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# Exploring The Scope And Limitations Of The Oxidative Deamination Of N-Acetyl Neuraminic Acid

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# EXPLORING THE SCOPE AND LIMITATIONS OF THE OXIDATIVE DEAMINATION OF *N*-ACETYL NEURAMINIC ACID

by

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## DEDICATION

I dedicate this dissertation to my beloved parents Mrs. Mymona and Mr. Bakr whom I don't have enough words to thank.

And I dedicate this dissertation to my heart (my wife) Ekram Adam who has been the main support during my PhD.

I thank my two beautiful kids Thamer and Zahir who are the joy of my life.

This dissertation is also dedicated to my brother Zakariya who passed away before I could finish my PhD

I thank my sister Asia and all my siblings who were behind my success.

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| Ac | Acetyl |
| AcO | Acetate |
| ax | Axial |
| B | Boat (conformation) |
| Bn | Benzyl |
| Boc | *tert*-Butyloxycarbonyl |
| Bu | Butyl |
| Bz | Benzoyl |
| c | Molar concentration |
| C | Celsius (use °C as unit abbreviation) |
| | Chair (conformation) |
| $^{13}$C NMR | Carbon nuclear magnetic resonance |
| $C_6D_6$ | Deuterated benzene |
| CAM | Ceric ammonium molybdate |
| $CCl_4$ | Carbon tetrachloride |
| $CDCl_3$ | Deuterated chloroform |
| COSY | Correlation spectroscopy |
| DANA | 2,3-Didehydro-2-deoxy-*N*-acetylneuraminic acid |
| DCM | Dichloromethane |
| EC 3.2.1.18 | a α-Neuraminidase |
| eq | Equatorial |
| equiv | Equivalent |
| ESI | Electrospray ionization |
| Et | Ethyl |
| gg | gauche-gauche |
| gt | gauche-trans |
| h | Hour(s) |

| | |
|---|---|
| $^{1}$H NMR | Proton nuclear magnetic resonance |
| H | Haemagglutinin |
| H1N1 | Spanish influenza |
| H2N2 | Asian influenza |
| H3N2 | Hong Kong influenza |
| H5N1 | Avian influenza |
| HAT | Hydrogen atom transfer |
| HMBC | Heteronuclear multiple bond correlation |
| HRMS | High resolution mass spectrometry |
| Hz | Hertz |
| IgG | Immunoglobulin G |
| *i*-Pr | Isopropyl |
| *i*-PrOH | Isopropyl alcohol |
| *J* | Coupling constant (NMR spectroscopy) |
| KDN | 2-keto-3-deoxy-D-glycero-D-galacto-nononic acid |
| m | Multiplet (spectra) |
| m/z | Mass-to-charge ratio |
| Man | Mannose |
| Man-6-P | Mannose-6-phosphate |
| Me | Methyl |
| mmol | Millimole |
| Ms | Methanesulfonyl |
| MS | Molecular sieves |
| N | Neuraminidase |
| $N_3$ | Azide |
| $NAc_2$ | *N*-Acetylacetamido |
| NANA | *N*-Acetyl neuraminic acid |
| NANA-aldolase | *N*-Acyl neuraminic acid-aldolase |
| Neu5Ac | *N*-Acetyl neuraminic Acid |

| | |
|---|---|
| Neu5Gc | *N*-Glycolylneuraminic acid |
| NHAc | Acetamido group |
| NIS | *N*-Iodosuccinimide |
| NMR | Nuclear magnetic resonance |
| nOe | Nuclear Overhauser effect |
| NOESY | Nuclear Overhauser enhancement spectroscopy |
| N-TFAHN | *N*-trifluoracetyl group |
| Nu | Nucleophile |
| P.T | Proton transfer |
| pa | Pseudoaxial |
| pe | Pseudoequatorial |
| PEP | Phosphoenolpyruvate |
| pH | Negative logarithm of hydrogen ion concentration |
| Ph | Phenyl |
| PhSH | Thiophenol |
| PhOH | Phenol |
| pK | Negative logarithm of equilibrium constant |
| p*K*a | p*K* for association |
| ppm | Parts per million |
| pTSA | 4-Toluenesulfonic acid |
| Py | Pyridine |
| q | Quartet (spectra) |
| SET | Single electron transfer |
| $S_N1$ | First-order nucleophilic substitution |
| $S_N2$ | Second-order nucleophilic substitution |
| $^tBu$ | Tert-butyl group |
| TE | $-(CH_2)_2SiMe_3$ |
| Tf | Triflyl |
| TFA | Trifluoroacetyl |

| | |
|---|---|
| TFE | Trifluoroethanol |
| TfOH | Trifluoromethanesulfonic acid |
| tg | Trans–gauche |
| THF | Tetrahydrofuran |
| UV | Ultraviolet |
| UV/vis | Ultraviolet–visible |
| $\alpha$ | Stereochemical descriptor |
| $\beta$ | Stereochemical descriptor |
| $\delta$ | NMR chemical shift in parts per million |
| $\lambda_{max}$ | Wavelength of maximum absorption |

# CHAPTER 1. INTRODUCTION

## 1.1 The importance of carbohydrates

Carbohydrates are vital components of living creatures and are abundant in nature. Carbohydrates are also called saccharides or sugars, and function in our body as a source of energy for many important biological activities. Almost all types of cellular organisms contain different kinds of saccharides, which mediate many cellular interactions.[1,2] Carbohydrates are frequently covalently bound to macromolecules and so form complicated structures of glycoproteins, glycolipids and glycoconjugates. The importance of carbohydrates makes them an area of study and interest in chemistry, biology and medicine.[1] Glycobiology and glycochemistry are two significant fields that dominate research on carbohydrates. Sugars mainly consist of carbon, hydrogen and oxygen in their basic formula $(CH_2O)_n$,[3] and they can be classified based on the number of carbons they possess. They also can be joined into monosaccharides, disaccharides, or oligosaccharides. Monosaccharides, which are the basic form of carbohydrates, are divided into two classes: aldoses and ketoses. The former contains an aldehyde group at the chain terminus, while the ketoses have an internal ketone group along the chain.[1] The simplest monosaccharide is glyceraldehyde (aldotriose) and has three carbons in its chain (**Figure 1**). Dihydroxyacetone (ketotriose) is the simplest ketonic monosaccharide with a three carbon chain (**Figure 1**).[1,4]

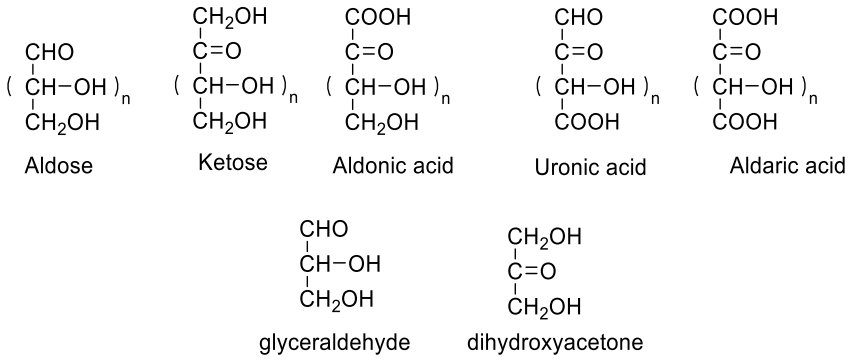



**Figure 1**. Examples of Basic Structures of Carbohydrates.[4]

Carbohydrates have in their structure, at least one chiral center. The number of isomers in carbohydrates increases with the increase in number of chiral centers present. Thus, the aldohexoses, with four stereogenic centers, have eight possible diastereomers, of which D-glucose, D-galactose, and D-mannose are common.[5] These common aldohexoses are supplemented by the common ketohexose D-fructose (**Figure 2**).

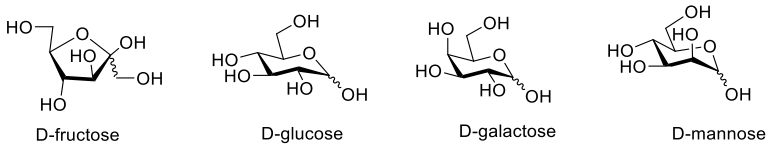
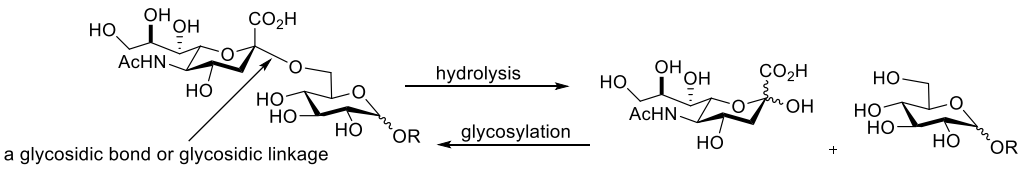



**Figure 2.** Common Six Carbons Sugars.

Oligosaccharides are constructed from two or more of monosaccharides connected by glycosidic linkages (**Scheme 1**). These linkages can be hydrolyzed and disconnected by suitable enzymes and reagents in important biochemical processes to form free monosaccharides.[5] To build an oligosaccharide, the glycosidic bond is formed by a glycosylation reaction, which is a very important transformation in carbohydrate chemistry; glycosylations are achieved in nature by glycosyl transferases[6] as well as in laboratory by using suitable promotors to connect between

glycosyl donor and accepter.[7] Carbohydrates participate in various important biological processes in living cells, which are involved in curing various diseases such as cancer, influenza or bacterial infections.[8,9]




**Scheme 1**. Hydrolysis and Formation of a Glycosidic Bond.

### 1.2 Discovery of the sialic acids

Sialic acid is a central molecule in the chemistry and glycobiology of carbohydrates. It is a polyhydroxy sugar acid and consists of a nine carbon backbone with an *N*-acetyl moiety attached to C5 (**Figure 3**).[1,2]

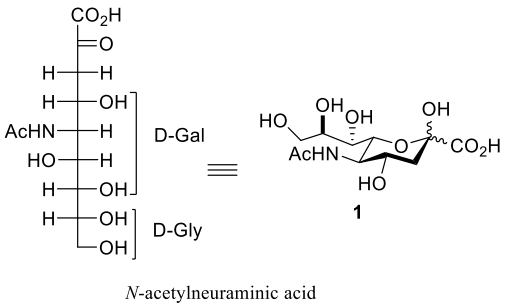
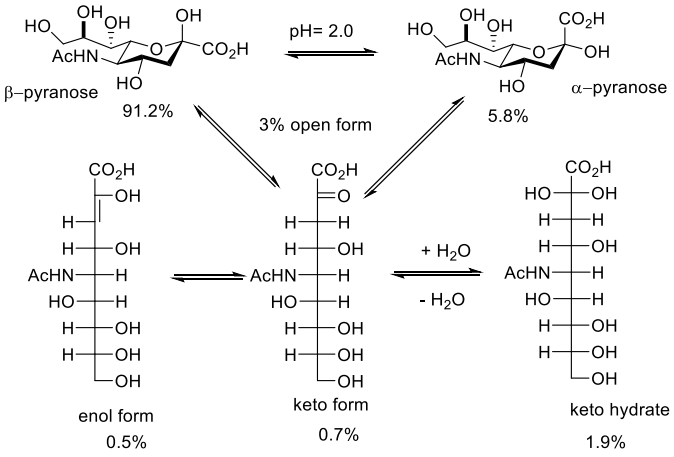



**Figure 3**. The Open and Closed Structures of *N*-Acetylneuraminic Acid (Sialic Acid).

The isolation and discovery of sialic acid was a challenging task owing to the lack of sophisticated instruments at the time for the characterization of its structure.[10] Its discovery opened a window to various applications in glycobiology and medicine. Blix in 1936 isolated a crystalline molecule from bovine submaxillary mucin that was later called sialic acid.[11,12] In

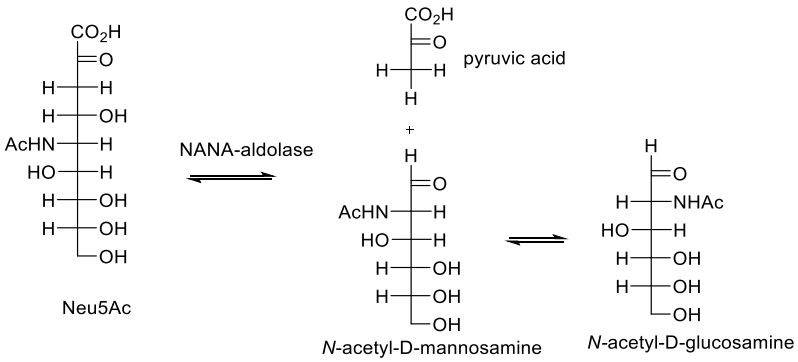
1941, Klenk also isolated sialic acid from brain gangliosides.[13] After this fascinating discovery, Blix, Klenk and Gottschalk published a formal nomenclature of the newly-isolated sialic acid and named it neuraminic acid.[14] According to this nomenclature *N*-acetylneuraminic acid (Neu5Ac) is the parent of the sialic acid family, and is more formally called 2-keto-5-acetamido-3,5-dideoxy-D-glycero-D-galactononulopyranos-1-onic acid. In NMR studies of $^{13}$C-labeled Neu5Ac at pH~2, Neu5Ac was found to exist as an equilibrium mixture of two cyclic forms as well as other minor acyclic forms.[15-17] The $\beta$-pyranose form of *N*-acetyl neuraminic acid is the major structure detected in solution in 91.2% at pH~2, whereas the $\alpha$-pyranose is found as a minor component in 5.8%. The acyclic structures including the keto-hydrate, enol and keto forms, occur in lower concentrations of 1.9%, 0.5%, and 0.7%, respectively (**Scheme 2**).[16] The detection of the correct forms of *N*-acetyl neuraminic acid is crucial for chemical and biological studies.




**Scheme 2.** The Various Forms of Neu5Ac at Equilibrium**.**

### 1.3 The diversity of sialic acids in nature

Sialic acids are present in the outmost end of most glycoproteins and glycolipids, and they are found in the wall cell membranes of vertebrate mammals and bacteria.[1,2] The rich variety of sialic acids that are found in animals, are distributed in deuterostomes specifically in vertebrates.[2] Some types of sialic acids in bacterial glycoproteins, exist as polysaccharides and lipopolysaccharides such as the conjugates of pseudaminic acid and legionaminic acid.[2] The numbers of naturally occurring sialic acids are increasing in the literature due to the fascinating role that they play nowadays in glycobiology research. The most common sialic acid found in nature is *N*-acetylneuraminic acid (Neu5Ac), which is found in the outmost terminal position of glycoproteins in vertebrates and invertebrates. Neu5Ac is abundant in humans and animals, and is considered the parent of most sialic acid derivatives.[2,3,18,19] *N*-Acetylneuraminic acid mediates many biological processes and it is frequently connected to the terminus of glycoproteins and glycolipids through $\alpha$(2-3) or $\alpha$(2-6) linkages.[2] The successful isolation of neuraminic acid led the scientific community become interested in its biosynthesis. NeuAc5 is synthesized from pyruvate and a naturally occurring *N*-acetylhexosamine. Rosemane and Comb successfully synthesized *N*-acetylneuraminic acid from pyruvic acid and *N*-acetyl-D-mannosamine using an aldolase type enzyme called *N*-acyl neuraminic acid-aldolase (NANA-aldolase).[12,20] *N*-Acetylglucosamine is believed to be an important component of NeuAc biosynthesis in that *N*-acetylglucosamine epimerizes to *N*-acetyl-D-mannosamine, which reacts with pyruvate in the presence of NANA-aldolase enzyme to form NeuAc5 (**Scheme 3**).




**Scheme 3.** Biosynthesis of *N*-Acetylneuraminic Acid.

*N*-Glycolylneuraminic acid (Neu5Gc) **2** is less abundant in nature compared to NeuAc5, but it is the second most abundant sialic acid in nature (**Figure 4**). Neu5Gc is mostly found in animals but is rare in humans, where it was found to be expressed at abnormal levels in human cancers.[3] The third most abundantly naturally occurring sialic acid is the deaminated neuraminic acid 2-keto-3-deoxy-D-glycero-D-galactononulosonic acid (KDN) **3**,[21,22] which occurs in many bacteria and lower vertebrates and is found in many of the glycoproteins and glycolipids.[23] KDN differs from the Neu5Ac structure at the 5-postion where the amide is replaced by a hydroxy group (**Figure 4**).

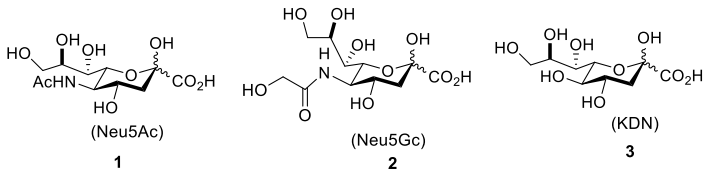



**Figure 4.** The Most Abundant Naturally Occurring Sialic Acids.

The sialic linkages that are abundant in nature, are $\alpha(2\rightarrow3)$, $\alpha(2\rightarrow4)$, $\alpha(2\rightarrow6)$, and $\alpha(2\rightarrow8)$. These types of linkages are found in NeuAc as well as KDN.[21] In animal cells, NeuAc exists mostly as a conjugate that is connected with other glycoproteins, whereas KDN is

abundant as a free monosaccharide form.[22] A large quantity of KDN as a free sugar is found in red blood cells as well as cancer cells.[22] KDN is formed by a biosynthesis pathway from mannose (Man), which is transformed to its 6-phosphate (Man-6-P). The condensation of (Man-6-P) with phosphoenolpyruvate (PEP) by the enzyme called KDN-9-P synthase (KPS), forms KDN-9-P that is a precursor of KDN (**Scheme 5**).[22,24]

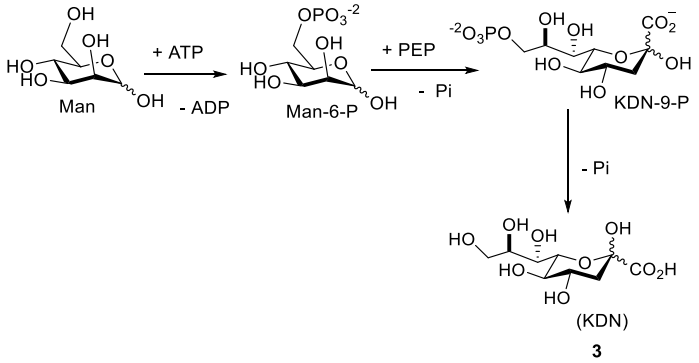



**Figure 5.** The Biosynthesis of KDN.

Much attention is focused on the synthesis of KDN and its derivatives because of their elevated observation level in some human cancer cells and tissues.[22]

**1.4 Biological significance of sialic acid.**

The presence or the absence of *N*-acetylneuraminic acid in glycoproteins was found to affect the inflammatory actions of human immunoglobulin G (IgG).[25] In vivo, sialic acids in general have an important role as glycoconjugates, for supplying of the negative charge on cellular membranes. Moreover, sialic acids play a vital role in the transfer of information between the cells as well as recognition and determination of the glycoprotein structures and bioactivities.[26] Sialic acid acids have important activities in masking cellular antigens and reducing the immunochemical reaction of degenerated cells.[27,28] Sialylatd glycoproteins play a

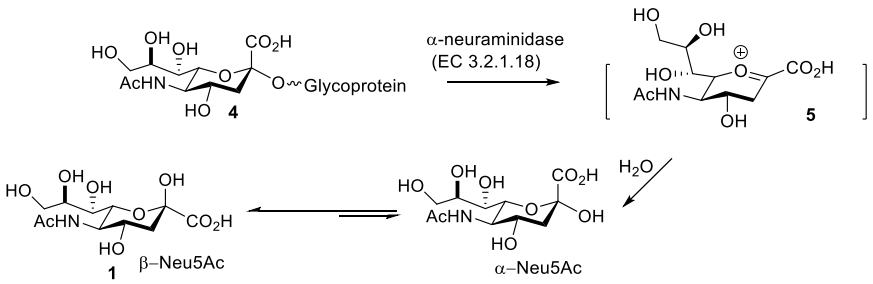
role in strengthening the cornea in the human eyeballs.[29] Recent studies suggested that metastatic breast cancer increases after targeting a sialic acid glycosides in tumor cells.[30] These many and varied biological activities make sialic acid research a central area of interest in medicine and the pharmaceutical sciences.

**1.5 Sialic acid-based inhibitors of neuraminidase**

Flu (cold) is a well-known epidemic infectious disease that both humans and animals have struggled to cope for millennia; it is caused by influenza viruses. Infection by the influenza viruses is harmful and can lead to death, especially among elders and children.[31,32] Influenza viruses are found to bind sialic acids in cell membranes.[33] Each type of influenza virus can recognize different types of sialic acid and the linkages that connect them.[3] There are three types of influenza virus: A, B, and C. Influenza A is the most common form that causes the flu, it contains the haemagglutinin (H) and neuraminidase (N) glycoproteins, which significantly impact the levels and so the activity of sialic acids in the living cells.[34,35] This leads to the classification of influenza A to several subtypes; Spanish influenza (H1N1), Asian influenza (H2N2), Hong Kong influenza (H3N2), and avian influenza (H5N1).[36,37] The treatment of influenza depends mostly on the regulation and manipulation of the enzymes that are responsible for the sialic acid behavior by means of their inhibition. Developing an inhibitor that would prevent the action of neuraminidase, is an important subject of interest in the drug discovery, and neuraminidase inhibitors are most effective drugs for treating influenzas, such that chemists became interested in developing sialic acid-based inhibitors using practical synthetic methods.[36,38,39]

### 1.5.1 The action of neuraminidase enzymes

Sialidases (neuraminidases) are a broad class of enzymes that have been isolated from animal tissue and bacteria. Neuraminidases (acetylneuraminyl hydrolases) have been isolated and crystallized to gain more insight to their biological and chemical actions. They occur in vertebrates and bacteria in animal cells as well as in influenza viruses.[28,40] Acetylneuraminyl hydrolase also called α-neuraminidase (EC 3.2.1.18) hydrolyzes the α-ketosidic linkages: *α*(2→3), *α*(2→6), and *α*(2→8) of the outmost sialoside residues in glycoproteins, gangliosides or colominic acids leading to release of free Neu5Ac, hence destroying the receptors for the virus (**Scheme 4**).[35,40-42]




**Scheme 4.** Neuraminidase (EC 3.2.1.18) Cleaves the Glycosidic Bond and Releases Sialic Acid.

### 1.5.2 The discovery of neuraminidase inhibitors

The first neuraminidase inhibitor reported was 2,3-didehydro-2-deoxy-*N*-acetylneuraminic acid (DANA) **6** (**Figure 6**), which is an unsaturated derivative of NeuAc5. Its structure is derived from neuraminic acid and its conformation resembles the intermediate that is formed as NeuAc5 is liberated from the terminal glycoprotein (**Scheme 4**).[43] DANA was not commercialized but its structure was used as a template for the synthesis of analogues to

discover new inhibitors of neuraminidase that could be more potent and effective as drugs. For instance, 2-deoxy-2,3-didehydro-*N*-trifluoracetylneuraminic acid **7** (**Figure 6**) was derived from DANA and displayed enhanced potent activity.[31, 32]

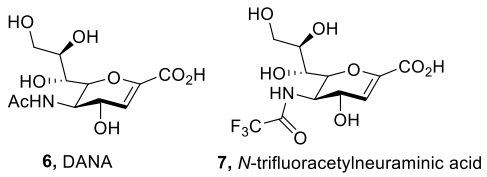
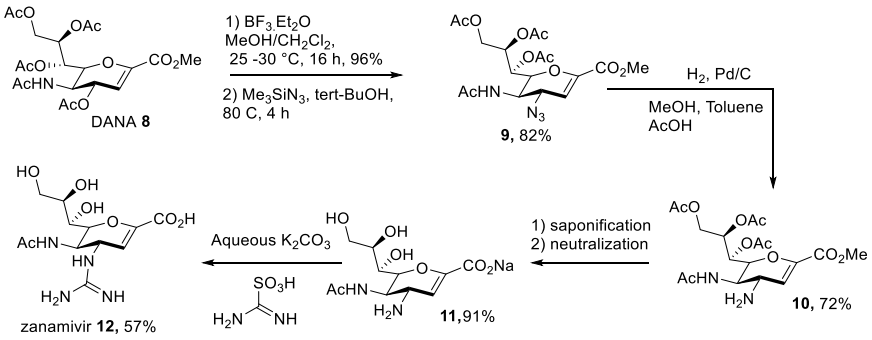



**Figure 6.** DANA and 5-*N*-Trifluroacetyl Inhibitors**.**

Zanamivir is another analogue of DANA and is considered to be the most effective neuraminidase inhibitor so far.[37] Zanamivir is commercialized as Relenza, and its structure is based on 2,3-didehydro-2,4-dideoxy-4-guanidinyl-*N*-acetylneuraminic acid. Its synthesis has been described multiple times,[39] but the first synthesis was reported by a group at Monash University in Australia who synthesized it from NANA (**Scheme 5**).[36,43] Zanamivir has been subjected to several rounds of structural modifications and many analogues were prepared to develop more potent inhibitors of neuraminidase.[43] The 4-guanidinyl moiety in Zanamivir is found to play an important role in binding the target protein.[36]




**Scheme 5.** The First Synthesis of Zanamivir.

Several further neuraminidase inhibitors have been discovered for influenza treatment, such as oseltamivir (Tamiflu), laninamivir and peramivir (**Figure 7**),[35] of which one, Tamiflu, has reached the market. It is derived from a cyclohexene ring and also mimics the intermediate structure **5** in the hydrolysis of the terminal sialic acid of glycoproteins.[44]

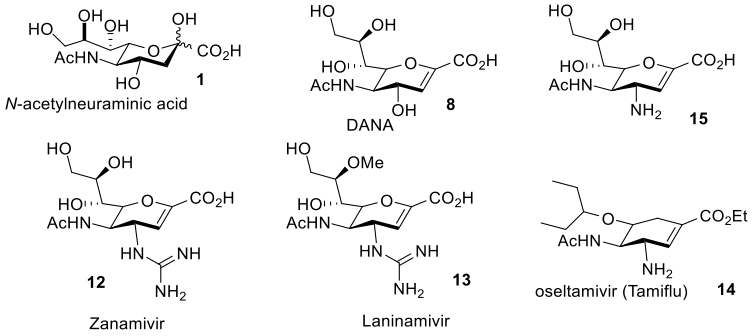
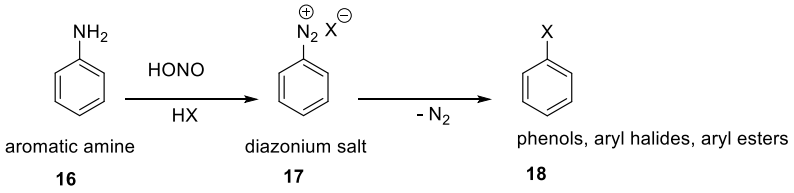



**Figure 7.** Further Inhibitors of Neuraminidase.

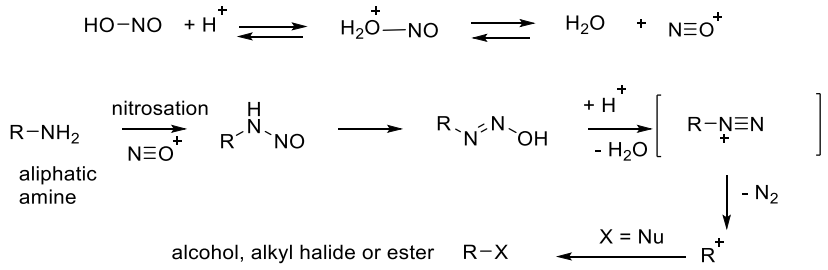
### 1.6 Oxidative deamination in organic synthesis

A deamination reaction is the transformation of an amino group to another non-nitrogen based functional group; they are widely used in organic syntheses. Synthetic chemists use deamination to convert anilines to phenols, aryl halides, and aryl esters. These conversions proceed via the formation of diazonium salt intermediates, which are susceptible to nucleophilic attack by various nucleophiles (**Scheme 6**).[45-47]




**Scheme 6.** Deamination in Aromatic Systems.

Aliphatic amines are also converted to the corresponding alcohols, alkyl halides and esters via the formation of alkane diazonium salts in a nitrosation reaction of amines (**Scheme 7**).[33] A general rule in oxidative deamination is that the acidity of the reaction media is crucial for a successful conversion.




**Scheme 7.** Deamination in Aliphatic Systems.

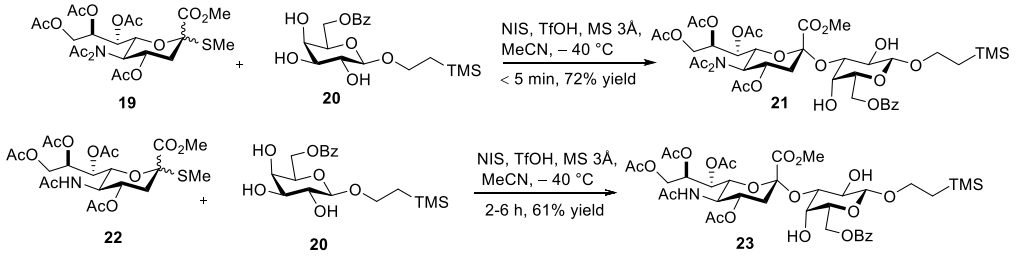
### 1.7 Modification of sialic acids

Many important modifications of sialic acid have been reported in the literature, giving rise to more diverse structures of sialic acids.[2,48] Even minor modifications in sialic acids can affect their biological role significantly.[2,4] Various chemical modifications of *N*-acetylneuraminic acid were achieved either to improve the chemical stereoselectivity of sialylation reactions or to develop the biology for medicinal and drug discovery purposes, such as the develop of carbohydrate-based drugs as antiviral or antibacterial agents. In particular, the chemical modification of the Neu5Ac at the 5-postion showed improved reactivity and selectivity in glycosylation reactions by influencing both sialic acid donors and acceptors.[48,49]

#### 1.7.1 Modification at the 5-postion of sialic acid.

The effect of modification at the 5-postion in sialic acid donors or acceptors was demonstrated by several labs. Boons and co-workers introduced the *N*-acetylacetamido ($NAc_2$)

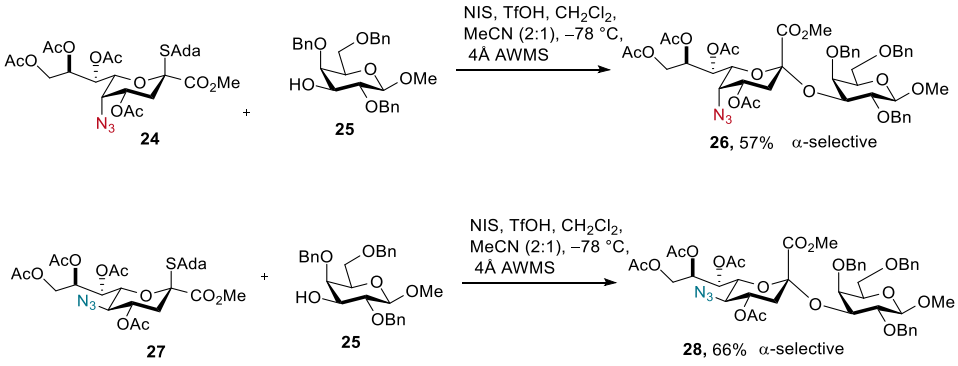
group in sialic acids in place of the original acetamido group (NHAc). This modification showed shorter time of the glycosylation reaction as well as increased yields. Thus, with the ($NAc_2$) group, the sialylation reaction was completed in 5 min. On the hand, with the native NHAc group in the sialic acid donor, sialylation reactions required 2-6 hours under comparable conditions (**Scheme 8**).[50]




**Scheme 8.** Comparison Between $NAc_2$ and NHAc Bearing Sialyl Donors**.**

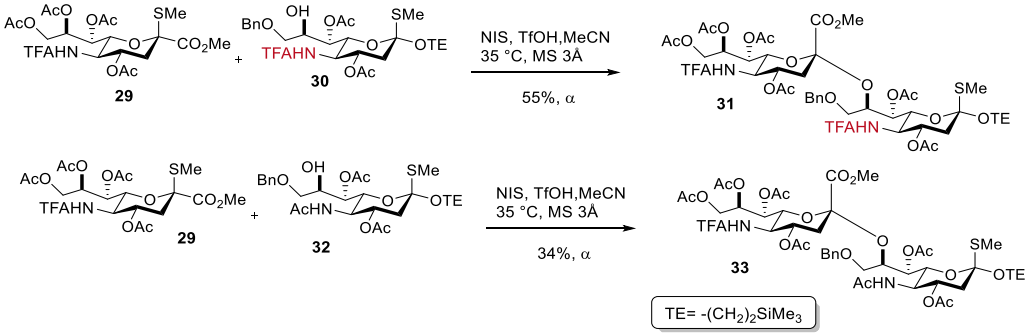
### 1.7.2 Modification as an azide group

The Crich lab achieved *α*-selective glycosylations in the synthesis of equatorial glycosides through modification at the 5-postion by the installation of an axial azide in the D-glycero-D-gulo sialic acid adamantanyl thioglycoside donor **24**. The high stereoselectivity of this reaction was accomplished due to the use of lower temperature – 78 °C, the installation of an azido moiety at the 5-postion of the donor, and the *trans–gauche* (*tg*) conformation of the side chain.[51,52] This modification enabled a coupling to even the least reactive acceptors, including hindered secondary alcohols such as **25**. In addition, the employment of an equatorial azide at the 5-potion of thioglycoside donor **27** provided the equatorial glycoside **28** under similar conditions (**Scheme 9**).




**Scheme 9**. $\alpha$-Selective Glycosylation Using a 5-Azido-Protected Donor.

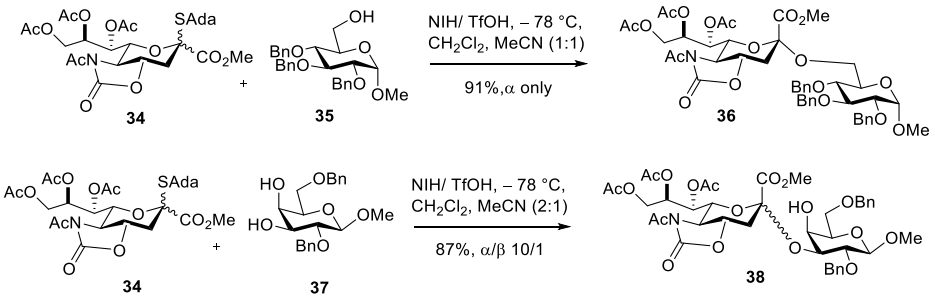
Schmidt[53] was able to introduce the azido group on C5 in the sialic acid by a Zbiral deamination reaction, and Wong[54] demonstrated improved α-selectivity with the azido protected sialic acid donors and acceptors. Introduction of a 5-N-trifluoracetyl group in place of the NHAc at the 5-postion in the glycosyl acceptor also revealed improved stereoselectivity, as well as enhanced yields in the glycosylation reaction compared to the original NHAc group (**Scheme 10**).[55]




**Scheme 10.** *N*-TFA and NHAc Groups in Acceptors

### 1.7.3 The *O*-4, *N*-5-oxazolidinone moiety

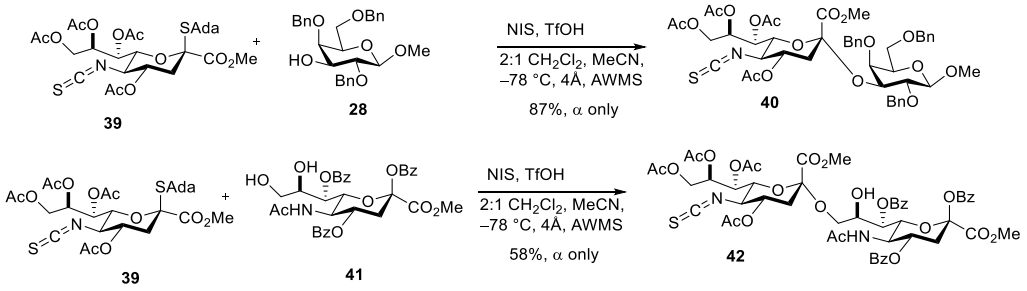
Modification of sialic acid can also be accomplished by the employment of an oxazolidinone moiety spanning the 4- and 5-postions of a sialyl donor **34**. The Crich lab has provided numerous examples of the advantageous use of the *O*-4, *N*-5-oxazolidinone-protected donor in α-selective sialylation at – 78 °C in a binary solvent of acetonitrile and dichloromethane (**Scheme 11**). This protecting group provides higher yields and high *α*-selective glycosylations.[56,57] The sialic acid oxazolidinone derivatives have been utilized widely in the synthesis of *α*-selective sialosides by many other labs.[56-61]




**Scheme 11.** The Use of Oxazolidinone-Protected Donors for *α*-Selective Glycosylation.

### 1.7.4 Modification of C5 by the isothiocyanato moiety

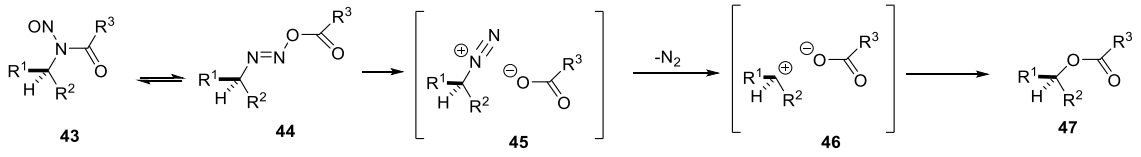
It was also found that modification of sialyl donors by installation of an isothiocyanato group at the 5-postion provides a practical access to the stereoselective *α*-sialosides as well as enabling the diversification of sialic acids. Thus, the Crich lab obtained high *α*-selectivity and high yields in coupling reactions conducted at – 78 °C, between a thiosialoside donor protected by the isothiocyanate functionality at C5 **39** and various glycosyl acceptors (**Scheme 12**).[62]




**Scheme 12.** Glycosylation Reactions Using an Isothiocyanato Derivative.

### 1.8 White's oxidative deamination

White used the deamination reaction oxidatively for the degradation of aliphatic amides through the decomposition of *N*-nitroso derivates **43**, followed by the extrusion of molecular nitrogen to provide the corresponding esters **44**. In the thermal conditions of the White method, the *N*-nitrosoamides of secondary and tertiary amides decompose to form the corresponding products **47** frequently with retention of configuration. The White reaction was suggested to proceed through the formation and degradation of two ion pairs **45** and **46** after acyl migration from nitrogen to oxygen (**Scheme 13**).[63-66]

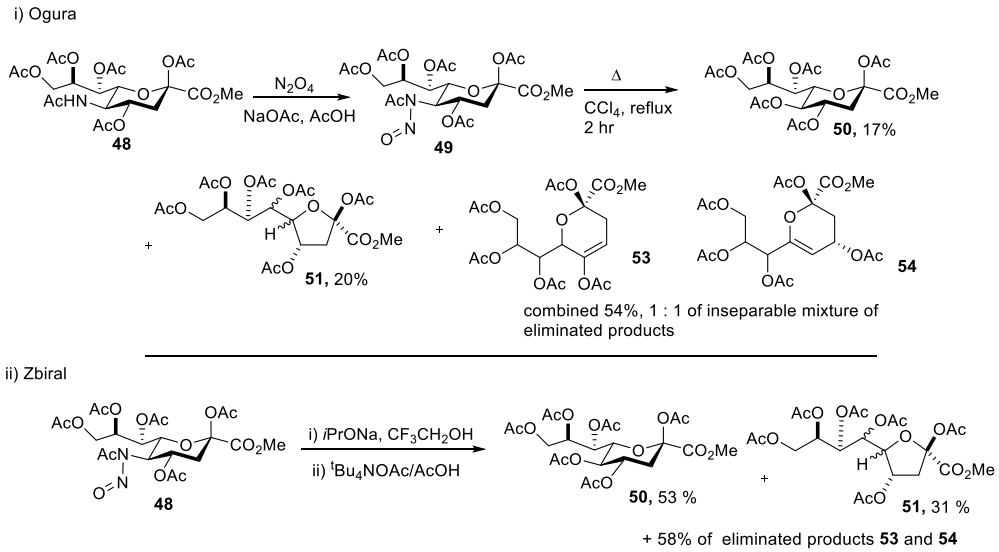



**Scheme 13.** White's Degradation of Aliphatic Amides**.**

### 1.9 Ogura and Zbiral's oxidative deamination

The primary application of the oxidative deamination reaction in carbohydrate chemistry is to convert *N*-acetylneuraminic acid to the biologically important molecule KDN. The oxidative deamination has also proven to be a pivotal transformation in the synthesis of

pseudaminic acid glycosides, which are found in the lipopolysaccharides from *Pseudomonas aeruginosa* and other pathogens.[51,67,68] Ogura was the first to apply the oxidative deamination in the transformation of an acetyl glycoside of Neu5Ac to obtain a KDN derivative; this transformation was accompanied by a ring contracted furan product, although no spectral data for the furanose ring were presented (**Scheme 14**).[69] Zbiral and Schreiner contributed a significant advance in the oxidative deamination by developing practical conditions. The formation of KDN resulted from the treatment of the *N*-nitrosoamide with sodium isopropoxide and trifluoroethanol followed by the addition of acetic acid. The Zbiral laboratory also observed the formation of and characterized the ring contracted product (**Scheme 14**), although they did not determine the configuration at both C5 and C6.[70]

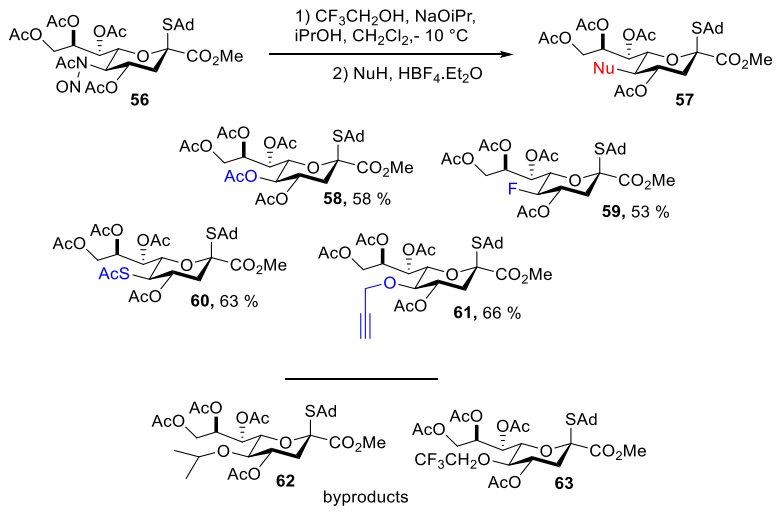



**Scheme 14.** Ogura's and Zbiral's Deamination.

### 1.10.1 Application of the Zbiral oxidative deamination in the Crich lab

The Crich lab have been studying intensively the oxidative deamination for modification and diversification of *N*-acetylneuraminic acid, with a view to achieving chemoselective and

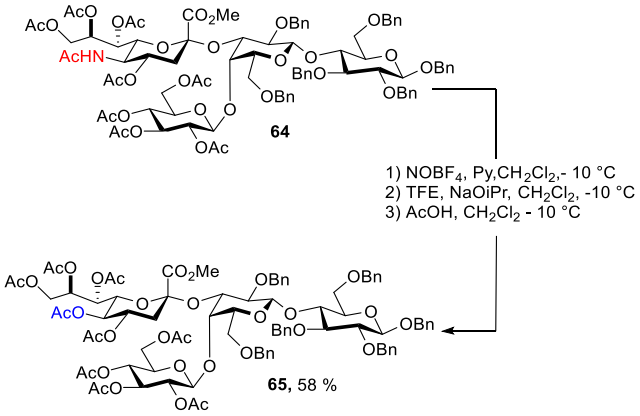
stereoretentive glycosyl donors. Prior to their work, acetic acid was the main nucleophile used in oxidative deamination to make KDN and its derivatives.[69,70] However, the Crich group demonstrated that thioacetic acid, (HF·pyridine), and propargyl alcohol can be used as nucleophiles in the presence of external acid ($HBF_4.Et_2O$) to functionalize Neu5Ac derivatives. The conditions used in these examples are the treatment of *N*-nitroso derivatives with trifluoroethanol, sodium isopropoxide and isopropanol at – 10 °C for 10 min, followed by the addition of a nucleophile and then, followed immediately by that of $HBF_4.Et_2O$. The deaminated products were reported as being isolated in reasonable yields accompanied by other byproducts. Retention of stereochemistry was apparent in all products. Attack by isopropanol as well as trifluoroethanol on C5 led to the isolation of undesirable side products that decreased the yield of the desired products (**Scheme 15**).[71]




**Scheme 15.** Deamination Reactions and Their Products Reported Recently by the Crich Lab.

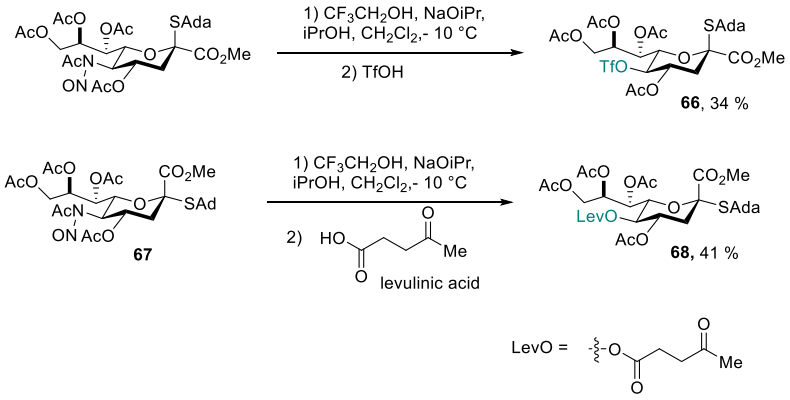
### 1.10.2 Deamination in late stage modification of oligosaccharides

To show further feasibility of the oxidative deamination transformation, application to oligosaccharides was shown for the first time to proceed smoothly and with high chemoselectivity (**Scheme 16**).[71]




**Scheme 16.** Oligosaccharide Modification by Oxidative Deamination Reaction.

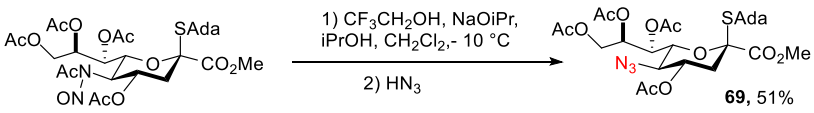
The triflate anion was also found to be a competent nucleophile in this chemistry.[72] Further, levulinic acid was shown to be a suitable nucleophile for the oxidative deamination and was used to functionalize the 5-postion (**Scheme 17**).[51,52]




**Scheme 17.** Triflate and Levulinate as Nucleophiles.

### 1.10.3 Use of azide as a nucleophile in oxidative deamination.

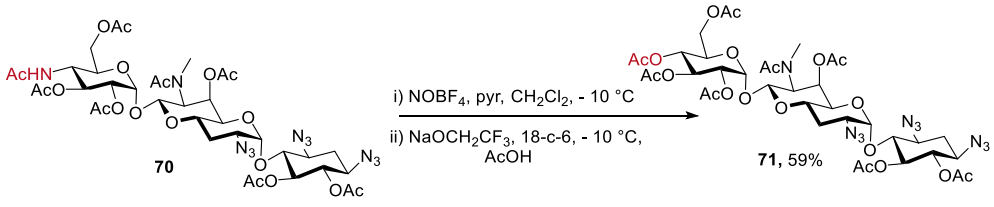
Oxidative deamination was very useful in the synthesis of pseudaminic acid donors. Traditionally, in order to introduce the azido group in a molecule, a good leaving group such as triflate is installed followed by $S_N2$ displacement by an azide source such as $LiN_3$. Interestingly, Zbiral's oxidative deamination enables the introduction of the azido group with the retention of configuration in one step (**Scheme 18**).[51,67,68] However, it is advisable to avoid the use of hydrogen azide unless in very small quantities with the appropriate safety precautions.




**Scheme 18.** Hydrogen Azide as a Nucleophile.

### 1.10.4 Oxidative deamination in aminoglycosides

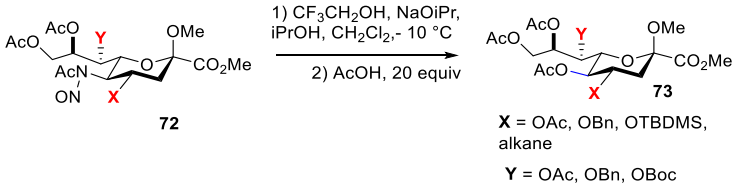
Application of the Zbiral deamination was also expanded by the Crich lab to the modification of aminoglycosides. Thus, Crich's modified conditions for the oxidative deamination enabled conversion of an acetamido group in an aminoglycoside derivative to the corresponding acetoxy group (**Scheme 19**).[73]




**Scheme 19.** Oxidative Deamination in an Aminoglycoside.

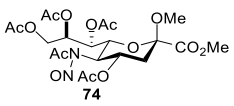
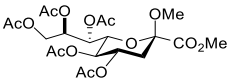
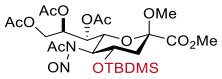
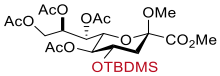
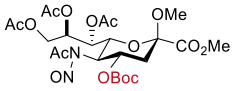
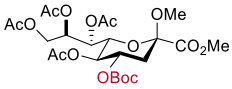
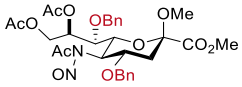
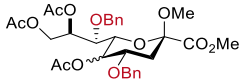
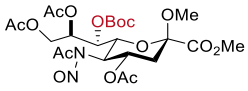
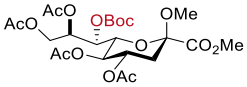
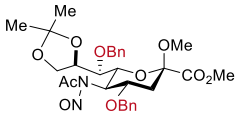
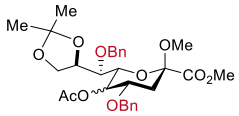
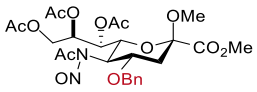
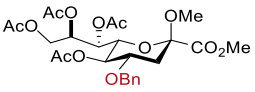
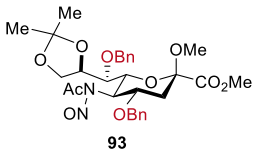
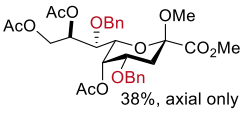
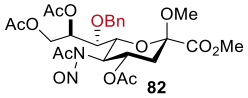
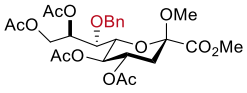
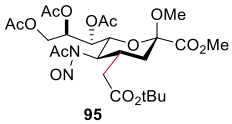
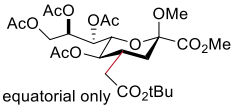
### 1.10.5 The mechanism of oxidative deamination and substituent effects.

The Crich lab conducted a detailed investigation of the oxidative deamination of *N*-acetyl neuraminic acid and derivatives. The protecting groups that surround the 5-postion of an *N*-nitrosoacetamide were varied to the probe the reasons behind the stereo-retentive nature of the process. Initially, it was presumed that the acetate on the 4-position or the 7-position controls the stereoselectivity by neighboring group participation. However, this assumption was invalidated through the use of different non-participating protecting groups such as *O*-benzyl, *tert*-butyldimethylsilyl (TBDMS), and *tert*-butyl ester at those positions (**Scheme 20**). In each case, substitution with retention of configuration was obtained leading to the conclusion that the ring oxygen participated in the stabilization of the resulting carbocation in C5, forming an oxonium ion intermediate followed by the equatorial substitution. Thus, the overall retention of configuration was observed. In **Table 1**, examples of deamination that have been evaluated using different non-participating protecting groups, are presented. Elimination products were found as byproducts in all examples.[74]



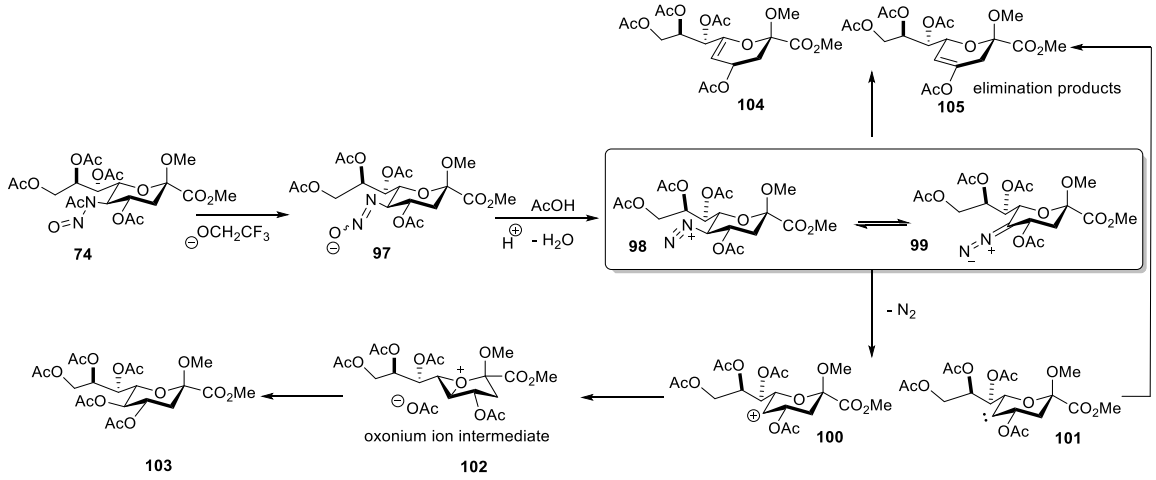

**Scheme 20.** Crich and Buda's Oxidative Deamination.

**Table 1.** Evaluation of Different Protecting Groups for the Deamination Reaction.

| Substrate | Product | Substrate | Product |
|---|---|---|---|
|  **74** |  **75,** 56%, equatorial only |  **84** |  **85,** 52%, equatorial only |
|  **76** |  **77,** 56%, equatorial only |  **86** |  **87** and **89,** 43%, eq/ax; 4.2: 1 |
|  **78** |  **79,** 45%, equatorial only |  **90** |  **91** and **92,** 40%, eq/ax; 1:1 |
|  **80** |  **81,** 46%, equatorial only |  **93** |  38%, axial only **94** |
|  **82** |  **83,** 27%, equatorial only |  **95** |  17%, equatorial only **96** |

Based on the results obtained in this study, a detailed mechanism for the oxidative deamination was proposed (**Scheme 21**). A selective *N*-deacetylation of *N*-nitrosoacetamide **74** by trifluoroethoxide generated in situ led to the formation of the hydroxydiazine **97**. Upon the acidification by the added nucleophile acetic acid, a subsequent protonation and removal of water from **97** gives the diazonium ion intermediates **98** or **99**. The diazonium ion **98** is in equilibrium with its conjugate base diazoalkane **99**. Since the media is acidic, the diazonium ion **98** is more favored. The loss of molecular nitrogen is presumed to form one of another two

possible intermediates; the carbenium ion **100** and the carbene **101**. The ultimate substitution product **103** is formed after the ring oxygen participation that stabilizes the carbocation of **100**. The elimination byproducts are formed either directly from the diazonium ion **98** or from the following intermediates **100** and **101** that resulted from the loss of molecular nitrogen (**Scheme 23**).




**Scheme 21.** General Mechanism of Oxidative Deamination in the Sialic Acids.

### 1.11 Overall goals

It is necessary to establish a deeper understanding of the mechanism of the oxidative deamination reaction of NeuAc and its outcomes. Toward this end, it was envisaged to use alternative nucleophiles that are weakly acidic and less nucleophilic to probe the reactivity of the diazonium ion intermediates. Phenols and thiophenols were selected accordingly for this oxidative deamination study. Additionally, with a long term goal of developing novel sialidase inhibitors with which to target drug resistant viruses, the application of the deamination reaction for the synthesis of new generations of neuraminidase inhibitors was chosen for study. Among the various possible nucleophiles hydroxylamines and nitrogen-based nucleophiles were selected

for the oxidative deamination to synthesize sialic acid derivatives that potentially function as neuraminidase inhibitors.

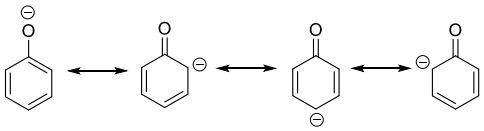
# CHAPTER 2. USE OF PHENOLS AS NUCLEOPHILES IN THE ZBIRAL OXIDATIVE DEAMINATION OF *N*-ACETYL NEURAMINIC ACID. ISOLATION AND CHARACTERIZATION OF TRICYCLIC 3-KETO-2-DEOXY-NONULOSONIC ACID (KDN) DERIVATIVES VIA AN INTERMEDIATE VINYL DIAZONIUM ION

## 2.1 Background

*N*-Acetyl neuraminic acid (Neu5Ac) is the most important member of the sialic acid family. Neu5Ac has been subjected to various modifications for chemical and biological purposes. The Zbiral oxidative deamination is one of the modifications that are applied to Neu5Ac to prepare KDN and other derivatives. In this chapter, phenols and thiophenols are employed as nucleophiles in the oxidative deamination of *N*-acetyl neuraminic acid in order to probe the reactivity of the diazonium ion intermediates and to provide syntheses of novel sialic acid derivatives that can potentially be used for medicinal applications.

## 2.2 The reactivity of phenolates

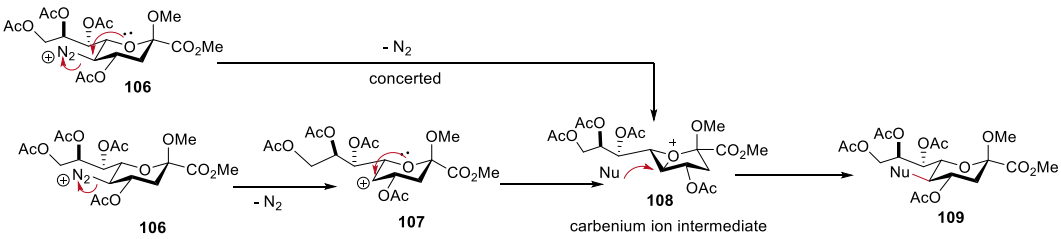
Phenols are ambident molecules whose resonance structures contain at least two sites of reactivity toward electrophiles (**Scheme 22**). The deprotonated phenol, a phenolate, has a negative charge delocalized on the oxygen and carbons within the ring.[75] Most phenols including the substituted phenols, are weakly acidic with p*K*a values in the ranges of 7-11.



**Scheme 22.** The Resonance Delocalization of a Phenolate.

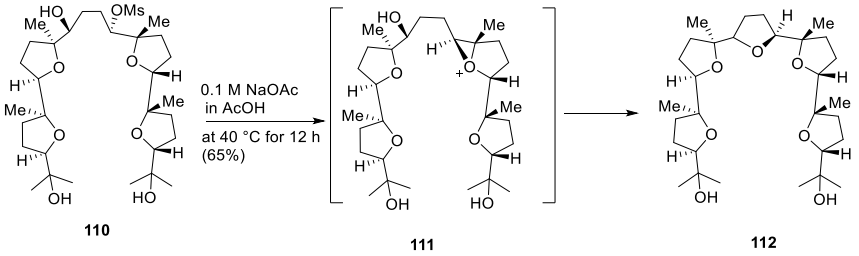
## 2.3 The mechanistic basis of the stereo-retentive nature of Zbiral's deamination

As discussed in chapter 1, the Crich lab conducted a detailed study suggesting that the retention of configuration in the oxidative deamination of NeuAc is caused by the pyranoside ring oxygen participation, via a 1-oxabicyclo[3.1.0]hexanium-type intermediate (carbenium ion) and not by the neighboring group participation of esters.[76] It is not yet clear whether the loss of nitrogen from the diazonium ion is concerted with participation by the ring oxygen or whether two steps are involved with formation of a carbenium ion as intermediate. The final nucleophilic attack occurs on the equatorial face resulting in overall retention of configuration at the 5-postion (**Scheme 23**).




**Scheme 23.** Formation and Opening of an Oxonium Ion.

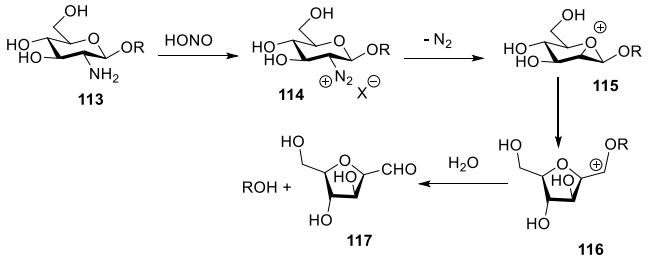
The participation of ether oxygens through comparable bicyclic oxonium ions was seen also in previous studies by several chemists. Thus, Corey and co-workers observed a ring oxygen participation during the total synthesis of glabrescol; the furanoside ring oxygen participated to stabilize the carbocation formed on departure of the mesylate group (**Scheme 24**).[77]



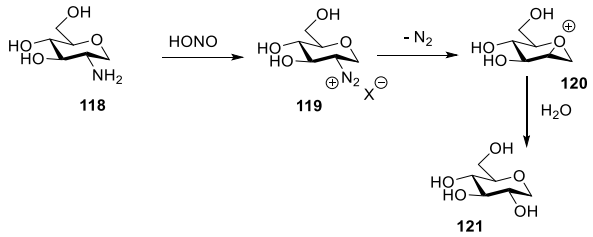

**Scheme 24.** Corey's Proposed Participation of an Ethereal Oxygen Via a Bicyclic Oxonium Ion.

## 2.4 Formation of a 5-membered ring contracted product

The treatment of 2-amino-2-deoxy-glucose **113** with nitrous acid led to the formation of a furanose through ring contraction (**Scheme 25**). Whereas in the absence of glycosidic oxygen such as in a 2-amino-1,5-anhydro sugar **118** , the deamination reaction mainly gave the product of substitution at C2 (**Scheme 26**).[78]

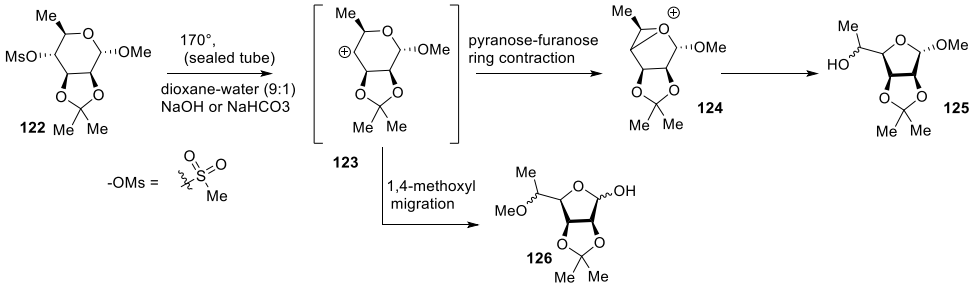



**Scheme 25.** Formation of a Contracted Furan Ring.




**Scheme 26.** Substitution at C2 Through Oxygen Participation in Absence of a Glycosidic Oxygen.

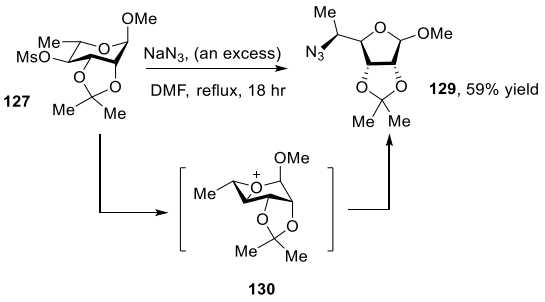
Similar observations were reported by Stevens,[79] Hanessian,[80] Horton,[81] and Cassinelli[82] in several examples of pyranoside to furanoside ring contractions (**Scheme 27**). Moreover, 1-thiabicyclo[3.1.0]hexanium[83] and 1-azabicyclo[3.1.0]hexanium[84] ions, which are equivalents to the ring oxygen oxonium ion, are commonly hypothesized in the literature.




**Scheme 27.** Hexanoside to Furanoside Ring Contraction by Stevens and Co-Workers.[79]

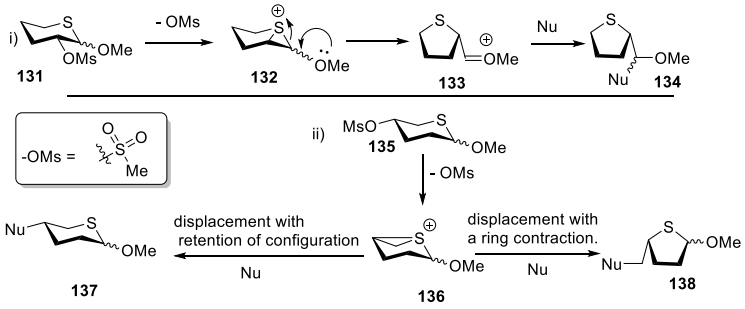
## 2.5 Hanessian's observation of ring contraction

Hanessian and co-workers obtained a furanoside from a rhamnopyranoside during an attempt at mesylate group displacement by the azido nucleophile (**Scheme 28**).[85] The furanoside ring was proposed to result from the oxygen ring participation after the departure of the mesylate group.




**Scheme 28.** Furanoside Ring Contraction by Hanessian and Co-Workers.

A related participation by sulfur was observed through the formation of thiabicyclo[3.1.0]hexanium ion in the synthesis of thiofuranose sugar from a thiopyranose ring. The two possible pathways; ring contraction or direct displacement with retention of configuration were suggested to take place leading to the isolation of a substituted product as well as a contracted thiofuranose (**Scheme 29**).[83]

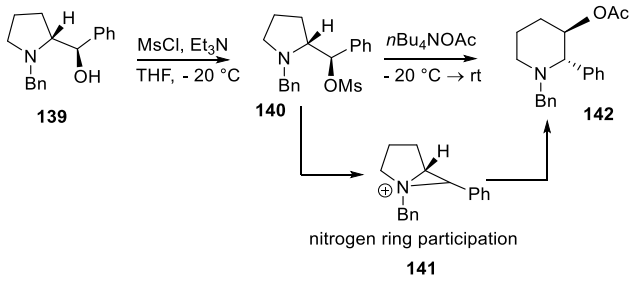



**Scheme 29.** Formation and Reactions of Thiabicyclo[3.1.0]hexanium Ions.

### 2.6 Ring expansion through nitrogen participation

Another example of the ring atom participation was reported in the synthesis of piperidines from prolinol derivatives. The nitrogen of the 5-membered ring prolinol participated to give a 1-azabicyclo[3.1.0]hexanium ion upon the departure of a *β*-leaving group. This was

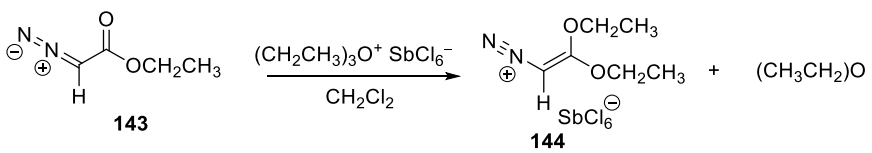
followed by the nucleophile attack on the bridged carbon, leading to the rearrangement and expansion of the ring to form a 6-membered ring (**Scheme 30**).[84]




**Scheme 30.** Nitrogen Participation Followed by Ring Expansion.

## 2.7 Synthesis and isolation of alkenediazonium ions

Although alkenediazonium ions are very reactive compounds and not isolable in the form of free ions, they have been isolated under harsh acidic conditions as hexachloroantimonate salts. Bott has reported the synthesis of series of the alkenediazonium ions with the use of strongly acidic reagents for the formation of resonance-stabilized salts.[86] The reaction between ethyl diazoacetate and triethyloxonium hexachloroantimonate in ethylene dichloride provided colorless crystals of an alkenediazonium salt in 50% yields; it was characterized by elemental analysis as well as infrared spectroscopy in which a sharp peak was observed near 2160 $cm^{-1}$, which was considered supportive of the presence of a diazo group (N≡N) (**Scheme 31**).[86,87]




**Scheme 31.** Formation of an Alkenediazonium **144** Ion from Ethyl Diazoacetate **143**.

Subsequently Glaser was able to obtain an X-ray structure of *β,β*-diethoxyethene diazonium hexachloroantimonate **144**, thereby putting the existence of this rare functional group beyond question (**Figure 8**).[88,89]

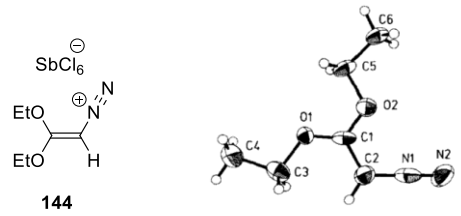
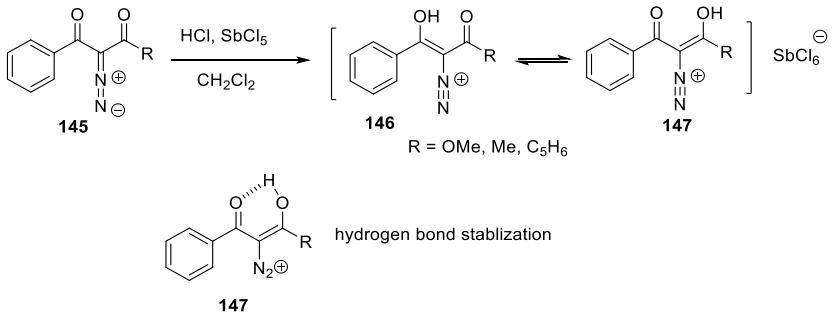


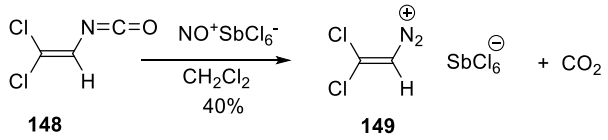

**Figure 8.** Literature X-Ray of Alkenediazonium Ion **144**.[88]

Some other stable alkenediazonium salts were isolated by the treatment of hydrogen chloride, and antimony pentachloride with methyl benzoyldiazoacetate or its derivatives in dichloromethane to provide the alkenediazonium salts as crystalline compounds **146** and **147**. The formation of an intramolecular hydrogen bond and the non-nucleophilic hexachloroantimonate counter ion stabilizes this kind of alkenediazonium ion of **147** (**Scheme 32**).[86,87]



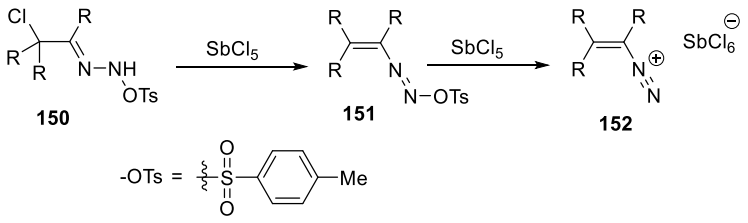

**Scheme 32.** Isolation of Alkenediazonium Salts from Benzoyldiazoacetates.

Additionally, alkenediazonium salts can be synthesized by the treatment of 2,2-dichlorovinyl isocyanate **148** with nitrosyl hexachloroantimonate in dichloromethane. The product **149** was formed in a 40% yield (**Scheme 33**).[86] Mechanistically, the reaction proceeds in two steps; *N*-nitrosation of 2,2-dichlorovinyl isocyanate, followed by the release of $CO_2$ gas.




**Scheme 33.** Synthesis of Alkenediazonium Salt **149** from Dichlorovinyl Isocyanate **148**.

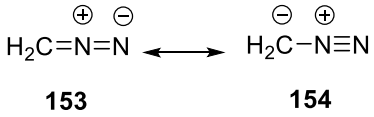
The preparation of alkenediazonium salts can also be achieved over two steps, by the treatment of a *β*-chloro-sulfonylhydrazone **150** with acids such as $AlCl_3$, $SbCl_5$ and $SnCl_4$.[90] The use of two equivalents of the acid is required to i) eliminate the halide, and ii) to facilitate the departure of tosylate group, leading to the formation of alkenediazonium salt **152** (**Scheme 34**).[86]




**Scheme 34.** Preparation of Alkenediazonium Salt **150** from Sulfonylhydrazone.

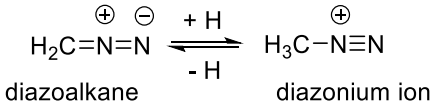
### 2.8 Reactivity of diazonium ions

Diazoalkanes are an important class of diazo compounds that have wide applications in organic synthesis. They have two resonance forms giving rise to the possibility of nucleophilic attack either by the nitrogen or by the carbon toward electrophiles (**Scheme 35**).

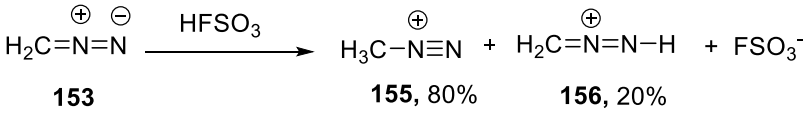



**Scheme 35**. Resonance of Diazomethane.

α-Protonation of diazoalkanes forms the corresponding diazonium ions, which are sources of carbocations (**Scheme 36**). Diazomethane is the simplest member of the diazoalkanes, and it is converted by protonation to the methyldiazonium **155** ion so that it acts as a methylating reagent under acidic conditions in organic synthesis.[91,92] However, the extreme reactivity of diazomethane disfavors its utilization in synthetic labs because it is toxic and potentially explosive.[93] Although the methyldiazonium ion **155** is very reactive and unstable, it was observed along with its protonated isomer methylene diazenium ion **156**, by a low temperature NMR at -106 °C in fluorosulfuric acid at - 120 °C (**Scheme 37**).[94]




**Scheme 36.** α-Protonation of Diazomethane.

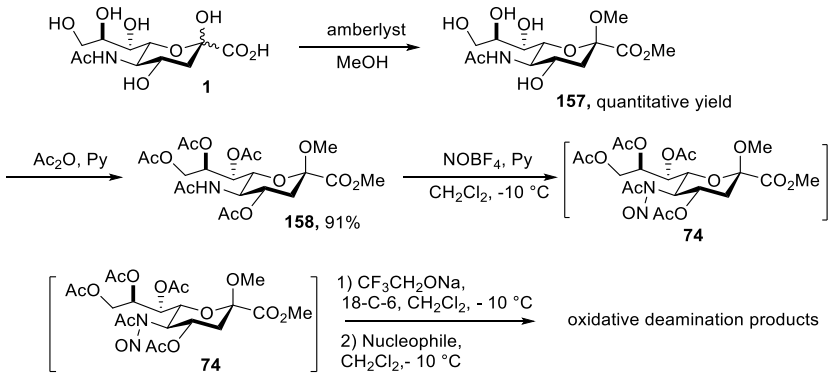



**Scheme 37.** Observation of Methyldiazonium ion **155** by a Low Temperature NMR.

## 2.9 Oxidative deamination using phenols and thiophenols

### 2.9.1 Synthesis of the substrate for deamination

The synthesis of methyl (methyl 4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-5-(*N*-nitrosoacetamido)-D-glycero-β-D-galacto-non-2-ulopyranosid)onate **74** was reproduced as reported in the literature[76,95] from the commercially available *N*-acetyl neuraminic **1**. Thus, compound **1** was treated with an acid source (Amberlyst® 15 hydrogen form) in anhydrous methanol to *O*-methylate the anomeric hydroxyl and the carboxylic acid group leading to methyl ester **157** in quantitative yield. This was followed by a global acetylation of the remaining hydroxy groups to furnish a per-acetylated *N*-acetyl neuraminic acid **158** in 91%. The *N*-nitroso compound **74** was obtained in a quantitative yield through *N*-nitrosylation by the treatment of per-acetylated *N*-acetylneuraminic acid **158** with nitrosyl tetrafluoroborate ($NOBF_4$) and pyridine in dichloromethane at – 10 °C. Compound **74** typically was used immediately without further purification for the oxidative deamination (**Scheme 38**).




**Scheme 38.** The Synthesis of the Starting Material **74** for the Deamination Reactions.

The conditions of the deamination used here were adapted from the previous work[76] by the treatment of the nitrosoamide **74** with sodium trifluoroethoxide in the presence of 18-crown-

6 in anhydrous dichloromethane at – 10 °C, followed after 10 minutes by an excess addition of phenolic nucleophile. After stirring for a further 5 minutes, the reactions were quenched by aqueous sodium bicarbonate, washed with aqueous sodium hydroxide to remove the excess of the nucleophile, and then subjected to chromatographic purification to afford series of the deaminated products (**Table 2**).

**2.10 Results**

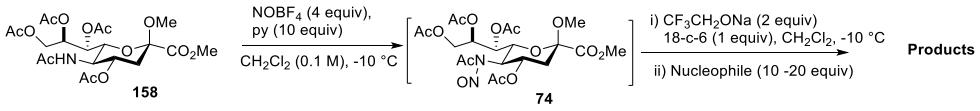
Levulinic acid with a p*K*a of 4.60[96] was used as a carboxylic acid nucleophile to establish the viability of the reaction conditions: it provided the direct substitution product **159** with retention of configuration in a 31% isolated yield. In addition to that, the regioisomeric elimination products **160** and **161** were isolated as byproducts in a 34% combined yield (**Table 2**, entry 1). The use of phenol as nucleophile led to the isolation of the disubstitution product **162**, in which the acetate substituent at C4 was displaced by phenol with the retention of configuration in addition to replacement of the nitrosoamide moiety at the 5-position with inversion of configuration (**Table 2**, entry 2). Additionally, enol ether **163** was isolated from this reaction in a 31% yield as byproduct.

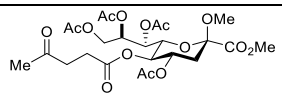
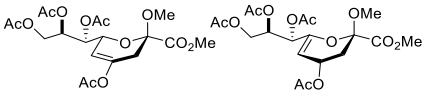
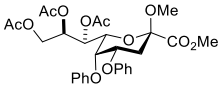
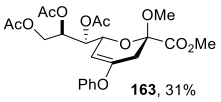
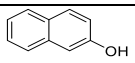
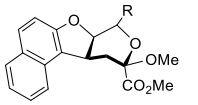
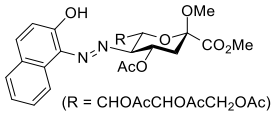
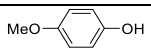
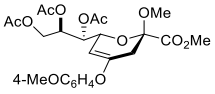
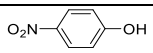
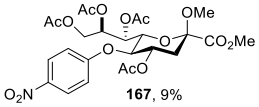
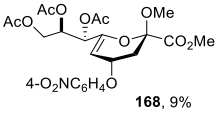
The use of *β*-naphthol as nucleophile gave the tricyclic product **164** in a 57% yield accompanied by the azo dye **165** in a 13% yield (**Table 2**, entry 3).

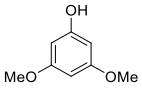
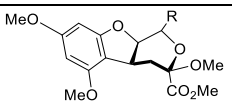
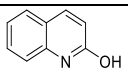
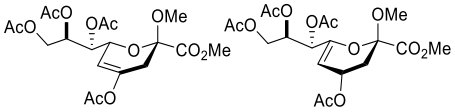
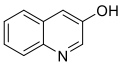
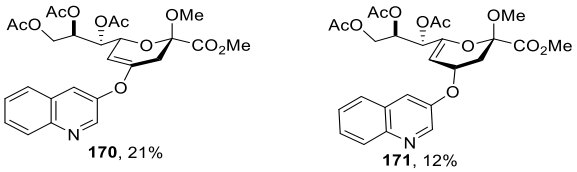
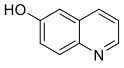
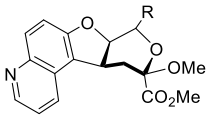
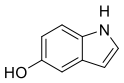
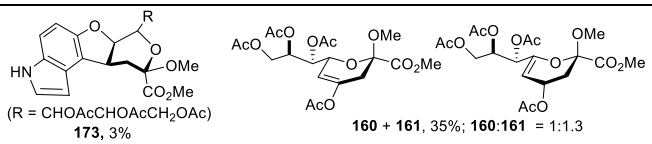
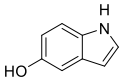
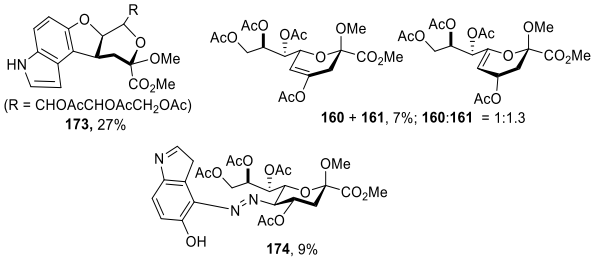
The use of *p*-methoxyphenol afforded a 36% yield of the enol ether **166** (**Table 2**, entry 4), whereas that of *p*-nitrophenol gave a 9% yield of the direct substitution product **167** at 5-position and a 9% yield of the elimination enol ether product **168** (**Table 2**, entry 5). The use of a disubstituted electron-rich phenol such as 3,5-dimethoxyphenol, on the other hand, provided the tricyclic adduct **169** in a 34% yield (**Table 2**, entry 6).

Turning to the use of heteroaromatic phenols as nucleophiles, the use of 2-quinolinol afforded only the elimination products **160** and **161** in a 86% combined yield (**Table 2**, entry 7), whereas 3-quinolinol gave the elimination enol ether products **170** and **171** in 21% and 12% yields, respectively (**Table 2**, entry 8). With the use of 6-quinolinol, on the other hand, similar reactivity was detected as that of *β*-naphthol and 3,5-dimethoxyphenol. This led to the isolation of the tricyclic product **172** in a 53% yield (**Table 2**, entry 9). This latter reaction was conducted in the poorly nucleophilic hexafluoroisopropanol[97,98] as a co-solvent to dissolve the nucleophile because the solubility of the nucleophile in dichloromethane was very limited. The same pattern was observed with 5-hydroxyindole leading to the isolation of the tricyclic product **173** in a 3% yield when the reaction was performed at –10 °C (**Table 2**, entry 10), and in a 27% yield when the reaction temperature was lowered to – 40 °C (**Table 2**, entry 11). The formation of **173** was accompanied by that of the normal elimination products **160** and **161** in 35% and 7% combined yields at –10 and – 40 °C, respectively (**Table 2**, entries 10 and 11), while a 9% yield of the azo dye **174** was also isolated from the reaction at the lower temperature (**Table 2**, entry 11).

**Table 2.** Application of Phenols in the Zbiral Reaction.




| Entry | Nucleophile | p*K*a | Products (% yield)[a] |
|---|---|---|---|
| 1 | Levulinic Acid | 4.60[96] |  **159**, 31%, eq only  **160** + **161**, 34%; **160** :**161** = 1:2.5 |
| 2 |  Phenol | 9.98[99] |  **162**, 33%  **163**, 31% |
| 3 |  β-Naphthol | 9.5[100] |  (R = CHOAcCHOAcCH$_2$OAc) **164**, 57%  (R = CHOAcCHOAcCH$_2$OAc) **165**, 13% |
| 4 |  4-Methoxyphenol | 10.21[99] |  **166**, 36% |
| 5 |  4-Nitrophenol | 7.15[99] |  **167**, 9%  **168**, 9% |

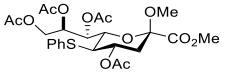
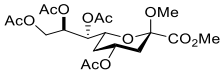
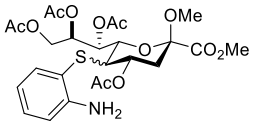
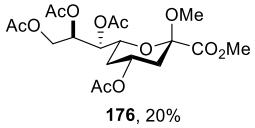
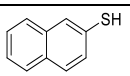
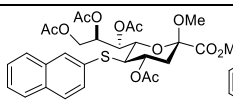
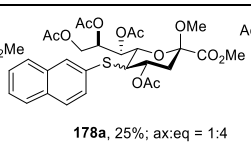
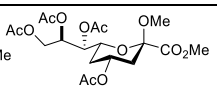
| | | | |
|---|---|---|---|
| 6 |  3,5-Dimethoxyphenol | 9.5 |  (R = CHOAcCHOAcCH$_2$OAc) **169**, 34% |
| 7 |  2-Hydroxyquinoline | 7.86[101] |  **160** + **161**, 86%; **160**:**161** = 2.5:1 |
| 8 |  3-Hydroxyquinoline | 8.03[101] |  **170**, 21% **171**, 12% |
| 9 [b] |  6-Hydroxyquinoline | 8.87[101] |  (R = CHOAcCHOAcCH$_2$OAc) **172**, 53% |
| 10 |  5-Hydroxyindole | - |  (R = CHOAcCHOAcCH$_2$OAc) **173,** 3% **160** + **161**, 35%; **160**:**161** = 1:1.3 |
| 11 [c] |  5-Hydroxyindole | - |  (R = CHOAcCHOAcCH$_2$OAc) **173,** 27% **160** + **161**, 7%; **160**:**161** = 1:1.3 **174**, 9% |

*a*) The elimination products were the side products in all deamination reactions and were not isolated in every reaction. *b*) Hexafluoroisopropanol was used to dissolve the nucleophile. *c*) the reaction was conducted at – 40 °C.

### 2.10.2 Thiophenols as nucleophiles

Attention was next turned to the use of thiophenols as nucleophiles. The typical substitution product **175** was isolated in a 23% yield with retention of configuration (**Table 3**, entry 1). This product was accompanied by the reduction product **176** in a 19% yield. On the other hand, the use of 2-aminothiophenol provided a 58% of the direct substitution product **177**, but as a mixture of isomers; 3:1 axial:equatorial (**Table 3**, entry 2), along with the reduction product **176** in a 20% yield. Finally, the use of 2-mercaptonaphthalene as nucleophile afforded the substitution with retention of configuration product **178** in a 30% yield, contaminated with a minor amount of the stereoisomer **178a** in a 25% yield, and the reduction product **176** in a 13% yield (**Table 3**, entry 3).

**Table 3.** Application of Thiophenols in the Zbiral Reaction.

| Entry | Nucleophile | p*K*a | Products (% yield)[a] |
|---|---|---|---|
| 1 |  Thiophenol | 6.6[100] |  **175**, 23%  **176**, 19% |
| 2 |  2-Aminothiophenol | 6.59[102] |  **177**, 58%; ax:eq = 1:3  **176**, 20% |
| 3 |  β-Mercaptonaphthalene | 5.9[100] |  **178**, 30%  **178a**, 25%; ax:eq = 1:4  **176**, 13% |

a) The elimination products were the side products in all deamination reactions and were not isolated in every reaction.

## 2.12 Structural elucidation

### 2.12.1 NMR data of the disubstituted and unusual tricyclic products

The structures of **159**, **167**, **175**, **176**, **177,** and **178** that were obtained from the direct substitution reaction, can be clearly characterized and confirmed by NMR analyses. However, the unexpected deamination products that resulted from either substitution-elimination or from solely elimination process in this reaction are worthy of further explanation. The disubstitution product **162** that resulted from using phenol as nucleophile, was characterized mainly by $^{1}$H-NMR with the focus on the measured data obtained from the $^{3}J_{H,H}$ coupling constants as well as nOe contacts that surround the pyranose ring (**Figure 9**).

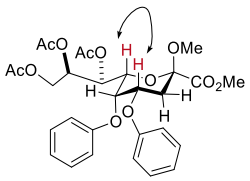



**Figure 9.** nOe Correlation in the Disubstitution Product **162.**

The $^{3}J_{H4,H5}$ and $^{3}J_{H5,H6}$ coupling constants of 4.5 and 2.0 Hz, respectively, were recorded in $C_6D_6$ due to the overlap of H's 5 and 6 in $CDCl_3$ in the structure of **162**. On the basis of these coupling constants, the substituents at C's 4, 5, and 6 were found to be in a *cis*-relationship. These findings were further supported by the nOe analysis between H's 4 and 6 (**Figure 10 and 11**).

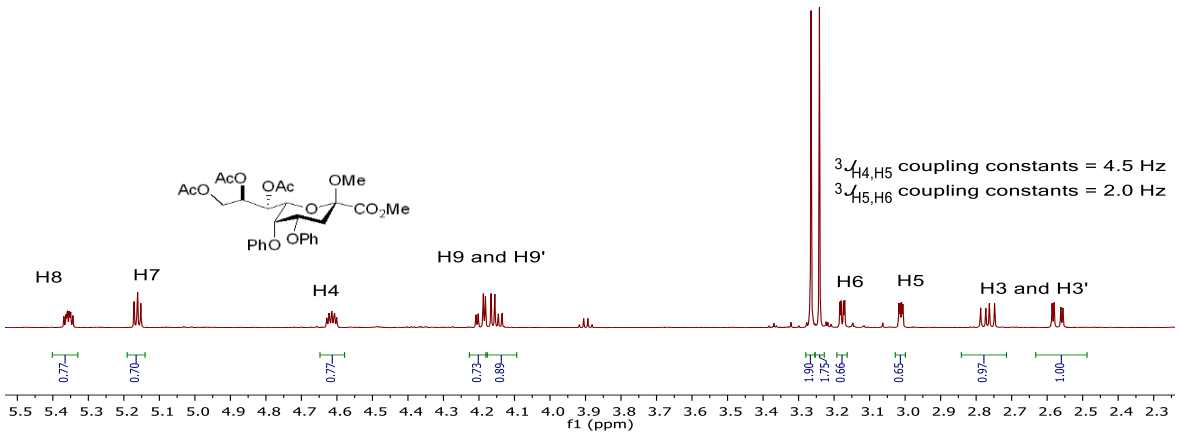



**Figure 10.** $^1$H NMR Recorded in $C_6D_6$ of the Disubstitution Product **108**.

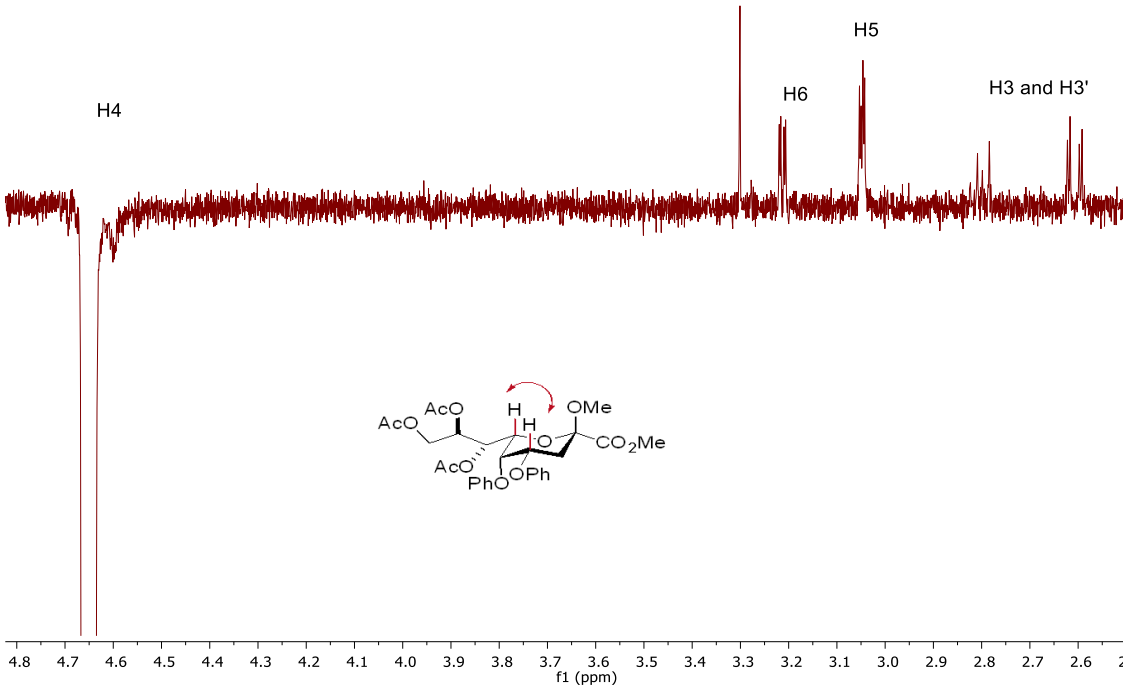



**Figure 11.** nOe Difference Spectrum of the Disubstitution Product **162** Obtained by Double Irradiation of H4.

### 2.12.2 The X-ray data for the tricyclic product 164

The tricyclic product **164** was crystallized from diethyl ether and its structure was determined by X-ray crystallography (**Figure 12**). Upon inspection of this crystal structure, the pyranose ring approximately was found to adopt a $^{3,6}B$ boat conformation (**Table 2**, entry 3).

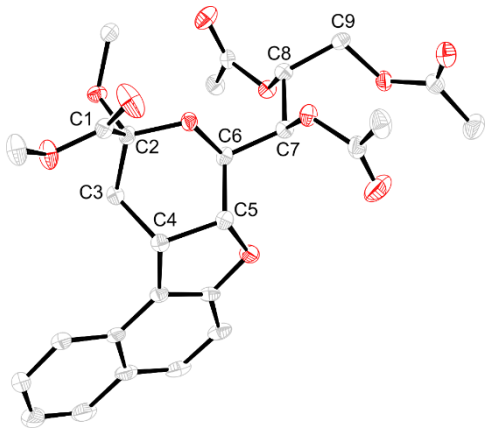



**Figure 12.** X-Ray Crystallographic Structure of Product **164** (CCDC 1941624).

This $^{3,6}B$ conformation also predominates in solution as indicated by the ensemble of $^{3}J$ scalar couplings in the $H_{3a,b}$, $H_4$, $H_5$, $H_6$ spin systems (**Table 4**) as well as by nOe interactions that were measured between one of the H3 protons and an aromatic proton (**Figure 13 and 14**).

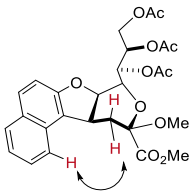



**Figure 13.** nOe Interactions of the Tricyclic Product **164**.

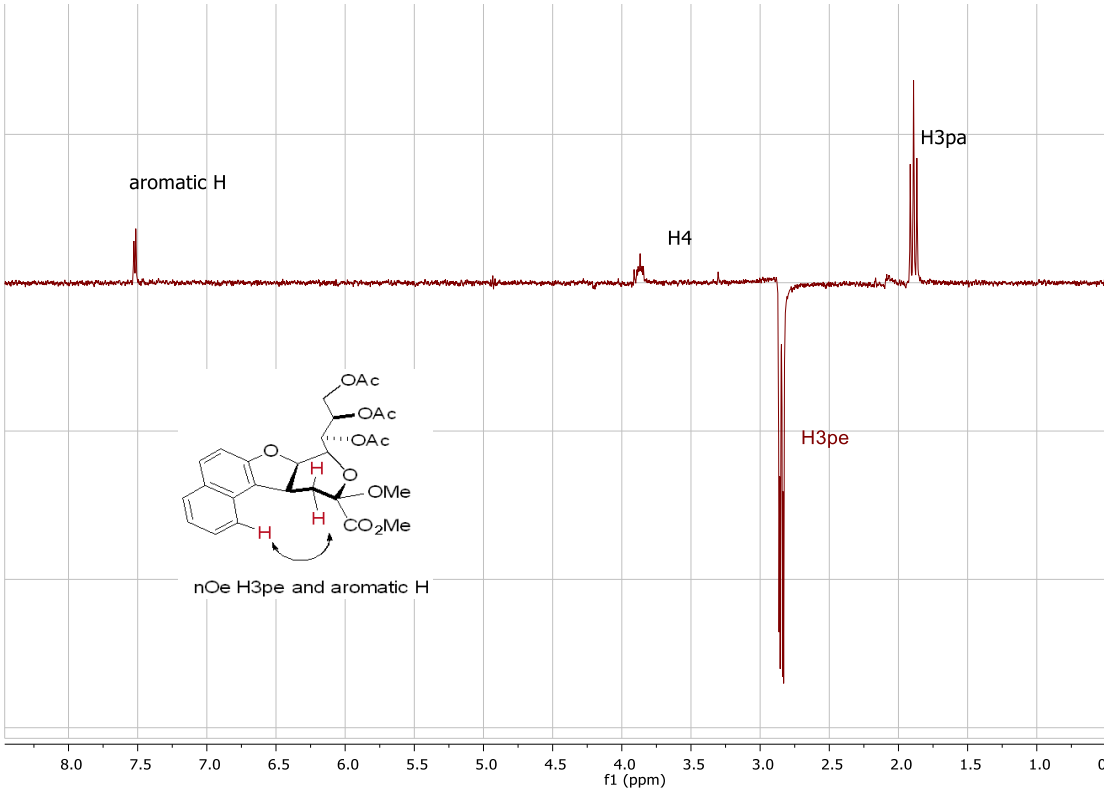



**Figure 14.** nOe Difference Spectrum of Tricyclic Product **164** on Double Irradiation of the Pseudoequatrial H3.

Although the tricyclic product **164** adopted a boat conformation, its side chain retains the conformation commonly found in NeuAc and its derivatives. Thus, the side chain of the tricyclic product **164** was found to adapt the *gauche,gauche*-conformation (*gg*),[103,104] ,which is similar to that found in the *N*-acetyl neuraminic acid (**Figures 15 and 16**).[105-111]

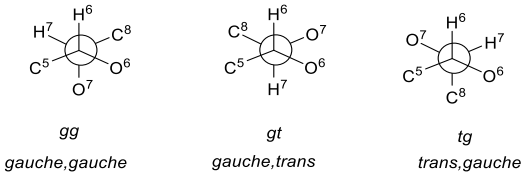



**Figure 15.** Possible Side Chain Conformations in NeuAc Systems.

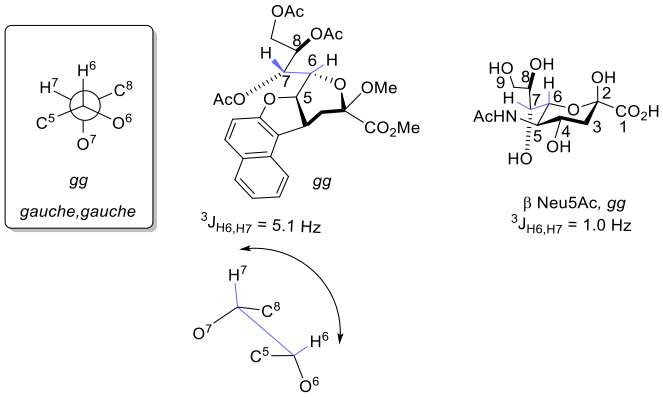



**Figure 16.** NeuAc and the Tricyclic Compound **164** Side Chain Conformations.

In addition, the disubstitution product **162** most likely does not adopt the *gg*-conformation because the axial phenoxy substituent at C5 with $^3J_{6,7}$ of ~ 2.0 Hz, forces the side chain to deviate from its original *gg*-conformation to a different conformation, along with the adopting of the standard $^2C_5$ chair conformation in **162**.[105-111] The strong dipolar and steric (syn-pentane) type interactions (**Figure 17**) are obviously present in between the C5-O5 and C7-O7 bonds in this conformation **162** (**Figure 17**). Thus, the side chain in this compound **162** takes up a different conformation in order to relieve the strain and the steric interaction (**Figure 17**).[112]

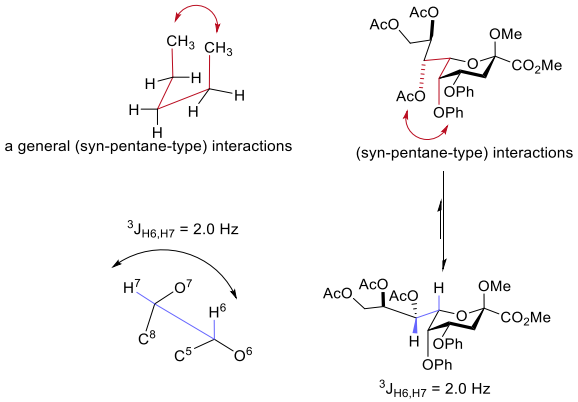



**Figure 17.** Demonstration of *Syn*-Pentane-Type Interaction and Its Influence on the Side Chain Conformation of **162**.

The tricyclic structures **169**, **172**, and **173** were assigned by analogy with **164** on the basis of NMR studies, with their coupling constants in the $H_{3a,b}$, $H_4$, $H_5$, $H_6$ spin system being very similar to those of the product **164** (**Table 2**). In each of the tricyclic products **164**, **169**, **172**, and **173** the $^3J$ coupling constant between the pseudo-axial H3 and H4 is found to be at the upper limit of the normal range (12.9-13.5 Hz) observed for a pair of coupled *trans*-diaxial spins in saturated aliphatic systems, presumably because there are no electronegative substituents in this spin system (**Table 4**).[113]

**Table 4**. Chemical Shifts and Diagnostic Coupling Constants for **162**, **164**, **169**, **172**, and **173**.[a]

| | chemical shifts (δ, ppm)[b] | | | | | | coupling constants (Hz) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| product | H3pa | H3pe | H4 | H5 | H6 | H7 | $^3J_{3pa,4}$ | $^3J_{3pe,4}$ | $^3J_{4,5}$ | $^3J_{5,6}$ | $^3J_{6,7}$ | $^2J_{3pa,pe}$ |
| **162** | 2.55 | 2.47 | 4.52 | 3.14 | 3.13 | 4.99 | 8.9 | 3.2 | 3.7 | - | 5.3 | 14.9 |
| **162**[c] | 2.77 | 2.57 | 4.61 | 3.01 | 3.18 | 5.16 | 8.8 | 3.4 | 4.5 | 2.0 | 5.7 | 14.8 |
| **164** | 1.90 | 2.86 | 3.87 | 4.94 | 4.21 | 5.69 | 13.5 | 5.0 | 9.2 | 9.4 | 5.1 | 14.9 |
| **169** | 1.79 | 2.63 | 3.47 | 4.70 | 4.03 | 5.59 | 12.9 | 5.4 | 9.1 | 9.4 | 4.6 | 14.9 |
| **172** | 1.92 | 2.78 | 3.88 | 4.99 | 4.21 | 5.68 | 13.4 | 5.1 | 8.9 | 9.3 | 5.0 | 14.9 |
| **173** | 2.02 | 2.72 | 3.77 | 4.82 | 4.12 | 5.67 | 12.8 | 5.5 | 8.8 | 9.4 | 5.0 | 14.9 |

*a*) All spectra were recorded in $CDCl_3$ unless otherwise stated. *b*) H3pa and H3pe mean pseudo-axial and pseudo-equatorial protons at C3, respectively. c) Recorded in $C_6D_6$.

### 2.12.3 Elucidation of structure of the enol ethers by chemical methods

Two possible regioisomeric structures for enol ethers **163**, **166**, and **170** could not be distinguished by normal $^{1}H$ and $^{13}C$ NMR spectroscopic methods because of the ambiguity in the multiplicity of the long range coupling constants around the pyranose ring. Therefore, it was unclear whether the nucleophile had attacked at the 4- position or the 5-position (**Figure 18**).

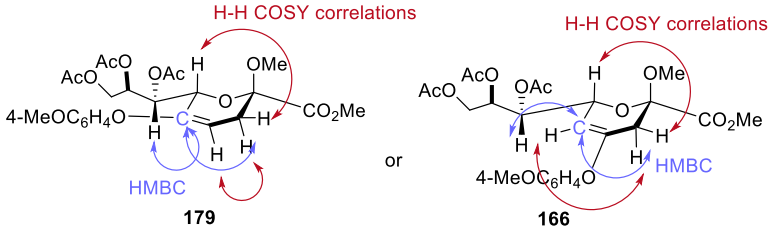
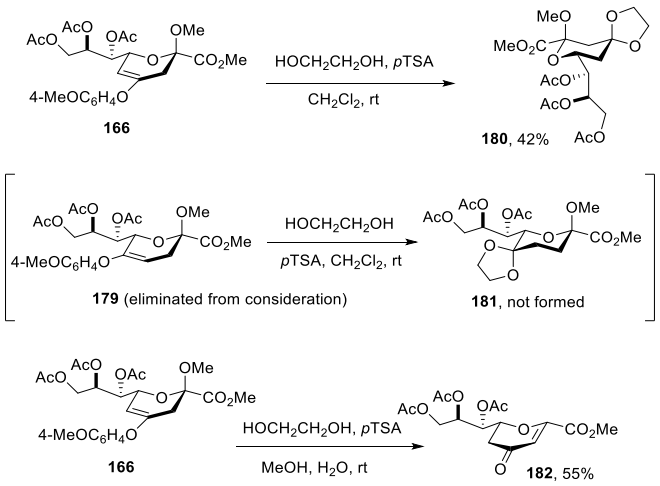



**Figure 18.** Ambiguous Long Range Couplings in The Possible Enol Ether Products **179** and **166**.

Eventually, a chemical reaction enabled to correctly assign the enol structures. Using **166** as a demonstrative example; it was treated with ethylene glycol in dichloromethane in the presence of *p*-toluenesulfonic acid at room temperature, and the cyclic ketal **180** was isolated in a 42% yield (**Scheme 39**). The two methylene spin systems in this ketal clearly indicate that the structure was **180** and not the other alternative ketal **181**. Thus, compound **166** was the product resulting from the deamination process and not the other presumed product **179**. Further, the structure of **166** was confirmed by the treatment with ethylene glycol and *p*-toluenesulfonic acid in wet methanol at room temperature when the enone **182** was isolated in a 55% yield (**Scheme 39**). The NMR spectra of the structures **163**, and **170** have a similar pattern of that for **166.**




**Scheme 39.** Chemical Elucidation of Enol Ether **16.**

With the structure of **166** in hand, the full complement of long range couplings in this product could be assigned (**Table 5**).

**Table 5.** Chemical Shifts and Coupling Constants for **166**.

| | chemical shifts (δ, ppm) | | | | | | coupling constants (Hz) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| product | H3pa | H3pe | H4 | H5 | H6 | H7 | $^3J_{3pe,5}$ | $^3J_{3pe,6}$ | $^3J_{4,5}$ | $^3J_{5,6}$ | $^3J_{6,7}$ | $^2J_{3pa,pe}$ |
| **166** | 2.53 | 2.64 | - | 4.51 | 4.45 | 5.23 | 2.0 | 2.5 | - | 1.9 | 5.3 | 17.1 |

The azo dyes **165** and **174** have intense yellow colors, which are typical of such derivatives. Their structures were further confirmed by $^1$H and $^{13}$C NMR, UV/visible spectra, and high resolution mass spectrometry (HRMS). Accordingly, NMR analysis showed that the diazo group (N=N) connects the 5-position of NeuAc with the C2 of *β*-naphthol moiety in the structure **165** as well as with the C4 of 5-hydroxyindole moiety in the azo dye **174**. Moreover, the aromatic protons in C2 of *β*-naphthol and in C4 of 5-hydroxyindole, which are distinct peaks in

$^{1}$H NMR, have disappeared but the remaining aromatic protons were clearly assigned in the both azo dyes. UV/Visible spectroscopy showed absorbance peaks at $\lambda_{max}$ 380 nm and $\lambda_{max}$ 365 nm for **165** and **174**, respectively. Finally, the retention of the azo moiety in both structures was confirmed by HRMS (**Table 6** and **Figure 19**).

**Table 6.** Characterization Data of the Diazo Dyes.

| Azo dye | UV/Visible spectra | Molecular formula | HRMS |
|---|---|---|---|
| **165** | $\lambda_{max}$ 380 nm (acetonitrile, $\varepsilon$ = 8699 $M^{-1}$ $cm^{-1}$) | $C_{29}H_{34}N_2O_{13}Na$ | 641.1964 |
| **174** | $\lambda_{max}$ 365 nm (dichloromethane, $\varepsilon$ = 2391 $M^{-1}cm^{-1}$) | $C_{27}H_{33}N_3O_{13}Na$ | 630.1904 |

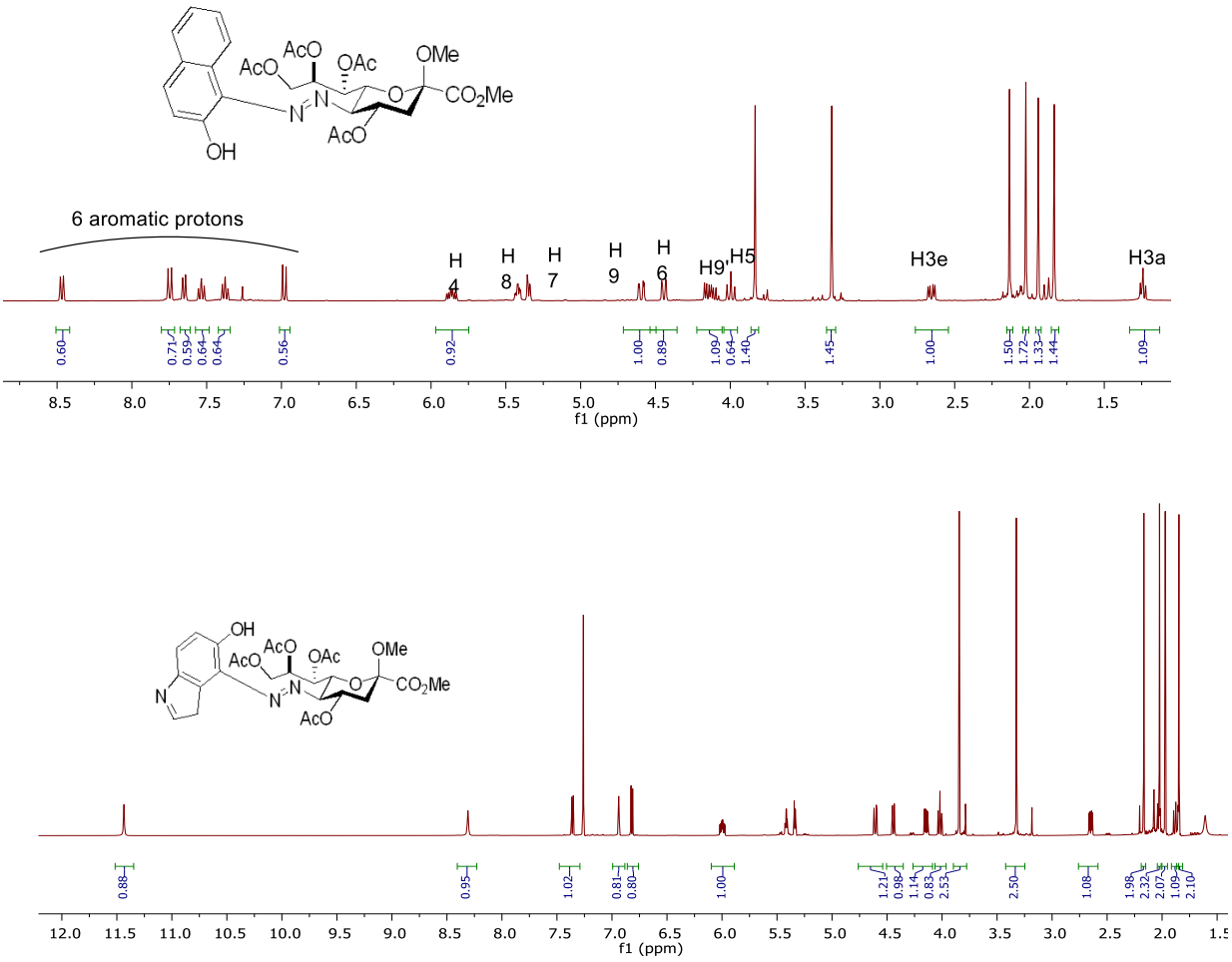



**Figure 19.** [1]H NMR of the Azo Dyes.

### 2.12.3 Determination of the configuration at the 5-position

The retentive nature of the configuration is confirmed by the measurement of the coupling constants of the protons residing in C4, C5 and, C6. When the substituent (nucleophile) at C5 is equatorial, the coupling constant of the axial proton is in between ~ 8-11. On the other hand, if the substituent is axial and the proton is equatorial, the coupling constant is approximately ~ 2-3. The structure **174** is shown as an example in (**Figure 20**) to determine the stereochemistry of H5 by the measurement of three bonds vicinal coupling constant.

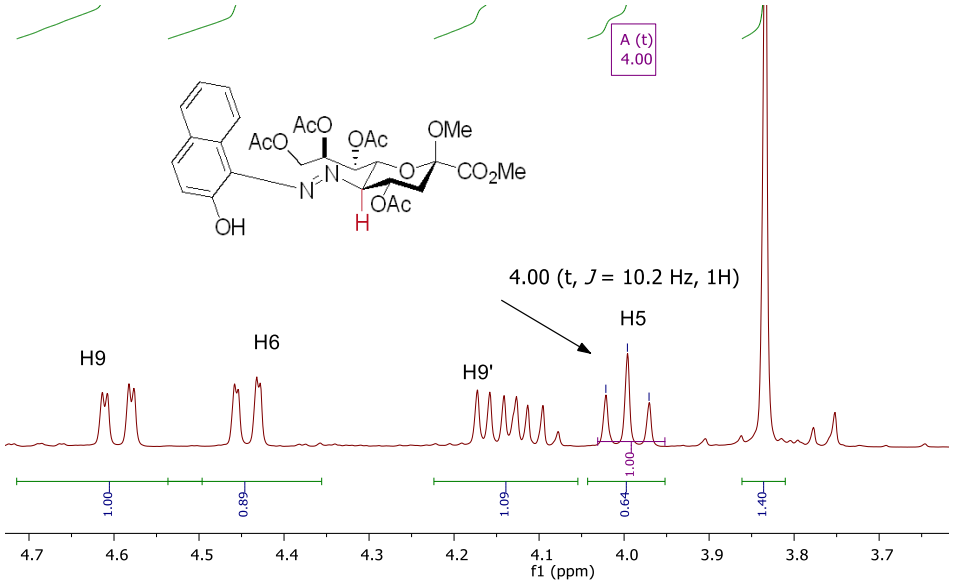
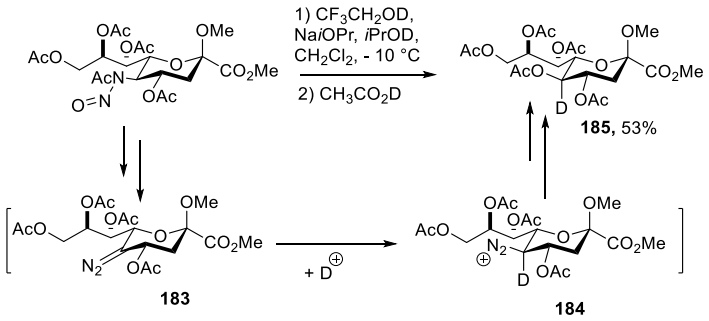



**Figure 20.** Determination of the Stereochemistry of H5 by Measuring the Coupling Constant**.**

## 2.13 Discussion

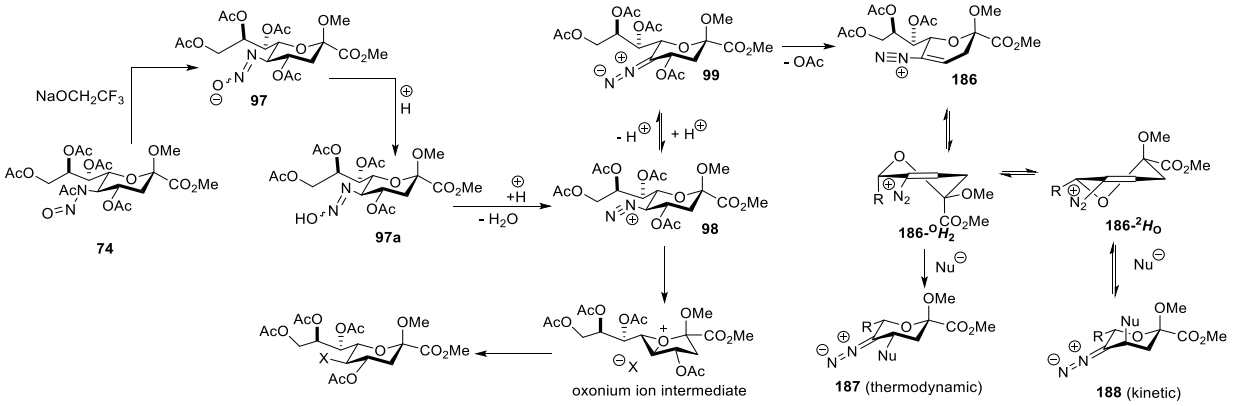
The ensemble of results may be explained according to the formation and reactions of a diazonium ion intermediate. Upon the addition of sodium trifluoroethoxide, the *N*-acetyl group is selectively removed from the acetamido moiety leading to the formation of hydroxydiazine **97a**. The protonated hydroxydiazine **97a** loses water after a second protonation, to form the diazonium ion **98**. It is suggested that the diazonium ion **98** undergoes reversible deprotonation to form its conjugate ion diazoalkane **99**, and both ions are in equilibrium. Depending on the acidity of the media, one of these two intermediates can predominate over another. Additionally, the formation of the azo dyes **165** and **174** is a strong evidence that the diazonium ion is involved as an intermediate in this process (**Table 2**).

The reversible deprotonation of the diazonium ion was previously confirmed by the Crich lab through the use of deuterioacetic acid as nucleophile. This led to the selective installation of a deuterium atom in the 5-position and formation of monodeuterio-KDN derivative (**Scheme 40**).[76]



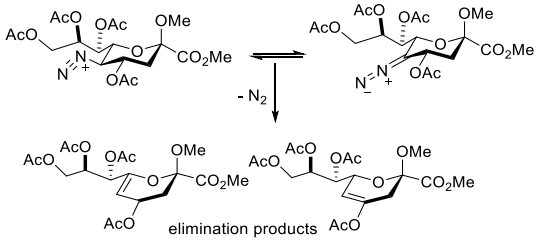

**Scheme 40.** The Incorporation of Deuterium at the 5-Position by the Crich Lab.

The diazonium ion **98**, which has electron withdrawing and acidity-enhancing *β*-C−O bonds, is expected to be more acidic than the simple methyldiazonium ion[114] (pKa ~ 10). In more acidic media, diazonium ion **98** is favored over the diazoalkane **99** leading to the loss of nitrogen followed by the formation of the standard substitution and normal elimination products (**Scheme 41**). In less acidic reaction media, such as that of phenols employed here, the diazoalkane **99** is formed and undergo *β*-elimination of the acetoxy group from the 4-position to afford the *α,β*-unsaturated diazonium ions **159** (**Scheme 41**).




**Scheme 41.** Overall Mechanism for Product Formation.

The normal elimination products that are regularly isolated in the oxidative deamination, are formed either directly by the loss of the molecular nitrogen from the diazonium ion followed by *β*-elimination or from the *N*-nitrosoacetamide **74** through the elimination by the anionic oxygen of the nitroso moiety (**Scheme 42**).




**Scheme 42.** The Formation of Elimination Products.

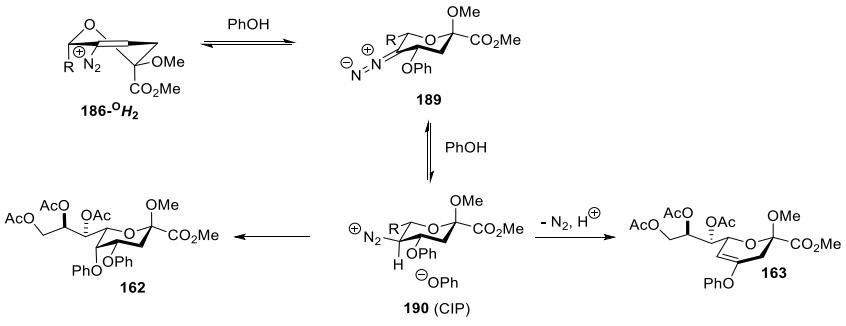
### 2.13.1 The formation of disubstitution product 162

The vinyl diazonium ion in this reaction is a reactive electrophile that can populate two possible half-chair conformers **186-$^{O}H_2$** and **186-$^{2}H_O$** and related boat conformers (**Scheme 42**). *β*-Face attack, occurs on the conformer **186-$^{2}H_O$** under kinetic Michael addition leading to the formation of a new chair structure of diazoalkane **188**. On the other hand, the nucleophile attack

from the bottom-face under thermodynamic Michael addition fashion leads to the equatorial delivery and formation of the chair conformation **187** (**Scheme 42**).

In the case of phenol as nucleophile, thermodynamic attack is followed by the protonation of the diazoalkane, and another molecule of phenol comes into play on the α-face leading to a contact ion pair (CIP) **190**. This loses the molecular nitrogen and forms the isolated product **162** with inversion of configuration (**Scheme 43**). Protonation of **189** from the α-face is also consistent with the earlier work by the Crich lab using the deuterium-labeling experiments (**Scheme 40**).[76] Finally, the enol ether **163** is formed from **190** by the loss of nitrogen followed by deprotonation in concerted fashion (**Scheme 43**).

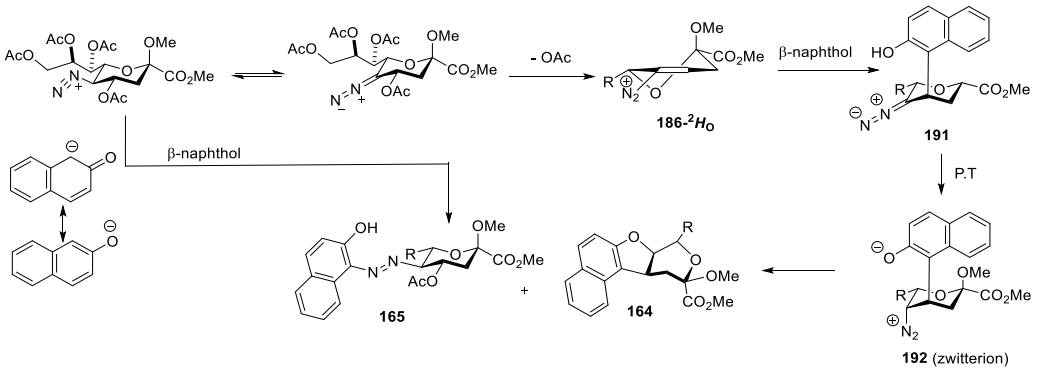
A similar pathway of elimination was observed for *p*-methoxyphenol and 3-quinolinol leading to the enol ethers **166**, **170**, and **171** as major products (**Table 2**, entries 4, 5, and 8). On the other hand, with the more acidic *p*-nitrophenol as nucleophile, the reprotonation of the diazonium ion **98** is competing with the elimination. Thus, the direct substitution product **168** is formed in minor quantity (**Table 2**, entry 5).




**Scheme 43.** Formation of Disubstitution Product **162**.

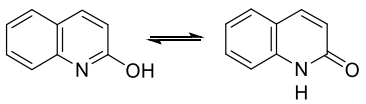
### 2.13.2. The formation of tricyclic product 164

In the case of *β*-naphthol, which is an ambident nucleophile, the kinetic Michael addition takes place and the intermediate **191** is trapped by intramolecular proton transfer leading to the formation of zwitterion **192**. The tricyclic product **164** is then formed by the ring closure of the zwitterion by the nitrogen displacement at C5 (**Scheme 44**).




**Scheme 44.** Formation of Tricyclic Product **164**.

2-Quinolinol is very weakly nucleophilic and no substitution product was observed because it exits mostly as quinolinone (**Scheme 45**). The normal regioisomeric elimination products are the only isolated products **160** and **161** of this reaction (**Table 2**, entry 7).

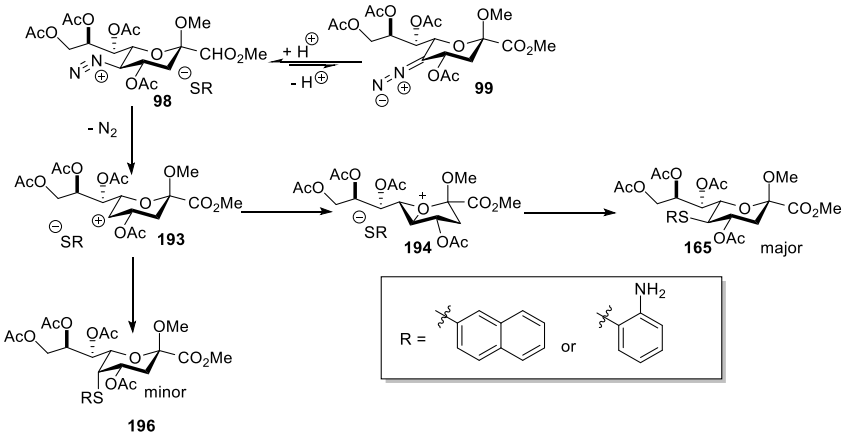



**Scheme 45.** The Tautomeric Forms of 2-Quinilinone.

### 2.13.3 Mechanism of reaction with thiophenols as nucleophile

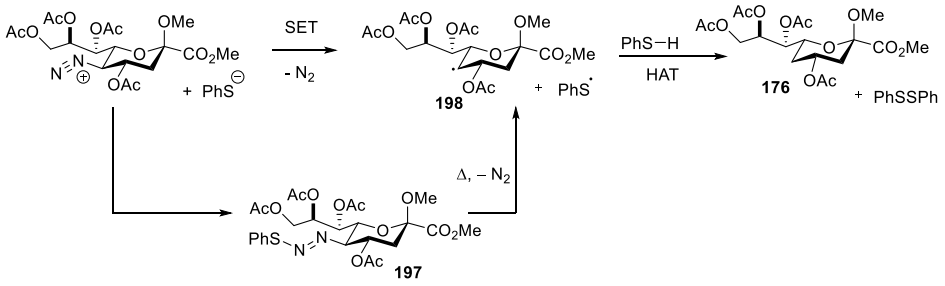
Because thiophenols are more acidic than phenols, the acidity of the reaction media is increased and diazonium ion **98** predominates over the diazoalkane **99.** Thus, the direct

substitution products are isolated with the retention of configuration (**Scheme 46**). However, minor amounts of the axial substitution products were observed with the inversion of configuration due to the direct displacement of nitrogen by the sulfur atom nucleophile, which is competitive with ring oxygen participation.




**Scheme 46.** Formation Equatorial and Axial Substitution in Thiophenols.

The reduction product **176** is formed possibly through a single electron transfer (SET) process. The diazonium ion **98** losses molecular nitrogen and receives a single electron from the thiophenolate to form alkyl radical **198**, which is converted to the reduction product **176** after hydrogen atom transfer (HAT) from another molecule of thiophenol. Alternatively, thiophenolate couples with the terminal nitrogen of the diazonium ion **98** to afford arylthiodiazene **197,** followed by homolytic scission to provide the alkyl radical **198** and followed, by HAT that leads to the reduction product **174** (**Scheme 47**). This reduction process is consistent with the proposed mechanism reported in the literature for the reduction of arenediazonium ions by thiophenols.[115] The formation of the reduction product therefore further supports the formation of the diazonium intermediate in the Zbiral deamination process.




**Scheme 47.** Mechanism for the Formation of the Reduction Product **176**.

## 2.14 Conclusion

The use of phenols and thiophenols as nucleophiles in the oxidative deamination has led to the discovery of a new branch of the Zbiral-type deamination reaction through the formation of a vinyl diazonium ion, a member of the little-studied class of alkenediazonium ions. The formation of different types of deamination products is a function of the acidity of the reaction media. More acidic media such as with thiophenols tend to favor the direct substitution products, while less acidic solutions lead to the formation of an electrophilic vinyl diazonium ion and, following Michael addition, disubstitution products.

# CHAPTER 3. THE ISOLATION AND CHARACTERIZATION OF NOVEL NEURAMINIC ACID DERIVATIVES FROM THE USE OF HYDROXYLAMINES AND RELATED COMPOUNDS AS NUCLEOPHILES IN THE ZBIRAL OXIDATIVE DEAMINATION OF *N*-ACETYL NEURAMINIC ACID

## 3.1 Background

### 3.1.1 Overview

Hydroxylamines are an under-appreciated functional group whose derivatives may be useful for pharmacological applications.[116] Hydroxylamines have been found to play a significant role in the immunogenic activity of *mycobacterial* ribonucleic acid vaccines in mice.[117] It was described that hydroxylamine derivatives may function as antifungal, antiviral and antifungal agents.[118] Oximes and hydroxamic acids are related structures derived from hydroxylamine (**Figure 21**).

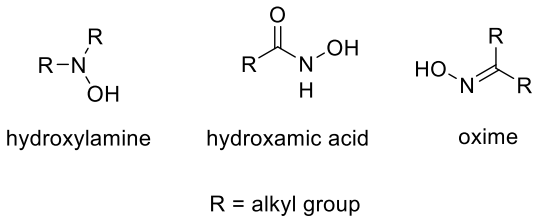



**Figure 21.** Structures of Hydroxylamines, Hydroxamic Acids and Oximes.

The hydroxamic acids are an important class of chemical compounds that are utilized in a wide range of biological and medicinal applications. For instance, the structures of hydroxamic acids mimic some functional groups that are present in protein structures.[119] Molecules containing a hydroxamic acid moiety are found to potentially function as inhibitors of *Helicobacter pylori urease*.[120] Both the oxygen and the nitrogen atoms in hydroxylamines and their derivatives, carry lone pairs, and so are potentially nucleophilic sites that can react with electrophiles.[121] These (N−OH)-containing organic molecules are weakly acidic and their p*K*a

values vary according to the substituents connected to nitrogen as well as the ability to release a proton from the terminal hydroxy group (**Figure 22**).[122-125]

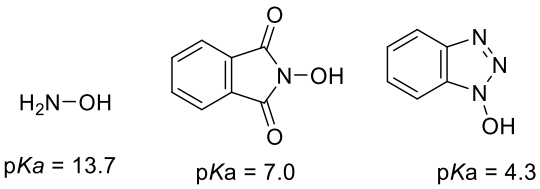
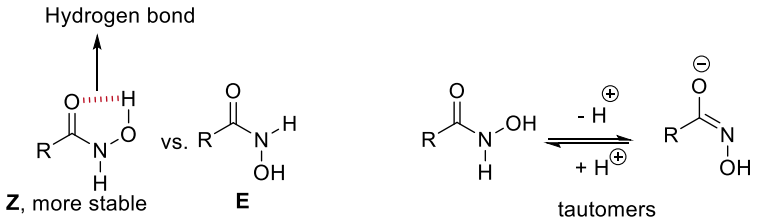



**Figure 22.** Examples of Hydroxylamine Derivatives and Their p*K*a Values.

One of the properties that accompanies these molecules is the α-effect, which describes the increase in nucleophilicity of molecules with two covalently bonded heteroatoms, which occurs due to the presence of lone pairs on adjacent atoms.[126]

The hydroxamic acid function has two possible acidic sites; hydroxyl O-H and amine N-H moieties, and a basic site in the form of the carbonyl oxygen. A hydroxamic acid can exist in two structures **E** and **Z**, but the **Z** structure is more stable due to the formation of a hydrogen bond between the oxygen of the carbonyl group and the proton of the hydroxy group.[122] A hydroxamic acid can also exist in two tautomeric forms in a keto-enol like equilibrium (**Scheme 48**).[126,127]



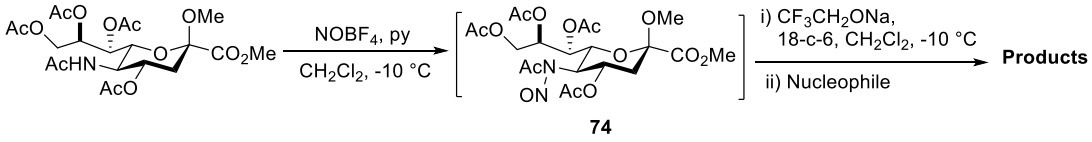

**Scheme 48**. Hydrogen Bond Stabilization and Tautomerism of Hydroxamic acids.

### 3.2 Research goal

As discussed in chapters 1 and 2, the oxidative deamination is a useful method to functionalize the 5-position of *N*-acetyl neuraminic acid with various nucleophiles and protecting groups. Accordingly, hydroxylamines, hydroxamic acids, oximes, nitrogen heterocycles and amines with variable p*K*a values, were screened as nucleophiles in the oxidative deamination of NeuAc to probe their reactivities and eventually probe the resulting products for potential use as sialic acid-based neuraminidase inhibitors.

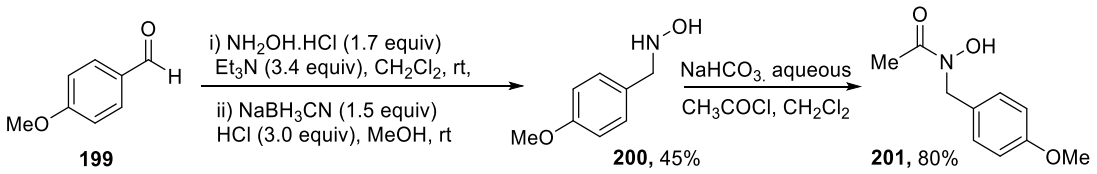
### 3.3 Results

The substrate **74** for the oxidative deamination was prepared according to the method reported in chapter 1. This nitrosyl sialoside **74** was treated with sodium trifluoroethoxide and 18-crown-6 in anhydrous dichloromethane at – 10 °C. Hydroxylamine, hydroxamic acid, or nitrogen-based nucleophiles were then added in the next step to afford the deaminated products (**Scheme 49**).



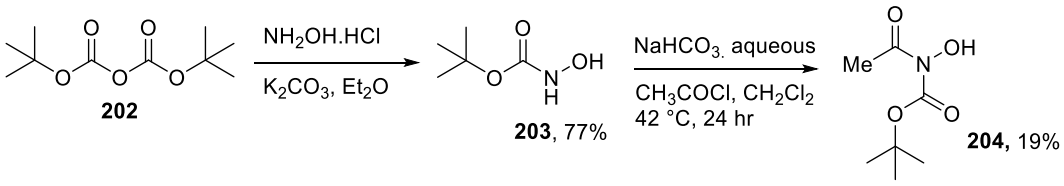

**Scheme 49.** Synthesis and Deamination of Nitrosyl Sialoside **74**.

Most nucleophiles in this study were purchased from commercial suppliers and were used in the deamination reactions without further purification. But, *N*-(*p*-methoxybenzyl)acetohydroxamic acid was prepared from 4-anisaldehyde by reproducing the literature procedure (**Scheme 50**).[128]




**Scheme 50.** Preparation of *N*-(*p*-Methoxybenzyl)acetohydroxamic Acid

*N*-Boc-Acetohydroxamic acid was prepared by following a literature protocol; it was synthesized from di-tert-butyl dicarbonate and hydroxylamine hydrochloride giving **203**, which was then acetylated using acetyl chloride (**Scheme 51**).[129]




**Scheme 51.** Preparation of *N*-Boc-Acetohydroxamic Acid.

### 3.3.1 Deamination Reactions

1-Hydroxybenzotriazole (HOBt) was the first nucleophile used in this study. This nucleophile gave the direct substitution product **205** with the retention of configuration in a 48% yield (**Table 7**, entry 1). Similarly, the use of *N*-hydroxysuccinimide (NHS) as nucleophile, provided the direct substitution product **206** at C5 with the retention of configuration in a 36% yield (**Table 7**, entry 2).

The use of *N*-hydroxyphthalimide (NHPI) as nucleophile, on the other hand, provided two deamination products; a mono-substitution product **207** at C5 isolated in a 36% yield, and a disubstitution product **208** at both C4 and C5 isolated in a 27% yield. These two products were

accompanied by the normal mixture of elimination products **160** and **161** in 23% yields and a 1:2.5 ratio (**Table 7**, entry 3).

The use of *N*,*N*-diethylhydroxylamine afforded only the normal elimination products **160** and **161** in a 36% yield; no substitution product was observed (**Table 7**, entry 4).

Attention was next turned to hydroxamic acids as nucleophiles. Acetohydroxamic acid, with a p*K*a of 9.40,[130] gave a novel bicyclic disubstitution product **209** at both the 4- and the 5-postions in 21% yield, accompanied by a single isomer of elimination product **161** in a 28% yield (**Table 7,** entry 5). In addition, a product **210,** possibly corresponding to a direct substitution on C5 by acetohydroxamic acid nucleophile, as determined by mass spectroscopy (**Figure 23**), was isolated in a 30% yield, but was found by $^{1}$H NMR spectroscopy to be an inseparable mixture of at least three products. Presumably, this mixture **210** arose because acetohydroxamic contains multiple forms of isomers resulting from tautomerism and keto-enol interconversion.[127] Unfortunately, it was not possible to separate this mixture and so the exact structures of the compounds could not be determined.

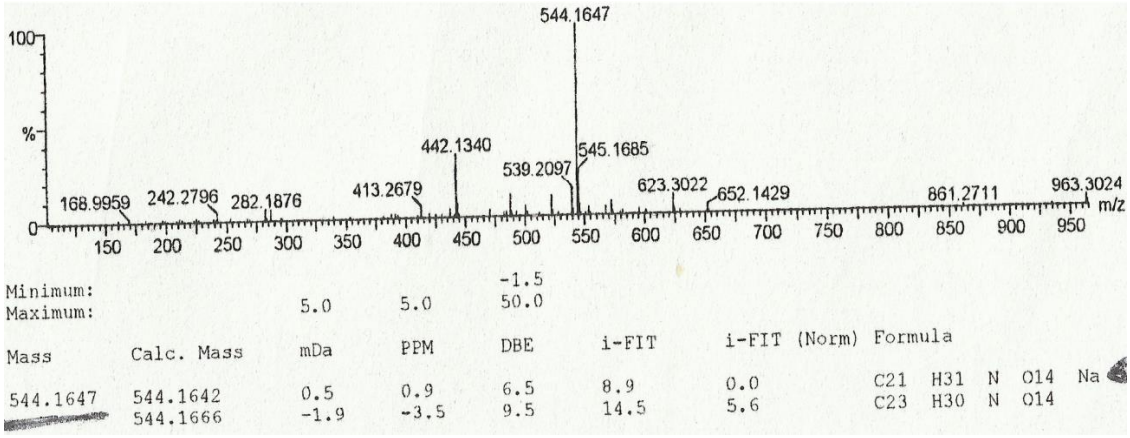
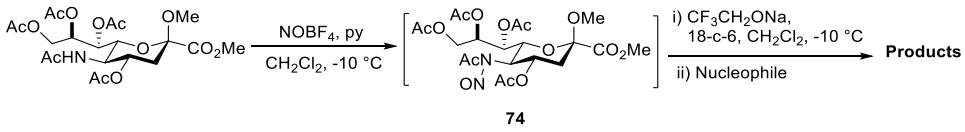



**Figure 23.** High Resolution Mass Spectroscopy for the Mixture **210** with 544.1647 m/z.

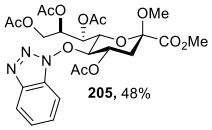
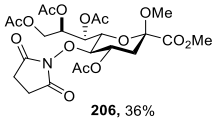
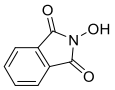
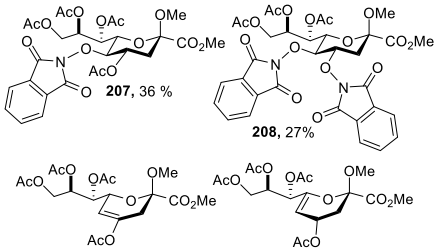
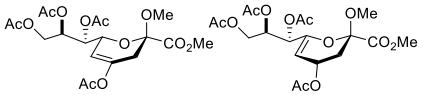
The hydroxamic acid derivatives; *N*-(*p*-methoxybenzyl)acetohydroxamic acid and *N*-Boc-acetohydroxamic acid (**Table 7**, entries 6 and 7), together provided the novel 4-deoxy-5-desacetamido non-4-eneulosonic acid derivative **211**, in 21% and 10% yields, respectively. Access to this type of alkene was only previously reported by Takahashi and coworkers when they constructed an unusual NeuAc derivative for the purpose of synthesizing gangliosides from $GM_3$ intermediates.[131] In both reactions (**Table 7**, entries 6 and 7), this alkene product **211** was accompanied by the elimination products **160** and **161** as side products in 18% and 41 % yields, respectively. With *N*-Boc-acetohydroxamic acid additional side products, the ketone **212** and enone **213** were formed as an inseparable and mixture isolated in 17% combined yield (**Table 7**, entry 7).

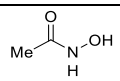
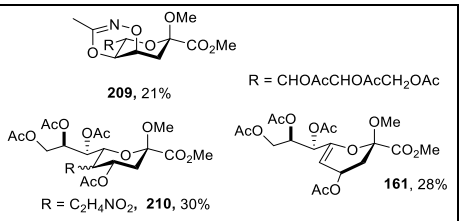
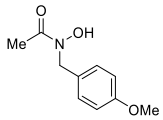
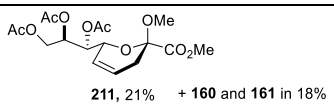
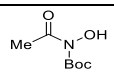
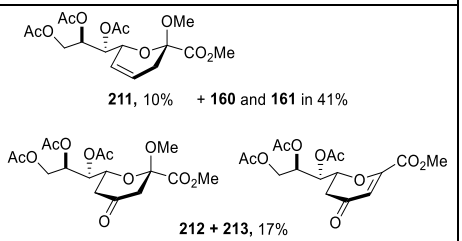
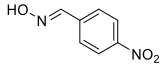
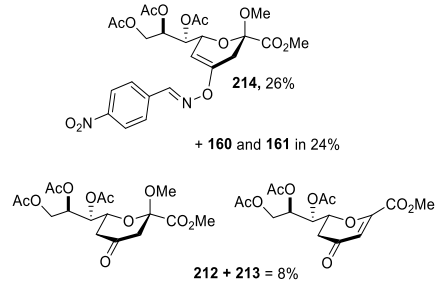
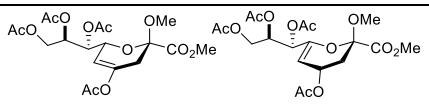
The oximes were examined starting with the use of *p*-nitrophenylbenzaldehyde oxime as nucleophile. Substitution at C4 was found to occur leading to the isolation of vinyl ether **214** in 26% yield, accompanied by an inseparable mixture of ketone **212** and enone **213** in 8% combined yield (**Table 7**, entry 8). On the other hand, acetone oxime was not effective as nucleophile for this oxidative deamination, and only the products of elimination **160** and **161** were isolated in a 38% yield (**Table 7**, entry 9).

**Table 7.** Oxidative Deamination Using Hydroxylamines Hydroxamic acids and Oximes.




74

| Entry | Nucleophile | p*K*a | Products (%yield)[a] |
|---|---|---|---|
| 1 |  Hydroxybenzotriazole (HOBt) | 4.3[132] |  **205,** 48% |
| 2 |  *N*-Hydroxysuccinimide | 6.0[133] |  **206,** 36% |
| 3 |  *N*-Hydroxyphthalimide | 6.1[134] |  **207,** 36 % **208,** 27% **160** + **161**, 23%; **160** :**161** = 1:2 |
| 4 | *N*,*N*-Diethylhydroxylamine | 8.33 |  **160** + **161**, 36%; **160** :**161** = 1:1 |

| | | | |
|---|---|---|---|
| 5 |  Acetohydroxamic acid | 9.40[130] |   |
| 6 |  *N*-(*p*-Methoxybenzyl)acetohydroxamic acid | 9.15[122] |   |
| 7 |  *N*-Boc-acetohydroxamic acid | - |   |
| 8 |  *p*-Nitrobenzaldehyde oxime | 10.5[135] |   |
| 9 |  Acetone oxime | 12.4[122] |   |

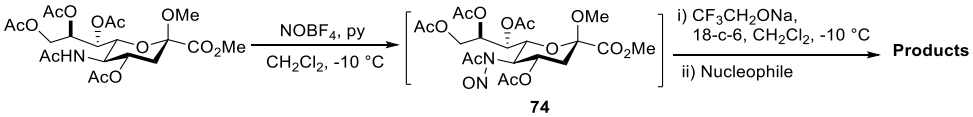
*a*) The elimination products were the side products in all deamination reactions and were not isolated in every reaction.

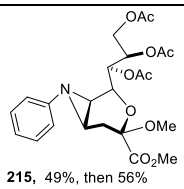
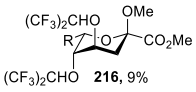
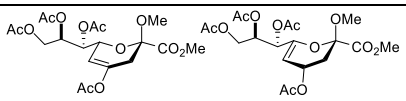
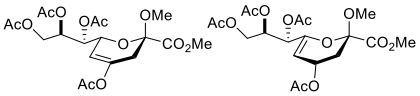
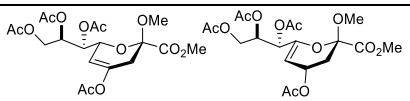
Attention was next shifted to the use of nitrogen nucleophiles. The use of aniline as nucleophile provided the aziridine **215** in a 49% yield (**Table 8**, entry 1). This reaction additionally produced a triazoline **230** as intermediate, detected by mass spectroscopy, which decomposed during the workup and/or in the process of the chromatographic purification. Alternatively, stirring the crude mixture of this latter deamination at room temperature for additional time (20-30 minutes), led to the intermediate triazoline **230** to convert to the aziridine product **215** with enhanced yield of 56%.

Attempted use of 3,5-dimethylpyrazole as nucleophile, gave a complex mixture and none of the desired substitution products were isolated. In this reaction, 3,5-dimethylpyrazole was insoluble in the optimal dichloromethane, and therefore, HFIP was used as a co-solvent. HFIP is known to be a practical reagent for dissolving organic compounds that are insoluble in typical organic solvents; it is weakly nucleophilic, but acidic with p*K*a of 9.3.[97,98,136-138] However, a novel disubstituted product **216** was isolated in a 9% yield (**Table 8**, entry 2)**.** This product resulted from the attack of two molecules of hexafluoroisopropanol (HFIP) at both the 4- and the 5-positions.

Finally, nitrogen-based heterocycles such as indole, 2-pyridone and *N*-hydroxypyridone-2-thione were surveyed as nucleophiles; each of them provided only a mixture of inseparable elimination products **160** and **161,** isolated in 80%, 32%, and 12% yields, respectively (**Table 8**, entries 3, 4, and 5).

**Table 8.** Oxidative Deamination Using Nitrogen-Based Nucleophiles.

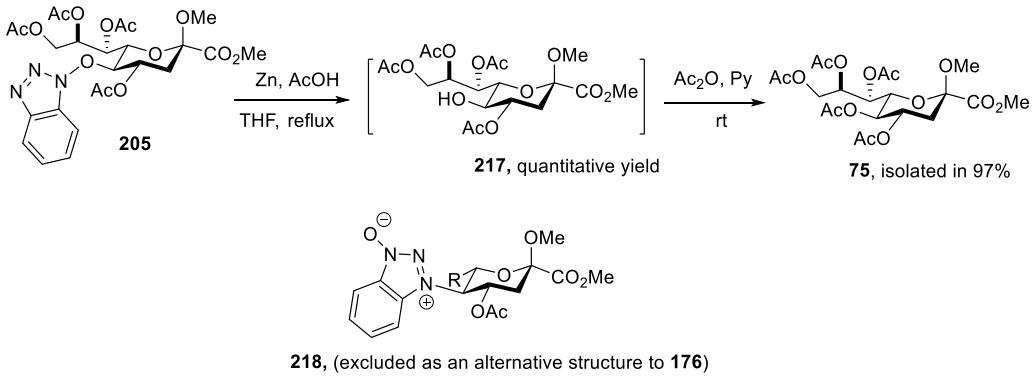



| Entry | Nucleophile | p*K*a | Products (% yield)[a] |
|---|---|---|---|
| 1 |  Aniline | 9.13[139] |  **215**, 49%, then 56% |
| 2[b] |  3,5-Dimethylpyrazole | ~ 19.8[140] |  **216**, 9% |
| 3 |  Indole | 16.72[141] |  **160** + **161**, 80%; **160** :**161** = 1:2 |
| 4 |  2-Pyridone | 11.62[142,143] |  **160** + **161**, 32%; **160** :**161** = 1:2 |
| 5 |  N-Hydroxypyridine-2-thione | 4.6[144] |  **160** + **161**, 12%; **160** :**161** = 1: 2.2 |

*a*) The elimination products were the side products in all deamination reactions and were not isolated in every reaction. *b*) Hexafluoroisopropanol was used to dissolve the nucleophile.

### 3.3.2 Structural elucidation of products

The deamination using HOBt as a nucleophile in principle could give two possible structures **205** and **218** since HOBt is an ambident nucleophile that can attack via oxygen or nitrogen. The product **205** was assigned as the correct structure following chemical confirmation by the treatment with zinc and acetic acid in refluxing tetrahydrofuran for 2 hours. Under these conditions, the N-O bond was cleaved and the KDN derivative **217** was observed in a quantitative yield. This product **217** was then acetylated by the treatment with acetic anhydride and pyridine, and the peracetylated KDN **75** was isolated with the retention of configuration in a 97% overall yield **(Scheme 52).** This method was previously reported in the literature for cleaving a N-O bond.[136] Thus, the alternative attack by the nitrogen of HOBt did not occur and the structure **218** was excluded.




**Scheme 52**. Probing Compound **205** and Formation of KDN Derivative **75**.

The structures of the direct substitution products **205**, **206** and **207** were assigned by NMR data based on the analysis of chemical shift and coupling constants. These products are consistent with the retention of configuration at C5 as previously discussed in chapter 2. The structures were confirmed by the measurement of the $^{3}J_{H4,H5}$ coupling constants of H5's giving 9.7, 9.7 and 9.4 Hz for the products **205**, **206** and **207**, respectively. Thus, H5 in all structures **205**, **206** and **207,** is in *trans*-relationship with both H4 and H6 with large $^{3}J_{H5,H6}$ coupling constants 10.1, 9.7, and 9.8, respectively.

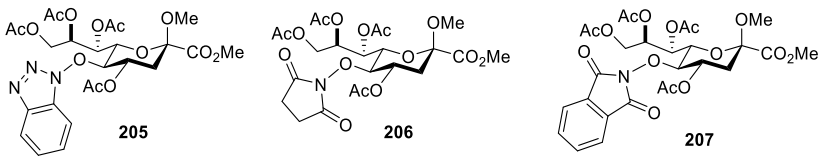



**Figure 24.** The Structures Derived by Direct Substitution with Retention of Configuration.

The alkene structure **211** was simply assigned from its $^{1}H$ and $^{13}C$ NMR data, whereas structures **160, 161** and **214** had spectral data that matched with the previously reported products of oxidative deamination from chapter 2.

### 3.3.3 Structural analyses of compounds 208, 209, 215 and 216

Products **208**, **209**, **215**, and **216** displayed interesting structural variations, which were confirmed by careful NMR analyses. The disubstitution product **208** arose from the double substitution with retention of configuration on both the 4- and the 5-positions. According to the $^{1}$H NMR spectrum of **208**, the $^{3}J_{H3e,H4}$, $^{3}J_{H3a,H4}$, and $^{3}J_{H4,H5}$ coupling constants are 10.5, 5.5, and 8.0 Hz , respectively, indicating that **208** is in the typical $^{2}C_{5}$ chair conformation with the all-*trans* configuration (**Table 8)**. Further, the $^{3}J_{H5,H6}$ coupling constant of 9.6 Hz, which is large, indicates that the H5 and H6 are in a 1,3-*trans*-diaxial relationship, which clearly matches the chair conformation (**Figure 25**).

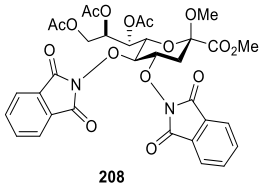



**Figure 25.** Configuration and Chair Conformation of Product **208.**

The structure of the bicyclic **209** most likely adopts the $^{2}C_{5}$ chair conformation carrying *cis* 4,5-disubstituents that comprise a heterocyclic ring. The configuration and conformation of **209** were deduced by study of the coupling constants in the H3's, H4, H5 and H6 spin system as well as from nOe correlations (**Table 8**). The $^{3}J_{H3e,H4}$, $^{3}J_{H3a,H4}$ coupling constants are 2.5 and 4.2 Hz, respectively. Further, the small value ~ 2.7 Hz for the $^{3}J_{H4,H5}$ coupling constant suggests that both H4 and H5 are in a *cis*-relationship. In addition, the $^{3}J_{H5,H6}$ coupling constant is ~10.0 Hz, a large value that is indicative of the *trans*-vicinal relationship **(Figure 26).** nOe contacts exist between H5 and H3 as well as H5 and H7. Further confirmation of the structure **209** was proved

by inspection of the HMBC spectrum, which shows that the imidate carbonyl carbon correlates with H5 (**Figure 27**), so eliminating from consideration the alternative structure **219** (**Figure 26**).

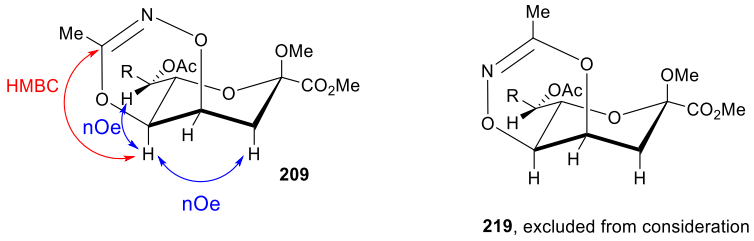



**Figure 26.** Key nOe and HMBC Correlations in Compound **209,** and the Alternative Structure **219**.

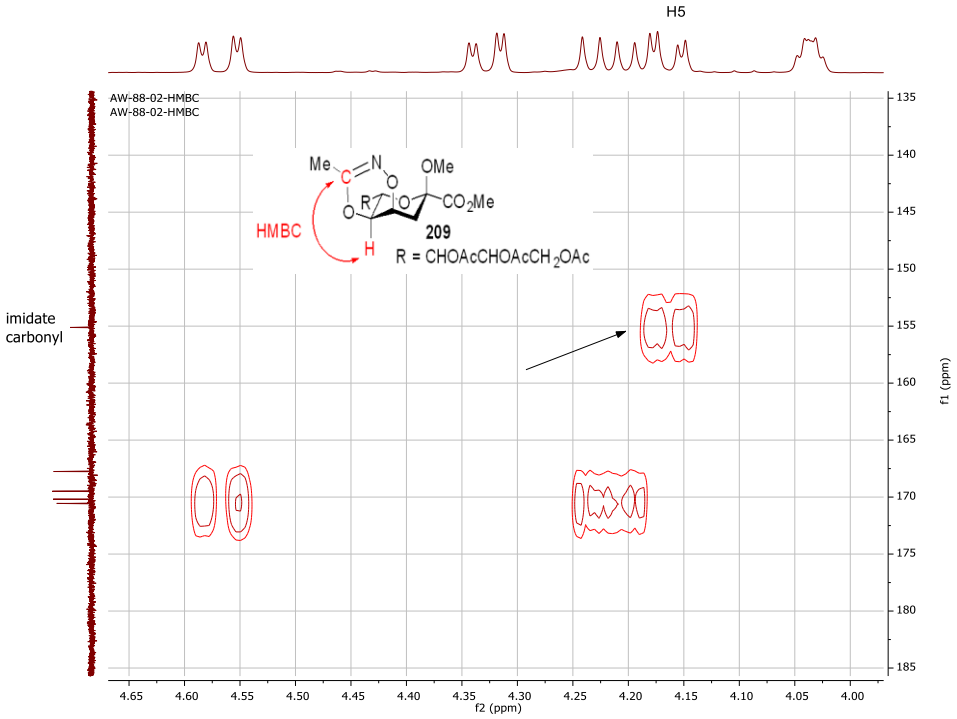



**Figure 27.** Three Bonds Correlations in HMBC Between H5 and the Imidate Carbonyl for **209.**

The aziridine **215** takes up a $^{3,6}B$ boat conformation according to the NMR analyses as well as comparison with the corresponding 2-naphthol-derived tricyclic **164** that was confirmed

by X-ray crystallography. The newly formed 3-membered ring in the structure **215** is *cis*-fused across C4 and C5, and the N-phenyl group is *exo* to the bicyclic nucleus. This was confirmed by nOe contacts found between both H4 and H5 and the aromatic *ortho*-protons of the phenyl ring. Further, nOe correlation was also observed between H5 and H7 of the side chain. The $^{3}J_{(CH4,\ CH5)}$ coupling constants of 7.0 Hz for the α-protons of H4 and H5, indicate that they are in *cis*-relationship **(Figure 28).**

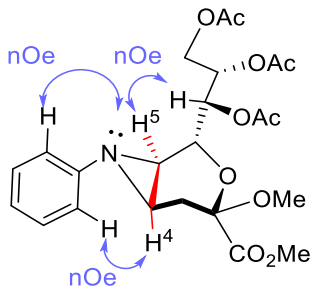



**Figure 28**. nOe Interactions and the H4-H5 Vicinal Coupling of the Aziridine **215.**

Finally, the configuration and conformation of the hexafluoroisopropanol adduct **216** are established by analysis of NMR coupling constants and nOe correlations. Thus, $^{3}J_{H4,H5}$ at 8.2 Hz indicates that H's 4 and 5 are either close to antiperiplanar or synperiplanar, while the $^{3}J_{H3ax,H4}$, $^{3}J_{H3eq,H4}$, and $^{3}J_{H5,H6}$ coupling constants of 6.1, 3.2, and 2.1 Hz, respectively, exclude axial orientations for both H4 and H5 (**Table 8**). This ensemble of information points to a chair-like conformation with axial substituents at C4 and C5, with twisting of the C4-C5 bond to minimize repulsion between the hexafluoroisopropyl groups, which forces the near-eclipsing of H's 4 and 5 (**Figure 29**). nOe correlations were observed between the 4-*O*-hexafluoroisopropyl proton and the ring protons H4 and H5, while no correlations were seen between H5 and either H3. One of the two trifluoromethyl groups in the same 4-*O*-hexafluoroisopropyl ether also showed

heteronuclear nOe correlations with H4 in the HOESY ($^{1}H$-$^{19}F$) spectrum further supporting the assigned conformation (**Figure 30**).

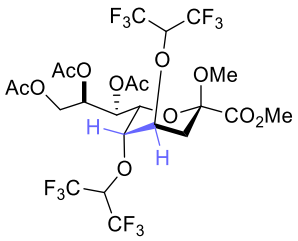



**Figure 29.** H4-H5 Vicinal Coupling of The Disubstitution Product **216**.

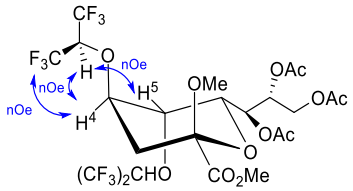



**Figure 30**. Key nOe Correlations in Structure **216**.

**Table 9.** Chemical Shifts and Coupling Constants for **208, 209, 215,** and **216.**

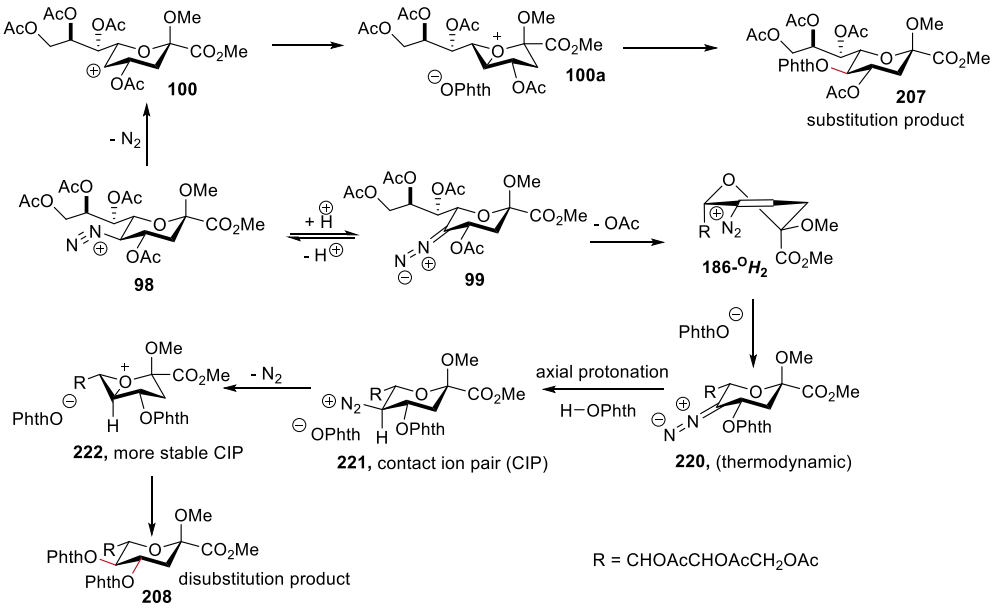
| | Chemical Shifts (δ, ppm) | | | | | | Coupling Constants (Hz) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Product | H3a | H3e | H4 | H5 | H6 | H7 | $^{3}J_{3a,4}$ | $^{3}J_{3e,4}$ | $^{3}J_{4,5}$ | $^{3}J_{5,6}$ | $^{3}J_{6,7}$ | $^{2}J_{3,3'}$ |
| **208** | 2.13 | 2.50 | 5.17 | 4.86 | 4.23 | 5.79 | 10.5 | 5.5 | 8.0 | 9.6 | 2.1 | 13.4 |
| **209** | 2.10 | 2.53 | 4.04 | 4.17 | 4.33 | 5.51 | 4.2 | 2.5 | 2.7 | 10.0 | 2.6 | 15.5 |
| **215** | 2.26 | 2.37 | 2.47 | 2.51 | 4.16 | 5.69 | 5.3 | 1.8 | 7.1 | 3.4 | 3.9 | 15.3 |
| **216** | 2.49 | 2.38 | 3.71 | 3.11 | 3.02 | 5.03 | 6.1 | 3.2 | 8.2 | 2.1 | 5.3 | 15.9 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | H3a | H3e | | | | | | | | | | |

**3.4 Discussion**

*N*-Hydroxybenzotriazole (HOBt) with a p*K*a ~ 4.3[132] and *N*-hydroxysuccinimide with a p*K*a ~ 6.0[133] both follow the usual mechanism of direct substitution at the 5-position with retention of configuration leading to the observed products **205** and **206**, respectively. These observations were anticipated because of the acidity of these nucleophiles.

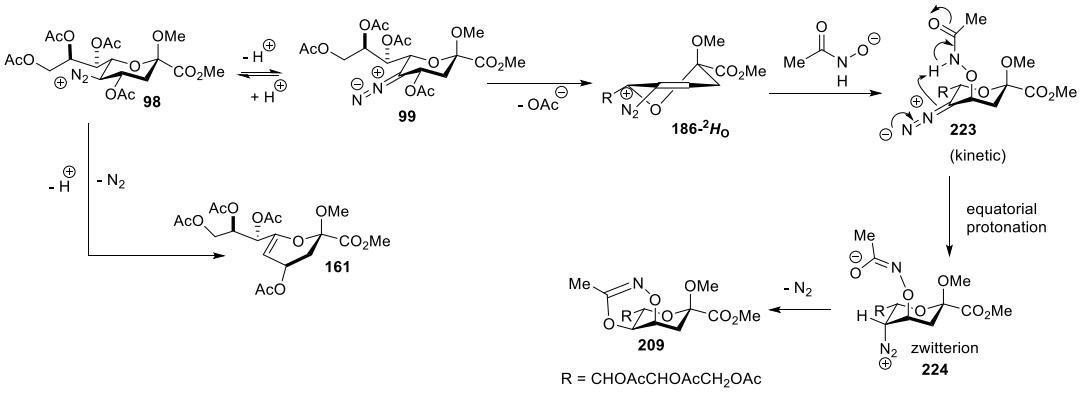
On the other hand, the use of NHPI as nucleophile gave the direct substitution product at the 5-position as well as the unanticipated disubstitution product at 4-and 5-postions. While the p*K*a of NHPI is ~ 6.1,[134] the diazonium ion **98** ~ diazoalkane **99** interconversion generates the two observed products **207** and **208** in almost equal amounts. The direct substitution at C5 leads to the anticipated product **207** from the diazonium ion. The formation of the disubstitution product **208** results directly from the β-elimination of the acetoxy group at C4 leading to the formation of vinyl diazonium ion **186**, by a mechanism similar to that observed with phenol as nucleophile discussed in chapter 2. This vinyl diazonium ion is then attacked at C4 by the *N*-oxyphthalimide anion under thermodynamic control to form **220**, followed by an intermolecular proton transfer from another molecule of NHPI to form the intermediate **221,** which then loses the molecular nitrogen to form the oxonium ion **222**. The intermediate **222** is finally substituted by *N*-hydroxyphthalimide, which approaches C5 from the backside leading to the observed disubstitution product **208** with overall retention of configuration (**Scheme 53**).




**Scheme 53.** Possible Mechanism Formation of the Products **207** and **208.**

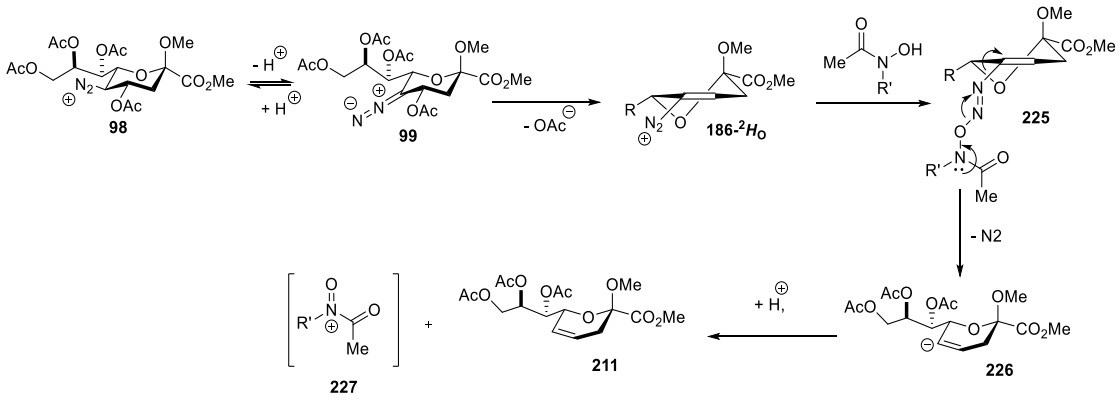
The formation of diazoalkane **99** predominates over the diazonium ion **98** in the case of acetohydroxamic acid, which has a p*K*a of 9.40.[135] Thus, the bicyclic product **209** isolated is the result of an attack by the two most nucleophilic sites of acetohydroxamic acid. The first substitution occurred at the 4-position of the vinyl diazonium ion **186-$^{2}$*H*** by the anionic oxygen of acetohydroxamic acid under kinetic Michael addition conditions leading to the intermediate **223**. An intramolecular proton transfer then takes place from the β-face of the intermediate **223** to form the zwitterion **224**. The second substitution at the 5-position occurs through the displacement of the nitrogen by the oxy-anion of the imidate moiety that resulted from the delocalization of the electrons leading to the isolated product **209** with retention of configuration. This reaction also produced a single elimination product **161** after possibly a concerted nitrogen loss and deprotonation of H6. Overall, the substitution at the 4-position occurred with inversion

of the configuration while that at the 5-position followed retention of the configuration (**Scheme 54**).



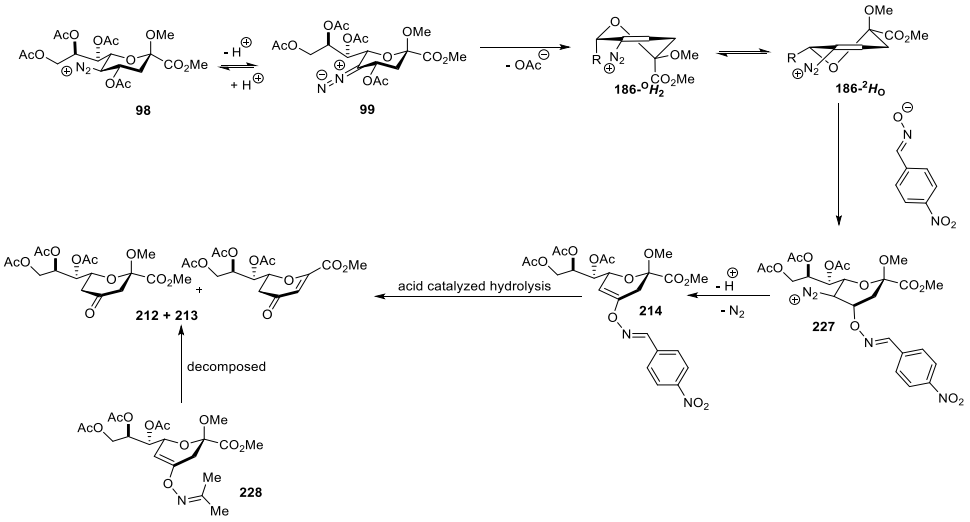

**Scheme 54.** Plausible Mechanism of Acetohydroxamic Acid Reaction with Vinyl Diazonium Ion.

The use of *N*-(4-methoxybenzyl)acetohydroxamic acid with a p*K*a of 9.15,[135] on the other hand, provided none of the substitution products but the alkene **211**, which was isolated for the first time. This alkene **211** possibly results from formation of and subsequent decomposition of intermediate **225**. This provides a vinyl anion **226**, which then is protonated to afford the alkene **211**. *N*-Boc-acetohydroxamic acid carries the bulky Boc group and is expected to follow a similar path of that with *N*-(4-methoxybenzyl)acetohydroxamic acid as nucleophile leading to the formation of alkene product **211** (**Scheme 55**).



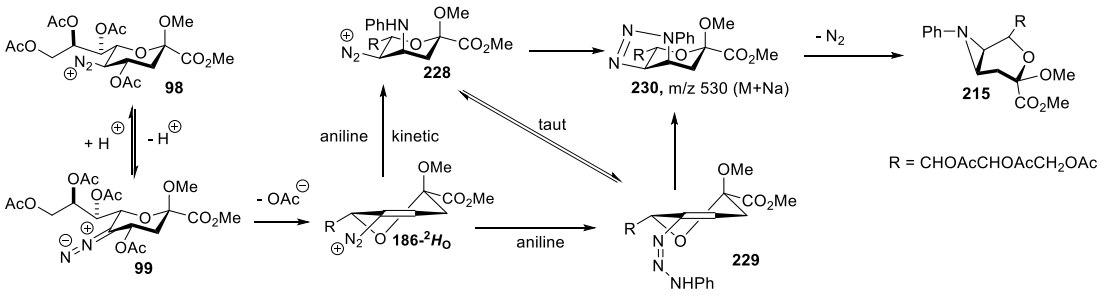
**Scheme 55.** Possible Mechanism Formation of the Alkene Product **211**.

The product **214** that was formed on use of *p*-nitrobenzaldoxime as nucleophile, likely occurs through conjugate addition to the vinyl diazonium ion, followed by loss of the molecular nitrogen and deprotonation of H4. The ketone **212** resulted from the acidic hydrolysis of the electron rich enol ether **214**. The enone **213** arose from the presence of more acid in the reaction medium (**Scheme 56**). The use of the more electron rich acetone oxime (p*K*a 12.4)[122] as nucleophile, led to the decomposition of the substitution adduct **228**. Thus, it provided the ketone **212** and enone **213** mixture in a 38% overall yield (**Scheme 56**).




**Scheme 56.** Mechanism Formation of Product **214** and the Decomposition of **228**.

The bicyclic aziridine product **215** is formed by the nucleophilic attack of aniline on the β-face of the vinyl diazonium ion in a kinetic Michael addition. This mechanism is similar to that postulated β-naphthol in chapter 2. Here, the diazonium intermediate **228** can tautomerize to **220**, followed by cyclization to form a triazoline **230**. Subsequently, the triazoline **230** decomposes with the loss molecular nitrogen to afford the aziridine **215**. Alternatively, comparing with the previous work on the reactions of arenes diazonium ions with amines,[145,146] aniline attacks the terminal nitrogen of the diazonium intermediate **186** to provide a vinyl triazene **229**, followed by cyclization and loss of nitrogen to give the observed aziridine **215** (**Scheme 57**). The triazoline intermediate **230** was detected by ESI mass spectrometry during the analysis of the crude reaction mixture from this reaction: an adduct of m/z 530 (M+Na) for **230** was recorded as a major ion peak, which disappeared over time to provide the aziridine **215** (m/z 501, M+Na) **(Figure 31).** The decomposition of triazolines by the loss of nitrogen to form the corresponding aziridines is a well established mechanism previously reported by Saalfrank and Ackerman.[147-150]




**Scheme 57.** Mechanism Formation of Bicyclic Product **215.**

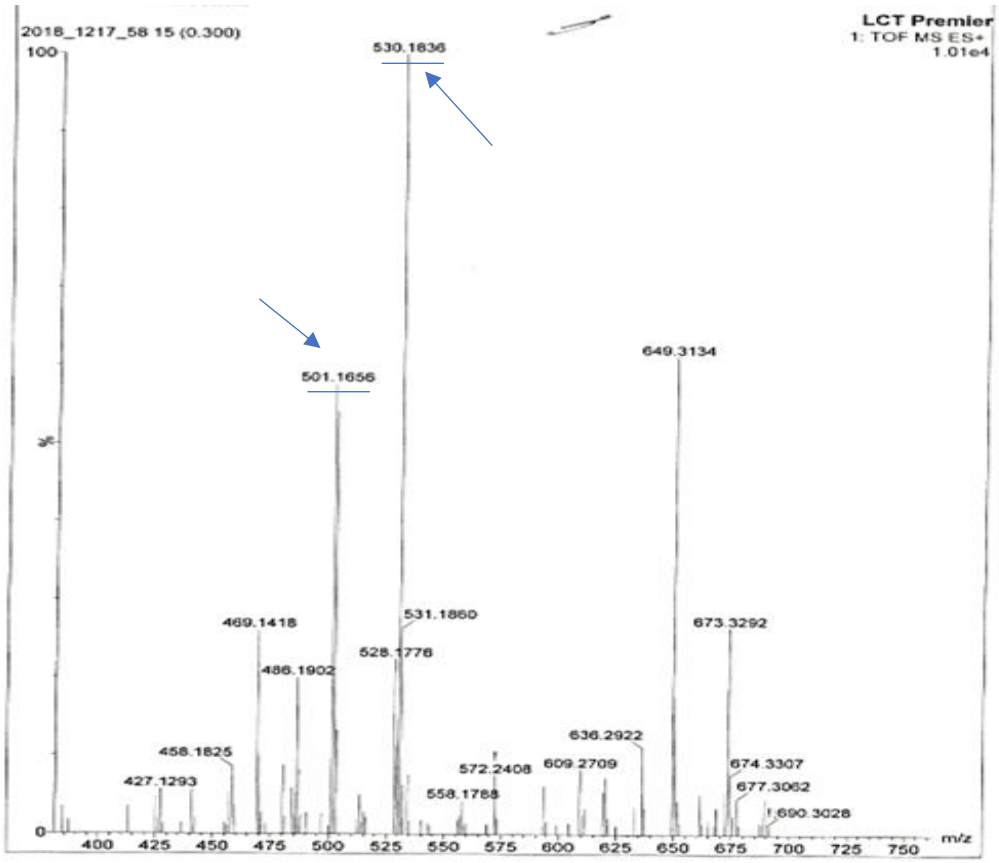
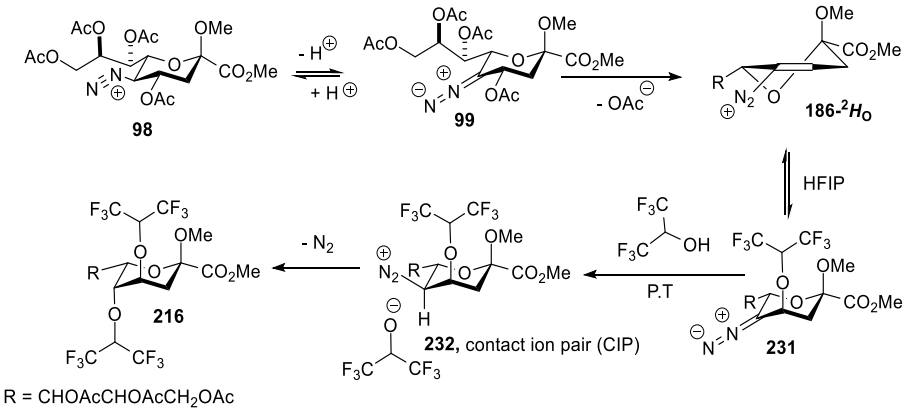



**Figure 31.** Mass Spectrum Showing Unstable Intermediate **230** (~ 530.1836 m/z).

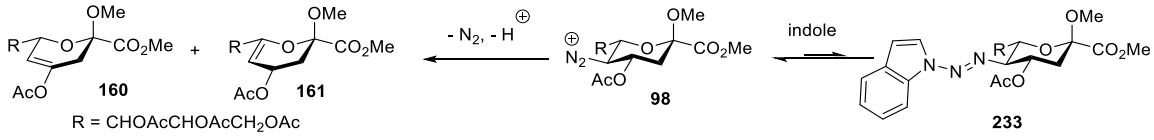
The deamination using 3,5-dimethylpyrazole as nucleophile, provided a novel disubstitution product **216**. This product resulted from use of HFIP as a solvent. It was formed by kinetic Michael addition on C4 of the vinyl diazonium ion that is similar the described

mechanisms in the previous reactions of 2-naphthol and acetohydroxamic acid. Although HFIP is a weakly acidic solvent with p*K*a value of 9.3[137] and is poorly nucleophilic,[97] substitution with inversion of configuration at C5 eventually afforded the product **216**. The high electrophilic reactivity of the vinyl diazonium and the absence of competitive nucleophiles play an important role in the isolation of the product **216** (**Scheme 58**).



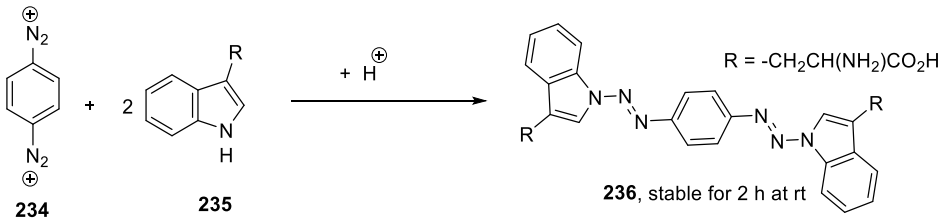

**Scheme 58**. Formation of Disubstitution Product **216**.

The attempted use of indole as nucleophile provided an inseparable mixture of the elimination products in high yield 80%. This reaction most likely reversibly produced an unstable triazene **233,** that restricts the formation of the vinyl diazonium ion. Eventual loss of nitrogen and the β-elimination of H4 and H6 lead to the isolated alkene products **160** and **161** (**Scheme 59**).




**Scheme 59**. Possible Decomposition of **233** and Formation of the Elimination Products.

The reaction of indoles with arene diazonium salts has been previously reported to provide the related *N*-arylazoindoles **236**, albeit they are sensitive and rapidly decompose (**Scheme 60**).[151]




**Scheme 60.** Literature Reaction of Indoles with Arene Diazonium Salts.

Finally, the use of 2-pyridone and *N*-hydroxypyridine-2-thione as nucleophiles afforded the usual elimination products. These two nucleophiles are in the keto form, which has very poor nucleophilic reactivity. It is also possible that they couple with the terminal nitrogen of the diazonium ion, similarly to the mechanism proposed for indole (**Scheme 59**) and retard formation of the elimination products **160** and **161**.

### 3.5 Conclusion

The use of hydroxylamines, hydroxamic acids, oximes and amines as nucleophiles in the oxidative deamination of *N*-acetyl neuraminic acid were examined. A diverse series of neuraminic acid derivatives were formed in these reactions testifying to the compatibility of this chemistry. HOBt, *N*-hydroxysuccinimide and *N*-hydroxyphthalimide afforded the anticipated deamination products with retention of configuration at the 5-position. However, NHPI provided an additional disubstitution product with the retention of configuration at C4 arising from Michael addition on an intermediate vinyl diazonium, followed the displacement by another molecule of NHPI at C5. Acetohydroxamic acid and aniline produced novel bicyclic products

with the different configurations and conformations. Oximes as nucleophiles afforded various alkenes and ketones as products. Following deprotection of the novel neuraminic acid derivatives obtained in this study could be candidates of interest as neuraminidase inhibitors and so as anti-influenza drugs.

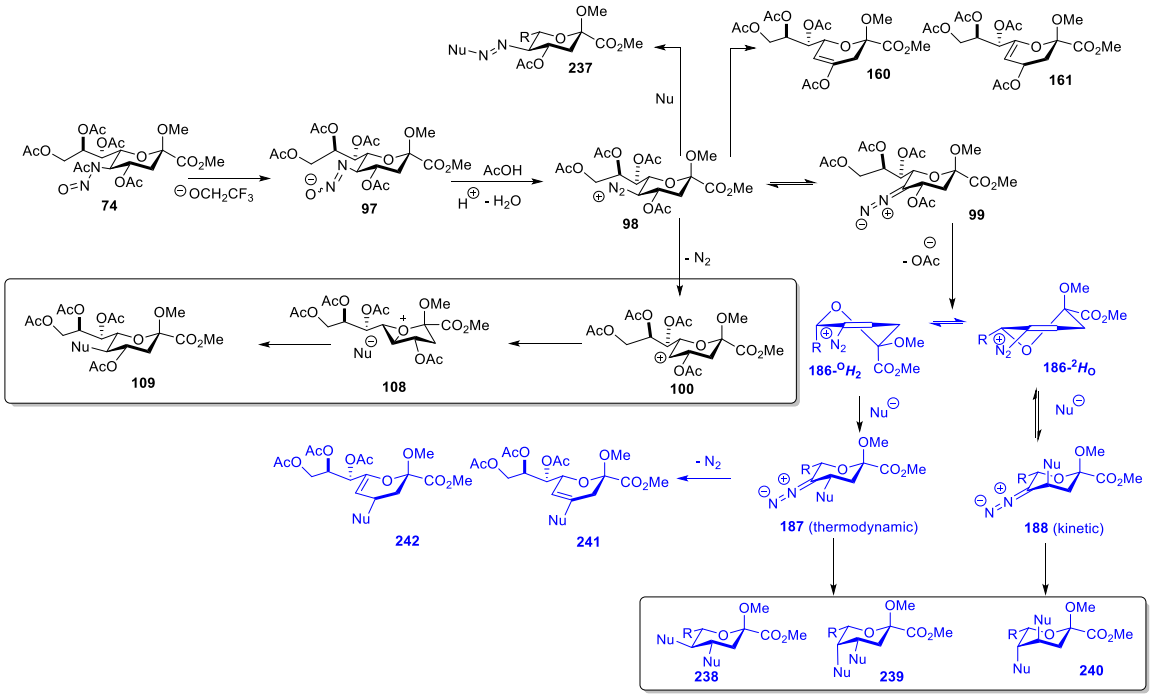
# CHAPTER 4. CONCLUSIONS

The utilization of the Zbiral oxidative deamination for the transformations of *N*-acetyl neuraminic to various sialic acid derivatives was accomplished in this thesis. The replacement of the *N*-acetyl moiety with the alternative described nucleophiles showed the feasibility of this deamination process. Phenols exhibited effective reactivities as nucleophiles in this deamination of the 5-position, although they are only weakly acidic. The use of phenol itself provided a novel disubstitution product, along with a product that resulted from β-elimination. β-Naphthol was an interesting nucleophile that led to the isolation of an unusual tricyclic product, which was found surprisingly to be in a boat conformation. Its structure was confirmed by X-ray crystallography. Similar tricyclic products were observed in reactions with 6-quinolinol, 5-hydroxyindole, and the electron rich phenols such as 3,5-dimethoxyphenol. On the other hand, the electron poor substituted phenols as well as the less acidic phenols such as 3-quinolinol, 4-nitrophenol and 4-methoxyphenol produced enol ether products. Thiophenols demonstrated the direct substitution process at the 5-position because of the presence of stronger sulfur atom as nucleophilic site and because of their higher p*K*a values compared to the simple phenols.

Further studies involved the use of hydroxylamines, hydroxamic acids, oximes, and amines as alternative nucleophiles. These studies further supported the potential significance of this deamination as these nucleophiles afforded a series of sialic acid derivatives with a hydroxyl amine (N-O) moiety at C5.

The investigations in this thesis are rationalized by the postulation of a central intermediate responsible for the syntheses of these novel and various deamination products, namely a vinyl diazonium ion. This intermediate is an example of class of alkenediazonium ions

that are under studied as useful intermediates in organic syntheses. An overall mechanism rationalizing formation of all products can be advanced (**Scheme 61**).




**Scheme 61.** Overall Oxidative Deamination Mechanism.

# CHAPTER 5. EXPERIMENTAL SECTION

## General Information:

All reactions were performed using oven-dried glassware under an atmosphere of argon. All reagents and solvents were purchased from commercial suppliers and used without further purification unless otherwise specified. Chromatographic purifications were performed on silica gel (230−400 mesh) columns (20−50 g) of silica gel per gram of crude compound. Reactions were monitored by analytical thin-layer chromatography (TLC) on precoated glassbacked plates (w/UV 254) and visualized by UV irradiation (254 nm) or by staining with 25% $H_2SO_4$ in EtOH or ceric ammonium molybdate solution. Specific rotations were measured on an automatic polarimeter with a path length of 100 mm in the solvent specified. Concentrations are given in g/100 mL. High-resolution mass spectra (HRMS) were recorded with an electrospray ionization (ESI) source coupled to a time-of-flight (TOF) mass analyzer. $^{1}H$, $^{13}C$, and $^{19}F$, spectra were recorded on a 400, 500, or 600 MHz spectrometer. NMR solvents were used without purification. Chemical shifts are given in ppm ($\delta$), and coupling constants ($J$) are given in Hertz (Hz). Multiplicities are given as singlet (s), broad singlet (br s), doublet (d), triplet (t), doublet of doublets (dd), triplet of doublets (td), multiplet (m), apparent quartet (app q), apparent pentet (app p), etc. Spectral assignments were made by a combination of correlated spectroscopy, heteronuclear single-quantum correlation, and heteronuclear multiple bond correlation spectra.

## General Procedure of Oxidative Deamination.

Using the quantities described in the individual experiments, sodium 2,2,2-trifluoroethoxide and 18-crown-6 were dissolved in anhydrous $CH_2Cl_2$ under Ar and cooled to

−10 °C. The solution was added to the nitrosyl sialoside (0.1 M solution in anhydrous $CH_2Cl_2$) at −10 °C under Ar. The mixture was stirred for 5 min at −10 °C. The nucleophile (10−20 equiv) dissolved in the solvent described under Ar at −10 °C was added to the reaction mixture in one portion. After stirring for 5 min, the reaction was quenched by the addition of saturated $NaHCO_3$ solution and diluted with dichloromethane. The reaction mixture was washed with NaOH (1 M) to remove excess phenolic nucleophile. The organic layer was washed with brine, dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure to afford the crude product, which was purified by column chromatography over silica gel.

**Methyl (Methyl 5-Acetamido-4,7,8,9-tetra-O-acetyl-3,5-dideoxyD-glycero-β-D-galacto-non-2-ulopyranosid)onate (158).**

Compound **158** (6 g, 95%) was obtained by a literature procedure[74] over two steps as a white solid from *N*-acetyl neuraminic acid (20 g, 64.7 mmol).

**Methyl (Methyl 4,7,8,9-Tetra-O-acetyl-3,5-dideoxy-5-(anti/synN-nitrosoacetamido)-D-glycero-β-D-galacto-non-2-ulopyranosid)onate (74).**

A solution of compound **74** (330 mg, 0.7 mmol) in dry dichloromethane (7 mL) was treated with dry pyridine (0.5 mL, 6.5 mmol, 10 equiv) and cooled to −10 °C. After stirring for 15 min, crushed nitrosyl tetrafluoroborate (382 mg, 3.0 mmol, 5 equiv) was added in one portion. The reaction mixture was stirred at −10 °C until TLC showed complete conversion (4−5 h). The mixture was diluted with cold dichloromethane (3 mL) and washed with cold 1 N HCl, saturated $NaHCO_3$, and brine. The organic layer was dried over anhydrous $Na_2SO_4$ and concentrated under 10 °C to obtain 5 as a yellowish foam, which was carried forward for the next reaction without further purification.

**Methyl (Methyl 4,7,8,9-Tetra-O-acetyl-3-deoxy-5-O-levulinyl-Dglycero-β-D-galacto-non-2-ulopyranosid)onate (159) and a Mixture of Methyl (Methyl 4,7,8,9-Tetra-O-acetyl-3,5-dideoxy-β-D-arabinonon-4-en-2-ulopyranosid)onate (160) and Methyl (Methyl 4,7,8,9Tetra-O-acetyl-3,5-dideoxy-β-D-ribo-non-5-en-2-ulopyranosid)onate (161).**

The nitrosyl sialoside **74** (267 mg, 0.5 mmol) in $CH_2Cl_2$ (5 mL) was deaminated using the general procedure for oxidative deamination with sodium 2,2,2-trifluoroethoxide (122 mg, 1 mmol), 18-crown-6 (291 mg, 1.1 mmol) in $CH_2Cl_2$ (2.5 mL), and levulinic acid (1.16 g, 10 mmol, 20 equiv) in $CH_2Cl_2$ (5 mL) to afford **159** after column chromatography over silica gel eluting with (hexane/ethyl acetate 3:1), as colorless crystals from methanol/$CH_2Cl_2$ (88 mg, 31%) and an inseparable mixture of **160** and **161** as a colorless oil (1:2.5 ratio, 75 mg, 34%).

Compound **159**: colorless crystals, mp = 132−134 °C; $[\alpha]^{D}_{20}$ − 5.7° (*c* 0.4, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$) δ 5.34−5.19 (m, 3H, H8, H7, H4), 4.87 (t, *J* = 9.9 Hz, 1H, H5), 4.65 (dd, *J* = 12.6, 2.4 Hz, 1H, H9), 4.09 (dd, *J* = 12.5, 6.7 Hz, 1H, H9′), 4.00 (dd, *J* = 10.1, 2.2 Hz, 1H, H6), 3.75 (s, 3H, $CH_3$), 3.21 (s, 3H, $CH_3$), 2.79−2.69 (m, 1H, H3e), 2.61−2.35 (m, 4H, $CH_2CH_2$), 2.11 (s, 3H, $CH_3$), 2.05 (s, 3H, $CH_3$), 2.02 (s, 3H, $CH_3$), 1.98 (s, 3H, $CH_3$), 1.97 (s, 3H, $CH_3$), 1.77 (dd, *J* = 13.0, 11.5 Hz, 1H, H3a). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 205.9, 171.7, 170.6, 170.2, 170.0, 167.2, 98.9, 70.9, 70.1, 68.7, 67.8, 67.6, 62.1, 52.7, 51.4, 37.9, 37.8, 37.0, 29.7, 28.0, 21.0, 20.9, 20.8, 20.7. HRMS (ESI-TOF) m/z: [M + Na]+ calcd for $C_{24}H_{34}NaO_{15}$ 585.1795; found: 585.1792.

Compound **161**: $^1$H NMR (400 MHz, $CDCl_3$) δ 5.51 (m, 1H, H8), 5.46 (m, 1H, H7), 5.25 (m, 1H, H4), 5.07 (dq, *J* = 4.4, 1.1 Hz, 1H, H5), 4.36 (dd, *J* = 12.1, 3.0 Hz, 1H, H9), 4.30 (dd, *J* = 12.1, 7.1 Hz, 1H, H9′), 3.75 (s, 3H, $CH_3$), 3.36 (s, 3H, $CH_3$), 2.31 (dd, *J* = 14.1, 3.6 Hz, 1H,

H3), 2.16 (dd, *J* = 14.2, 5.3 Hz, 1H, H3′), 2.11 (s, 3H, $CH_3$), 2.04 (s, 3H, $CH_3$), 2.03 (s, 3H, $CH_3$), 1.96 (s, 3H, $CH_3$). $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 170.8, 170.1, 170.0, 169.3, 167.7, 149.8, 99.2, 98.0, 70.4, 70.3, 63.0, 61.9, 52.7, 52.2, 34.6, 21.1, 20.9, 20.9.

Compound **160** was identified in the mixture by the following diagnostic signals: $^1H$ NMR (400 MHz, $CDCl_3$) δ 5.43 (dd, *J* = 6.1, 2.5 Hz, 1H, H8), 5.33−5.29 (m, 2H, H7, H5), 4.58 (ddd, *J* = 12.6, 2.4, 1.3 Hz, 1H, H9), 4.51 (dq, *J* = 4.7, 2.5 Hz, 1H, H6), 4.19 (ddd, *J* = 12.5, 5.9, 1.3 Hz, 1H, H9′), 3.78 (s, 3H, $CH_3$), 3.24 (s, 3H, $CH_3$), 2.68 (ddd, *J* = 17.0, 3.9, 2.4 Hz, 1H, H3). $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 170.7, 170.4, 169.9, 168.5, 168.0, 144.5, 110.0, 98.1, 70.7, 70.1, 69.2, 62.4, 52.7, 51.5, 34.8, 21.0, 20.9, 20.7. HRMS (ESI-TOF) m/z: [M + Na]+ calcd for $C_{19}H_{26}NaO_{12}$ 469.1322; found: 469.1322.

**Methyl (Methyl 7,8,9-Tri-O-acetyl-3-deoxy-4,5-di-O-phenyl-Dglycero-β-D-gulo-non-2-ulopyranosid)onate (162) and Methyl (Methyl 7,8,9-Tri-O-acetyl-3,5-dideoxy-4-O-phenyl-β-D-arabinonon-4-en-2-ulopyranosid)onate (163).**

The nitrosyl sialoside **74** (200 mg, 0.4 mmol) in $CH_2Cl_2$ (4 mL) was deaminated using the general procedure for oxidative deamination with sodium 2,2,2-trifluoroethoxide (90 mg, 0.7 mmol), 18-crown-6 (195 mg, 0.7 mmol) in $CH_2Cl_2$ (2 mL), and phenol (188 mg, 2 mmol, 5 equiv) in $CH_2Cl_2$ (1 mL) followed by column chromatography over silica gel eluting with (hexane/ethyl acetate 1:1) to afford **162** (71 mg, 33%) and **163** (56 mg, 31%).

Compound **162**: colorless oil, $[\alpha]^D_{20}$ −32.4° (c 0.25, $CHCl_3$). $^1H$ NMR (600 MHz, $CDCl_3$) *δ* 7.29−7.23 (m, 4H, ArH), 7.09 (dt, *J* = 7.7, 1.1 Hz, 2H, ArH), 7.04 (t, *J* = 7.3 Hz, 1H, ArH), 6.96 (t, *J* = 7.3 Hz, 1H, ArH), 6.87 (d, *J* = 8.5 Hz, 2H, ArH), 5.19 (td, *J* = 5.8, 3.7 Hz, 1H, H8), 4.99 (t, *J* = 5.3 Hz, 1H, H7), 4.52 (dt, *J* = 8.9, 3.7 Hz, 1H), 4.20 (dd, *J* = 12.3, 3.6 Hz, 1H, H9),

4.14 (dd, *J* = 12.2, 6.3 Hz, 1H, H9′), 3.56 (s, 3H, $CH_3$), 3.48 (s, 3H, $CH_3$), 3.17−3.12 (m, 2H, H6 and H5), 2.55 (dd, *J* = 14.9, 8.9 Hz, 1H, H3a), 2.47 (dd, *J* = 14.9, 3.2 Hz, 1H, H3e), 2.07 (s, 3H, $CH_3$), 2.04 (s, 3H, $CH_3$), 2.02 (s, 3H, $CH_3$). $^1$H NMR (600 MHz, $C_6D_6$) δ 7.28−7.26 (m, 2H, ArH), 7.08 (dt, *J* = 8.6, 7.3 Hz, 4H, ArH), 6.99−6.96 (m, 2H, ArH), 6.84 (tt, *J* = 7.3, 1.2 Hz, 1H, ArH), 6.78 (tt, *J* = 7.4, 1.2 Hz, 1H, ArH), 5.36 (ddd, J = 6.2, 5.7, 3.6 Hz, 1H, H8), 5.16 (t, *J* = 5.7 Hz, 1H, H7), 4.61 (ddd, *J* = 8.8, 4.6, 3.4 Hz, 1H, H4), 4.20 (dd, *J* = 12.3, 3.6 Hz, 1H, H9), 4.15 (dd, J = 12.2, 6.3 Hz, 1H, H9′), 3.26 (s, 3H, $CH_3$), 3.24 (s, 3H, $CH_3$), 3.18 (dd, *J* = 5.7, 2.1 Hz, 1H, H6), 3.01 (dd, *J* = 4.5, 2.0 Hz, 1H, H5), 2.77 (dd, *J* = 14.8, 8.8 Hz, 1H, H3a), 2.57 (dd, *J* = 14.8, 3.4 Hz, 1H, H3e), 1.65 (s, 3H, $CH_3$), 1.63 (s, 3H, $CH_3$), 1.57 (s, 3H, $CH_3$). $^{13}$C NMR (151 MHz, $CDCl_3$) δ 170.6, 170.1, 169.7, 168.3, 157.4, 154.4, 129.8, 129.7, 123.3, 122.1, 118.8, 116.0, 101.3, 71.6, 70.6, 70.5, 61.6, 57.4, 54.1, 52.8, 50.4, 37.1, 20.9, 20.8, 20.8. $^{13}$C NMR (151 MHz, C6D6) δ 169.8, 169.6, 169.3, 168.1, 158.1, 155.1, 129.9, 129.9, 128.2, 128.1, 127.9, 123.3, 122.1, 119.3, 116.6, 101.8, 72.6, 71.2, 71.0, 61.7, 57.6, 54.4, 52.1, 50.2, 37.4, 20.4, 20.2, 20.1. ESIHRMS calculated for ($C_{29}H_{34}NaO_{12}$): ([M + Na]+) m/z: 597.1948; found: 597.1943.

Compound **163**: colorless oil, $[\alpha]^D_{20}$ −32.1° (c 0.26, $CHCl_3$). 1H NMR (600 MHz, $CDCl_3$) δ 7.32 (t, *J* = 7.9 Hz, 2H, ArH), 7.12 (t, *J* = 7.4 Hz, 1H, ArH), 6.98 (d, *J* = 7.7 Hz, 2H, ArH), 5.44 (dd, *J* = 6.2, 2.3 Hz, 1H, H8), 5.26 (dd, *J* = 6.4, 2.7 Hz, 1H, H7), 4.69 (t, *J* = 1.9 Hz, 1H, H5), 4.57 (dd, *J* = 12.5, 2.4 Hz, 1H, H9), 4.48 (p, *J* = 2.6 Hz, 1H, H6), 4.21 (dd, *J* = 12.5, 6.1 Hz, 1H, H9′), 3.83 (s, 3H, $CH_3$), 3.31 (s, 3H, $CH_3$), 2.65 (ddd, *J* = 17.2, 3.7, 2.2 Hz, 1H, H3), 2.54 (dd, *J* = 17.2, 2.6 Hz, 1H, H3′), 2.08 (s, 3H, $CH_3$), 2.04 (s, 3H, $CH_3$), 2.03 (s, 3H, $CH_3$). $^{13}$C NMR (151 MHz, $CDCl_3$) δ 170.8, 170.0, 169.9, 168.4, 154.6, 151.0, 129.8 (two carbons), 124.4,

120.2 (two carbons), 99.4, 98.5, 71.3, 70.2, 69.4, 62.5, 52.8, 51.6, 34.5, 21.0, 20.9 (two carbons). ESI-HRMS calcd for (C23H28NaO11): ([M + Na]+) m/z: 503.1529; found: 503.1529.

**Methyl (Methyl 7,8,9-Tri-O-acetyl-3,4-dideoxy-4-C,5-O-(naphthalen-1,2-diyl)-D-glycero-β-D-talo-non-2-ulopyranosid)onate (164) and Methyl (Methyl 4,7,8,9-Tetra-O-acetyl-3,5-dideoxy-5-(2-hydroxynaphthalen-1-diazenyl)-D-glycero-β-D-galacto-non-2ulopyranosid)onate (165).**

The nitrosyl sialoside **74** (534 mg, 1 mmol) in $CH_2Cl_2$ (10 mL) was deaminated using the general procedure for oxidative deamination with sodium 2,2,2-trifluoroethoxide (244 mg, 2 mmol), 18-crown-6 (582 mg, 2 mmol) in $CH_2Cl_2$ (5 mL), and 2-naphthol (2.88 g, 20 mmol, 20 equiv) in $Et_2O$ (10 mL) to afford, after flash chromatography over silica gel eluting with (hexane/ethyl acetate 1:1), **164** as white crystals (282 mg, 57%) from diethyl ether and **165** as deep yellow crystals (81 mg, 13%) from methanol/$CH_2Cl_2$.

Compound **164**: white crystals, mp = 107−109 °C; $[\alpha]^{D}_{20}$ −116.0° (c 1.0, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.2 Hz, 1H, ArH), 7.69 (d, *J* = 8.8 Hz, 1H, ArH), 7.53 (dd, *J* = 8.0, 1.2 Hz, 1H, ArH), 7.46 (ddd, *J* = 8.3, 6.7, 1.2 Hz, 1H, ArH), 7.32 (ddd, *J* = 8.1, 6.7, 1.3 Hz, 1H, ArH), 7.10 (d, *J* = 8.8 Hz, 1H, ArH), 5.69 (dd, *J* = 6.0, 5.1 Hz, 1H, H7), 5.47 (td, *J* = 6.0, 2.7 Hz, 1H, H8), 4.94 (t, *J* = 9.2 Hz, 1H, H5), 4.48 (dd, *J* = 12.3, 2.7 Hz, 1H, H9), 4.35 (dd, *J* = 12.3, 6.0 Hz, 1H, H9′), 4.21 (dd, *J* = 9.4, 5.1 Hz, 1H, H6), 3.92 (s, 3H, $CH_3$), 3.87 (ddd, *J* = 13.5, 9.2, 5.0 Hz, 1H, H4), 3.31 (s, 3H, $CH_3$), 2.86 (dd, *J* = 14.9, 5.0 Hz, 1H, H3pe), 2.18 (s, 3H, $CH_3$), 2.10 (s, 3H, $CH_3$), 2.09 (s, 3H, $CH_3$), 1.90 (dd, *J* = 14.9, 13.5 Hz, 1H, H3pa). $^{13}$C NMR (101 MHz, CDCl3) δ 170.8, 170.2, 169.9, 169.3, 157.1, 130.4, 130.0, 129.8, 129.1, 127.2, 123.4,

122.1, 119.8, 112.5, 99.4, 80.0, 70.6, 69.8, 69.6, 61.8, 53.0, 51.7, 37.1, 34.1, 21.0, 20.9. ESI-HRMS calcd for ($C_{27}H_{30}O_{11}Na$): ([M + Na]+) m/z: 553.1686; found: 553.1686.

Compound **165**: deep yellow crystals; mp = 163−165 °C; $[\alpha]^{D}_{20}$ −21.6° (c 0.7, $CHCl_3$). $^1$H NMR (400 MHz, CDCl3) δ 8.47 (d, *J* = 8.3 Hz, 1H, ArH), 7.75 (d, *J* = 9.2 Hz, 1H, ArH), 7.65 (d, *J* = 7.9 Hz, 1H, ArH), 7.53 (ddd, *J* = 8.3, 7.0, 1.4 Hz, 1H, ArH), 7.38 (ddd, *J* = 8.1, 7.1, 1.3 Hz, 1H, ArH), 6.98 (d, *J* = 9.3 Hz, 1H, ArH), 5.86 (ddd, *J* = 11.2, 10.0, 5.1 Hz, 1H, H4), 5.42 (td, *J* = 6.1, 2.4 Hz, 1H, H8), 5.35 (dd, *J* = 6.5, 1.9 Hz, 1H, H7), 4.60 (dd, *J* = 12.5, 2.5 Hz, 1H, H9), 4.44 (dd, *J* = 10.4, 1.9 Hz, 1H, H6), 4.18−4.07 (m, 1H, H9), 4.00 (t, *J* = 10.2 Hz, 1H, H5), 3.83 (s, 3H, $CH_3$), 3.32 (s, 3H, $CH_3$), 2.66 (dd, *J* = 12.9, 5.1 Hz, 1H, H3), 2.13 (s, 3H, $CH_3$), 2.02 (s, 3H, $CH_3$), 1.94 (s, 3H, $CH_3$), 1.83 (s, 3H, $CH_3$), 1.26−1.22 (m, 1H, H3′). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 170.7, 170.1, 169.7, 169.5, 167.4, 161.9, 138.1, 133.3, 129.7, 128.5, 128.4, 128.0, 125.1, 122.5, 121.3, 99.0, 70.4, 70.2, 69.5, 68.9, 67.5, 62.1, 52.8, 51.5, 36.7, 21.0, 20.8, 20.7, 20.7. UV/vis λmax = 380 nm (acetonitrile, ε = 8699 M−1 cm−1). ESIHRMS calcd for ($C_{29}H_{34}N_2O_{13}Na$): ([M + Na]+) m/z: 641.1959; found: 641.1964.

**Methyl (Methyl 7,8,9-Tri-O-acetyl-3,5-dideoxy-4-O-(4-methoxyphenyl)-β-D-arabino-non-4-en-2-ulopyranosid)onate (166).**

The nitrosyl sialoside **74** (267 mg, 0.5 mmol) in $CH_2Cl_2$ (5 mL) was deaminated using the general procedure for oxidative deamination with sodium 2,2,2-trifluoroethoxide (122 mg, 1 mmol), 18-crown-6 (291 mg, 1.1 mmol) in $CH_2Cl_2$ (2.5 mL), and 4-methoxyphenol (1.24 g, 10 mmol, 20 equiv) in $CH_2Cl_2$ (5 mL) to afford, after flash column chromatography over silica gel eluting with (toluene/ethyl acetate 3:1), **166** as a colorless oil (92 mg, 36%); $[\alpha]^{D}_{20}$ −10.9° (c 0.7, $CH_2Cl_2$). $^1$H NMR (600 MHz, $CDCl_3$) δ 6.93−6.87 (m, 2H, ArH), 6.87−6.80 (m, 2H, ArH), 5.42

(td, *J* = 6.2, 2.3 Hz, 1H, H8), 5.23 (dd, *J* = 6.3, 2.7 Hz, 1H, H7), 4.56 (dd, *J* = 12.5, 2.4 Hz, 1H, H9), 4.51 (t, *J* = 1.9 Hz, 1H, H5), 4.45 (dt, *J* = 5.3, 2.6 Hz, 1H, H6), 4.19 (dd, *J* = 12.5, 6.1 Hz, 1H, H9′), 3.83 (s, 3H, $CH_3$), 3.78 (s, 3H, $CH_3$), 3.30 (s, 3H, $CH_3$), 2.64 (ddd, *J* = 17.1, 3.5, 2.0 Hz, 1H, H3), 2.53 (dd, *J* = 17.1, 2.5 Hz, 1H, H3′), 2.07 (s, 3H, $CH_3$), 2.03 (s, 3H, $CH_3$), 2.02 (s, 3H, $CH_3$). $^{13}$C NMR (151 MHz, $CDCl_3$) δ 170.8, 170.0, 169.8, 168.5, 156.6, 152.0, 147.6, 121.8, 114.8, 98.4, 96.9, 71.4, 70.2, 69.4, 62.5, 55.7, 52.8, 51.6, 34.6, 21.0, 20.9 (two carbons). HRMS (ESITOF) m/z: [M + Na]+ calcd for $C_{24}H_{30}NaO_{12}$ 533.1635; found: 533.1636.

**Methyl (Methyl 4,7,8,9-Tetra-*O*-acetyl-3-deoxy-5-*O*-(4-nitrophenyl)-D-glycero-*β*-D-galacto-non-2-ulopyranosid)onate (167) and Methyl (Methyl 7,8,9-Tri-*O*-acetyl-3,5-dideoxy-4-*O*-(4-nitrophenyl)-*β*-D-arabino-non-4-en-2-ulopyranosid)onate (168).**

The nitrosyl sialoside **74** (267 mg, 0.5 mmol) in $CH_2Cl_2$ (5 mL) was deaminated using the general procedure for oxidative deamination with sodium 2,2,2-trifluoroethoxide (122 mg, 1 mmol), 18-crown-6 (291 mg, 1.1 mmol) in $CH_2Cl_2$ (2.5 mL), and 4-nitrophenol (1.39 g, 10 mmol, 20 equiv) in tetrahydrofuran (THF) (5 mL) to afford **167** (27 mg, 9%), and **168** (25 mg, 9%), and an inseparable mixture of **160** and **161** (52 mg, 23%) after flash column chromatography over silica gel eluting with (toluene/ethyl acetate 3:1).

Compound **167**: colorless oil, $[\alpha]^{D}_{20}$ −3.7° (c 0.8, $CHCl_3$). $^1$H NMR (600 MHz, $CDCl_3$) δ 8.17 (d, *J* = 9.3 Hz, 2H, ArH), 6.97 (d, *J* = 9.2 Hz, 2H, ArH), 5.42 (dd, *J* = 4.8, 2.2 Hz, 1H, H7), 5.30 (ddd, *J* = 7.2, 4.9, 2.5 Hz, 1H, H8), 5.14 (dd, *J* = 10.1, 9.3 Hz, 1H, H5), 4.88 (ddd, *J* = 11.3, 9.2, 4.9 Hz, 1H, H4), 4.77 (dd, *J* = 12.5, 2.5 Hz, 1H, H9), 4.14 (dd, *J* = 12.5, 7.1 Hz, 1H, H9′), 4.11 (dd, *J* = 10.1, 2.2 Hz, 1H, H6), 3.82 (s, 3H, $CH_3$), 3.31 (s, 3H, $CH_3$), 2.66 (dd, *J* = 13.3, 4.9 Hz, 1H, H3e), 2.14 (s, 3H, $CH_3$), 2.08 (s, 3H, $CH_3$), 2.03 (s, 3H, $CH_3$), 1.95 (dd, *J* = 13.3, 11.3

Hz, 1H, H3a), 1.87 (s, 3H, $CH_3$). $^{13}C$ NMR (151 MHz, $CDCl_3$) δ 170.6, 170.5, 170.2, 169.6, 167.1, 162.6, 142.2, 126.1, 115.6, 99.1, 74.3, 71.3, 70.6, 68.4, 67.6, 62.3, 53.1, 51.6, 37.3, 21.1, 20.9, 20.8 (two carbons). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{25}H_{31}NNaO_{15}$ 608.1591; found: 608.1595.

Compound **168**: colorless oil, $[\alpha]^{D}_{20}$ −46.8° (*c* 0.6, $CHCl_3$). $^1H$ NMR (600 MHz, $CDCl_3$) δ 8.20 (d, *J* = 9.2 Hz, 2H, ArH), 6.90 (d, *J* = 9.2 Hz, 2H, ArH), 5.56−5.51 (m, 2H, H8 and H7), 5.18 (d, *J* = 3.6 Hz, 1H, H5), 5.04 (tdd, *J* = 5.5, 3.8, 1.2 Hz, 1H, H4), 4.41 (dd, *J* = 12.2, 2.7 Hz, 1H, H9), 4.33 (dd, *J* = 12.1, 7.1 Hz, 1H, H9′), 3.79 (s, 3H, $CH_3$), 3.41 (s, 3H, $CH_3$), 2.43 (dd, *J* = 13.8, 5.6 Hz, 1H, H3), 2.37 (dd, *J* = 13.8, 5.3 Hz, 1H, H3′), 2.14 (s, 3H, CH3), 2.07 (s, 3H, $CH_3$), 2.065 (s, 3H, $CH_3$). $^{13}C$ NMR (151 MHz, $CDCl_3$) δ 170.8, 170.1, 169.4, 167.4, 162.0, 149.9, 142.0, 126.2, 126.1, 118.2, 115.6, 115.5, 99.4, 97.9, 70.5, 70.4, 66.9, 61.9, 53.0, 52.4, 34.5, 21.0, 20.94, 20.92. HRMS (ESI-TOF) m/z: [M + Na] + calcd for $C_{23}H_{27}NNaO_{13}$ 548.1380; found: 548.1389.

**Methyl (Methyl 7,8,9-Tri-*O*-acetyl-3,4-dideoxy-4-C,5-*O*-(3,5-dimethoxyphenyl-2,1-diyl)-D-glycero-*β*-D-talo-non-2-ulopyranosid)onate (169).**

The nitrosyl sialoside **74** (267 mg, 0.5 mmol) in $CH_2Cl_2$ (5 mL) was deaminated using the general procedure for oxidative deamination with sodium 2,2,2-trifluoroethoxide (122 mg, 1 mmol), 18-crown-6 (291 mg, 1.1 mmol) in $CH_2Cl_2$ (2.5 mL), and 3,5-dimethoxyphenol (1.54 g, 10 mmol, 20 equiv) in $CH_2Cl_2$ (5 mL) to afford **169**, after flash column chromatography over silica gel eluting with (hexane/ethyl acetate 1:1), as a colorless oil in (92 mg, 34%); $[\alpha]^{D}_{20}$ −79.8° (*c* 0.93, $CH_2Cl_2$). $^1H$ NMR (600 MHz, $CDCl_3$) δ 6.02 (d, *J* = 2.0 Hz, 1H, ArH), 5.97 (d, *J* = 2.0 Hz, 1H, ArH), 5.59 (dd, *J* = 6.4, 4.6 Hz, 1H, H7), 5.39 (td, *J* = 6.1, 2.6 Hz, 1H, H8), 4.70 (t, *J* =

9.4 Hz, 1H, H5), 4.41 (dd, *J* = 12.3, 2.7 Hz, 1H, H9), 4.28 (dd, *J* = 12.4, 5.8 Hz, 1H, H9′), 4.03 (dd, *J* = 9.4, 4.6 Hz, 1H, H6), 3.82 (s, 3H, $CH_3$), 3.73 (s, 3H, $CH_3$), 3.72 (s, 3H, $CH_3$), 3.47 (ddd, *J* = 12.9, 9.1, 5.4 Hz, 1H, H4), 3.25 (s, 3H, $CH_3$), 2.63 (dd, *J* = 14.9, 5.4 Hz, 1H, H3pe), 2.14 (s, 3H, $CH_3$), 2.06 (s, 6H, $CH_3$), 1.79 (dd, *J* = 14.9, 12.9 Hz, 1H, H3pa). $^{13}C$ NMR (151 MHz, $CDCl_3$) δ 170.7, 170.1, 169.7, 169.4, 162.1, 161.1, 157.1, 107.5, 99.4, 91.8, 88.7, 79.5, 70.2, 69.7, 69.2, 61.7, 55.6, 55.3, 52.8, 51.5, 35.2, 33.7, 21.0, 20.8. ESIHRMS calcd for ($C_{25}H_{32}NaO_{13}$): ([M + Na]+) m/z: 563.1741; found: 563.1715.

**Deamination of Nitrosyl Sialoside 74 with 2-Quinolinol as Nucleophile.**

The nitrosyl sialoside **74** (306 mg, 0.6 mmol) in $CH_2Cl_2$ (5 mL) was deaminated using the general procedure for oxidative deamination with sodium 2,2,2-trifluoroethoxide (140 mg, 1.1 mmol), 18-crown-6 (300 mg, 1.1 mmol) in $CH_2Cl_2$ (3 mL), and 2-quinolinol (165 mg, 1.1 mmol) in $Et_2O$ (10 mL) to afford, after flash column chromatographic separation over silica gel (hexane/ethyl acetate 1:1), a mixture of compounds **160** and **161** (1:2.5 ratio; 220 mg, 86%).

**Methyl (Methyl 7,8,9-Tri-*O*-acetyl-3,5-dideoxy-4-*O*-(quinolin-3yl)-*β*-D-arabino-non-4-en-2-ulopyranosid)onate (170) and Methyl (Methyl 7,8,9-Tri-*O*-acetyl-3,5-dideoxy-4-*O*-(quinolin-3-yl)-*β*-D-ribonon-5-en-2-ulopyranosid)onate (171).**

The nitrosyl sialoside **74** (330 mg, 0.6 mmol) in $CH_2Cl_2$ (5 mL) was deaminated using the general procedure for oxidative deamination with sodium 2,2,2-trifluoroethoxide (146 mg, 1.2 mmol), 18-crown-6 (317 mg, 1.2 mmol) in $CH_2Cl_2$ (3 mL), and 3-quinolinol (1.2 g, 8.5 mmol) in $Et_2O$ (10 mL) to afford, after flash column chromatography over silica gel eluting with (hexane/ethyl acetate 1:2), **170** as a colorless oil in (68 mg, 21%) and **171** as a colorless oil in (40 mg, 12%).

Compound **170**: $[\alpha]^{D}_{20}$ −42.1° (*c* 0.28, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.69 (d, *J* = 2.8 Hz, 1H, ArH), 8.11 (d, *J* = 8.5 Hz, 1H, ArH), 7.77 (d, *J* = 8.2 Hz, 1H, ArH), 7.73 (d, *J* = 2.7 Hz, 1H, ArH), 7.67 (ddd, *J* = 8.4, 6.7, 1.5 Hz, 1H, ArH), 7.56 (t, *J* = 7.5 Hz, 1H, ArH), 5.46 (td, *J* = 6.3, 2.5 Hz, 1H, H8), 5.29 (dd, *J* = 6.5, 2.8 Hz, 1H, H7), 4.89 (t, *J* = 2.0 Hz, 1H, H5), 4.56 (dd, *J* = 12.5, 2.4 Hz, 1H, H9), 4.52 (q, *J* = 2.7 Hz, 1H, H6), 4.21 (dd, *J* = 12.5, 6.0 Hz, 1H, H9′), 3.84 (s, 3H, $CH_3$), 3.34 (s, 3H, $CH_3$), 2.73 (ddd, *J* = 17.0, 3.7, 2.1 Hz, 1H, H3), 2.61 (dd, *J* = 17.1, 2.4 Hz, 1H, H3′), 2.12 (s, 3H, $CH_3$), 2.04 (s, 3H, $CH_3$), 2.03 (s, 3H, $CH_3$). $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 170.8, 170.0, 169.8, 168.1, 150.6, 148.1, 145.6, 129.4, 128.5, 127.5, 127.3, 122.9, 101.3, 98.4, 71.1, 70.0, 69.3, 62.4, 52.8, 51.7, 34.3, 21.0, 20.9, 20.8. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for C26H29NO11Na 554.1638; found: 554.1636.

Compound **171**: [α]D 20 −26.2° (*c* 0.2, $CHCl_3$). $^1H$ NMR (600 MHz, $CDCl_3$) δ 8.57 (d, *J* = 2.8 Hz, 1H, ArH), 8.03 (d, *J* = 8.3 Hz, 1H, ArH), 7.72 (d, *J* = 8.1 Hz, 1H, ArH), 7.57 (t, *J* = 7.6 Hz, 1H, ArH), 7.51 (t, *J* = 7.5 Hz, 1H, ArH), 7.40 (d, *J* = 2.9 Hz, 1H, ArH), 5.58− 5.53 (m, 2H, H8, H7), 5.24 (d, *J* = 3.8 Hz, 1H, H5), 5.06 (tdd, *J* = 5.3, 3.7, 1.3 Hz, 1H, H4), 4.43 (dd, *J* = 12.2, 2.8 Hz, 1H, H9), 4.36 (dd, *J* = 12.1, 7.2 Hz, 1H, H9′), 3.80 (s, 3H, $CH_3$), 3.42 (s, 3H, $CH_3$), 2.51 (dd, *J* = 13.8, 5.4 Hz, 1H, H3), 2.40 (dd, *J* = 13.8, 5.3 Hz, 1H, H3′), 2.13 (s, 3H, $CH_3$), 2.06 (s, 6H, 2 × $CH_3$). $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 170.8, 170.1, 169.4, 167.5, 150.2, 149.6, 128.7, 127.5, 126.9, 99.4, 98.3, 70.5, 70.4, 66.8, 61.9, 53.0, 52.4, 34.4, 21.0, 20.9 (two carbons). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{26}H_{29}NO_{11}Na$ 554.1638; found: 554.1636.

**Methyl (Methyl 7,8,9-Tri-*O*-acetyl-3,4-dideoxy-4-C,5-*O*-(quinoline-5,6-diyl)-D-glycero-β-D-talo-non-2-ulopyranosid)onate (172).**

The nitrosyl sialoside **74** (200 mg, 0.4 mmol) in $CH_2Cl_2$ (4 mL) was deaminated using the general procedure for oxidative deamination with sodium 2,2,2-trifluoroethoxide (91 mg, 0.7 mmol), 18-crown-6 (195 mg, 0.7 mmol) in $CH_2Cl_2$ (3 mL), and 6-quinolinol (1.1 g, 7.6 mmol) in hexafluoroisopropanol (3 mL) to afford, after flash column chromatography over silica gel eluting with (hexane/ethyl acetate 1:2), **172** as a light yellow oil (105 mg, 53%) and an inseparable mixture of **160** and **161** as a colorless oil (25 mg, 11%).

Compound **172**: $[\alpha]^{D}_{20}$ −85.1° (*c* 0.37, $CH_2Cl_2$). $^1$H NMR (600 MHz, $CDCl_3$) δ 8.78 (dd, *J* = 4.2 Hz, 1H, ArH), 8.01 (d, *J* = 9.0 Hz, 1H, ArH), 7.91 (d, *J* = 8.3 Hz, 1H, ArH), 7.39 (dd, *J* = 8.4, 4.2 Hz, 1H, ArH), 7.34 (d, *J* = 9.0 Hz, 1H, ArH), 5.68 (dd, *J* = 6.1, 5.0 Hz, 1H, H7), 5.46 (td, *J* = 6.0, 2.6 Hz, 1H, H8), 4.99 (dd, *J* = 9.3, 8.9 Hz, 1H, H5), 4.48 (dd, *J* = 12.3, 2.7 Hz, 1H, H9), 4.34 (dd, *J* = 12.3, 6.0 Hz, 1H, H9′), 4.21 (dd, *J* = 9.3, 5.0 Hz, 1H, H6), 3.91 (s, 3H, $CH_3$), 3.88 (ddd, *J* = 13.4, 8.9, 5.1 Hz, 1H, H4), 3.31 (s, 3H, $CH_3$), 2.78 (dd, *J* = 14.9, 5.1 Hz, 1H, H3pe), 2.18 (s, 3H, $CH_3$), 2.10 (s, 3H), 2.09 (s, 3H), 1.92 (dd, *J* = 14.9, 13.4 Hz, 1H, H3pa). $^{13}$C NMR (151 MHz, $CDCl_3$) δ 170.8, 170.3, 169.9, 169.2, 157.3, 147.3, 133.2, 131.6, 130.4, 125.5, 121.9, 119.8, 115.9, 99.2, 80.5, 70.5, 69.8, 69.5, 61.7, 53.1, 51.8, 36.9, 34.3, 21.2, 21.1, 21.0. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{26}H_{29}NO_{11}Na$ 554.1638; found: 554.1634.

**Methyl (Methyl 7,8,9-Tri-O-acetyl-3,4-dideoxy-4-C,5-O-(indol-4,5-diyl)-D-glycero-β-D-talo-non-2-ulopyranosid)onate (173) and Methyl (Methyl 4,7,8,9-Tetra-O-acetyl-3,5-dideoxy-5-(5-hydroxyindol-4-diazenyl)-D-glycero-β-D-galacto-non-2-ulopyranosid)onate (174)**

The nitrosyl sialoside **74** (267 mg, 0.5 mmol) in $CH_2Cl_2$ (5 mL) was deaminated using the general procedure for oxidative deamination with sodium 2,2,2-trifluoroethoxide (122 mg, 1

mmol), 18-crown-6 (291 mg, 1.1 mmol) in $CH_2Cl_2$ (2.5 mL), and 5-hydroxyindole (1.33 g, 10 mmol, 20 equiv) in THF (5 mL) to afford, after flash column chromatography over silica gel eluting with (hexane/ethyl acetate 1:1), **173** as a colorless oil (72 mg, 27%), **174** (28 mg, 9%) as deep yellow crystals from methanol/$CH_2Cl_2$, and an inseparable mixture of **160** and **161** (16 mg, 7%).

Compound **173**: colorless oil, $[\alpha]^{D}_{20}$ −104.8° (*c* 0.4, $CH_2Cl_2$). $^{1}$H NMR (600 MHz, $CDCl_3$) δ 8.13 (s, 1H, NH), 7.22 (t, *J* = 2.9 Hz, 1H, ArH), 7.17 (d, *J* = 8.6 Hz, 1H, ArH), 6.74 (d, *J* = 8.6 Hz, 1H, ArH), 6.32 (ddd, *J* = 3.1, 2.0, 1.0 Hz, 1H, ArH), 5.67 (dd, *J* = 6.1, 5.0 Hz, 1H, H7), 5.47 (td, *J* = 6.1, 2.8 Hz, 1H, H8), 4.82 (dd, *J* = 9.4, 8.8 Hz, 1H, H5), 4.46 (dd, *J* = 12.3, 2.8 Hz, 1H, H9), 4.32 (dd, *J* = 12.3, 6.1 Hz, 1H, H9′), 4.12 (dd, *J* = 9.4, 5.0 Hz, 1H, H6), 3.88 (s, 3H), 3.77 (ddd, *J* = 12.8, 8.8, 5.5 Hz, 1H, H4), 3.28 (s, 3H, $CH_3$), 2.72 (dd, *J* =14.9, 5.5 Hz, 1H, H3pe), 2.17 (s, 3H, $CH_3$), 2.09 (s, 3H, $CH_3$), 2.07 (s, 3H, $CH_3$), 2.02 (dd, *J* =14.9, 12.8 Hz, 1H, H3pa). $^{13}$C NMR (151 MHz, $CDCl_3$) δ 170.9, 170.3, 169.9, 169.6, 153.3, 132.3, 126.0, 124.5, 116.9, 110.9, 106.0, 99.5, 99.4, 78.7, 70.7, 69.9, 69.6, 61.9, 53.0, 51.6, 37.6, 34.2, 21.1, 21.0. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{25}H_{29}NNaO_{11}$ 542.1638; found: 542.1637.

Compound **174**: mp = 209 − 210 °C; $[\alpha]^{D}_{20}$ −51.1° (*c* 0.45, $CHCl_3$). $^{1}$H NMR (600 MHz, $CDCl_3$) δ 11.44 (s, 1H), 8.31 (s, 1H, ArH), 7.36 (d, *J* = 8.7, 0.9 Hz, 1H, ArH), 6.94 (ddd, *J* = 2.9, 2.0, 0.8 Hz, 1H, ArH), 6.82 (d, *J* = 8.8 Hz, 1H, ArH), 6.00 (ddd, *J* = 11.4, 9.9, 5.1 Hz, 1H, H4), 5.42 (td, *J* = 6.1, 2.6 Hz, 1H, H8), 5.34 (dd, *J* = 6.3, 1.9 Hz, 1H, H7), 4.61 (dd, *J* = 12.5, 2.5 Hz, 1H, H9), 4.44 (dd, *J* = 10.4, 1.9 Hz, 1H, H6), 4.14 (dd, *J* = 12.5, 6.0 Hz, 1H, H9′), 4.02 (t, *J* = 10.1 Hz, 1H, H5), 3.84 (s, 3H, $CH_3$), 3.32 (s, 3H, $CH_3$), 2.65 (dd, *J* = 12.9, 5.1 Hz, 1H, H3e), 2.17 (s, 3H, $CH_3$), 2.02 (s, 3H, $CH_3$), 1.97 (s, 3H, $CH_3$), 1.87 (dd, *J* = 12.8, 11.6 Hz, 1H, H3a),

1.85 (s, 3H, $CH_3$). $^{13}C$ NMR (151 MHz, $CDCl_3$) δ 170.9, 170.2, 169.9, 169.5, 167.7, 149.3, 130.6, 128.9, 126.6, 118.1, 113.2, 101.4, 99.1, 74.2, 70.4, 70.2, 69.1, 67.5, 62.2, 52.9, 51.5, 36.5, 21.1, 20.9 (three carbons). UV/ vis λmax = 365 nm (dichloromethane, ε = 2391 M−1 cm−1). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{27}H_{33}N_3NaO_{13}$ 630.1911; found: 630.1904.

**Methyl (Methyl 4,7,8,9-Tetra-O-acetyl-3,5-dideoxy-5-phenylthio-D-glycero-β-D-galacto-non-2-ulopyranosid)onate (175) and Methyl (Methyl 4,7,8,9-Tetra-O-acetyl-3,5-dideoxy-β-D-gluco-non-2ulopyranosid)onate (176).**

The nitrosyl sialoside **74** (200 mg, 0.4 mmol) in $CH_2Cl_2$ (4 mL) was deaminated using the general procedure for oxidative deamination with sodium 2,2,2-trifluoroethoxide (90 mg, 0.7 mmol), 18-crown-6 (97 mg, 0.4 mmol) in $CH_2Cl_2$ (2 mL), and thiophenol (0.8 mL, 7.4 mmol) to afford **175** (48 mg, 23%) and **176** (32 mg, 19%) after flash column chromatography over silica gel eluting with (hexane/ethyl acetate 1:1).

Compound **175**: yellow oil, $[\alpha]^{D}_{20}$ −59.4° (*c* 0.5, $CHCl_3$). $^1H$ NMR (600 MHz, $CDCl_3$) δ 7.45−7.40 (m, 3H, ArH), 7.36−7.32 (m, 2H, ArH), 5.98 (dd, *J* = 4.7, 1.8 Hz, 1H, H7), 5.29 (td, *J* = 10.9, 5.0 Hz, 1H, H4), 5.23 (ddd, *J* = 7.2, 4.7, 2.6 Hz, 1H, H8), 4.71 (dd, *J* = 12.4, 2.5 Hz, 1H, H9), 4.12 (dd, *J* = 12.4, 7.1 Hz, 1H, H9′), 3.87 (dd, *J* = 11.1, 1.9 Hz, 1H, H6), 3.78 (s, 3H), 3.17 (s, 3H), 2.88 (t, *J* = 10.9 Hz, 1H, H5), 2.53 (dd, *J* = 12.8, 4.9 Hz, 1H, H3e), 2.08 (s, 3H), 2.04 (s, 3H), 2.00 (s, 3H), 1.92 (s, 3H), 1.73 (dd, *J* = 12.8, 11.1 Hz, 1H, H3a). $^{13}C$ NMR (151 MHz, $CDCl_3$) δ 170.6, 170.4, 169.6, 169.5, 167.4, 134.8, 133.8, 132.09, 132.03, 131.3, 122.3, 98.5, 71.7, 71.3, 69.7, 69.0, 62.2, 52.6, 51.3, 48.7, 37.9, 29.6, 20.96, 20.91, 20.7, 20.3. ESI-HRMS calcd for ($C_{25}H_{32}NaO_{12}S$): ($[M + Na]^+$) m/z: 579.1512; found: 579.1519.

Compound **176**: colorless oil, $[\alpha]^{D}_{20}$ −21.9° (*c* 2.1, $CHCl_3$). $^1$H NMR (600 MHz, $CDCl_3$) δ 5.33 (td, *J* = 6.0, 2.6 Hz, 1H, H8), 5.26 (dd, *J* = 6.2, 3.2 Hz, 1H, H7), 5.20 (m 1H, H4), 4.56 (dd, *J* = 12.8, 2.6 Hz, 1H, H9), 4.22 (dd, *J* = 12.6, 5.9 Hz, 1H, H9), 3.99 (dd, *J* = 11.9, 3.2 Hz, 1H, H6), 3.78 (s, 3H, $CH_3$), 3.19 (s, 3H, $CH_3$), 2.35 (dd, *J* = 12.8, 4.9 Hz, 1H, H3e), 2.14 (s, 3H, $CH_3$), 2.07 (s, 3H, $CH_3$), 2.04 (s, 3H, $CH_3$), 2.02 (s, 3H, $CH_3$), 1.64−1.56 (m, 2H, H5e, H3a), 1.38 (q, *J* = 12.0 Hz, 1H, H5a). $^{13}$C NMR (151 MHz, $CDCl_3$) δ 170.7, 170.2, 170.1, 170.1, 168.1, 99.4, 71.7, 70.3, 68.2, 66.5, 62.0, 52.7, 50.9, 37.3, 32.2, 21.2, 21.0, 20.8 (two carbons). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{19}H_{28}NaO_{12}$ 471.1478; found: 471.1479.

**Methyl (Methyl 4,7,8,9-Tetra-O-acetyl-3,5-dideoxy-5-(2-aminophenyl-thio)-D-glycero-β-D-galacto/gulo-non-2-ulopyranosid)onate (177) and Methyl (Methyl 4,7,8,9-Tetra-O-acetyl-3,5-dideoxy-β-D-gluco-non-2-ulopyranosid)onate (176)**

The nitrosyl sialoside **74** (267 mg, 0.5 mmol) in $CH_2Cl_2$ (5 mL) was deaminated using the general procedure for oxidative deamination with sodium 2,2,2-trifluoroethoxide (122 mg, 1 mmol), 18-crown-6 (291 mg, 1.1 mmol) in $CH_2Cl_2$ (2.5 mL), and 2-aminothiophenol (1.25 g, 10 mmol, 20 equiv) in $CH_2Cl_2$ (5 mL) to afford, after flash column chromatography over silica gel eluting with (hexane/ethyl acetate 2:1), **177** (167 mg, 58%) as a mixture of two isomers (ratio; axial/equatorial = 1:3) and **176** (64 mg, 28%).

Major isomer (D-glycero-D-galacto): colorless oil, $^1$H NMR (600 MHz, $CDCl_3$) δ 7.33 (dd, *J* = 7.7, 1.5 Hz, 1H, ArH), 7.09 (ddd, *J* = 8.0, 7.3, 1.5 Hz, 1H, ArH), 6.67 (dd, *J* = 8.1, 1.3 Hz, 1H, ArH), 6.65 (td, *J* = 7.6, 1.2 Hz, 1H, ArH), 5.97 (dd, *J* = 5.1, 1.5 Hz, 1H, H7), 5.27 (ddd, *J* = 6.8, 5.1, 2.5 Hz, 1H, H8), 5.22 (td, *J* = 10.6, 5.0 Hz, 1H, H4), 4.67 (dd, *J* = 12.5, 2.5 Hz, 1H, H9), 4.14 (dd, *J* = 12.5, 6.9 Hz, 1H, H9′), 3.96 (dd, *J* = 11.1, 1.6 Hz, 1H, H6), 3.75 (s, 3H, $CH_3$),

3.15 (s, 3H, $CH_3$), 2.94 (t, *J* = 10.7 Hz, 1H, H5), 2.51 (dd, *J* = 12.8, 5.1 Hz, 1H, H3e), 2.07 (s, 3H, $CH_3$), 2.03 (s, 3H, $CH_3$), 2.02 (s, 3H, $CH_3$), 1.89 (s, 3H, $CH_3$), 1.63 (dd, *J* = 12.8, 10.9 Hz, 1H, H3a). $^{13}$C NMR (151 MHz, $CDCl_3$) δ 170.7, 170.5, 170.0, 169.8, 167.5, 136.7, 130.6, 118.7, 115.4, 113.7, 98.5, 71.7, 71.7, 70.1, 70.0, 62.4, 52.6, 51.3, 47.0, 37.6, 21.1, 20.9, 20.6.

Minor isomer (D-glycero-D-gulo): $^1$H NMR (600 MHz, $CDCl_3$) δ 7.44 (dd, *J* = 8.3, 1.4 Hz, 1H, ArH), 7.04 (td, *J* = 7.7, 1.5 Hz, 1H, ArH), 5.86 (dd, *J* = 7.6, 4.1 Hz, 1H, H7), 5.41 (dt, *J* = 6.0, 4.6 Hz, 1H), 4.37 (dd, *J* = 12.0, 4.8 Hz, 1H, H9), 4.18 (dd, *J* = 12.0, 5.9 Hz, 1H, H9′), 4.09 (dd, *J* = 7.6, 1.7 Hz, 1H, H6), 3.80 (s, 3H, $CH_3$), 3.21 (s, 3H, $CH_3$), 2.66 (dd, *J* = 12.9, 12.0 Hz, 1H, H3), 2.10 (s, 3H, $CH_3$), 2.09 (s, 3H, $CH_3$), 2.05 (s, 3H, $CH_3$), 1.46 (s, 3H, $CH_3$). $^{13}$C NMR (151 MHz, $CDCl_3$) δ 170.3, 170.0, 167.5, 148.8, 137.0, 129.8, 118.8, 116.5, 115.5, 98.9, 71.2, 70.3, 69.5, 61.4, 52.8, 51.0, 48.0, 32.7, 21.0, 20.9, 20.8, 20.2.

Compounds **177**: ESI-HRMS calcd for ($C_{25}H_{33}NNaO_{12}S$): ($[M + Na]^+$) m/z: 594.1621; found: 594.1621.

**Methyl (Methyl 4,7,8,9-Tetra-O-acetyl-3,5-dideoxy-5-(naphthalen-2-thio)-D-glycero-β-D-galacto/gulo-non-2-ulopyranosid)onate (178) and Methyl (Methyl 4,7,8,9-Tetra-O-acetyl-3,5-dideoxy-Dgluco-non-2-ulopyranosid)onate (176).**

The nitrosyl sialoside **74** (267 mg, 0.5 mmol) in $CH_2Cl_2$ (5 mL) was deaminated using the general procedure for oxidative deamination with sodium 2,2,2trifluoroethoxide (122 mg, 1 mmol), 18-crown-6 (291 mg, 1.1 mmol) in $CH_2Cl_2$ (2.5 mL), and 2-naphthalenethiol (1.60 g, 10 mmol, 20 equiv) in $CH_2Cl_2$ (5 mL) to afford, after flash column chromatography over silica gel eluting with (hexane/ethyl acetate 3:1), **178** as a colorless oil (92 mg, 30%), a mixture of **178** and

its stereoisomer **178a** as a colorless oil (76 mg, 25%) in the axial/ equatorial ratio 1:4 by 1H NMR, and **176** (30 mg, 13%).

Compound **178** (D-glycero-D-galacto): colorless oil (92 mg, 30%), $[\alpha]^{D}_{20}$ −34.7° (*c* 2.5, $CH_2Cl_2$). $^1$H NMR (600 MHz, $CDCl_3$) δ 7.97 (d, *J* = 1.8 Hz, 1H, ArH), 7.79 (dd, *J* = 7.8, 1.6 Hz, 2H, ArH), 7.77 (d, *J* = 8.5 Hz, 1H, ArH), 7.52 (dd, *J* = 8.6, 1.9 Hz, 1H, ArH), 7.48 (m, 2H, ArH), 6.08 (dd, *J* = 4.8, 1.9 Hz, 1H, H7), 5.38 (td, *J* = 10.9, 5.0 Hz, 1H, H4), 5.25 (ddd, *J* = 7.2, 4.8, 2.6 Hz, 1H, H8), 4.69 (dd, *J* = 12.4, 2.6 Hz, 1H, H9), 4.12 (dd, *J* = 12.4, 7.1 Hz, 1H, H9), 3.94 (dd, *J* = 11.0, 1.9 Hz, 1H, H6), 3.77 (s, 3H, $CH_3$), 3.12 (s, 3H, $CH_3$), 3.03 (t, *J* = 10.9 Hz, 1H, H5), 2.54 (dd, *J* = 12.9, 5.1 Hz, 1H, H3e), 2.03 (s, 3H, $CH_3$), 2.01 (s, 3H, $CH_3$), 1.96 (s, 3H, $CH_3$), 1.80 (s, 3H, $CH_3$), 1.76 (dd, *J* = 12.9, 11.1 Hz, 1H, H3a). $^{13}$C NMR (151 MHz, $CDCl_3$) δ 170.7, 170.6, 169.8, 169.5, 167.6, 133.6, 132.9, 132.7, 130.3, 129.4, 128.7, 127.7, 127.7, 126.8, 126.7, 98.7, 71.8, 71.7, 70.0, 69.4, 62.5, 52.7, 51.4, 48.8, 38.1, 21.0, 21.0, 20.9, 20.4. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{29}H_{34}O_{12}SNa$ 629.1669; found: 629.1669.

The minor D-glycero-D-gulo isomer **178a** was identified from a mixture with the major isomer by the following signals: $^1$H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 1.8 Hz, 1H, ArH), 7.81−7.75 (m, 3H, ArH), 7.59 (dd, *J* = 8.6, 1.9 Hz, 1H, ArH), 7.48−7.43 (m, 2H, ArH), 5.94 (dd, *J* = 4.8, 1.9 Hz, 1H, H7), 5.52 (ddd, *J* = 7.2, 4.8, 2.6 Hz, 1H, H8), 5.38 (m, 1H, H4), 4.46 (dd, *J* = 12.4, 2.6 Hz, 1H, H9), 4.18−4.10 (m, 2H, H6, H9), 3.95 (m, 1H, H5), 3.82 (s, 3H, $CH_3$), 3.24 (s, 3H, $CH_3$), 2.60 (dd, *J* = 12.9, 11.1 Hz, 1H, H3), 2.16 (dd, *J* = 12.9, 5.1 Hz, 1H, H3), 2.12 (s, 3H, $CH_3$), 2.09 (s, 3H, $CH_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 170.8, 170.4, 170.2, 169.7, 167.4, 133.7, 132.7, 132.0, 131.1, 129.4, 129.3, 128.2, 127.3, 126.6, 126.2, 98.9, 71.8, 70.7, 69.7, 68.9, 61.6, 52.8, 50.9, 49.9, 29.7, 20.8, 20.7, 20.6, 20.1.

**Methyl (Methyl 7,8,9-Tri-O-acetyl-3,5-dideoxy-4,4-*O*-ethylene-dioxy-β-D-arabino-non-2-ulopyranosid)onate (180).**

Dry ethylene glycol (20 μL) and a few crystals of dry *p*-toluenesulfonic acid were added to compound **166** (30 mg, 0.06 mmol) dissolved in $CH_2Cl_2$ (5 mL). The mixture was stirred at rt until the substrate was consumed (25 h). The reaction mixture was diluted with $CH_2Cl_2$ (5 mL), and the organic layer was washed with sat. $NaHCO_3$ and brine, dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure. Purification by column chromatography over silica gel eluting with (hexane/ethyl acetate 1:1) then gave compound **180** as a colorless oil (11 mg, 42%); $[\alpha]^{D}_{20}$ −16.4° (*c* 0.45, $CHCl_3$). $^1$H NMR (600 MHz, $CDCl_3$) δ 5.35 (td, *J* = 6.0, 2.5 Hz, 1H, H8), 5.29 (dd, *J* = 5.9, 3.3 Hz, 1H, H7), 4.60 (dd, *J* = 12.5, 2.5 Hz, 1H, H9), 4.23 (dd, *J* = 12.5, 6.0 Hz, 1H, H9), 4.19 (ddd, *J* = 12.2, 3.4, 2.1 Hz, 1H, H6), 4.10 − 3.86 (m, 4H), 3.78 (s, 3H, $CH_3$), 3.23 (s, 3H, $CH_3$), 2.19 (dd, *J* = 14.2, 2.2 Hz, 1H, H5), 2.13 (s, 3H, $CH_3$), 2.07 (s, 3H, $CH_3$), 2.03 (s, 3H, $CH_3$), 1.89 (d, *J* = 14.1 Hz, 1H, H5′), 1.71 (dt, *J* = 13.2, 2.2 Hz, 1H, H3e), 1.58 (dd, *J* = 13.1, 12.1 Hz, 1H, H3a). $^{13}$C NMR (151 MHz, $CDCl_3$) δ 170.8, 170.3, 170.2, 168.5, 105.8, 99.3, 71.9, 70.5, 68.0, 65.5, 64.1, 62.0, 52.7, 51.5, 40.5, 35.8, 21.1, 20.9. HRMS (ESITOF) m/z: $[M + Na]^+$ calcd for $C_{19}H_{28}NaO_{12}$ 471.1478; found: 471.1471.

**Methyl (7,8,9-Tri-*O*-acetyl-2,3,5-tri-deoxy-*β*-D-arabino-non-2-en-4-oxo-2-ulopyranosid)onate (182).**

A solution of compound **166** (25 mg, 0.05 mmol), a few drops of wet methanol, and a few crystals of *p*-toluenesulfonic acid in $CH_2Cl_2$ (5 mL) were stirred at rt until TLC showed complete consumption of the starting material (4 h). The reaction mixture was diluted with $CH_2Cl_2$ (5 mL), and the organic layer was washed with sat. $NaHCO_3$ and brine, dried over

anhydrous $Na_2SO_4$, and concentrated under reduced pressure. Purification by column chromatography over silica gel eluting with (toluene/ethyl acetate 4:1) gave compound **182** as a colorless oil (10 mg, 55%); $[\alpha]^{D}_{20}$ −26.8° (*c* 0.2, $CHCl_3$). $^1$H NMR (600 MHz, $CDCl_3$) δ 6.24 (d, *J* = 1.1 Hz, 1H, H3), 5.41 (ddd, *J* = 7.3, 4.9, 2.5 Hz, 1H, H8), 5.38 (dd, *J* = 7.1, 2.8 Hz, 1H, H7), 4.71 (ddd, *J* = 13.5, 3.8, 2.8 Hz, 1H, H6), 4.49 (dd, *J* = 12.6, 2.5 Hz, 1H, H9), 4.25 (dd, *J* = 12.6, 4.9 Hz, 1H, H9), 3.88 (s, 3H, $CH_3$), 2.58 (dd, *J* = 16.9, 13.6 Hz, 1H, H5), 2.49 (ddd, *J* = 16.9, 3.8, 1.1 Hz, 1H, H5′), 2.14 (s, 3H, $CH_3$), 2.08 (s, 3H, $CH_3$), 2.06 (s, 3H, $CH_3$). $^{13}$C NMR (151 MHz, $CDCl_3$) δ 191.8, 170.7, 169.8, 161.7, 158.3, 109.5, 77.7, 77.4, 77.2, 76.9, 70.1, 69.5, 61.7, 53.4, 37.8, 21.0, 20.8, 20.6. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{16}H_{20}NaO_{10}$ 395.0954; found: 395.0950.

**Methyl (methyl 4,7,8,9-tetra-*O*-acetyl-3-deoxy-5-*O*-(benzotriazol-1-yl)-D-glycero-β-D-galacto-non-2-ulopyranosid)onate (205).**

The nitrosyl sialoside **74** (150 mg, 0.3 mmol) in $CH_2Cl_2$ (3 mL) was deaminated using the general procedure for oxidative deamination with sodium 2,2,2-trifluoroethoxide (68 mg, 0.6 mmol), 18-crown-6 (74 mg, 0.3 mmol) in $CH_2Cl_2$ (2 mL) and HOBt (380 mg, 2.8 mmol, 10 equiv) in HFIP (2 mL) to afford **205** after flash column chromatography over silica gel eluting with hexane/ ethyl acetate (1:1), as a colorless oil (78 mg, 48%); $[\alpha]^{20}_{D}$ + 45.7° (*c* 0.45, $CH_2Cl_2$).$^1$H NMR (600 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.4 Hz, 1H, ArH), 7.49 (d, *J* = 3.5 Hz, 2H, ArH), 7.36 (dt, *J* = 8.0, 3.8 Hz, 1H, ArH), 5.91 (dd, *J* = 5.0, 2.3 Hz, 1H, H7), 5.60 (ddd, *J* = 11.0, 9.4, 5.5 Hz, 1H, H4), 5.39 (ddd, *J* = 7.3, 5.0, 2.6 Hz, 1H, H8), 4.95 (t, *J* = 9.7 Hz, 1H, H5), 4.76 (dd, *J* = 12.5, 2.6 Hz, 1H, H9), 4.40 (dd, *J* = 10.1, 2.2 Hz, 1H, H6), 4.20 (dd, *J* = 12.4, 6.8 Hz, 1H, H9’), 3.80 (s, 3H, $CH_3$), 3.34 (s, 3H, $CH_3$), 2.60 (dd, *J* = 13.1, 5.5 Hz, 1H, H3e), 2.32 (s, 3H,

$CH_3$), 2.11 (s, 3H, $CH_3$), 2.04 (s, 3H, $CH_3$), 1.67 (dd, *J* = 13.1, 11.2 Hz, 1H, H3a), 1.12 (s, 3H, $CH_3$). $^{13}C$ NMR (151 MHz, $CDCl_3$) δ 170.8, 170.6, 170.0, 169.3, 166.9, 143.3, 128.4, 127.9, 124.8, 120.3, 108.8, 98.7, 82.8, 71.2, 70.0, 69.3, 68.5, 62.3, 52.9, 51.8, 36.8, 21.1, 21.0, 20.9, 20.1. ESI-HRMS Calcd. for $C_{25}H_{31}N_3NaO_{13}$ :($[M+Na]^+$) m/z: 604.1755; found: 604.1756.

**Methyl (methyl 4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-5-*O*-(succinimido-N-yl)-D-glycero-β-D-galacto-non-2-ulopyranosid)onate (206).**

The nitrosyl sialoside **74** (200 mg, 0.4 mmol) in $CH_2Cl_2$ (4 mL) was deaminated using the general procedure for oxidative deamination with sodium 2,2,2-trifluoroethoxide (98 mg, 0.8 mmol), 18-crown-6 (105 mg, 0.4 mmol) in $CH_2Cl_2$ (2 mL), and *N*-hydroxysuccinimide (460 mg, 4 mmol, 10 equiv) in HFIP (1 mL) after flash column chromatography over silica gel eluting with (hexane/ ethyl acetate 1:1) to afford **206** as a colorless oil in (77 mg, 36%); $[\alpha]^{21}{}_D$ – 33.6° (*c* 0.25, $CHCl_3$). $^1H$ NMR (600 MHz, $CDCl_3$) δ 5.58 (dd, *J* = 6.0, 1.8 Hz, 1H, H7), 5.46 (ddd, *J* = 10.8, 8.4, 5.2 Hz, 1H, H4), 5.34 (td, *J* = 6.0, 2.6 Hz, 1H, H8), 4.61 (dd, *J* = 12.5, 2.7 Hz, 1H, H9), 4.27 (dd, *J* = 9.7, 8.4 Hz, 1H, H5), 4.18 (dd, *J* = 9.7, 1.9 Hz, 1H, H6), 4.12 (ddd, *J* = 12.5, 6.1 Hz, 1H, H9'), 3.79 (s, 3H, $CH_3$), 3.25 (s, 3H, $CH_3$), 2.73 – 2.60 (m, 4H, $CH_2CH_2$), 2.55 (dd, *J* = 13.3, 5.3 Hz, 1H, H3e), 2.17 (s, 3H, $CH_3$), 2.09 (s, 3H, $CH_3$), 2.04 (s, 3H, $CH_3$), 2.02 (s, 3H, $CH_3$), 1.81 (dd, *J* = 13.3, 10.7 Hz, 1H, H3a). $^{13}C$ NMR (151 MHz, $CDCl_3$) δ 171.2, 170.8, 170.4, 170.3, 169.6, 167.3, 98.4, 79.9, 76.9, 70.5, 69.6, 68.9, 62.1, 52.8, 51.6, 36.4, 21.1, 21.1, 20.9. ESI-HRMS Calcd. for $C_{23}H_{31}NNaO_{15}$ :($[M+Na]^+$) m/z: 584.1591; found: 584.1595.

**Methyl (methyl 4,7,8,9-tetra-*O*-acetyl-3-deoxy-5-*O*-(phthalimido-N-yl)-D-glycero-β-D-galacto-non-2-ulopyranosid)onate (207).**

The nitrosyl sialoside **74** (267 mg, 0.5 mmol) in $CH_2Cl_2$ (5 mL) was deaminated using the general procedure for oxidative deamination with sodium 2,2,2-trifluoroethoxide (90 mg, 0.7 mmol), 18-crown-6 (195 mg, 0.7 mmol) in $CH_2Cl_2$ (2 mL) and *N*-hydroxyphthalimide (1.2 g, 7.4 mmol, 20 equiv) to afford **207** after flash column chromatography over silica gel eluting with hexane/ ethyl acetate (1:1), as a colorless oil (115 mg, 36%) and **208** as a colorless oil (102 mg, 27%), and an inseparable mixture of elimination products **160** and **161** as a colorless oil (1:2.5 ratio, 53 mg, 23%).

Compound **207**; $[\alpha]_D^{20}$ – 52.0° (*c* 0.4, $CHCl_3$).$^1$H NMR (600 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 5.5, 3.1 Hz, 2H, ArH), 7.75 (dd, *J* = 5.5, 3.1 Hz, 2H, ArH), 5.80 (dd, *J* = 5.3, 2.0 Hz, 1H, H7), 5.53 (ddd, *J* = 11.0, 9.0, 5.4 Hz, 1H, H4), 5.39 (ddd, *J* = 6.7, 5.3, 2.7 Hz, 1H, H8), 4.67 (dd, *J* = 12.4, 2.7 Hz, 1H, H9), 4.44 (t, *J* = 9.4 Hz, 1H, H5), 4.23 (p, *J* = 9.8, 2.1 Hz, 1H, H6), 4.16 (dd, *J* = 12.4, 6.7 Hz, 1H, H9'), 3.78 (s, 3H, $CH_3$), 3.29 (s, 3H, $CH_3$), 2.66 (dd, *J* = 13.2, 5.4 Hz, 1H, H3e), 2.25 (s, 3H), 2.10 (s, 3H, $CH_3$), 2.04 (s, 3H, $CH_3$), 1.72 (s, 3H, $CH_3$), 1.69 (dd, *J* = 13.1, 11.0 Hz, 1H, H3a). $^{13}$C NMR (151 MHz, $CDCl_3$) δ 170.8, 170.5, 170.2, 169.4, 167.3, 163.3, 134.8, 128.9, 123.7, 98.6, 79.5, 71.0, 70.2, 69.4, 68.9, 62.4, 52.8, 51.7, 36.4, 21.1, 21.1, 20.9, 20.8. ESI-HRMS Calcd. for $C_{27}H_{31}NNaO_{15}$ :($[M+Na]^+$) m/z: 632.1591 ; found: 632.1592.

**Methyl (methyl 7,8,9-tri-*O*-acetyl-3-deoxy-4,5-di-*O*- (phthalimido-*N*-yl))-D-glycero-β-D-galacto-non-2-ulopyranosid)onate (208).**

Compound **208**; $[\alpha]_D^{20}$ – 32.0 ° (*c* 0.25, $CHCl_3$). $^1$H NMR (600 MHz, $CDCl_3$) δ 7.79 (dd, *J* = 5.5, 3.1 Hz, 2H, ArH), 7.73 – 7.68 (m, 4H, ArH), 7.67 (dd, *J* = 5.5, 3.0 Hz, 2H, ArH), 5.79 (dd, *J* = 5.7, 2.1 Hz, 1H, H7), 5.39 (td, *J* = 6.2, 2.7 Hz, 1H, H8), 5.17 (ddd, *J* = 10.5, 8.0, 5.5 Hz, 1H, H4), 4.86 (dd, *J* = 9.6, 7.9 Hz, 1H, H5), 4.67 (dd, *J* = 12.4, 2.7 Hz, 1H, H9), 4.23 (dd, *J* = 9.6, 2.1

Hz, 1H, H6), 4.16 (dd, *J* = 12.4, 6.5 Hz, 1H, H9'), 3.80 (s, 3H, $CH_3$), 3.23 (s, 3H, $CH_3$), 2.50 (dd, *J* = 13.4, 5.5 Hz, 1H, H3e), 2.32 (s, 3H, $CH_3$), 2.13 (dd, *J* = 13.4, 10.5 Hz, 1H, H3a), 2.10 (s, 3H, $CH_3$), 2.03 (s, 3H, $CH_3$). $^{13}$C NMR (151 MHz, $CDCl_3$) δ 170.9, 170.4, 170.2, 167.4, 163.6, 163.3, 134.7, 134.3, 129.3, 128.8, 123.8, 123.6, 98.9, 82.5, 78.8, 70.8, 69.2, 68.6, 62.3, 53.0, 51.5, 35.5, 21.2, 20.9, 14.3. ESI-HRMS Calcd. for $C_{33}H_{32}N_2NaO_{16}$ :([M+Na]$^+$) m/z: 735.1650 ; found: 735.1650.

**Methyl (methyl 7,8,9-tri-*O*-acetyl-3-deoxy-4-*O*,5-*O*-(ethanimin-1-yl-*N*-yl)-D-glycero-β-D-talo-non-2-ulopyranosid)onate (209).**

The nitrosyl sialoside **74** (200 mg, 0.4 mmol) in $CH_2Cl_2$ (4 mL) was deaminated using the general procedure for oxidative deamination with sodium 2,2,2-trifluoroethoxide (90 mg, 0.7 mmol), 18-crown-6 (195 mg, 0.7 mmol) in $CH_2Cl_2$ (3 mL) and acetoxyhydroxamic acid (555 mg, 7.4 mmol, 20 equiv) to afford **209** after flash column chromatography over silica gel eluting with hexane/ ethyl acetate (1:1), as a colorless oil (62 mg, 36%) and the single elimination product **161** as a colorless oil (46 mg, 28%).

Compound **209**; $[\alpha]_D^{20}$ – 15.3$^o$ (*c* 0.85, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$) δ 5.51 (dd, *J* = 5.6, 2.6 Hz, 1H, H7), 5.34 (td, *J* = 6.2, 2.6 Hz, 1H. H8), 4.57 (dd, *J* = 12.5, 2.7 Hz, 1H, H9), 4.33 (dd, *J* = 10.0, 2.6 Hz, 1H, H6), 4.22 (dd, *J* = 12.5, 6.3 Hz, 1H, H9'), 4.17 (dd, *J* = 10.0, 2.8 Hz, 1H, H5), 4.04 (dt, *J* = 4.2, 2.6 Hz, 1H, H4), 3.78 (s, 3H, $CH_3$), 3.23 (s, 3H, $CH_3$), 2.53 (dd, *J* = 15.5, 2.5 Hz, 1H, H3), 2.14 (s, 3H, $CH_3$), 2.10 (dd, *J* = 15.5, 4.2 Hz, 1H, H3'), 2.07 (s, 3H, $CH_3$), 2.03 (s, 3H. $CH_3$), 1.92 (s, 3H, $CH_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 170.7, 170.3, 169.6, 167.9, 155.2, 97.7, 77.5, 77.2, 76.8, 70.5, 69.1, 68.8, 66.8, 66.1, 62.1, 52.8, 51.8, 34.9, 21.1, 20.8, 20.8, 17.4. ESI-HRMS Calcd. for $C_{19}H_{27}NNaO_{12}$ :([M+Na]$^+$) m/z: 484.1431 ; found: 484.1400.

**Methyl (methyl 4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-β-D-ribo-non-5-en-2-ulopyranosid)onate (161).**

Compound **161**; $[\alpha]_D^{20}$ – 57.0° (*c* 0.5, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$) δ 5.54 (ddd, *J* = 7.3, 4.4, 3.0 Hz, 1H, H8), 5.49 (dt, *J* = 4.6, 1.1 Hz, 1H, H7), 5.28 (dt, *J* = 5.6, 4.3 Hz, 1H, H4), 5.10 (dt, *J* = 4.4, 0.9 Hz, 1H, H5), 4.39 (dd, *J* = 12.2, 2.8 Hz, 1H, H9), 4.33 (dd, *J* = 12.2, 7.1 Hz, 1H, H9'), 3.78 (s, 3H, $CH_3$), 3.39 (s, 3H, $CH_3$), 2.34 (dd, *J* = 14.2, 4.3 Hz, 1H, H3), 2.20 (dd, *J* = 14.2, 5.4 Hz, 1H, H3'), 2.13 (s, 3H, $CH_3$), 2.06 (s, 6H, $CH_3$), 1.99 (s, 3H, $CH_3$). $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 170.8, 170.1, 170.1, 169.3, 167.7, 149.9, 99.3, 98.2, 77.5, 77.2, 76.8, 70.5, 70.4, 63.1, 62.0, 52.7, 52.2, 34.7, 21.2, 21.0, 20.9.ESI-HRMS Calcd. for $C_{19}H_{26}NaO_{12}$ :($[M+Na]^+$) m/z: 469.1322 ; found: 469.1322.

**Methyl (methyl 7,8,9-tri-*O*-acetyl-3,4,5-trideoxy-β-D-arabino-non-4-en-2-ulopyranosid)onate (211).**

The nitrosyl sialoside **74** (267 mg, 0.5 mmol) in $CH_2Cl_2$ (5 mL) was deaminated using the general procedure for oxidative deamination with sodium 2,2,2-trifluoroethoxide (122 mg, 1 mmol), 18-crown-6 (291 mg, 1.1 mmol) in $CH_2Cl_2$ (2.5 mL) and *N*-(4-methoxybenzyl)acetyl hydroxamic caid (975 mg, 5 mmol, 10 equiv) in $CH_2Cl_2$ (5 mL) to afford **211** after flash column chromatography over silica gel eluting with hexane/ ethyl acetate (3:1), as a colorless oil (41 mg, 21%) and an inseparable mixture of elimination products **160** and **161** as a colorless oil (40 mg, 18%).

Compound **211**; $[\alpha]_D^{20}$ – 10.1° (*c* 1.3, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$) δ 5.82 (ddt, *J* = 10.0, 4.9, 2.3 Hz, 1H, H4), 5.63 (ddt, *J* = 10.5, 3.0, 1.5 Hz, 1H, H5), 5.45 (td, *J* = 6.2, 2.3 Hz,

1H, H8), 5.37 (dd, *J* = 6.2, 2.7 Hz, 1H, H7), 4.61 (dd, *J* = 12.5, 2.3 Hz, 1H. H9), 4.43 (tdq, *J* = 4.9, 2.6, 1.5, 0.9 Hz, 1H, H6), 4.22 (dd, *J* = 12.5, 6.1 Hz, 1H, H9'), 3.80 (s, 3H, $CH_3$), 3.28 (s, 3H, $CH_3$), 2.40 (ddt, *J* = 17.8, 4.0, 2.6 Hz, 1H, H3 ), 2.32 (dddd, *J* = 17.8, 4.8, 3.2, 1.4 Hz, 1H, H3'), 2.06 (s, 6H, $2CH_3$), 2.04 (s, 3H, $CH_3$). $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 170.8, 170.1, 170.0, 169.0, 123.8, 123.8, 97.6, 71.3, 70.3, 69.2, 62.5, 52.6, 51.5, 32.1, 21.0, 20.9, 20.8.ESI-HRMS Calcd. for $C_{27}H_{24}NaO_{10}$ :($[M+Na]^+$) m/z: 411.1262 ; found: 411.1248.

**Deamination of nitrosyl sialoside 74 with *N*-($^t$Butyloxycarbonyl)acetyl hydroxamic acid as nucleophile.**

**Methyl (7,8,9-tri-*O*-acetyl-3,5-dideoxy-β-D-arabino-non-4-oxo-2-ulopyranosid)onate (212) and Methyl (7,8,9-tri-*O*-acetyl-2,3,5-trideoxy-β-D-arabino-non-2-en-4-oxo-2-ulopyranosid) onate (213).**

The nitrosyl sialoside **74** (267 mg, 0.5 mmol) in $CH_2Cl_2$ (5 mL) was deaminated using the general procedure for oxidative deamination with sodium 2,2,2-trifluoroethoxide (122 mg, 1 mmol), 18-crown-6 (291 mg, 1.1 mmol) in $CH_2Cl_2$ (2.5 mL) and *N*-($^t$butyloxycarbonyl)acetyl hydroxamic acid (525 mg, 3 mmol, 6 equiv) in $CH_2Cl_2$ (5 mL) to afford **211** after flash column chromatography over silica gel eluting with hexane/ ethyl acetate (3:1), as a colorless oil (20 mg, 10%), an inseparable mixture of elimination products **160** and **161** as a colorless oil (91 mg, 41%) and another inseparable mixture of compounds **212** and **213** (1.27:1 ratio, 35 mg, 17%) as a colorless oil.

Compound **212**; $^1H$ NMR (400 MHz, $CDCl_3$) δ 6.24 (d, *J* = 1.1 Hz, 1H, H3), 5.39 (ddd, *J* = 7.9, 5.3, 2.5 Hz, 1H, H8), 5.38 (dd, *J* = 7.9, 2.8 Hz, 1H, H7), 4.71 (ddd, *J* = 13.3, 4.1, 2.7 Hz, 1H, H6), 4.49 (dd, *J* = 12.5, 2.3 Hz, 1H, H9), 4.25 (m, 1H, H9), 3.87 (s, 3H, $CH_3$), 2.57 (dd, *J* =

16.9, 13.7 Hz, 1H, H5), 2.48 (dd, *J* = 16.9, 3.8 Hz, 1H, H5'), 2.14 (s, 3H, $CH_3$), 2.07 (s, 3H, $CH_3$), 2.06 (s, 3H, $CH_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 191.8, 170.7, 170.0, 161.7, 158.3, 109.5, 77.7, 77.4, 77.2, 76.9, 70.1, 69.5, 61.7, 53.4, 37.8, 21.0, 20.8, 20.6.

Compound **213** was identified in the mixture by the following diagnostic signals; $^1$H NMR (400 MHz, $CDCl_3$) δ 5.35 (ddd, *J* = 6.0, 5.7, 2.5 Hz, 1H, H8), 5.29 (dd, *J* = 6.0, 3.1 Hz, 1H, H7), 4.58 (dd, J=12.5, 2.6 Hz, 1H, H9), 4.25 (m, 1H, H6), 4.21 (dd, *J* = 12.5, 5.8 Hz, 1H, H9'), 3.82 (s, 3H, $CH_3$), 3.24 (s, 3H, $CH_3$), 2.74 (d, *J* = 14.9 Hz, 1H, H3), 2.61 (d, *J* = 14.9 Hz, 1H, H3'), 2.39 (br s, 1H, H5), 2.37 (br s, 1H, H5'), 2.13 (s, 3H, $CH_3$), 2.05 (s, 3H, $CH_3$), 2.04 (s, 3H, $CH_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 201.6, 170.7, 170.2, 169.8, 167.2, 100.2, 71.3, 70.2, 69.0, 62.0, 53.0, 51.5, 48.0, 42.1, 21.0, 20.8, 20.8.

**Methyl (methyl 7, 8, 9-tri-*O*-acetyl-3,5-dideoxy-4-*O*-(4-nitrophenylmethanimin-*N*-yl)-β-D-arabino-non-4-en-2-ulopyranosid)onate (214).**

The nitrosyl sialoside **74** (267 mg, 0.5 mmol) in $CH_2Cl_2$ (5 mL) was deaminated using the general procedure for oxidative deamination with sodium 2,2,2-trifluoroethoxide (122 mg, 1 mmol), 18-crown-6 (291 mg, 1.1 mmol) in $CH_2Cl_2$ (2.5 mL) and 4-nitrobenzaldehyde oxime (1.66 g, 10 mmol, 20 equiv) in THF (5 mL) to afford **214** after flash column chromatography over silica gel eluting with hexane/ ethyl acetate (1:1), as a colorless oil (72 mg, 26%), an inseparable mixture of elimination products **160** and **161** as a colorless oil (53 mg, 24%) and another inseparable mixture of compounds **212** and **213** (17 mg, 8%) as a colorless oil.

Compound **214**; $[\alpha]_D^{20}$ – 15.5° (*c* 0.9, $CHCl_3$). $^1$H NMR (600 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.8 Hz, 2H, ArH), 8.02 (s, 1H, NCH), 7.73 (d, *J* = 8.8 Hz, 2H, ArH), 5.57 (ddd, *J* = 7.3, 4.5, 2.8

Hz, 1H, H8), 5.53 (dt, *J* = 4.6, 1.2 Hz, 1H, H7), 5.20 (d, *J* = 4.2 Hz, 1H, H5), 4.87 (dt, *J* = 6.4, 5.0 Hz, 1H, H4), 4.42 (dd, *J* = 12.2, 2.8 Hz, 1H, H9), 4.36 (dd, *J* = 12.1, 7.4 Hz, 1H, H9'), 3.74 (s, 3H, $CH_3$), 3.39 (s, 3H, $CH_3$), 2.56 (dd, *J* = 14.0, 4.8 Hz, 1H, H3), 2.25 (dd, *J* = 14.0, 5.2 Hz, 1H, H3'), 2.15 (s, 3H, $CH_3$), 2.07 (s, 3H, $CH_3$), 2.06 (s, 3H, $CH_3$). $^{13}C$ NMR (151 MHz, $CDCl_3$) δ 170.9, 170.1, 169.4, 167.8, 149.7, 148.6, 147.2, 138.2, 127.8 (2 Carbons), 124.1(2 Carbons), 99.4, 98.5, 72.3, 70.5, 70.5, 62.0, 52.7, 52.3, 34.7, 21.0, 20.9 (2 Carbons). ESI-HRMS Calcd. for $C_{24}H_{28}N_2NaO_{13}$ :($[M+Na]^+$) m/z: 575.1484 ; found: 575.1486.

**Deamination of nitrosyl sialoside 74 with acetone oxime as nucleophile.** The nitrosyl sialoside **74** (267 mg, 0.5 mmol) in $CH_2Cl_2$ (5 mL) was deaminated using the general procedure for oxidative deamination with sodium 2,2,2-trifluoroethoxide (122 mg, 1 mmol), 18-crown-6 (291 mg, 1.1 mmol) in $CH_2Cl_2$ (2.5 mL) and acetone oxime (731 mg, 10 mmol, 20 equiv) in $CH_2Cl_2$ (5 mL) to afford **160** and **161**, after flash column chromatography over silica gel eluting with hexane/ ethyl acetate (1:1), as a colorless oil (84 mg, 38%).

**Methyl (methyl 7,8,9-tri-*O*-acetyl-3,4,5-trideoxy-4-*N*,5-*N*-phenylaziridinyl-D-glycero-β-D-talo-non-2-ulopyranosid)onate (215).**

The nitrosyl sialoside **74** (267 mg, 0.5 mmol) in $CH_2Cl_2$ (5 mL) was deaminated using the general procedure for oxidative deamination with sodium 2,2,2-trifluoroethoxide (122 mg, 1 mmol), 18-crown-6 (291 mg, 1.1 mmol) in $CH_2Cl_2$ (2.5 mL) and aniline (0.83 mL, 9.2 mmol, 20 equiv) to afford **215**, after flash column chromatography over silica gel eluting with hexane/ ethyl acetate (1:1), as a yellowish oil (110 mg, 49%).

Compound **215**; $[\alpha]_D^{20}$ – 45.0° (*c* 0.5, $CH_2Cl_2$).$^1$H NMR (600 MHz, $CDCl_3$) δ 7.22 (dd, *J* = 8.5, 7.3 Hz, 2H, ArH), 6.98 – 6.94 (m, 3H, ArH), 5.69 (dd, *J* = 6.0, 3.9 Hz, 1H, H7), 5.52 (td, *J* = 5.9, 2.8 Hz, 1H, H8), 4.59 (dd, *J* = 12.5, 2.8 Hz, 1H, H9), 4.32 (dd, *J* = 12.5, 5.9 Hz, 1H, H9'), 4.16 (t, *J* = 3.6 Hz, 1H, H6), 3.80 (s, 3H, $CH_3$), 3.22 (s, 3H, $CH_3$), 2.51 (dd, *J* = 7.1, 3.4 Hz, 1H, H5), 2.47 (ddd, *J* = 7.1, 5.3, 1.7 Hz, 1H, H4), 2.37 (dd, *J* = 15.3, 1.8 Hz, 1H, H3pe), 2.26 (dd, *J* = 15.3, 5.3 Hz, 1H, H3pa), 2.15 (s, 3H, $CH_3$), 2.09 (s, 3H, $CH_3$), 2.08 (s, 3H, $CH_3$). $^{13}$C NMR (151 MHz, $CDCl_3$) δ 170.8, 170.4, 170.2, 169.4, 153.4, 129.2, 123.1, 120.6, 97.6, 71.4, 70.3, 70.2, 62.2, 52.7, 52.0, 37.1, 35.3, 31.2, 21.1, 21.0, 20.9. ESI-HRMS Calcd. for $C_{23}H_{29}NNaO_{10}$ :([M+Na]$^+$) m/z: 502.1689; found: 502.1682.

An enhanced yield (130 mg, 56%) of **215** was obtained by stirring the crude mixture at room temprarure for 30 minutes. Compound **215** was then isolated using the previousely described chromotoghraphic procedure.

**Deamination of nitrosyl sialoside 74 with indole as nucleophile.** The nitrosyl sialoside **74** (267 mg, 0.5 mmol) in $CH_2Cl_2$ (5 mL) was deaminated using the general procedure for oxidative deamination with sodium 2,2,2-trifluoroethoxide (122 mg, 1 mmol), 18-crown-6 (291 mg, 1.1 mmol) in $CH_2Cl_2$ (2.5 mL) and indole (1.17 g, 10 mmol, 20 equiv) in $CH_2Cl_2$ (5 mL) to afford **160** and **161**, after flash column chromatography over silica gel eluting with hexane/ ethyl acetate (1:1), as a colorless oil (182 mg, 81%).

**Methyl (methyl 7,8,9-tri-*O*-acetyl-3-deoxy-4,5-di-*O*-hexafluoroisopropyl-D-glycero-β-D-ido-non-2-ulopyranosid)onate (216).**

The nitrosyl sialoside **74** (267 mg, 0.5 mmol) in $CH_2Cl_2$ (5 mL) was deaminated using the general procedure for oxidative deamination with sodium 2,2,2-trifluoroethoxide (122 mg, 1 mmol), 18-crown-6 (291 mg, 1.1 mmol) in $CH_2Cl_2$ (2.5 mL) and 3,5-dimethylpyrazole (960 mg, 10 mmol, 20 equiv) dissolved in HFIP (5 mL) to afford **216**, after flash column chromatography over silica gel eluting with hexane/ ethyl acetate (3:1), as a colorless oil (31 mg, 9%).

Compound **216**; $[\alpha]_D^{20}$ – 17.5° (*c* 1.5, $CH_2Cl_2$). $^1$H NMR (600 MHz, $CDCl_3$) δ 5.24 (td, *J* = 6.0, 3.4 Hz, 1H, H8), 5.10 (p, *J* = 6.0 Hz, 1H, CH), 5.03 (t, *J* = 5.5 Hz, 1H, H7), 4.75 (p, *J* = 6.0 Hz, 1H, CH), 4.34 (dd, *J* = 12.3, 3.4 Hz, 1H, H9), 4.17 (dd, *J* = 12.3, 6.2 Hz, 1H, H9'), 3.80 (s, 3H, $CH_3$), 3.71 (ddd, *J* = 8.7, 6.0, 3.2 Hz, 1H, H4), 3.39 (s, 3H, $CH_3$), 3.11 (dd, *J* = 8.2, 2.1 Hz, 1H, H5), 3.02 (dd, *J* = 5.3, 2.1 Hz, 1H, H6), 2.49 (dd, *J* = 15.9, 6.1 Hz, 1H, H3a), 2.38 (dd, *J* = 15.9, 3.2 Hz, 1H, H3e), 2.11 (s, 3H, $CH_3$), 2.08 (s, 3H, $CH_3$), 2.05 (s, 3H, $CH_3$). $^{13}$C NMR (151 MHz, $CDCl_3$) δ 170.6, 170.0, 169.7, 166.7, 101.1, 78.4, 73.5, 73.2, 73.0, 72.8, 72.6, 70.5, 69.8, 69.6, 69.4, 69.2, 68.9, 68.7, 61.6, 58.4, 53.2, 53.0, 52.7, 36.1, 20.7, 20.7.

$^{13}$C{$^{19}$F,$^1$H}NMR (126 MHz, $CDCl_3$) δ 170.7, 170.0, 169.7, 166.7, 121.7, 121.5, 121.3, 121.2, 101.2, 78.5, 73.1, 70.5, 69.8, 69.2, 61.6, 58.4, 53.3, 53.1, 52.7, 36.2, 20.8, 20.7.

$^{19}$F NMR (471 MHz, $CDCl_3$) δ -75.42 (q, *J* = 8.0, 7.1 Hz), -75.47 – -75.59 (m), -76.46 (h, *J* = 8.5, 7.3 Hz), -76.80 (qd, *J* = 9.2, 6.0 Hz).

ESI-HRMS Calcd. for $C_{23}H_{26}F_{12}NaO_{12}$ :($[M+Na]^+$) m/z: 745.1130 ; found: 745.1125.

**Methyl (methyl 4,5,7,8,9-penta-O-acetyl-3-deoxy-D-glycero-β-D-galacto-non-2-ulopyranosid)onate (75).**

In a dry round bottom flask, compound **205** (22 mg, 0.04 mmole) was dissolved in anhydrous THF (0.2 mL), glacial acetic acid (0.8 mL). Zn-dust (50 mg) was added in one portion. The reaction was left under reflux for 2 h until starting material was consumed, and formation of the product was monitored by TLC and mass spectrometry. The reaction was then quenched with water and filtered through Celite. The filtrate was washed with water and brine. The organic layer was dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure. The crude mixture was then acetylated using acetic anhydride (1 mL) and pyridine (0.5 mL) at rt until the reaction was completed (1 hr). The crude acetylated mixture was purified by column chromatography over silica gel eluting with (hexane/ ethyl acetate 1:1) to afford **75** as a white foam in (22 mg, 97%). Compound **75**; the spectral data is consistent with reported literature.[74]

## X-Ray Crystal Structure Determination.

### X-Ray Crystal Structure Determination of 164 (CCDC 1941624)

Single crystals of **164** $C_{27}H_{30}O_{11}$ were obtained by slow cooling of a saturated solution in diethyl ether. A suitable crystal was selected and mounted on a 'Bruker APEX-II CCD' diffractometer. The crystal was kept at 100.1 K during data collection. Using Olex2,[152] the structure was solved with the ShelXT[153] structure solution program using Intrinsic Phasing and refined with the ShelXL[154] refinement package using Least Squares minimization.

Refinement model description

Number of restraints - 0, number of constraints - unknown.

Details:

1.Fixed Uiso

At 1.2 times of:

All C(H) groups, All C(H,H) groups

At 1.5 times of:

All C(H,H,H) groups

2.a Ternary CH refined with riding coordinates:

C6(H6), C5(H5), C7(H7), C8(H8), C4(H4)

2.b Secondary CH2 refined with riding coordinates:

C9(H9A,H9B), C3(H3A,H3B)

2.c Aromatic/amide H refined with riding coordinates:

C21(H21), C20(H20), C27(H27), C24(H24), C25(H25), C26(H26)

2.d Idealised Me refined as rotating group:

C16(H16A,H16B,H16C), C15(H15A,H15B,H15C), C13(H13A,H13B,H13C),

C17(H17A,H17B,

H17C), C11(H11A,H11B,H11C)

| **Table 10.** Crystal data and structure refinement for **164** | |
|---|---|
| Identification code | AW6302_2_0m (**164**) |
| Empirical formula | $C_{27}H_{30}O_{11}$ |
| Formula weight | 530.51 |
| Temperature/K | 100.1 |
| Crystal system | orthorhombic |
| Space group | $P2_12_12_1$ |
| a/Å | 6.7275(5) |
| b/Å | 13.0314(13) |
| c/Å | 32.146(3) |

| | |
|---|---|
| α/° | 90 |
| β/° | 90 |
| γ/° | 90 |
| Volume/Å$^3$ | 2818.2(4) |
| Z | 4 |
| $\rho_{calc}$g/cm$^3$ | 1.250 |
| μ/mm$^{-1}$ | 0.097 |
| F(000) | 1120.0 |
| Crystal size/mm$^3$ | 0.415 × 0.391 × 0.242 |
| Radiation | MoKα (λ = 0.71073) |
| 2Θ range for data collection/° | 2.534 to 50.756 |
| Index ranges | -8 ≤ h ≤ 7, -15 ≤ k ≤ 15, -38 ≤ l ≤ 35 |
| Reflections collected | 58714 |
| Independent reflections | 5160 [$R_{int}$ = 0.0566, $R_{sigma}$ = 0.0419] |
| Data/restraints/parameters | 5160/0/348 |
| Goodness-of-fit on F$^2$ | 1.040 |
| Final R indexes [I>=2σ (I)] | $R_1$ = 0.0366, w$R_2$ = 0.0758 |

| | |
|---|---|
| Final R indexes [all data] | $R_1 = 0.0541$, $wR_2 = 0.0809$ |
| Largest diff. peak/hole / e $Å^{-3}$ | 0.18/-0.20 |
| Flack parameter | 0.4(3) |

**Table 11.** Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for AW6302_2_0m (**164**). $U_{eq}$ is defined as 1/3 of the trace of the orthogonalised $U_{IJ}$ tensor.

| **Atom** | ***x*** | ***y*** | ***z*** | **U(eq)** |
|---|---|---|---|---|
| O8 | 6859(2) | 2801.0(12) | 7187.3(5) | 17.5(4) |
| O2 | 7902(2) | 4133.0(13) | 6755.1(5) | 16.9(4) |
| O9 | 8801(2) | 6055.1(12) | 6536.2(5) | 18.2(4) |
| O5 | 4215(2) | 6006.2(12) | 7116.1(5) | 16.3(4) |
| O11 | 4508(3) | 4788.6(13) | 5913.6(5) | 22.2(4) |
| O3 | 5952(2) | 7901.5(13) | 6847.8(5) | 20.6(4) |
| O1 | 9477(2) | 1582.0(13) | 6650.7(6) | 24.9(5) |
| O6 | 4689(3) | 5253.7(15) | 7738.7(6) | 27.8(5) |
| O7 | 11181(3) | 3024.4(15) | 6762.1(7) | 36.6(5) |
| O4 | 8879(3) | 8688.8(14) | 6726.6(6) | 28.6(5) |
| O10 | 8020(3) | 6923.0(17) | 5955.3(6) | 41.2(6) |
| C1 | 9640(4) | 2585(2) | 6728.5(8) | 17.9(6) |
| C19 | 3478(4) | 3982(2) | 5749.4(7) | 18.3(6) |

| | | | | |
|---|---|---|---|---|
| C12 | 3591(4) | 5524.5(18) | 7464.4(8) | 17.8(6) |
| C9 | 6870(4) | 7247.3(19) | 7153.6(8) | 18.1(6) |
| C2 | 7562(4) | 3065.3(19) | 6787.1(8) | 16.9(6) |
| C16 | 7963(4) | 3233(2) | 7527.6(8) | 18.9(6) |
| C6 | 6353(3) | 4694.4(18) | 6549.9(7) | 15.7(6) |
| C14 | 9246(4) | 6642(2) | 6201.4(8) | 23.0(6) |
| C5 | 6324(4) | 4375.5(19) | 6097.5(8) | 17.8(6) |
| C3 | 6018(3) | 2681.9(19) | 6482.9(8) | 16.2(6) |
| C21 | 743(4) | 3248(2) | 5395.4(8) | 26.1(7) |
| C7 | 6735(4) | 5818.9(19) | 6616.3(8) | 16.2(6) |
| C8 | 6341(3) | 6151.3(19) | 7063.2(7) | 15.6(6) |
| C4 | 6237(4) | 3190.2(18) | 6053.9(7) | 16.5(6) |
| C10 | 7137(4) | 8601(2) | 6655.4(8) | 23.3(6) |
| C22 | 1624(4) | 2272(2) | 5427.0(8) | 24.9(7) |
| C20 | 1642(4) | 4113(2) | 5549.7(7) | 23.5(7) |
| C18 | 4387(4) | 3054.3(19) | 5793.4(7) | 16.9(6) |
| C23 | 3519(4) | 2171(2) | 5625.3(7) | 20.7(6) |

| | | | | |
|---|---|---|---|---|
| C15 | 11410(4) | 6863(2) | 6185.4(9) | 30.6(7) |
| C13 | 1398(4) | 5372(2) | 7449.4(8) | 23.1(6) |
| C27 | 4420(5) | 1186(2) | 5636.6(8) | 28.5(7) |
| C17 | 11321(4) | 1023(2) | 6605.2(9) | 27.1(7) |
| C24 | 703(5) | 1386(2) | 5261.0(9) | 36.5(8) |
| C11 | 5982(5) | 9206(2) | 6347.1(9) | 35.6(8) |
| C25 | 1595(6) | 455(3) | 5279.5(9) | 47.2(9) |
| C26 | 3490(5) | 354(2) | 5465.8(9) | 39.6(8) |

**Table 12.** Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for AW6302_2_0m (**164**). The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

| **Atom** | **$U_{11}$** | **$U_{22}$** | **$U_{33}$** | **$U_{23}$** | **$U_{13}$** | **$U_{12}$** |
|---|---|---|---|---|---|---|
| O8 | 16.6(8) | 21.4(10) | 14.4(9) | 0.2(8) | 0.2(8) | -1.8(8) |
| O2 | 15.3(8) | 14.0(10) | 21.4(9) | 1.9(8) | -3.9(7) | -0.6(7) |
| O9 | 14.4(8) | 18.6(10) | 21.7(9) | 3.4(8) | 4.2(8) | -0.7(8) |
| O5 | 11.0(8) | 20.1(10) | 17.9(9) | 1.2(8) | 2.0(7) | 0.2(7) |

| | | | | | | |
|---|---|---|---|---|---|---|
| O11 | 24.5(9) | 18.9(10) | 23.2(10) | -2.2(8) | -8.8(8) | 5.6(8) |
| O3 | 22.5(9) | 14.8(10) | 24.6(10) | 2.2(8) | -2.2(8) | -1.0(8) |
| O1 | 15.1(9) | 16.5(11) | 43.1(12) | 1.3(9) | 4.1(8) | 3.6(8) |
| O6 | 20.5(9) | 36.0(12) | 26.8(10) | 11.3(9) | 0.7(9) | 3.6(9) |
| O7 | 15.3(10) | 27.2(12) | 67.4(15) | -13.6(10) | 3.7(10) | -1.1(9) |
| O4 | 29.7(11) | 23.5(11) | 32.5(11) | 3.1(9) | 2.8(9) | -4.1(9) |
| O10 | 40.1(12) | 53.5(15) | 30.1(12) | 19.4(11) | -3.6(11) | -8.6(11) |
| C1 | 15.9(13) | 18.8(16) | 19.1(14) | 2.4(12) | 1.1(11) | -0.2(12) |
| C19 | 18.4(13) | 24.6(16) | 12.0(13) | -3.3(12) | 0.8(11) | 1.7(12) |
| C12 | 18.4(13) | 13.6(14) | 21.3(15) | 1.3(12) | 2.9(12) | -0.1(11) |
| C9 | 16.7(12) | 21.2(15) | 16.4(13) | 1.9(12) | -2.0(11) | 2.3(11) |
| C2 | 18.9(13) | 15.9(15) | 15.8(14) | 3.0(12) | 2.8(11) | -2.0(11) |
| C16 | 18.8(13) | 19.5(15) | 18.3(14) | 2.8(12) | -0.6(12) | 0.0(11) |
| C6 | 11.7(12) | 16.7(14) | 18.7(13) | 3.4(11) | 0.4(11) | 2.5(11) |
| C14 | 30.9(16) | 17.1(15) | 21.0(15) | -0.1(12) | 7.6(14) | -1.4(13) |
| C5 | 16.2(12) | 18.2(14) | 19.2(14) | 1.5(11) | 0.7(11) | 1.3(11) |
| C3 | 11.4(12) | 16.2(14) | 21.1(14) | -0.6(11) | -0.4(10) | 0.2(11) |

| | | | | | | |
|---|---|---|---|---|---|---|
| C21 | 19.8(14) | 45(2) | 13.6(14) | 2.1(13) | -2.5(11) | -3.6(14) |
| C7 | 11.6(12) | 18.9(15) | 18.1(13) | 1.0(11) | 0.5(11) | -0.9(11) |
| C8 | 8.0(11) | 20.1(15) | 18.9(13) | 1.8(11) | -1.2(10) | -1.2(11) |
| C4 | 15.3(12) | 17.2(14) | 16.9(13) | -1.6(11) | 3.1(11) | 2.0(11) |
| C10 | 30.8(17) | 16.8(15) | 22.3(15) | -4.1(13) | 0.9(13) | 1.8(13) |
| C22 | 27.2(15) | 34.8(19) | 12.9(13) | 1.3(12) | -1.3(12) | -10.2(14) |
| C20 | 22.0(14) | 34.0(18) | 14.5(13) | -0.4(13) | 0.2(11) | 10.0(13) |
| C18 | 17.8(13) | 20.1(15) | 12.9(12) | -0.7(11) | 2.2(11) | 1.1(12) |
| C23 | 28.4(14) | 22.9(16) | 10.8(13) | 1.5(11) | 0.2(12) | -3.4(13) |
| C15 | 29.4(15) | 25.5(17) | 36.9(17) | 1.5(13) | 11.3(14) | -6.2(13) |
| C13 | 20.3(13) | 23.4(16) | 25.6(15) | 0.0(12) | 3.3(12) | -3.9(12) |
| C27 | 44.7(17) | 24.6(18) | 16.1(14) | 1.8(12) | -5.7(13) | -5.7(15) |
| C17 | 18.4(13) | 18.1(15) | 44.8(17) | -0.1(13) | 8.1(13) | 3.8(12) |
| C24 | 47(2) | 43(2) | 19.3(15) | 5.5(15) | -7.9(14) | -22.2(18) |
| C11 | 47.6(19) | 26.1(17) | 33.2(17) | 7.2(14) | -2.7(15) | 6.7(15) |
| C25 | 77(3) | 36(2) | 28.6(17) | 4.8(15) | -20.2(18) | -24(2) |
| C26 | 74(2) | 19.9(17) | 24.9(16) | 1.0(13) | -11.6(17) | -5.2(17) |

**Table 13.** Bond Lengths for AW6302_2_0m (**164)**

| Atom | Atom | Length/Å | | Atom | Atom | Length/Å |
|---|---|---|---|---|---|---|
| O8 | C2 | 1.413(3) | | C12 | C13 | 1.490(3) |
| O8 | C16 | 1.437(3) | | C9 | C8 | 1.500(4) |
| O2 | C2 | 1.414(3) | | C2 | C3 | 1.512(3) |
| O2 | C6 | 1.434(3) | | C6 | C5 | 1.513(3) |
| O9 | C14 | 1.354(3) | | C6 | C7 | 1.503(4) |
| O9 | C7 | 1.446(3) | | C14 | C15 | 1.485(4) |
| O5 | C12 | 1.350(3) | | C5 | C4 | 1.552(4) |
| O5 | C8 | 1.453(3) | | C3 | C4 | 1.537(3) |
| O11 | C19 | 1.365(3) | | C21 | C22 | 1.406(4) |
| O11 | C5 | 1.460(3) | | C21 | C20 | 1.372(4) |
| O3 | C9 | 1.440(3) | | C7 | C8 | 1.524(3) |
| O3 | C10 | 1.360(3) | | C4 | C18 | 1.510(4) |
| O1 | C1 | 1.335(3) | | C10 | C11 | 1.486(4) |
| O1 | C17 | 1.446(3) | | C22 | C23 | 1.431(4) |
| O6 | C12 | 1.203(3) | | C22 | C24 | 1.415(4) |

| | | | | | | |
|---|---|---|---|---|---|---|
| O7 | C1 | 1.189(3) | | C18 | C23 | 1.400(4) |
| O4 | C10 | 1.200(3) | | C23 | C27 | 1.420(4) |
| O10 | C14 | 1.200(3) | | C27 | C26 | 1.367(4) |
| C1 | C2 | 1.544(3) | | C24 | C25 | 1.355(5) |
| C19 | C20 | 1.403(4) | | C25 | C26 | 1.415(5) |
| C19 | C18 | 1.363(4) | | | | |

**Table 14.** Bond Angles for AW6302_2_0m (**164)**.

| **Atom** | **Atom** | **Atom** | **Angle/°** | | **Atom** | **Atom** | **Atom** | **Angle/°** |
|---|---|---|---|---|---|---|---|---|
| C2 | O8 | C16 | 115.11(18) | | O11 | C5 | C4 | 107.4(2) |
| C2 | O2 | C6 | 114.70(18) | | C6 | C5 | C4 | 111.1(2) |
| C14 | O9 | C7 | 118.32(19) | | C2 | C3 | C4 | 111.8(2) |
| C12 | O5 | C8 | 117.62(18) | | C20 | C21 | C22 | 122.1(2) |
| C19 | O11 | C5 | 107.32(18) | | O9 | C7 | C6 | 110.27(19) |
| C10 | O3 | C9 | 117.13(19) | | O9 | C7 | C8 | 105.95(18) |
| C1 | O1 | C17 | 116.2(2) | | C6 | C7 | C8 | 112.4(2) |
| O1 | C1 | C2 | 110.2(2) | | O5 | C8 | C9 | 109.55(19) |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| O7 | C1 | O1 | 124.1(2) | | O5 | C8 | C7 | 104.18(18) |
| O7 | C1 | C2 | 125.7(2) | | C9 | C8 | C7 | 114.3(2) |
| O11 | C19 | C20 | 122.0(2) | | C3 | C4 | C5 | 110.6(2) |
| C18 | C19 | O11 | 114.5(2) | | C18 | C4 | C5 | 101.41(19) |
| C18 | C19 | C20 | 123.4(2) | | C18 | C4 | C3 | 111.6(2) |
| O5 | C12 | C13 | 110.1(2) | | O3 | C10 | C11 | 110.7(2) |
| O6 | C12 | O5 | 123.6(2) | | O4 | C10 | O3 | 123.3(2) |
| O6 | C12 | C13 | 126.3(2) | | O4 | C10 | C11 | 126.0(3) |
| O3 | C9 | C8 | 109.25(19) | | C21 | C22 | C23 | 119.4(2) |
| O8 | C2 | O2 | 111.1(2) | | C21 | C22 | C24 | 121.7(3) |
| O8 | C2 | C1 | 108.4(2) | | C24 | C22 | C23 | 118.9(3) |
| O8 | C2 | C3 | 106.16(19) | | C21 | C20 | C19 | 117.0(3) |
| O2 | C2 | C1 | 104.11(19) | | C19 | C18 | C4 | 108.9(2) |
| O2 | C2 | C3 | 112.9(2) | | C19 | C18 | C23 | 120.2(2) |
| C3 | C2 | C1 | 114.2(2) | | C23 | C18 | C4 | 130.9(2) |
| O2 | C6 | C5 | 108.16(19) | | C18 | C23 | C22 | 117.9(2) |
| O2 | C6 | C7 | 107.92(19) | | C18 | C23 | C27 | 123.7(2) |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| C7 | C6 | C5 | 114.0(2) | | C27 | C23 | C22 | 118.4(2) |
| O9 | C14 | C15 | 110.7(2) | | C26 | C27 | C23 | 120.7(3) |
| O10 | C14 | O9 | 123.0(2) | | C25 | C24 | C22 | 121.3(3) |
| O10 | C14 | C15 | 126.3(2) | | C24 | C25 | C26 | 120.1(3) |
| O11 | C5 | C6 | 107.38(19) | | C27 | C26 | C25 | 120.6(3) |

**Table 15**. Hydrogen Atom Coordinates (Å×$10^4$) and Isotropic Displacement Parameters (Å$^2$×$10^3$) for AW6302_2_0m (**164)**.

| **Atom** | ***x*** | ***y*** | ***z*** | **U(eq)** |
|---|---|---|---|---|
| H9A | 6400.27 | 7437.09 | 7435.1 | 22 |
| H9B | 8331.11 | 7334.36 | 7145.07 | 22 |
| H16A | 7699.85 | 2837.03 | 7780.94 | 28 |
| H16B | 7555.86 | 3946.97 | 7570.06 | 28 |
| H16C | 9386.77 | 3208.06 | 7463.8 | 28 |
| H6 | 5049.55 | 4511.05 | 6679.52 | 19 |
| H5 | 7517.66 | 4652.45 | 5949.91 | 21 |
| H3A | 4675.36 | 2827.24 | 6594.31 | 19 |

| | | | | |
|---|---|---|---|---|
| H3B | 6150.84 | 1929.01 | 6452.41 | 19 |
| H21 | -513.53 | 3309.56 | 5263.08 | 31 |
| H7 | 5876.4 | 6227 | 6423.77 | 19 |
| H8 | 7075.1 | 5689.35 | 7258.35 | 19 |
| H4 | 7435.7 | 2924.17 | 5904.8 | 20 |
| H20 | 1047.22 | 4771.04 | 5522.41 | 28 |
| H15A | 12152.8 | 6216.07 | 6184.41 | 46 |
| H15B | 11790.65 | 7268.82 | 6429.28 | 46 |
| H15C | 11713.55 | 7249.67 | 5931.78 | 46 |
| H13A | 1047.12 | 4986.31 | 7198.28 | 35 |
| H13B | 734.26 | 6041.81 | 7444.18 | 35 |
| H13C | 968.79 | 4989.15 | 7695.83 | 35 |
| H27 | 5684.15 | 1104.3 | 5764.26 | 34 |
| H17A | 12153.84 | 1136.18 | 6851.15 | 41 |
| H17B | 12023.23 | 1266.09 | 6356.87 | 41 |
| H17C | 11036.62 | 289.17 | 6576.8 | 41 |
| H24 | -567.08 | 1444.78 | 5133.93 | 44 |

| | | | | |
|---|---|---|---|---|
| H11A | 6213.59 | 9939.96 | 6393.47 | 53 |
| H11B | 4562.92 | 9056.38 | 6379.21 | 53 |
| H11C | 6408.22 | 9021.86 | 6065.36 | 53 |
| H25 | 947.42 | -130.73 | 5167.3 | 57 |
| H26 | 4121.79 | -297.72 | 5472.3 | 47 |

**Table 16.** Solvent masks information for AW6302_2_0m (**164)**.

| **Number** | **X** | **Y** | **Z** | **Volume** | **Electron count** | **Content** |
|---|---|---|---|---|---|---|
| 1 | -0.479 | 0.250 | 0.000 | 175.5 | 37.2 | ? |
| 2 | -0.134 | 0.750 | 0.500 | 175.5 | 37.2 | ? |

# APPENDIX



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## ABSTRACT

## EXPLORING THE SCOPE AND LIMITATIONS OF THE OXIDATIVE DEAMINATION OF N-ACETYL NEURAMINIC ACID

by

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**Major**: Chemistry (Organic)

**Degree**: Doctor of Philosophy

Sialic acids are molecules of importance in the fields of carbohydrate chemistry and glycoscience, and their diversity make them even more attractive to scientific research. Modifications of sialic acid derivatives may lead to several biological and chemical features that can be utilized for medicinal purposes. The modern drug therapy is dependent on the chemical discoveries of potent and effective molecules. *N*-Acetyl neuraminic acid is the parent and most common molecule in sialic acid family that received considerable attention in glycochemical research. This dissertation explores the scope as well as the limitations of the Zbiral oxidative deamination of *N*-acetyl neuraminic acid (NeuAc) by using various nucleophiles and protecting groups leading to the discovery of new general reaction pathway that may be useful for organic synthesis.

Chapter one discusses an overview and definition of carbohydrates and their importance in biology and chemistry. Common monosaccharides as well as construction of polysaccharides

by the glycosidic linkages are defined. These are followed by brief discussion about sialic acid discovery as well as explanation of their diverse presence in nature. In chapter one also general discussion about deamination reaction is introduced. This is supported by literature review of sialic acid modification approaches. Finally, previously reported examples of oxidative deamination utilization in carbohydrate syntheses are also presented.

Chapter two proves that use of phenols and thiophenols are effective as nucleophiles for oxidative deamination of NeuAc with the discovery of novel intermediate vinyl diazonium ion. Firstly, chapter one introduces brief literature examples of a ring atom participation as well as ring contractions followed by earlier reported synthetic pathways of alkenediazonium ions. Then, novel and unusual structures of neuraminic acid derivatives are described to be isolated and characterized by the use of phenols nucleophiles in modified conditions of oxidative deamination. The weakly acidic nature of phenols plays an important role in the formation of the vinyl diazonium ion intermediate, which was a result of β-elimination of 4-acetoxy group after diazonium ion and diazoalkane interconversion. This is influenced by the p*K*a values of the nucleophiles that lead to the formation of the variety of products. Finally, the plausible mechanisms of products formation are explained according to the acidity of the reaction media.

Chapter three further supports the finding of the formation of vinyl diazonium ion as an intermediate, which afforded new products of sialic acid derivatives. Furthermore, chapter three describes the expansion of the range of nucleophiles for oxidative deamination of *N*-acetyl neuraminic acid showing that modifications at the 5-position of NeuAc by building N-O bond are accomplishable. Hydroxylamines, hydroxamic acids, oximes, amines are the nucleophile

used to isolate structurally novel cyclic and substitution products with potential medicinal applications.

Chapter four illustrates the conclusions and the main contributions in this dissertation giving an overall reaction mechanism of the products formation in this oxidative deamination.

Chapter five describes the substrates syntheses and experimental procedures as well as the materials used for the characterization of the products.

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### Publications

- "Use of Hydroxylamines, Hydroxamic Acids, Oximes and Amines as Nucleophiles in the Zbiral Oxidative Deamination of *N*-Acetyl Neuraminic Acid. Isolation and Characterization of Novel Mono- and Disubstitution Products"
  **Mohammed Hawsawi**, Michael G. Pirrone, Anura Wickramasinghe, and David Crich. *Carbohydr. Res*. **2020**, 107921.

- "Use of Phenols as Nucleophiles in the Zbiral Oxidative Deamination of N-Acetyl Neuraminic Acid: Isolation and Characterization of Tricyclic 3-Keto-2-deoxy-nonulosonic Acid (KDN) Derivatives via an Intermediate Vinyl Diazonium Ion"
  **Mohammed Hawsawi**, Anura Wickramasinghe, and David Crich. *J. Org. Chem*. **2019**, 84, 22, 14688-14700.

### Presentations

- "Studies Towards the Total Synthesis of Aplydactone: A Model Study"
  *Oral Poster Presentation* at the Graduate Research and Creativity Symposium RIT, Rochester, NY, February 27, 2015.
- "Oxidative Deamination of Sialic Acids using Various Nucleophiles"
  *Oral Poster Presentation* at the 14th Annual Midwest Carbohydrate and Glycobiology Symposium, East Lansing, MI, September 21st – 22nd, 2018
- "Phenols as Nucleophiles in the Oxidative Deamination of *N*-Acetyl Neuraminic Acid"
  *Oral Poster Presentation* at the ACS Fall 2019 National Meeting & Exposition in San Diego, CA, August 25th – 29th, 2019.
- "Phenols as Nucleophiles in the Oxidative Deamination of *N*-Acetyl Neuraminic Acid"
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