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Review

C-5 Modifications in *N*-acetyl-neuraminic acid: scope and limitations

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Abstract—Glycoconjugates containing sialic acid are involved in a large variety of biological phenomena, including cell–cell adhesion, recognition by viruses and bacteria, and oncogenesis. Therefore, they are important synthetic targets for the design of drugs and vaccines. In the last decades, different methodologies that improve yield and stereoselectivity in sialylation reactions have been investigated. This review summarizes the latest developments in the synthesis of C-5 modified sialic acid glycosyl donors and glycosyl acceptors and their application in the synthesis of α-sialosides.

Keywords: Sialylation; Amino protecting groups; Glycosylation; Stereoselectivity

Contents

1. Introduction

Glycoconjugates containing sialic acid are important synthetic targets due to their active participation in a wide variety of biological phenomena, ranging from cell–cell adhesion and recognition, to pathogen attack and oncogenesis.[1–4] The most widespread sialic acid is *N*-acetyl-neuraminic acid (Neu5Ac, Fig. 1), which is naturally found α-(2→3) or α-(2→6)-linked to galactose and α-(2→6)-linked to *N*-acetyl-galactosamine (e.g., α-Neu5Ac-(2→3)-Gal, α-Neu5Ac-(2→6)-Gal, and α-Neu5Ac-(2→6)-GalNAc). The disialosyl structures α-Neu5Ac-(2→8)-Neu5Ac and α-Neu5Ac-(2→9)-Neu5Ac have also been found as constituents of glycoproteins and glycolipids (Fig. 1).[2]

The stereoselective synthesis of α-sialosides in high yield is extremely challenging mainly due to the destabilizing presence of the C-1 carboxylic group and to the lack of a hydroxyl group at C-3. Thus, upon the departure of the leaving group, the resulting carbocation is not assisted by a stereocontrolling neighboring group and therefore an anomeric mixture is often produced.

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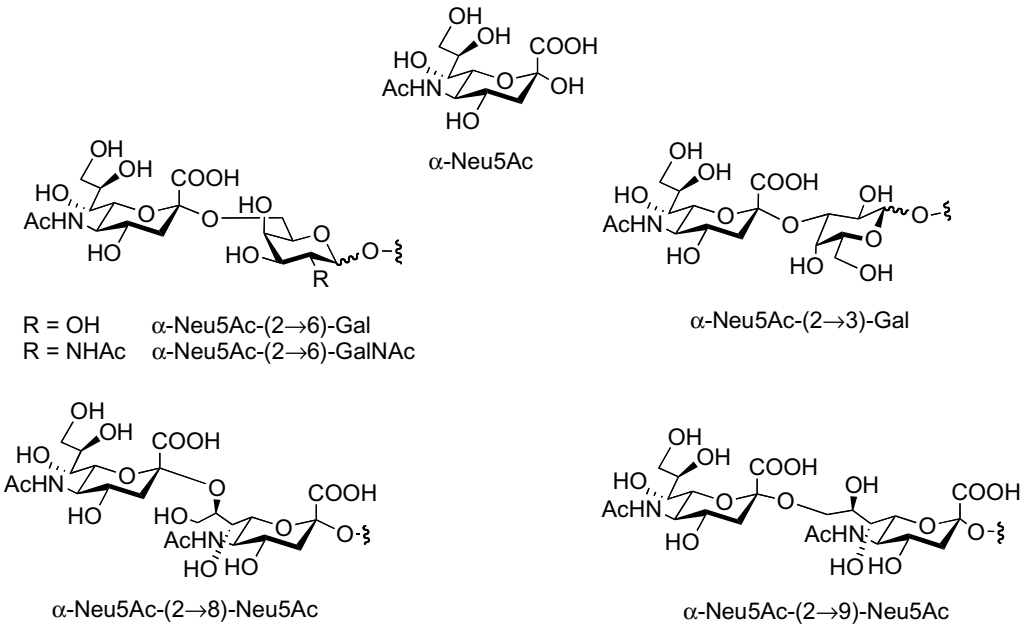
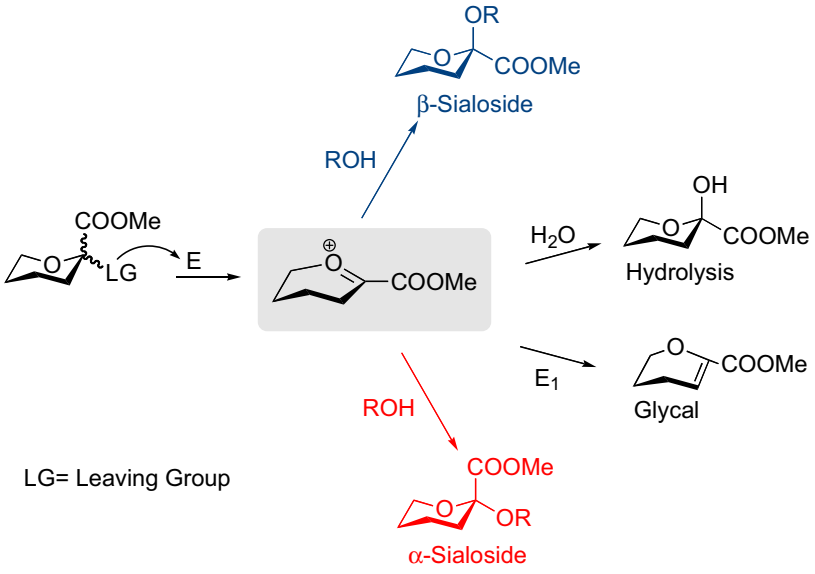


Figure 1. *N*-Acetyl-neuraminic acid and its natural linkages.



Scheme 1. General mechanism of sialylation reactions.

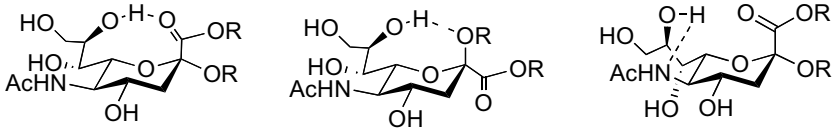


Figure 2. Proposed H-bonds of 8-OH.

In addition, competition with E1 elimination and nucleophilic attack of water (hydrolysis) are other factors that decrease the overall yield (Scheme 1). The synthesis of the disialosyl structure α-Neu5Ac-(2→8)-Neu5Ac linkages is further complicated by the low reactivity of the hydroxyl group at C-8 in the sialosyl acceptor, which has been related to its involvement in H-bonds (Fig. 2).[5–8]