

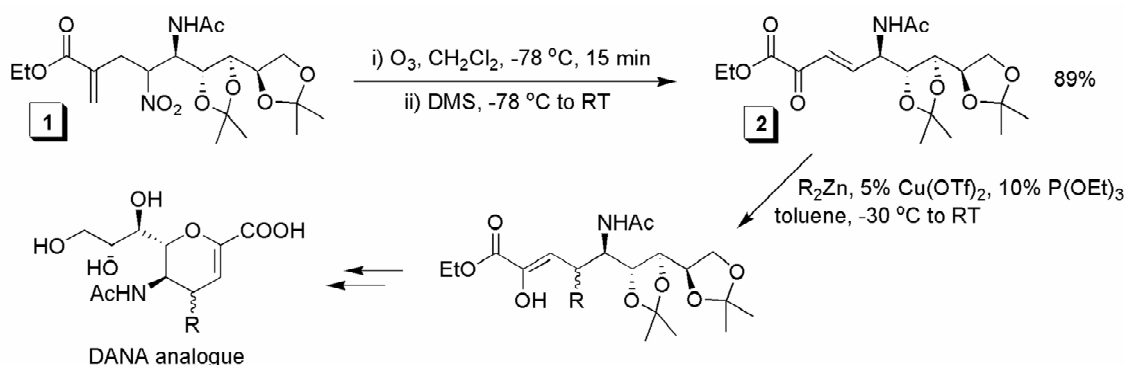
NEW ROUTES TO C4-SUBSTITUTED SIALIC ACID DERIVATIVES AS POTENTIAL INFLUENZA SIALIDASE INHIBITORS

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Sialic acids and sialidases have been implicated in influenza infection [1]. Viral sialidase activity is necessary for proliferation of newly-formed virus particles and thus inhibition of influenza sialidase has emerged as a target for minimizing influenza infectivity, evidenced by the success of such anti-influenza drugs as Relenza and Tamiflu. While structural variants at other positions of sialic acid have been synthesized, few modifications at C4 have been made. Many sialic acid derivatives are synthesized by coupling pyruvate with an appropriate aldose (ManNAc in the case of sialic acid synthesis) using sialic acid aldolase which invariably installs a hydroxy group at C4 [2]. We have devised a modular synthetic route that allows generation of a diverse array of C4-substituted sialic acid derivatives as potential sialidase inhibitors.

Starting from arabinose, we obtained an unexpected enone **2** in seven steps following ozonolysis of the precursor enone **1**. Copper-catalyzed conjugate addition of dialkylzinc reagents to enone **2** allows installation of an alkyl group at C4. These products can be further elaborated to sialic acid derivatives and the variety of potential dialkylzinc reagents allows the generation of diverse libraries of C4-substituted sialic acid derivatives. We have converted our compounds to analogues of 2-deoxy-2,3-dehydro-*N*-acetylneuraminic acid (DANA), a known sialidase inhibitor, for comparison of their inhibitory activities against influenza sialidase. The syntheses and inhibitory activities of several C4-modified sialic acid derivatives will be presented.



[1] Taylor, G. *Curr. Opin. Struct. Biol.*, **1996**, 6, 830-837

[2] Lin, C-C. ; Lin, C-H. ; Wong, C-H. *Tetrahedron Lett.*, **1997**, 38, 2649-2652