sulfonamide linkage. After peptide
synthesis, the sulfonamide is activated by cyano-
methylation and then cleaved with a thiol nucleo-
phile. This general synthetic approach permits ac-
cess to unprecedented quantities of homogeneous
glycoproteins.

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