12-1988

Synthesis of N and C Nucleosides via Cycloaddition Reactions a New Approach to an Old Problem

Glenn L. Heise
Western Michigan University

Follow this and additional works at: https://scholarworks.wmich.edu/dissertations

Part of the Chemistry Commons

Recommended Citation
https://scholarworks.wmich.edu/dissertations/2181

This Dissertation—Open Access is brought to you for free and open access by the Graduate College at ScholarWorks at WMU. It has been accepted for inclusion in Dissertations by an authorized administrator of ScholarWorks at WMU. For more information, please contact maira.bundza@wmich.edu.
SYNTHESIS OF N AND C NUCLEOSIDES VIA CYCLOADDITION REACTIONS:
A NEW APPROACH TO AN OLD PROBLEM

by

Glenn L. Heise, Ph.D.

A Dissertation
Submitted to the
Faculty of The Graduate College
in partial fulfillment of the
requirements for the
Degree of Doctor of Philosophy
Department of Chemistry

Western Michigan University
Kalamazoo, Michigan
December 1988
SYNTHESIS OF N AND C NUCLEOSIDES VIA CYCLOADDITION REACTIONS: A NEW APPROACH TO AN OLD PROBLEM

Glenn L. Heise, Ph.D.
Western Michigan University, 1988

This dissertation describes the synthesis and subsequent 1,3-dipolar cycloaddition reactions of the N-methyl nitrone derived from 2,5-anhydro-D-allose. The 1,3-dipolar cycloaddition strategy provided a novel entry into the synthesis of C-nucleosides. To complement the above approach, N-nucleosides were synthesized through the use of the cycloaddition reaction of glutaraldehyde salts and suitably protected ribofuranosyl isothiocyanates and acyclic isothiocyanates. The final facet of this study explored the synthesis of glucopyranosyl and ribofuranosyl N-diethyl phosphoroamidates derived from glucopyranosyl and ribofuranosyl azides.

With the discovery that nucleosides blocked in the 3' and 5' positions could serve as chain terminators during DNA replication, an attempt was made to introduce the 2',3' double bond into the cycloadduct 1-(β-D-ribofuranosyl)-2(1H)-thiono-3-pyridine carboxaldehyde. This effort was successful. When coupled with acyclic nucleoside analogs, it provided a series of compounds which may have biological activity against various DNA viruses.

The potential use of the N-methyl nitrone derived from 2,5-anhydro-D-allose for the synthesis of C-nucleosides has only just begun. These unique nitrone derivatives were found to be very
reactive 1,3 dipoles in 1,3-dipolar cycloaddition reactions with assorted electron poor dipolarophiles. Five membered ring synthesis through the use of 1,3-dipolar cycloaddition reactions, originally introduced by R. Husigen in 1960, now has been successfully applied to the synthesis of synthetically challenging C-nucleosides.
Synthesis of N and C nucleosides via cycloaddition reactions: A new approach to an old problem

Heise, Glenn Leslie, Ph.D.
Western Michigan University, 1988
ACKNOWLEDGEMENTS

This work is dedicated to my coworkers and committee members at Western Michigan University, Kalamazoo, Michigan, whose helpful comments and suggestions have helped guide this dissertation to a successful completion. To my dissertation advisor, respected professor and friend, Dr. Robert E. Harmon, I owe the greatest thanks. His keen insight and vast knowledge have guided this research project to its conclusion. I also wish to thank The Graduate College for two travel grants which helped fund my trips to the American Chemical Society National Meetings to present some of the results obtained in these experiments. The tedious work of typing and retyping this manuscript was shared by two special people in my life, namely Corinna Heise and Julie Jones. Lastly, I would like to thank my family and friends for their unfailing support of my continued endeavors in the field of chemistry.

Glenn L. Heise, Ph.D.
# TABLE OF CONTENTS

ACKNOWLEDGEMENTS ............................................. ii

CHAPTER

I. INTRODUCTION. ............................................. 1

II. STATEMENT OF THE PROBLEM .................................. 3

III. EXPERIMENTAL. ............................................. 4

   Instrumentation. ............................................. 4

   General .................................................... 4

   Materials .................................................. 5

Preparations. .................................................. 5

1-2,3,5-Tri-O-benzoyl-α-D-ribofuranosyl bromide 1 ........ 5

1-2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl cyanide 2 .... 6

1-2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl cyanide 2
   Alternative preparation, (41,42) ................ 7

1-2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl isothiocyanate 3 .... 7

1,3-Diphenyl-2-(2,3,5-tri O-benzoyl-β-D-
   ribofuranosyl) imidazolidine 4 ...................... 8

1,3-Diphenyl-2-(β-D-ribofuranosyl) imidazolidine 5 .... 9

1,3-Diphenyl-2-(2,3,5-tri O-benzyl-β-D-ribofuranosyl)
   imidazolidine 6 ................................. 10

2,5-Anhydro-3,4,6-tri-O-benzoyl-β-D-allose 7 ...... 10

2,5-Anhydro-3,4,6-tri-O-benzoyl-β-D-allose 7 ...... 11

2,5-Anhydro-3,4,6-tri-O-benzyl-β-D-allose 9 .... 12

2,5-Anhydro-3,4,6-tri-O-benzoyl-β-D-allose N-methyl
   nitrone 10 ................................. 13

2,5-Anhydro-3,4,6-tri-O-benzyl-β-D-allose N-methyl
   nitrone 8 ................................. 13

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
| **3-(2',3',5'-Tri-o-benzyl-β-D-ribofuranosyl)-2-**<br>**methyl-2H-isoxazole-4,5-dicarboxylic acid dimethyl ester** | 11 |
| **3-(2',3',5'-Tri-O-benzoyl-β-D-ribofuranosyl)-2,5-**<br>**dimethyl-2,5H-pyrrole 3,4-d isoxazolidine-4,6-dione** | 12 |
| **3-(2',3',5'-Tri-o-benzyl-p-D-ribofuranosyl)-2-**<br>**methyl-2H-isoxazolidine-4,5-dicarboxylic acid diethyl ester** | 13 |
| **3-(2,3,5-Tri-o-benzyl-β-D-ribofuranosyl)-2-methyl-**<br>**2H-isoxazole-4,5-dicarboxylic acid dimethyl ester** | 14 |
| **3-(2',3',5'-Tri-O-benzoyl-p-D-ribofuranosyl)-2,5-**<br>**dimethyl-2,5H-pyrrole 3,4-d isoxazolidine-4,6-**<br>**dione** | 15 |
| **3-(2',3',5'-Tri-o-benzyl-β-D-ribofuranosyl)-2-methyl-**<br>**2H-isoxazolidine-4,5-dicarboxylic acid diethyl ester** | 16 |
| **1-(2',3',5'-Tri-o-benzoyl-β-D-ribofuranosyl)-2(1H)-**<br>**thiono-3-pyridine carboxaldehyde** | 17 |
| **1-(β-D-Ribofuranosyl)-2(1H)-thiono-3-pyridine carboxaldehyde** | 18 |
| **1-(2',3'-Dideoxy-2',3'-didehydro-β-D-ribofuranosyl)-2(1H)-thiono-3-pyridine carboxaldehyde** | 19 |
| **1-(2,3,4-Tri-o-benzoyl-β-D-ribofuranosyl)azide** | 20 |
| **1-(2,3,5-Tri-o-benzoyl-β-D-ribofuranosyl)-triethyl iminophosphorane** | 21 |
| **1-(2,3,5-Tri-o-benzoyl-β-D-ribofuranosyl)-N-diethyl-phosphoramidate** | 22 |
| **1-(2,3,4,6-Tetra-o-acetyl-β-D-glucopyranosyl)azide** | 23 |
| **1-(2,3,4,6-Tetra-o-acetyl-β-D-glucopyranosyl)-**<br>**diethyl-N-iminophosphorane** | 24 |
| **1-(2,3,4,6-Tetra-o-acetyl-β-D-glucopyranosyl)-**<br>**diethyl-N-phosphoroamidate** | 25 |
### TABLE OF CONTENTS CONTINUED

1-(2,3,4,6-Tetra-O-acetyl-β-D-galactopyranosyl) azide 26 .................................. 25

1-(2,3,4,6-Tetra-O-acetyl-β-D-galactopyranosyl)-diethyl-N-iminophosphorane 27 .............. 25

1-(2,3,4,6-Tetra-O-acetyl-β-D-galactopyranosyl)-N-diethyl-phosphoramidate 28 ................... 26

N-Ethyl-2,5-anhydro-3,4,6-tri-O-benzoyl-β-D-allononitrilium tetrafluoroborate 29 .................. 27

N-Ethyl-2,5-anhydro-3,4,6-tri-O-benzoyl-β-D-allononimine 30 ..................................... 27

2,5-Anhydro-3,4,6-tri-O-benzoyl-β-D-allose An alternative approach 7 ............................. 28

3-(2',3',5'-Tri-O-benzoyl-β-D-ribofuranosyl)-2(1H) thiono-6-methyl-3H-1,3-oxazine-4-one 32 .... 28

6-Methyl-4-thiomethyl-3-acetyl-2(1H)-thiono-1-phenylpyridine 33 .................................. 29

2-Amino-4,7-dimethyl-6-phenyl-5-thiono-6H-pyrido 4, 3d-pyrimidine 34 ............................. 29

2-Trimethylsilylethoxymethylisothiocyanate 35 .......................................................... 30

1-(2'-Trimethylsilylethoxymethyl)-2(1H)-thiono-3-carboxaldehyde 36 ................................ 31

2-Acetoxy-ethoxy-methyl-isothiocyanate 37 ................................................................. 31

1-(2-Acetoxy-ethoxy-methyl)-2(1H)-thiono-3-carboxaldehyde 38 ..................................... 32

IV. RESULTS AND DISCUSSION ................................................. 34

V. CONCLUSIONS AND RECOMMENDATIONS ....................... 58

REFERENCES ................................................................. 59

APPENDIX ................................................................. 66

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
CHAPTER I

INTRODUCTION

This work had its origins in a series of conversations that I had had with my mentor Dr. Robert E. Harmon. Because much of his past work was with compounds of medicinal interest with an emphasis on carbohydrate analogs, and because of the renewed interest in nucleoside derivatives as agents against DNA related diseases, it was decided that new synthetic approaches to N and C nucleosides would provide a formidable synthetic problem for research. Since synthetic approaches starting from noncarbohydrate reactants or readily available meso compounds require a conventional optical resolution step and a recycling of the undesired enantiomer, it was decided to use the natural carbohydrate precursors in the synthesis. In the past, the heterocyclic moiety of N and C nucleosides was synthesized in several steps and then attached to the sugar utilizing the normal electrophilicity of the anomeric carbon atom. Efficient syntheses of heterocycles utilizing a cycloaddition methodology was known, yet had not been ever rigorously applied to a total synthesis of N and C nucleosides. In particular, use of the 1,3 dipole nitrene could be used to generate a variety of 5-membered ring heterocycles if it could be successfully attached to the sugar moiety. With this in mind, a novel strategy was developed for the synthesis of a ribofuranosyl nitrene as a synthon for C-nucleoside synthesis. In connection with past research in our
laboratories using the isothiocyanate functionality as a synthon for pyridine heterocycles, we decided to use this functionality when attached to a carbohydrate moiety as an entry into substituted pyridine nucleoside. Using these novel pyridine nucleosides as substrates, literature deoxygenation procedures were applied with great success. The promising antiviral activity of several nucleoside analogues in which the ribose moiety has been replaced by an acyclic moiety provided an incentive for the production of an acyclic N-nucleoside with an attached substituted pyridine heterocycle. Lastly, because of the utility of many new silicon reagents, an application utilizing trimethsilyl azide to convert protected carbohydrates into their corresponding anomeric azides and subsequent derivatives should prove valuable.
CHAPTER II

STATEMENT OF THE PROBLEM

This research was undertaken to study:

1. The synthesis and subsequent 1,3-dipolar cycloaddition reactions of N-alkyl-nitrones derived from 1-(2,3,5-tri-O-benzoyl-\beta-D-ribofuranosyl)cyanide.

2. The cycloaddition reactions of ribofuranosyl isothiocyanates and acyclic isothiocyanates to the potassium salt of glutaraldehyde.

3. The synthesis of glucopyranosyl and ribofuranosyl N-diethyl phosphoroamidates derived from glucopyranosyl and ribofuranosyl azides.
CHAPTER III

EXPERIMENTAL

Instrumentation

General

Melting points (uncorrected) were determined on a Thomas-Hoover Unimelt instrument in open capillary tubes, and are expressed in degrees Celsius. Compounds were identified by IR, $^1$H NMR, and $^{13}$C NMR, and melting point (for those compounds with literature precedent for which a new method of synthesis was developed) IR spectra were run either as KBr pellets or as thin films between NaCl plates on a Nicolet 5D x C FT-IR spectrophotometer. All NMR spectra were determined in appropriate deuterated solvents, and the chemical shifts expressed in $\delta$ values (ppm) relative to TMS as internal standard. The $^1$H NMR spectra were determined at 200 MHz with a Brucker Model AC200 Fourier transform spectrometer. The $^{13}$C NMR spectra were determined at 50.3 MHz and were broad band proton decoupled. Microanalysis were carried out at Midwest Microlab, Ltd., Indianapolis, IN and at Galbraith Laboratories, Inc., Knoxville, TN. TLC was performed on silica gel plates (Merck, 60, F$_{254}$, precoated, 0.2mm, fluorescent indicator) to follow the progress of reactions and as an indicator of purity. These thin layer chromatograms were visualized with UV light or iodine vapor. Flash chromatography was performed on
silica gel 60 (230-400 mesh, E. Merck) and on Florisil (60-100 mesh, Aldrich).

Materials

Fgansteihl Chemical Co. was the source of the carbohydrate precursors, other chemicals and solvents were supplied by Aldrich, Sargent Welch, Burdick and Jackson, etc. Reaction solvents as well as chromatography solvents were dried and redistilled before use. Reactions were carried out in oven dried flasks and were run under N₂ or Ar atmospheres. Syringes were used for small liquid transfers when needed.

Preparations

1-2,3,5-Tri-O-benzoyl-α-D-ribofuranosyl bromide 1

A solution of 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose (63g, 0.12mol) in anhydrous benzene (250ml) was saturated under ice cooling with gaseous dry hydrogen bromide. The reaction mixture was stirred in a 500ml triple necked flask which had been fitted with two inlet hydrogen bromide tubes that reached nearly to the bottom of the flask and a single vent tube which was connected to a suitable hydrogen bromide trap. The hydrogen bromide was bubbled into the reaction for 30 minutes and then the reaction was allowed to warm to room temperature for an additional 30 minutes. The benzene was then evaporated under vacuum to yield a golden syrup which was coevaporated with an additional 200ml portion of benzene to remove water. The product was prone to rapid hydrolysis and was used

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
immediately in the preparation of \(1-(2,3,5\text{-Tri-O-benzoyl-}D\text{-ribofuranosyl})\) cyanide. The reaction mixture was concentrated to one half its original volume and was seeded with crystals obtained from chromatography on silica gel, using 20:1 benzene-ether as eluent, and allowed to crystallize at room temperature over night. The crystals were collected using vacuum filtration and washed with cold ethanol.

\[1-2,3,5\text{-Tri-O-benzoyl-}D\text{-ribofuranosyl cyanide}\]

To a solution of \(1-2,3,5\text{-Tri-O-benzoyl-}D\text{-ribofuranosyl bromide (39,40) (65.7g, 0.125mmol)}\) dissolved in 150ml of nitromethane, was added (60.0g, 0.237mol) of powdered mercuric cyanide (predried at 14°C/15mm Hg for 5 hours). The reaction mixture was stirred at room temperature for 20 hours, and the precipitate was filtered off and washed with 100ml of benzene. The filtrate was concentrated under reduced pressure to the consistence of a syrup which was dissolved in 250ml of ethyl acetate. This solution was washed with two 100ml portions of 5% aqueous potassium iodide, two 50ml portions of water, and then dried over sodium sulfate. The solution was once again concentrated to a syrup and then dissolved in 100ml of absolute ethanol. The ethanolic solution was concentrated to one half of its original volume, seeded with crystals which were obtained from flash chromatography of an analytical sample on silica gel using (20:1) benzene ether as eluent. The fraction containing the product was concentrated to yield 52g (two crops), 88% yield, mp 78.0-89.0°C, IR (neat), (C=O) 1735.9 cm\(^{-1}\), \(^1\)H NMR (CDCl\(_3\)), \(\delta\) 8.10,
multiplet, (5H), δ 7.57, multiplet, (10H), δ 6.7, doublet (H₄), δ 5.86, triplet, (H₃), δ6.06, triplet (H₂), δ 4.84, multiplet (δₐ, δₐ, δₐ), J₁₂ 4.5 Hz, J₂₃ 5.0 Hz, C¹³NMR (CDCl₃), 170.83, 166.77, 165.84, 133.13, 132.83, 129.60, 129.52, 128.19, 128.10, 100.26, 79.92, 78.79, 76.16, 72.41, 71.43.

1-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl cyanide

Anhydrous stannic chloride (20.8g, 9.33ml, 80.0mmol) was added using a syringe in one portion to a solution of 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose (40.3g, 80.0mmol), 1,2-dichloroethane (100ml), and cyanotrimethylsilane (15.84gm 160.0mmol) in a 500ml round bottom flask. The rapidly darkening solution was stirred for 2 minutes and then poured into saturated sodium bicarbonate (800ml) and stirred for an additional 5 minutes. The pH of this solution was 7.0. One liter of chloroform was added to the neutralized reaction mixture and then the resulting solution was filtered through Celite, the chloroform layer was separated and dried with magnesium sulfate and then evaporated under reduced pressure. The yellow-orange syrup that resulted was dissolved in hot anhydrous ethanol, decolorized with Norit, filtered through Celite, and then allowed to crystallize in long white needles to yield 30g (80%).

1,2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl isothiocyanate

To a solution of 1,2,3,5-tri-O-benzoyl-β-D-ribofuranosyl bromide (13.1g, 25.0mmol) in 150ml of anhydrous benzene was added (4.2g, 25.0mmol) of silver thiocyanate. This mixture was
refluxed for 30 minutes and filtered hot through a rayon filter. The precipitated yellow-silver bromide was washed with two 50ml portions of anhydrous benzene. The benzene solution was concentrated under reduced pressure to yield 47.6g (94%) of an orange solid mp (123-125°C). An alternative to the use of expensive silver thio-
cyanate in this procedure was the use of lead (II) thiocyanate (43-
45) (8.1g, 25.0mmol) which leads to a slightly lower yield (87%) of the product, IR (neat thin film), (N=C=S) 2017.2 cm⁻¹, (C=O) 1735.9
cm⁻¹, ¹H NMR (CDCl₃) 8.08, multiplet (5H), 7.55, multiplet (10H),
6.75, doublet (1H), 5.56 multiplet (2H) (H₂and H₃), 4.67, multiplet, (3H) (H₄a, H₄b, and H₄), C¹³NMR (CDCl₃), 170.00, 166.01, 165.20,
133.13, 132.88, 129.91, 129.59, 128.28, 128.15, 105.17, 78.77, 75.60,
72.55, 64.82.

₁,₃-Diphenyl-2-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl) imidazolidine

To a vigorously stirred suspension of Raney nickel (75.0g) in a solution of monosodium hypophosphite (50.0g, 5.68.3mmol), and N,N'-
diphenylethylene diamine (21.1g, 100mmol), in a mixture of pyridine (375.0ml, 4.63mol), glacial acetic acid (185.0ml, 3.23mol), and water (185.0ml, 10.28mol), was added 1-2,3,5-tri-O-benzoyl-β-D-ribofuranosyl cyanide (25.0gm, 53.0mmol). The mixture was stirred at room temperature for 1.25 hours and then filtered. The precipitate was washed thoroughly with chloroform (3 x 200ml), and the combined filtrates were diluted to a volume of 2.5 liters with chloroform and subsequently washed with water (3 x 200ml). The chloroform solution was dried with magnesium sulfate, filtered, and concentrated.
under reduced pressure leaving a syrup (46-52) that crystallized upon the addition of methanol yielding 26g (74%) of the product with mp 154-155°C, IR (neat thin film), (C=O) 1735.9 cm⁻¹, ¹H NMR (CDCl₃), 5.86, broad singlet, (C₁H), δ 4.79 doublet, (C₂H), δ 5.70, doublet of doublets, (C₃H), δ 5.50, multiplet, (C₄H), δ 4.45, multiplet, (C₅H, C₆H), δ 3.7 multiplet (4H, N-CH₂), δ 6.8, multiplet (4H, Ph), 7.3, multiplet, (15H, Bz), δ 7.9, multiplet, (6H, Ph), J₁₂=1H₂, J₂₃=6H₂, J₃₄=6Hz, J₅₆, J₆₇ not resolved, ¹³C NMR (CDCl₃) δ 166.07, 166.00, 165.37, 146.42, 133.26, 133.15, 132.87, 129.71, 129.65, 129.58, 129.38, 129.19, 129.09, 128.33, 128.27, 128.21, 116.04, 113.58, 113.26, 83.29, 79.52, 73.44, 72.72, 64.13, 47.31.

1,3-Diphenyl-2-(β-D-ribofuranosyl)imidazolidine 5

A solution of 4,1,3-diphenyl-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)imidazolidine (19.8g, 29.6mmol) in 200ml of chloroform was added to methanolic sodium methoxide (200ml of 0.75M), and the mixture was stirred at room temperature for 2.5 hours. The solution was then neutralized by the addition of 3.0g of Dowex 50 (H⁺) resin (50-100 Mesh) with stirring, followed by filtration and concentration of the resulting solution under reduced pressure. The light brown syrup that resulted was flash chromatographed to remove methyl benzoate on a column of silica gel (1 Kg) using first (1:1) chloroform-ethyl acetate and then ethyl acetate as eluents. The product can be recrystallized from aqueous methanol to yield 7.5g (73%) of the product mp 169-170°C IR (neat thin film) (OH), 3220 cm⁻¹, ¹H NMR (pyridine d₅, D₂O), δ 5.97 broad singlet (C₁H), δ 4.87 broad doublet (C₂H), δ 4.52 doublet of doublets (C₃H), δ 4.4 multiplet (C₄H, C₅H),
δ 3.91 singlet (C₆H), δ 3.56, 3.84 multiplets (4H, NCH₂), δ 7.0 multiplet (10H, Ph's), J₁₂=1Hz, J₂₃=6Hz, J₄₅ not resolved, J₅₆=0 Hz.

1,3-Diphenyl-2-(2,3,5-tri-O-benzyl-β-D-ribofuranosyl)imidazolidine

Previously dried 1,3-diphenyl-2-(β-D-ribofuranosyl)imidazolidine (10.4g, 29.0mmol) was added to a stirred suspension of sodium hydride (13.2g, 552mmol) in 500ml of dimethylsulfoxide (DMSO) under argon. The reaction was stirred for 30 minutes at room temperature at which time benzyl chloride (98ml, 828mmol) was added dropwise. Following the addition, the reaction was heated to 60°C for 2 hours, and then allowed to stand at room temperature for an additional 12 hours. The reaction mixture was then diluted with 2 liters of chloroform and washed with 500ml of 2N acetic acid, 500ml of saturated aqueous sodium bicarbonate, and then 500ml of water. The organic phase was dried with calcium chloride, and then concentrated under reduced pressure to the consistency of a syrup that was chromatographed on silica gel using hexane-ether (4:1) as the eluent, to yield 14.5g (80%) of the product mp 92-94°C, ¹H NMR (CDCl₃), δ 5.52 doublet (C₁H), δ 4.52 doublet of doublets (C₂H), δ 3.78 doublet of doublets (C₃H), δ 4.14 doublet of doublets (C₄H), δ 3.2-3.6 multiplets (C₅H, C₆H), δ 3.5 multiplet (4H, N-CH₂), δ 4.28, 4.38, 4.42 singlets (6H, OCH₂Ph), J₁₂=1Hz, J₂₃=5Hz, J₄₅=5Hz, J₅₆ unresolved.

2,5-Anhydro-3,4,6-tri-O-benzoyl-β-D-allose

Method 1: To a solution of 1,3-diphenyl-2-(2,3,5-tri-O-
benzoyl-β-D-ribofuranosyl)imidazolidine (6.7g, 10.0mmol) in a mixture of 500ml of tetrahydrofuran and 250ml of water was added Dowex 50 (H⁺) resin (32.5g, 20–50 mesh). The mixture was stirred under reflux for 5 hours while being constantly monitored by TLC (thin layer chromatography) using (2:1) ether hexane. Upon completion of the reaction, the mixture was filtered and the resin was washed with tetrahydrofuran. The solution was then concentrated under reduced pressure to yield 4.0g (68%) of an oil after rapid chromatography on a column of silica gel using ether hexane (2:1) as the eluent, IR (neat thin film) (CHO) 1700 cm⁻¹, ¹H NMR (CDCl₃) δ 9.77 doublet, J₁₂=1.5Hz.

2,5-Anhydro-3,4,6-tri-O-benzoyl-β-D-allose

Method 2: A solution of (355mg, 1.87mmol) of p-toluene-sulfonic acid monohydrate in 10.0ml of acetone was added with stirring to an ice cooled solution of 4 in 25.0ml of dichloromethane. After 5 minutes at 0°C the mixture was allowed to come to room temperature over a period of 40 minutes. Because the reaction was found to be incomplete by TLC, an additional portion (50mg) of p-toluene sulfonic acid in 5ml of acetone was added. The reaction was found to be complete after 30 minutes at which time it was filtered to remove the p-toluene sulfonic acid salt of 1,2-dianilino-ethane. This salt was washed with 2 x 50ml of dichloromethane, and the combined filtrates were concentrated under vacuum without heating. The yellow-brown oil which resulted was redissolved in 50ml of dichloromethane and washed with cold water (3 x 50ml), dried with...
MgSO₄, and once again concentrated under vacuum. This material was
found to still contain some unreacted 4 by TLC, thus it was
chromatographed on silica gel using ether-hexane (2:1) as the
eluent. In this way 240mg (68%) of the aldehyde 7 was obtained.
This material was very unstable and was used soon after its production.

2,5-Anhydro-3,4,6-tri-O-benzyl-β-D-allose 9

Method 1: To a solution of 6 1,3-diphenyl-2-(2',3',5'-tri-
O-benzyl-β-D-ribofuranosyl)imidazolidine (6.26g, 10.0mmol) in a
mixture of 500ml of tetrahydrofuran and 250ml of water was added
Dowex 50 (H⁺) resin (32.5g, 20-50 mesh). The mixture was stirred
under reflux for 5 hours while being constantly monitored by TLC
using (2:1) ether hexane. After this period of time some unreacted
6 still remained thus an additional portion (15.0g, 20-50 mesh) of
Dowex 50 (H⁺) resin was added. The resulting mixture was then
filtered upon completion (2 hours) and the resin was washed with
2 x 150ml of tetrahydrofuran. The filtrates were combined and
concentrated under reduced pressure to yield 4.11g, (95%) of 9 as
a colorless oil, IR (neat thin film) (CHO) 1695 cm⁻¹.

Method 2: A solution of (52.31g, 275mmol) of p-toluenesulfonic
acid monohydrate in 200ml of acetone was added with stirring to an
ice cooled solution of (69.5g, 0.110mol) of 6 1,3-diphenyl-2-(2',3',
5'-tri-O-benzyl-β-D-ribofuranosyl)imidazolidine in 250ml of
dichloromethane. After 5 minutes at 0°C the mixture was allowed to
come to room temperature over a period of 1 hour. The reaction was
found to still contain some unreacted 6 after this period of time.
and was thus subjected to flash chromatography on silica gel using (2:1) ether hexane as eluent. The fractions containing the product were then combined to yield 22.8g (48%) of a colorless oil.

2,5-Anhydro-3,4,6-tri-0-benzoyl-β-D-allose N-methyl nitrone 10

A mixture of (1.12g, 1.90mmol) of 2,5-anhydro-3,4,6-tri-O-benzoyl-β-D-allose, (0.161g, 1.93mol) of N-methyl-hydroxylamine hydrochloride, and (0.183g, 2.23mmol) of sodium acetate in 5ml of water was stirred for 12 hours at room temperature. The resulting solution was extracted with chloroform, and the combined extracts were combined, dried with CaCl₂, and concentrated under reduced pressure to yield 736mg, (77%) of a yellow solid after flash chromatography on silica gel using 10:1 hexane ethyl acetate as eluent, mp (112-114°C), IR (neat thin film CH₂Cl₂), (C=O) 1714.8 cm⁻¹, (C=O) 1595.3, 1525.0 cm⁻¹, (N-O), 1264.8, ¹H NMR (CDCl₃), δ 7.88-8.15 multiplet (5H, 6'Bz), δ 7.71 doublet (C₃H), δ 7.15-7.50 multiplet (10H, 4', 5'Bz), δ 6.54 doublet of doublets (C₂H), δ 5.27 doublet of doublets (C₂H), δ 5.21 singlet (NCH₃), δ 4.01 multiplet (C₁H, C₅H), δ 3.62, ¹³C NMR (CDCl₃) δ 165.447, 165.446, 165.445, 150.104, 146.532, 132.744, 129.195, 122.941, 125.531, 115.275, 112.426, 57.654, 52.297, Analysis calculated for C₂₆H₂₅N0₇, C 66.79, H 5.01, N 2.78, found: C 68.90, H 5.08, N 2.65.

2,5-Anhydro-3,4,6-tri-0-benzyl-β-D-allose N-methyl nitrone 8

A mixture of 2,5-anhydro-3,4,6-tri-0-benzyl-β-D-allose (1.119g, 1.90mmol) of N-methyl hydroxylamine hydrochloride, and
(.183g, 2.23mmol) of sodium acetate in 5ml of water was stirred for 12 hours at room temperature. The resulting solution was extracted with 3 x 25ml of chloroform, and the combined extracts were combined, dried with CaCl₂, and concentrated under reduced pressure to yield .657g, 80% after flash chromatography using 4:1 petroleum ether:chloroform then 2:1 petroleum ether:chloroform as eluents, mp 133-135°C, IR (neat thin film CH₂Cl₂) (C=N) 1318.2 cm⁻¹, (N-O) 1264.8 cm⁻¹, ¹H NMR (CDCl₃) δ 8.07 doublet (C₁H), δ 7.25-7.53 multiplet (15H, C₃, C₅, C₆, Bn), δ 7.00 broad singlet (C₂H, C₃H), δ 4.74 multiplet (C₄H, C₅H, C₆H₉, C₆H₇) δ 4.69 singlet (NCH₃), δ 3.9 broad singlet (6H, CH₂Ar), ¹³C NMR (CDCl₃) δ 148.299, 138.294, 132.778, 128.348, 128.291, 128.090, 126.333, 116.645, 112.278, 104.566, 87.052, 85.142, 72.012, 66.479, 54.672, 48.026. Analysis calculated for C₂₈H₃₁N₀₅, C 72.86, H 6.77, N 3.04, found: C 73.25, H 6.75, N 3.03.

3-(2',3',5'-Tri-O-benzoyl-β-D-ribofuranosyl)-2-methyl-2H-isoxazole-4,5-dicarboxylic acid dimethyl ester 11

A solution of (503mg, 1.0mmol) of 2,5-anhydro-3,4,6-tri-O-benzoyl-β-D-allose-N-methyl-nitrone 10 and (156mg, 1.1mmol) of dimethyl acetylene dicarboxylate in 5ml of anhydrous benzene was heated to reflux for 6.0 hours or until reaction was complete as shown by TLC. The reaction mixture was allowed to cool to room temperature at which time it was subjected to flash chromatography on silica gel using 1:1 chloroform:ethyl acetate as the eluent. The yield of pure product (yellow oil) was 432mg, (67%) and had the following characteristics: IR (CH₂Cl₂ neat thin film) (C=O)
1724 cm⁻¹, ¹H NMR (CDCl₃) δ 9.63 singlet (C₁H), δ 8.0-8.12 multiplet (5H, C₆Bz), δ 7.63-7.35 multiplet (10H, C₅, C₄, Bz), δ 7.22 doublet (C₂H, C₃H), δ 6.66 doublet (C₄H), δ 5.36 singlet (N-CH₃), δ 5.24 multiplet (C₅H), δ 3.92-3.65 multiplet (C₆H₉, C₆H₅), δ 3.73 broad singlet (2H, CO₂Me) Analysis calculated for C₃₅H₉₅NO₁₂, C 63.25, H 4.84, N 2.17, found C 63.76, H 4.91, N 2.12.

3-(2',3',5'-Tri-O-benzoyl-β-D-ribofuranosyl)-2,5-dimethyl-2,5H-Pyrrole 3,4-d isoxazolidine-4,6-dione 12

A solution of (503mg, 1.0mmol) of 2,5-anhydro-3,4,6-tri-O-benzoyl-β-D-allose-N-methyl-nitrone 1£ and (122mg, 1.1mmol) of N-methyl maleimide in 5ml of anhydrous benzene was heated to reflux for 3 hours or until complete by TLC. The reaction mixture was then allowed to cool to room temperature at which time it was subjected to flash chromatography on silica gel using 2:1 chloroform ethyl acetate as the eluent. The yield of product (a yellow oil) was 601mg, 97% and had the following characteristics: IR (neat thin film), (C=O) 1712 cm⁻¹, 1735 cm⁻¹, ¹H NMR (CDCl₃) δ 8.10-7.94, multiplet (C₅', Bz, 5H), δ 7.58-7.26 multiplet (C₄', C₃', Bz 10H), δ 5.83-5.70 multiplet (C₃H, C₅'H), δ 4.66-4.41 multiplet (C₄'H, C₅'H, C₄'H, C₃'H, C₅'H), δ 4.03-3.66 doublet of doublets (C₅H), δ 3.55-3.47 doublet of doublets (C₃H), δ 2.97 singlet (N₂-CH₃), δ 2.76 doublet (N₃-CH₅), ¹³C NMR δ 175.665, 17.629, 166.426, 165.426, 165.251, 133.396, 133.174, 129.695, 129.404, 199.452, 83.265, 81.213, 79.873, 79.773, 77.641, 73.762, 72.735, 72.276, 71.175, 64.000, 63.633, 52.176, 51.265, 46.256, 45.666, 25.227.
Analysis calculated for C_{33}H_{30}N_{2}O_{10}, C 64.49, H 4.92, N 4.56, found C 64.67, H 5.02, N 4.52.

3-(2',3',5'-Tri-O-benzoyl-β-D-ribofuranosyl)-2-methyl-2H-imidazolidine-4,5-dicarboxylic acid diethyl ester 13

A solution of (503mg, 1.0mmol) of 2,5-anhydro-3,4,6-tri-O-benzoyl-β-D-allose-N-methyl nitrone 10 and (189mg, 1.1mmol) of diethylmaleate in 5ml of benzene was heated to reflux for 12 hours or until complete by TLC. The reaction mixture was then allowed to cool to room temperature at which time it was subjected to flash chromatography on silica gel using 1:1 chloroform:ethyl acetate as the eluent. The yield of product (a colorless oil) was 540mg, 80% and had the following characteristics: IR (neat thin film) (C=O) 1735.9 cm\(^{-1}\), 1728.2 cm\(^{-1}\). Analysis calculated for C_{36}H_{37}N_{2}O_{12}, C 64.00, H 5.52, N 2.07, found C 64.31, H 5.70, N 1.94.

3-(2,3,5-Tri-O-benzyl-β-D-ribofuranosyl)-2-methyl-2H-imidazole-4,5-dicarboxylic acid dimethyl ester 14

A solution of (923mg, 2.0mmol) of 2,5-anhydro-2,3,5-tri-O-benzyl-β-D-allose-N-methyl nitrone 8 and (313mg, 2.2mmol) of dimethyl acetylene dicarboxylate in 10ml of anhydrous benzene was heated to reflux for 12 hours or until complete by TLC. The reaction mixture was then concentrated under reduced pressure and subjected to flash chromatography on silica gel using 2:1 chloroform:ethyl acetate as eluent to yield 760mg, 63% of a yellow oil, having the following characteristics: IR (neat thin film) (C=O) 1728.9 cm\(^{-1}\). Analysis calculated for C_{31}H_{37}N_{2}O_{9}, C 67.65, H 6.18, N 2.32, found C 67.52,


H 5.79, N 2.30.

3-(2',3',5'-Tri-O-benzyl-β-D-ribofuranosyl)-2,5-dimethyl-2,5H-
pyrrole 3,4-d isoxazolidine-4,6-dione 15

A solution of (923mg, 2.0mmol) of 2,5-anhydro-2,3,5-tri-O-
benzyl-β-D-allose-N-methyl nitrone 8 and (244mg, 2.2mmol) of N-methyl
maleimide in 10ml of anhydrous benzene was heated to reflux for 12
hours or until the reaction was shown to be complete by TLC. The
reaction mixture was then concentrated under reduced pressure and
subjected to flash chromatography on silica gel using 1:1 chloroform:
ethyl acetate as the eluent to yield 710mg, 62% of a colorless oil
having the following characteristics: IR (neat thin film) (C=O)
1709.2 cm⁻¹. Analysis calculated for C₃₅H₃₆N₂O₇, C 69.21, H 6.34,
N 4.89, found C 69.43, H 6.41, N 5.01.

3-(2',3',5'-Tri-O-benzyl-β-D-ribofuranosyl)-2-methyl-2H-
isoxazolidine-4,5-dicarboxylic acid diethyl ester 16

A solution of (923mg, 2.0mmol) of 2,5-anhydro-2,3,5-tri-O-
benzyl-β-D-allose-N-methyl nitrone 8 and (.32ml, 2.0mmol) of diethyl
maleate in 5.0ml of anhydrous benzene was heated to reflux for 12
hours or until the reaction was shown to be complete by TLC. The
reaction mixture was then concentrated under reduced pressure and
subjected to flash chromatography on silica gel using 5:1 chloroform:
ethyl acetate as the eluent to yield 612mg, 82% of a yellow oil with
the following characteristics: IR (neat thin film) (C=O) 1736.2
cm⁻¹. Analysis calculated for C₅₆H₄₅N₂O₉, C 68.23, H 6.84, N 2.21,
found C 68.09, H 6.72, N 2.35.

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
A solution of (500mg, 1.0mmol) of 1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-isothiocyanate and (150mg, 1.1mmol) of the potassium salt of glutaconaldehyde in 15ml of DMF (dimechylformamide) is heated to 60°C for 5.5 hours with stirring. A second portion of the potassium salt of glutaconaldehyde (150mg) was added and the reaction stirred for an additional 2 hours. The dark red reaction mixture was allowed to cool to room temperature and was then poured into 50ml of cool water at 0°C. This orange-red mixture was placed in a lighter than water extractor and subsequently extracted with ether for 3 weeks. The ether fractions were collected every three days and concentrated to yield 414mg, 71% of the crude product which still contained some unreacted isothiocyanate. To remove this contaminant the ether concentrate was flash chromatographed on silica gel using 3:1 hexane:ethyl acetate to yield 396mg, 68% of the pure product with the following characteristics: mp (58-59°C) orange crystals very hygroscopic, IR (neat thin film CH₂Cl₂), (C=O) ester 1735.9 cm⁻¹, (C=H) aldehyde 2853.9 cm⁻¹, ¹H NMR (CDCl₃) δ 10.65 singlet (C=H ald), δ 8.33-7.76 multiplet (5H, C₃', Bz), δ 7.43-7.13 multiplet (12H, C₃', C₄', Bz, ABX pyridine ring protons), δ 5.81-5.54 multiplet (C₂H, C₃H, C₄H), δ 4.66-4.55 multiplet (C₄H, C₃aH, C₃bH), ¹³C NMR (CDCl₃) δ 169.143, 163.998, 163.766, 162.989, 13.912, 130.760, 130.611, 127.278, 126.980, 126.667, 126.631, 126.221, 125.998, 125.661, 124.939, 98.042, 93.704, 89.403, 77.001, 74.702, 62.852. Analysis calculated...
1-(g-P-Ribofuranosyl)-2(1H)-thiono-3-pyridine carboxaldehyde 18

The pyridine nucleoside 17, (1.16 g, 2.0 mmol) was added to a solution of NaOH (150 mg, 3.75 mmol) in 21 ml of dry methanol and was then stirred overnight at room temperature. After the reaction was deemed complete by TLC, the solution was concentrated under reduced pressure and the residue added to 100 ml of water and then extracted with 3 x 200 ml portions of benzene (to remove methyl benzoate). The combined benzene extracts were then washed once with 100 ml of water and then discarded. The water solutions were then combined and concentrated under high vacuum bath temperature no higher than 80°C. The light orange oil was then flash chromatographed on Florisil using 4:1 chloroform methanol as the eluent to yield (531 mg, 98.5%) of the deprotected nucleoside as a light yellow powder. The compound had the following characteristics: mp (90–94°C) with decomposition, IR (nujol mull) (C=O) aldehyde 1685.2 cm⁻¹, (C-S) 1225.5 cm⁻¹, (C-H) aldehyde 2850.7 cm⁻¹, ¹H NMR (D₂O+DMSO₆), ¹³C NMR (D₂O+DMSO₆) δ 169.949, 169.807, 169.612, 169.370, 168.985, 81.373, 70.995, 69.262, 66.753, 62.928. Analysis calculated for C₉H₈N₂O₅S, C 48.70, H 4.83, N 5.16, S 11.82, found C 48.63, H 4.51, N 5.13, S 11.41.

1-(2',3'-Dideoxy-2',3'-didehydro-β-D-ribofuranosyl)-2(1H)-thiono-3-pyridine carboxaldehyde 19

A suspension of (1.90 g, 7.0 mmol) of the deprotected nucleosides
20

18 in 70ml of acetonitrile was treated with 7ml of 10:1 acetonitrile/water and (4.2ml, 28.0mmol) of α-acetoxyisobutryl bromide. The solution was stirred at room temperature for 1 hour. The clear yellow solution which resulted was treated with aqueous sodium bicarbonate (100ml) and was then extracted with 3 x 50ml of ethyl acetate. Analysis of the extract showed 2 bonds via TLC which corresponded to the formation of an isomeric pair of 2',3' trans bromo acetates. The extracts were concentrated under reduced pressure to a yellow oil which was then dissolved in (35ml, 371mmol) of acetic anhydride. To this stirred solution was added (35.0ml, 434mmol) of dry pyridine and (0.7g, 5.6mmol) of DMAP (4-dimethyl amino-pyridine). This reaction mixture was allowed to stand undisturbed overnight at room temperature. The reaction mixture was then poured into 400ml of ice water and then extracted with 3 x 200ml of chloroform. The chloroform extracts were combined, washed with 3 x 250ml of water, dried (CaCl₂), and then concentrated under reduced pressure. The residue which resulted was then dissolved in 70ml of DMF and stirred with 20g of zinc-copper couple for 1 hour at room temperature. Filtration of the mixture through Celite, concentration under reduced pressure, and deacylation with KCN/MeOH at room temperature, followed by chromatography on Fluorosil (2:1) chloroform/methanol, yielded (1.20g, 72%) of the product with the following characteristics: mp 150-160°C IR (nujol mull), (6=0) 1685 cm⁻¹. Analysis calculated for C₁₁H₁₃NO₃S, C 55.68, H 4.67, N 5.90, S 13.52, found C 55.74, H 4.61, N 5.86, S 13.60.

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
To a solution of (12.61g, 25.0mmol) of 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl acetate in 75ml of dry nitromethane was added (9.95ml, 75.0mmol) of trimethylsilylazide and stirred while being warmed to 35-37°C. Freshly redistilled boron trifluoride etherate (6.15ml, 50.0mmol) was then added and the reaction was stirred for at least 12 hours. After this time the mixture was concentrated under reduced pressure and the residue dissolved in 80ml of dichloromethane. The dichloromethane solution was then washed successively with saturated aqueous Na₂HCO₃ (2 x 25ml), water (2 x 25ml), and then dried with Na₂SO₄. This solution was once again concentrated to yield (9.02g, 74%) of the product as a yellow oil having the following characteristics: IR (neat thin film), (N=N=N) 2122.6 cm⁻¹, (C=O) 1735.9 cm⁻¹. Analysis calculated for C₂₁H₂₁N₃O₇, C 64.06, H 4.34, N 8.62, found C 64.42, H 4.33, N 8.68.

Triethyl phosphite (4.29ml, 25.0mmol) was added to a solution of the ribofuranosyl azide 20 (12.18g, 25.0mmol) in 50ml of anhydrous benzene. The solution was stirred for 6 hours at room temperature and then allowed to stand for 72 hours (during which time the N₂(g) was allowed to escape through a cannula inserted in the septum). The solution was then concentrated under vacuum to yield yellow-brown crystals which can be recrystallized from anhydrous diethylether or flash chromatographed on silica gel using first 2:1 hexane/
ethylacetate then 1:1 hexane/ethylacetate. The yield of the product was (15.3g, 98%) and the following characteristics: IR (neat thin film) (C=O) 1735.9 cm\(^{-1}\), (N=P) 1980.2 cm\(^{-1}\), \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 8.12-7.92 multiplet, (5H, C\(_5\)' Bz), \(\delta\) 7.58-7.30 multiplet (10H, C\(_4\)', C\(_3\)' Bz), \(\delta\) 5.81-5.77 multiplet, (C\(_1\)' H), \(\delta\) 5.50-5.30, multiplet (C\(_2\)' H), \(\delta\) 4.66-4.48, multiplet (C\(_3\)' H, C\(_4\)' H), \(\delta\) 4.22-3.99 multiplet, (8H, C\(_5\)' H\(_a\), C\(_5\)' H\(_b\), -CH\(_2\)O), \(\delta\) 1.44-1.17 multiplet, (9H, CH\(_3\)), \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 166.116, 165.264, 133.376, 133.138, 129.657, 129.657, 129.024, 128.437, 128.334, 85.948, 78.739, 78.188, 75.029, 72.523, 64.374, 63.523, 62.644, 15.973, 15.855. Analysis calculated for C\(_{32}\)H\(_{36}\)NO\(_{10}\), C 61.44, H 5.80, N 2.24, P 4.95, found C 57.74, H 5.60, N 3.33, P 5.60.

1-(2,3,5-Tri-O-benzoyl-\(\beta\)-D-ribofuranosyl)-N-diethyl-phosphoroamidates

Water (45.0mg, 2.50mmol) was added to a solution of the ribofuranosyl iminophosphorane \(21\) (1.56g, 2.50mmol) in 7ml of anhydrous benzene. The mixture was stirred at reflux for one hour and then dried using MgSO\(_4\). The solution crystallizes almost immediately upon cooling to yield (1.45g, 97%) of the product as white crystals mp (122-123°C), IR (CH\(_2\)Cl\(_2\) thin film) (N-H) 3227.5 cm\(^{-1}\), (P=O) 1284.2 cm\(^{-1}\), \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 8.12-7.91 multiplet (5H, C\(_5\)' Bz), \(\delta\) 7.55-7.29 multiplet (10H, C\(_4\)', C\(_3\)' Bz), \(\delta\) 5.86 triplet (C\(_1\)' H), \(\delta\) 4.67-4.54 multiplet (C\(_3\)' H, C\(_4\)' H, C\(_5\)' H\(_a\)), \(\delta\) 4.16-4.00 multiplet (5H C\(_5\)' H\(_a\),-CH\(_2\)O), \(\delta\) 1.34-1.13 triplet (6H, CH\(_3\)-), \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 165.985, 165.137, 133.191, 132.909, 129.526, 129.151, 128.951, 128.193, 86.031, 78.490, 75.151, 71.664, 64.485, 62.389, 15.751.

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
Analysis calculated for C_{30}H_{52}O_{10}N_{P}, C 60.30, H 5.40, N 2.34, P 5.18,
found C 60.37, H 5.42, N 2.33, P 5.12.

1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl-azide 23

To a solution of (9.75g, 25.0mmol) of β-D-glucose pentaacetate
in 75ml of dry nitromethane was added (9.95ml, 75.0mmol) of
trimethylsilylazide and stirred while being warmed to 35-37°C.
Freshly distilled boron trifluoride etherate (6.15ml, 50.0mmol)
was then added and the reaction was stirred for 12 hours. After
this time, the mixture was concentrated under vacuo and the residue
was dissolved in 80ml of dichloromethane. This solution was washed
successively with saturated aqueous NaHCO₃ (2 x 25ml), water (2 x
25ml), and then dried over Na₂SO₄. The dry dichloromethane solution
was again concentrated under reduced pressure to a volume of 15ml
at which time absolute ethyl alcohol was added (25-50ml). The
product crystallized out of the solution as white needles (6.63g,
71%) with the following characteristics: mp (123-124°C), IR (CH₂Cl₂
thin film) (N=N=N) 2122.6 cm⁻¹, (C=O) 1750.0 cm⁻¹, ¹H NMR (CDCl₃)
δ 5.29-4.91 multiplet (3H, C₁'H, C₂'H; C₃'H), δ 4.66 doublet (C₄'H)
δ 4.31-4.19 (2H, C₅'H, C₆'H), δ 3.67-3.62 multiplet (C₆'H), δ 2.10-
1.98 four singlets (12H, CH₃'s), ¹³C NMR (CDCl₃) δ 170.294, 169.822,
169.097, 168.955, 87.731, 73.947, 72.552, 70.658, 67.956, 61.623,
20.403, 20.278. Analysis calculated for C_{14}H_{19}N_{3}O_{6}, C 45.04,
H 5.03, N 11.26, found C 45.25, H 5.03, N 11.23.

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
Triethyl phosphite (1.08ml, 6.29mmol) was added at 25-30°C to a stirred solution of the glucopyranosyl azide 23 (2.35g, 6.29mmol) in 20ml of benzene and 2ml of dichloromethane. The solution was stirred for 6 hours and then allowed to stand undisturbed for 72 hours during which time the N₂(g) was released through a cannula inserted in the septum. Following this period, the solution is concentrated under vacuum. The crystals (3.12g) which result can be recrystallized from benzene and are obtained in 97% yield. The compound had the following characteristics: mp (110-112°C), IR (KBr pellet), (N=P) 2115.6 cm⁻¹, ¹H NMR (CDCl₃), δ 5.11-4.52 multiplet (5F C₁'H, C₂'H, C₃'H, C₄'H, C₅'H), δ 4.15-3.49 multiplet and quartet (8H, C₆'Hₐ, C₆'Hₗ, CH₂), δ 1.98-1.68 multiplet (12H, CH₃'s of acetate), δ 1.23-1.13 triplet (9H CH₃'s of ethyl). Analysis calculated for C₁₀H₁₅N₃O₁₂P, C 46.97, H 6.70, N 2.74, P 6.05, found C 44.87, H 5.66, N 3.89, P 7.93.

Water (33mg, 1.83mmol) was added to a solution of the N-glucosyl iminophosphorane 24 (937mg, 1.83mmol) in 10ml of benzene. The mixture was stirred at reflux for one hour. The resulting solution was then dried over MgSO₄ and allowed to crystallize. The compound, a white crystalline solid, was obtained in 95% yield (855mg) and had the following characteristics: mp 103-105°C, IR (CHCl₃ thin film) (P=O) 2129.7 cm⁻¹, (C=O) 1735.9 cm⁻¹. Analysis calculated for C₁₂H₁₅N₃O₁₂P, C 44.72, H 6.25, N 2.90, P 6.41, found C 44.69, H 5.72, N 3.01.
1-(2,3,4,6-Tetra-O-acetyl-β-D-galactopyranosyl) azide 26

To a solution of (9.75g, 25.0mmol) of β-D-galactose pentaacetate in 75ml of dry nitromethane was added (9.95ml, 75.0mmol) of trimethylsilylazide and stirred while being warmed to 35-37°C. Freshly distilled boron trifluoride etherate (6.15ml, 50.0mmol) was then added and the reaction was stirred for 12 hours. After this period the mixture was concentrated under reduced pressure and the residue was dissolved in 80ml of dichloromethane. This solution was washed successively with saturated aqueous NaHCO₃ (2 x 25ml), water (2 x 25ml) and then dried over Na₂SO₄. The dry dichloromethane solution was once again concentrated to a volume of 15ml at which time absolute ethyl alcohol was added (25-50ml) to initiate crystallization. The yield of the product was (6.34g, 68%) and had the following characteristics: mp (98-100°C), IR (CH₂Cl₂ thin film) (N=N=N) 2122.6 cm⁻¹, (C=O) 1750.0 cm⁻¹, ¹H NMR (CDCl₃) δ 5.24 doublet (C₁'H), δ 5.20-5.04 (doublet of doublets) (C₂'H, C₃'H), δ 4.66 doublet (C₄'H), δ 4.20-4.09 multiplet (C₅'H, C₆'Hₐ, C₆'Hₕ), δ 2.27-1.88 four singlets (12H, CH₃'s) ¹³C NMR (CDCl₃) δ 169.834, 169.677, 169.441, 166.880, 87.833, 72.573, 70.411, 67.931, 66.752, 60.956, 20.044. Analysis calculated for C₁₄H₁₅N₃O₉, C 45.04, H 5.13, N 11.26, found C 45.31, H 4.97, N 10.99.

1-(2,3,4,6-Tetra-O-acetyl-β-D-galactopyranosyl)-diethyl-N-iminophosphorane 27

Triethyl phosphite (2.55ml, 14.8mmol) was added to a stirred
solution of the galactopyranosyl azide $\text{26}$ (5.55g, 14.8mmol) in 20ml of anhydrous benzene and 2ml of dichloromethane. The solution was stirred for 6 hours and then allowed to stand undisturbed for 72 hours during which time the $N_2$(g) was allowed to escape through a cannula inserted through the septum of the flask. After this period of time, the solution was concentrated under reduced pressure to yield (11.7g) and had the following characteristics: IR (neat thin film), (N=P) 2115.6 cm$^{-1}$, (C=O) 1750.0 cm$^{-1}$, $^1$H NMR (DMSO$_d$$_6$) $\delta$ 6.15 doublet ($C_1'H$), $\delta$ 5.25-4.96 multiplet ($C_6'H_a, C_6'H_b$), $\delta$ 4.21-3.83 multiplet ($C_5'H, C_6'H_a, C_6'H_b$), $\delta$ 3.37 singlet (9H, CH$_3$'s acetates), $\delta$ 2.14-1.89 multiplet (12H, CH$_3$ acetate, CH$_3$'s ethyl), $\delta$ 1.26-1.14 (6H,-CH$_2$'s). $^{13}$C NMR (DMSO$_d$$_6$) $\delta$ 169.949, 169.747, 169.370, 166.985, 81.372, 70.995, 69.464, 67.653, 64.766, 62.928, 20.270, 15.998. Analysis calculated for C$_{20}$H$_{33}$NO$_{12}$P, C 46.97, H 6.70, N 2.74, P 6.05, found C 43.29, H 6.59, N 2.53, P 6.11.

1-(2,3,4,6-Tetra-O-acetyl-8-D-glactopyranosyl)-N-diethyl phosphoramoide $\text{28}$

Water (0.33, 1.83mmol) was added to a solution of the galactopyranosyl iminophosphorane (937mg, 1.83mmol) in 25ml of benzene. The mixture was stirred at reflux for one hour. The resulting solution was then dried over MgSO$_4$ and then allowed to crystallize. The product obtained in 84% yield 889mg has the following characteristics: mp 136-138°C, IR (neat thin film) (C=O) 1750 cm$^{-1}$, (P=O) 2115.6 cm$^{-1}$. Analysis calculated for C$_{18}$H$_{30}$NO$_{12}$P, C 44.72, H 6.25, N 2.90, P6.41, found C 44.84, H 6.17, N 2.94, P 6.49.
N-Ethyl-2,5-anhydro-3,4,6-Tri-O-benzoyl-β-D-allononitrilium tetrafluoroborate 29

To a stirred solution of (8.51g, 18.0mmol) of 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl cyanide 2 in 20ml of dichloromethane was added (18.0ml, 18.0mmol) of triethyloxonium tetrafluoroborate via syringe. The reaction was stirred at 25°C under argon and was found to be complete by TLC within 5-10 minutes. Upon addition of ethyl Meerwein's reagent, the golden yellow solution became bright orange. The solution was then stored in the refrigerator under Argon until the next step (because of its powerful electrophilicity the salt was easily converted to the amide upon exposure to water, thus it was handled under an inert atmosphere). The yield of the compound prepared in the above manner was nearly quantitative.

N-Ethyl-2,5-anhydro-3,4,6-tri-O-benzoyl-β-D-allono-imine 30

To the refrigerated reaction mixture of the nitrilium salt 29 was added (3.51ml, 22.0mmol) (1.2eq.) of triethylsilane and the reaction mixture was stirred under argon for 7 hours. During the reaction period, the solution turned color from bright orange to an opaque yellow. The reaction mixture was filtered and the dichloromethane solution containing the imine was concentrated under vacuum. The yellow oil was transferred only under an inert atmosphere and had the following characteristics: IR (neat thin film) (C=\text{N}) (C=\text{O}). Analysis calculated for C_{29}H_{27}NO_{7}, C 69.45, H 5.43, N 2.79, found C 69.63, H 5.51, N 2.71.
2,5-Anhydro-3,4,6-tri-O-benzoyl-β-D-allose 7 (An alternative approach)

The N-ethyl imine derived from 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl-cyanide 30 (9.02g, 18.0mmol) was treated with 200ml of a 1:1 mixture of tetrahydrofuran and water and the mixture was stirred at reflux for 3 hours. The reaction mixture was then concentrated under reduced pressure to yield a yellow-brown oil which is almost entirely aldehyde contaminated with some unhydrolyzed imine. Since this aldehyde was very unstable as mentioned earlier, it was used soon after its production. The spectral characteristics of this compound have been described already, see compound 7.

3-(2',3',5'-Tri-O-benzoyl-β-D-ribofuranosyl)-2-thiono-6-methyl-3H-1,3-oxazine-4-one 32

A solution of (2.52g, 5.0mmol) of 1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl) isothiocyanate and (1.07g, 7.5mmol) of 2,2,6-timethyl-1,3-dioxin-4-one was stirred and heated at 120-130°C for 15-20 minutes. The acetone produced during the reaction was removed during the heating period. After cooling of the reaction mixture, the oily residue was flash chromatographed on silica gel using a gradient elution sequence of first 4:1 hexane/ethylacetate, 3:1 hexane/ethylacetate, and then 1:1 hexane/ethylacetate. The product isolated in the second fraction was a yellow crystal with mp (°C) obtained in 58% (1.65g) yield: IR (neat thin film) (C=O) 1735.9 cm⁻¹, (C=S) 1100.3 cm⁻¹, ¹H NMR (CDCl₃) δ 7.58-7.13 multiplet (16H, 2',3',5',Bz C₅H oxazine) δ 6.54 singlet (3H, C₁'H, C₂'H, C₃'H), δ 5.29 singlet
(3H, C_4'H, C_5'H_a, C_5'H_b), δ 2.08 singlet (3H, CH₃ oxazine ring),

$^{13}$C NMR (CDCl₃) δ 200.332, 175.617, 149.056, 146.436, 141.156,
129.897, 128.080, 127.349, 110.035, 29.302. Analysis calculated for
C₃₁H₂₅N₀₂S, C 65.14, H 4.41, N 2.45, S 5.61, found C 65.22, H 4.41,
N 2.51, S 5.67.

6-Methyl-4-thiomethyl-3-acetyl-2(1H)-thiono-1-phenyl-pyridine 33

A solution of (7.43g, 55.0mmol) of phenylisothiocyanate in 25ml
of dimethylsulfoxide was added to a stirred solution of the enolate
derived from 1,5-dimethyl-3-thiomethyl-pentane-dione (9.7g, 50.0mmol)
in 25ml of dimethylsulfoxide. The mixture was stirred for 1 hour at
40°C and was then poured into water at 0°C. This solution was
stirred for an additional 30 minutes, then saturated with sodium
chloride, and the pH adjusted to 7.0 by the addition of 4N HCl.
The precipitated product was filtered, dried, and recrystallized
from benzene. It was obtained in 66% yield (9.55g) and had a
melting point consistent with that reported in the literature
(213-214°C).

2-Amino-4,7-dimethyl-6-phenyl-5-thiono-6(H)-pyrido 4,3-d pyrimidine 34

A solution of (2.89g, 10.0mmol) of the substituted pyridine
thione 40, (955mg, 10.0mmol) of guanidine HCl, and (902mg, 11.0mmol)
of sodium acetate in 20ml of ethyl alcohol was heated at reflux for
two hours or until complete by TLC. The reaction mixture was then
cooled at which time yellow crystals of the product began to form.
The product was obtained in 82% yield (2.22g) and had the following characteristics: mp (°C), IR (CH₂Cl₂ thin film) (N-H) 3225.0 cm⁻¹ (N-C=S) 1100.3 cm⁻¹, ¹H NMR (CDCl₃) δ 7.51-7.43 multiplet (3H, phenyl), δ 7.12-7.09 multiplet (2H, phenyl), δ 6.52 singlet (1H, pyridine ring), δ 2.57 singlet (3H, CH₃ pyridine ring), δ 2.45 singlet (3H, CH₃), δ 2.03 singlet (2H, NH₂). Analysis calculated for C₁₄H₁₃N₄S, C 61.97, H 5.57, N 20.65, S 11.81, found C 63.24, H 5.71, N 19.87, S 11.87.

2-Trimethylsilylethoxymethylisothiocyanate 35

To a stirred solution of 1,3-deoxolane (10.2g, 138mmol) in cyclohexane (30.0ml) at -78°C under N₂ was added cooled trimethylsilyliodide (25.0g, 125mmol). Conversion to the product iodomethyl ether was essentially complete in less than 10 minutes; ¹H NMR (CDCl₃) δ 0.02 singlet (9H, Si(CH₃)₃), δ 3.67 multiplet (4H, CH₂CH₂), δ 5.87 singlet (2H, ICH₂0). To this reaction mixture was added (22.9g, 138mmol) of silverthiocyanate and the reaction was heated to reflux 15-20 minutes or until the precipitation of yellow-silver iodide ceases. The reaction mixture was filtered and the precipitate washed with cyclohexane. The filtrant and the washings were combined, concentrated under reduced pressure, and the residue vacuum distilled (67-72°C at 500 um Hg) to yield 23.4g of the product (91.0%), IR (neat thin film) (N=C=S) 2103.7 cm⁻¹, ¹H NMR (CDCl₃) δ 0.20 singlet (9H, Si(CH₃)₃), δ 3.79 multiplet (4H, CH₂CH₂), δ 4.92 multiplet (2H, OCH₂NCS). Analysis calculated for C₇H₁₃N₀₂SSi, C 40.94, H 7.36, N 6.82, S 15.62, found C 41.28, H 7.52, N 6.65, S 15.56.
1-(2'-Trimethylsilylethoxymethyl)-2(1H)-thione-3-pyridine-carboxaldehyde 36

To a solution of glutaraldehyde potassium salt (1.36g, 10.0mmol) in 10ml of DMF was added the 2-Trimethylsilylethoxymethyl isothiocyanate 45 (2.05g, 10.0mmol). The mixture was stirred for 25 hours at 50-60°C or until complete by TLC. The reaction mixture was then poured on 100ml of ice water and extracted with chloroform (3 x 100ml). The dark red solution was then concentrated under reduced pressure and subjected to flash chromatography on silica gel using first 1:1 ether/hexane then 4:1 chloroform/methanol. The product was isolated in 48% yield (1.37g) as a viscous red oil with the following characteristics: IR (neat thin film in CH₂Cl₂), ν(C=O) aldehyde 1679.7 cm⁻¹, ¹H NMR (CDCl₃) δ 9.45 singlet (1H, aldehyde), δ 7.57 doublet of doublets (1H, X of ABX system), δ 7.40 doublet of doublets (1H, A of ABX system), δ 7.23 singlet (1H, B of ABX system), δ 4.98 broad singlet (2H, -OCH₂-N), δ 4.45-3.59 multiplet (4H, -CH₂CH₂-), δ 0.02 singlet (9H, (CH₃)₃Si). Analysis calculated for C₁₂H₁₉N₀₃S₅Si, C 50.50, H 6.71, N 4.91, S 11.23, found C 50.41, H 6.58, N 5.07, S 11.26.

2-Acetoxy-ethoxy-methyl-isothiocyanate 37

Freshly distilled acetylchloride (39.2g, 500mmol) was added dropwise to (55.5g, 750mmol) of 1,3-dioxolane with stirring in a flame dried flask. After one third of the acetyl chloride was added, the temperature was raised to 70°C or until the mixture begins to reflux. The remaining two thirds of acetyl chloride was added over
a period of 45 minutes. Upon completion of the acetyl chloride addition, the solution was refluxed for 8 hours and then fractionally distilled to give 67.0g (88%) of a colorless liquid with boiling point 74-76°C at 5.0 torr: ¹H NMR (CDCl₃) δ 2.05 singlet (3H, CH₃CO), δ 3.80 multiplet (2H, CH₂O), δ 4.20 multiplet (2H, AcOCH₂⁻), δ 5.50 singlet (2H, OCH₂Cl). To a solution of (67.0g, 440mmol) of the chloromethoxy ethyl acetate in 100ml of toluene was added (55.5g, 530mmol) of potassium thiocyanate. The solution was stirred at reflux for 10 hours. The pale yellow solution was filtered and the filtrate fractionally distilled to give 58.7g (76%) of a colorless liquid with a boiling point of 93°C at 0.65 torr: IR (neat thin film) (N=S=O) 2150.2 cm⁻¹, (C=O) 1735.0 cm⁻¹; ¹H NMR (CDCl₃) δ 2.05 singlet (3H, CH₃CO), δ 3.80 multiplet (2H, CH₂O), δ 4.20 multiplet (2H, AcOCH₂⁻), δ 5.0 singlet (2H, OCH₂N), ¹³C NMR (CDCl₃).

1-(2-Acetoxy-ethoxy-methyl)-2(1H)-thiono-pyridine-carboxaldehyde

A solution of (4.38g, 25.0mmol) of 2-acetoxy-ethoxy-methyl-isothiocyanate and (3.41g, 25.0mmol) of the potassium salt of glutaconaldehyde in 15ml of DMF was stirred at 72°C for 36 hours. The reaction mixture upon completion was poured on 150ml of cold water and then stirred for 2 hours. This solution was then extracted with 3 x 600ml portions of ethylacetate. The extracts were combined, dried over MgSO₄, and concentrated under reduced pressure to yield 2.7g (42%) of a dark red syrup which was subjected to flash chromatography on silica gel using 4:1 chloroform/methanol as the eluent. The isolated product had the following characteristics: IR (neat...
thin film), (C=O) acetate 1728.9 cm⁻¹, (C=O) aldehyde 1686.7 cm⁻¹.

Analysis calculated for C₁₁H₁₃NO₄S, C 51.75, H 5.13, N 5.49, S 12.56,
found C 48.33, H 5.84, N 5.43, S 12.60.
The synthesis of C-nucleosides has always been a challenging problem for synthetic chemists. C-nucleosides are a group of molecules containing ribose bound to the carbon atom of a heterocyclic aglycon, some of which are known to exhibit significant antibacterial, antiviral, and antitumor activities (1-38). Our entry into a new series of C-nucleosides involved the homologation of a suitable carbohydrate substrate with its inherent chirality. The desired configuration at the anomeric carbon of this substrate was $\beta$ since the majority of naturally occurring and bioactive C-nucleosides possess the $\beta$ configuration. The starting substrate chosen was 1-O-acetyl-2,3,5-tri-O-benzoyl-$\beta$-D-ribofuranose. This compound was homologated via cyanide ion with complete retention on configuration at the anomeric carbon atom. This transformation was accomplished through the use of the two pathways outlined below in Scheme 1 (39-42) and produced an anomerically pure C-glycoside 2.

Scheme 1

\[
\begin{align*}
\text{BzO} & \quad \text{OAc} \\
\text{BzO} & \quad \text{O} \\
\text{BzO} & \quad \text{BzO}
\end{align*}
\]

HBr(g), benzene

\[
\begin{align*}
0^\circ \text{C, 30 min, 88\%}
\end{align*}
\]

\[
\begin{align*}
\text{BzO} & \quad \text{O} \\
\text{BzO} & \quad \text{BzO} \\
\text{BzO} & \quad \text{Br}
\end{align*}
\]

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
Since the objective of this synthesis was the production of the N-methyl-nitrone, it was necessary to change the oxidation state of the nitrile to that of an aldehyde. This transformation was accomplished through a procedure developed by J. Moffatt and coworkers (46-49). The homoligated ribose aldehyde (2,3-anhydro-D-allose) was used in the synthesis of a number of nucleoside antibiotics such as showdomycin and pyrazomycin as well as pseudouridine (46-47). In our hands, use of the aldehyde was the most direct route to the target nitrone. Thus, reductive hydrolysis of the cyano function of 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl cyanide (see Scheme 2) in the presence of N,N'-diphenylethylenediamine, sodium hypophosphite, and Raney nickel in a mixture of pyridine, acetic acid, and water at 25°C led to the rapid synthesis of crystalline 1,3-diphenyl-2-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl) imidazolidine 4. The N,N'-diphenylethylenediamine reagent was developed by Wanzlick and Lochel for the selective conversion of aldehydes into 1,3-diphenylimidazolidine derivatives and has previously been used to trap aldehydes formed by the hydrogenation of nitriles (50,51).
The imidazolidine ring is very stable toward base but can be easily hydrolyzed to the corresponding aldehyde under acidic conditions. This property allows for modifications in the protecting benzoyl groups of the sugar moiety (see Scheme 3).

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
As shown in Scheme 3, treatment of the 1,3 diphenylimidazolidine derivative 4 with methanolic sodium methoxide led to smooth cleavage of the benzoyl protecting groups and resulted in the production of 1,3-diphenyl-2(β-D-ribofuranosyl) imidazolidine 5. This compound was subsequently benzylated using benzyl chloride and sodium hydride in dimethyl sulfoxide to give the tri-O-benzyl ether 6 (49).

As mentioned earlier, regeneration of the free aldehyde function from 1,3-diphenylimidazolidine derivatives was usually achieved by treatment with a heterogeneous mixture of ether and 3-6N hydrochloric acid. For our purposes a much milder condition was sought. The current literature suggested two possible routes (49) to the free aldehyde. The first method utilized p-toluenesulfonylic acid monohydrate in a mixture of acetone and methylene chloride at 0-20°C. This treatment led to the rapid precipitation of the p-toluenesulfonate salt of N,N'-diphenylethylenediamine which was easily removed by filtration or aqueous extraction. This method usually was only 85-90% complete (as shown by TLC) and the unreacted 1,3-diphenylimidazolidine derivative was found in later worked up products. An alternative method which was found to be more applicable to our unique needs was the use of Dowex 50(H+) resin (styrene sulfonic acid type). This resin required longer reaction times and heating to 50-60°C to complete the hydrolysis but produced chromatographically pure aldehyde. The required solvent system for Dowex treatment was aqueous tetrahydrofuran. This system was found suitable for the subsequent reaction to form the nitrone, so only an intermediate filtration step was necessary for the direct synthesis of the nitrone from the 1,3-diphenylimidazolidine compounds.
6 and 7. The procedure was very convenient since all traces of the basic hydrolysis products are bound by the resin which is removed in the intermediate filtration. Thus, upon completion of the hydrolysis as indicated by TLC, the reaction mixture was filtered and immediately one equivalent of N-methylhydroxylamine hydrochloride was added and the reaction stirred till completion (see Schemes 4 and 5).

**Scheme 4**

```
Ph
\[Ph\]
\[Ph\]
\[Ph\]
TsCH, aceton 0°C, 30 min.
Dowex 50 (H+), 2/1 THF/H2O, reflux, 5 hrs., 68%
```

```
TsOH, acetone/CH2Cl2, 0°C, 30 min., 68%
```

or

```
Dowex 50(H+), 2/1 THF/H2O, reflux, 5 hrs., 68%
```

---

**Scheme 4**

```
BzO--O
\[\text{CHO}\]
\[\text{BzO}\]
\[\text{BzO}\]
BzO BzO
```

```
BzO--O
\[\text{CHO}\]
\[\text{BzO}\]
\[\text{BzO}\]
BzO BzO
```

---

**Scheme 10**

```
H
\[\text{C=N}^+\]
\[\text{Me}\]
BzO--O
\[\text{BzO}\]
\[\text{BzO}\]
BzO BzO
```

```
NaOAc, 2/1 THF/H2O, MeNHOH·HCl, 12 hrs., 77%
```
These unique nitrone derivatives of 2,5-anhydro-D-allose were found to be very reactive 1,3-dipoles in subsequent 1,3-dipolar cycloaddition reactions with various electron poor dipolarophiles. The use of the 1,3-dipolar cycloaddition reaction for the synthesis of five-membered rings was introduced in 1960 by R. Huisgen and coworkers and has since become an important synthetic method (52).
Since this time, the versatility of this reaction has found its way into the realm of the carbohydrate chemist. A synthesis of 1,3-dipoles consisting of a carbohydrate moiety bound to a heteroallylic unit have been reported by A. Vasella and coworkers (53-57). Their systems were directed toward the asymmetric synthesis of compounds such as various captopril analogues which incorporated 5-oxaproline in place of the proline moiety (55). Our focus was to synthesize novel C-nucleosides from the nitrones 8 and 10. With this in mind, these nitrones were reacted with three electron poor dipolarophiles known for their high reactivity in 1,3-dipolar cycloaddition reactions (Scheme 6).

Scheme 6

(A) = Dimethylacetylenedicarboxylate, 67%
(B) = N-Methylmaleimide, 97%
(C) = Diethylmaleate, 80%
The 1,3-dipolar cycloadditions just described can be rationalized if molecular orbital analysis is invoked. This analysis suggests that the basis of the reactivity can be explained by the distribution of electron density in the HOMO and LUMO of the reacting molecules. For electron poor dipolarophiles like those used in our synthesis, the LUMO is presumed to react with the HOMO of the 1,3-dipole of the nitrone. In this manner the greatest overlap of the orbital pairs is achieved (see Scheme 7).
The 1,3-dipolar cycloaddition reactions of the 2,5-anhydro-β-D-allose N-methyl nitrones just described yielded a series of novel C-nucleosides in good yields. These compounds represent only a small fraction of the potential C-nucleosides available through this unique route.

To compliment the use of the carbohydrate derived nitrone described above, we found that likewise a novel series of N-nucleosides could be synthesized using another cycloaddition approach. Our past experience in the synthesis and reactions of glucopyranosyl isothiocyanates suggested that a ribofuranosyl analog could be likewise synthesized. Starting from our previous substrate 1-O-acetyl-2,3,5-
tri-O-benzoyl-β-D-ribofuranose, 2,3,5-tri-O-benzoyl-β-D-isothiocyanate 3 was synthesized through anhydrous bromination and subsequent substitution by the thiocyanate ion (see Scheme 8).

**Scheme 8**

This synthesis has also been achieved through the use of lead(II) thiocyanate which circumvents the use of expensive silver thiocyanate (43). Several studies have appeared in the literature that describe
the use of isothiocyanates as substrates for the synthesis of N-nucleosides (44-45). These studies demonstrated the high reactivity of the thiocarbonyl carbon of the isothiocyanate group to incoming carbon or nitrogen nucleophiles. Other investigations (58-64) into the chemistry of organic isothiocyanates by J. Becher and coworkers demonstrated that these compounds reacted readily with the ambident anion of glutaconaldehyde. The products of these reactions were substituted 2(1H)-pyridinethiones. Having successfully applied this technology to glycosyl isothiocyanates, it seemed reasonable to assume that ribofuranosyl isothiocyanates would also react with the potassium salt of glutaconaldehyde to form a ribosyl substituted 2(1H)-pyridinethione (see Scheme 9).

Scheme 9

1) DMF, 70-80°C, 7.5 hrs., 68%
2) extraction with ether 3 weeks

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
As expected, the reaction produced the desired product. But, to have any potential biological activity, nucleside adducts must be fully deprotected. Deprotection of 17 with methanolic sodium hydroxide yielded compound 18, namely 1-ribofuranosyl-2-thiono-3-pyridine carboxaldehyde (see Scheme 10).

Scheme 10

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
With the discovery that nucleosides blocked in the 3' and 5' positions could serve as chain terminators during DNA replication, a surge of research was initiated into the synthesis of nucleoside analogs which possessed the necessary structural attributes. T. Lin and W. Prusoff had synthesized various 3'-azido, 3'-amino, 2',3'-unsaturated, and 2',3'-dideoxy analogs and tested their respective activities in the leukemia virus (M-MULV) and found that many of their compounds had significant activity (33-35). With this in mind, an attempt was made to introduce the 2',3' double bond into our N-nucleoside analog 18. Early work by J. Moffatt and coworkers (65) utilized 2-acetoxy isobutyryl chloride to synthesize 2,2'-anhydro-l-(3'-O-acetyl-β-D-arabinofuranosyl)cytosine. This synthesis had its basis in the conversion of the 2',3' cis diol function of the carbohydrate moiety into a reactive 2',3'-acetoxonium ion which was then opened by attack of chloride ion to form an isomeric mixture of 2',3'-trans chloro acetates. This reaction, named an abnormal Mattocks reaction (66, 67), was discovered during an attempted synthesis of α-acetoxy-α-methylbutyryl esters of retronecine, as part of a study of semi-synthetic pyrrolizidine alkaloids. The result of the reaction with retronecine was chlorination and acetylation of the primary and secondary hydroxyl groups. This unique result was then tested with vicinal diols, and the same mixture of chloroacetates were once again formed. Recently, M. Robbins and coworkers (68) found that under carefully controlled conditions, the transbromo acetate of adenosine could be converted to 2',3'-dideoxy adenosine. This was accomplished by treating the isomeric mixture of trans-bromo acetates with zinc.
copper couple to effect the reductive elimination to form the double bond which was then later hydrogenated to form the 2',3'-dideoxy nucleoside. Application of this sequence (69-71) to our deprotected nucleoside resulted in the synthesis of l-(2',3'-dideoxy-2',3'-didehydro-β-D-ribofuranosyl)-2-thiono-3-pyridine carboxaldehyde 19 (see Scheme 11).
Another potential entry into N-nucleosides was envisioned through the use of a suitably protected ribofuranosyl or glucopyranosyl azide. Since early methods used displacement reactions utilizing potentially explosive sodium azide with the α halogenated sugar to synthesize the target azido sugar, a new method seemed desirable. There was a report (72) in the literature that generated trimethylsilyl azide in-situ by the reaction of trimethylsilyl chloride and sodium azide in DMF, but application of this system was limited to aldehydes and ketones by forming their respective azido-trimethylsiloxy derivatives. A more recent report derivatized tertiary alcohols by reaction of preformed trimethylsilyl azide with the alcohol in the presence of a suitable Lewis acid (73). This approach with the necessary modifications led to a highly efficient synthesis of azido sugars in one step from the corresponding acetates. Our procedure eliminated the need to first synthesize the α-halo sugar and resulted in the synthesis of chromatographically pure azido sugars. The synthesis of 1-(2,3,5-tri-O-benzoyl 8-D-ribofuranosyl)-azide 20, 1-(2,3,4,6-tetra-O-acetyl-8-D-glucopyranosyl)-azide 23, and 1-(2,3,4,6-tetra-O-acetyl-8-D-galactopyranosyl)-azide 26 was accomplished from the corresponding acetates by treatment with trimethylsilyl azide and boron trifluoride etherate in benzene at room temperature. Application of the Staudinger reaction (73) to each of the above azides afforded the corresponding iminophosphoranes which could then be directly converted into the respective diethyl N-(ribofuranosyl or pyranosyl) phosphoramidates. This sequence of reactions leading to the phosphoramidates is outlined in Schemes 12-14.
Scheme 12

\[\text{Scheme 12}\]

\[\text{Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.}\]
Scheme 13

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
Scheme 14

\[ \text{TMSN}_3, \text{CH}_3\text{NO}_2, \text{BF}_3\text{OEt}_2, \]
\[ 35^\circ\text{C}, 12\text{ hrs.}, 68\% \]

\[ \text{(EtO)}_3\text{P}, \text{Ph-H}, \]
\[ 25^\circ\text{C}, 78\text{ hrs.}, 92\% \]

\[ \text{H}_2\text{O}, \text{Ph-H}, \text{reflux}, 1\text{ hr.}, 84\% \]

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
Because of our earlier need for the selective synthesis of 2,5-anhydro-D-allose, we had continually sought to improve and expand the present methodology concerning this critical intermediate. Reports (74-77) of the potential utility of silane reductions to effect the conversion of compounds such as acid chlorides, amides, and nitriles to the corresponding hydrocarbons, amines, and aldehydes suggested to us that this may be an alternative approach to the known (and difficult) route to 2,5-anhydro-D-allose. As a result, we attempted to convert \(1-(2,3,5\text{-tri-}O\text{-benzoyl-}D\text{-ribofuranosyl})\) cyanide to 2,5-anhydro-D-allose by first N-alkylation with ethyl Meerweins reagent (75, 76) followed by partial triethylsilane reduction to the N-alkylaldimine. The N-alkylaldimine 30 was then steam distilled (with subsequent hydrolysis) to afford the aldehyde 2,5-anhydro-D-allose in fair yield (see Scheme 15).

Scheme 15

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
The facile cycloaddition reactions of the acylketene generated from the thermolysis of 2,2,6-trimethyl-4H-1,3-dioxin-4-one (78-80) prompted us to investigate the synthesis of a novel N-nucleoside derived from 1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-isothiocyanate 3. The mechanism of this reaction involved initial retro-Diels-Alder fragmentation of the "diketene-acetone adduct" (2,2,6-trimethyl-4H-1,3-dioxin-4-one) to form acetyl ketene, which was then attacked by the N of the isothiocyanate moiety followed by subsequent cycloaddition to form the 3H-1,3-oxazine ring 3 (see Scheme 16).
Scheme 16

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
Our investigations into the unique cycloaddition reactions of glutaraldehyde led us to study briefly the reactions of the pyridine thione adduct with a nucleophile such as guanidine hydrochloride. A compound 33 with a literature precedent (59) was prepared by the cycloaddition of phenylisothiocyanate and the sodium salt of the diketone derived from 2,6-dimethyl-4-pyranthione. This compound was then reacted with guanidine hydrochloride to give the condensation product 34 (see Scheme 17). Since nucleophilic displacements of thiomethyl groups on pyridine and related systems is known, this result was not unexpected.

Scheme 17

[Chemical structure and reaction conditions diagram]
The final facet of this research endeavor dealt with the synthesis of some interesting acyclic N-nucleosides which may possess some antiviral activity (81-89). The known compound 9-[(2-hydroxyethoxy)methyl]guanine (acycloguanosine) is an example of a compound found to possess potent antiviral activity with low host toxicity. This compound demonstrated that the intact cyclic carbohydrate moiety was not necessary in order to mimic nucleoside binding to enzymes. Furthermore, acycloguanosine was proved to have selective inhibitory activity against herpes viruses, in that it was specifically phosphorylated to the monophosphate derivative in herpes-infected cells and upon conversion to the triphosphate, inhibited herpes virus DNA polymerisation more effectively than cellular DNA synthesis (85-86).

Our related analogs were synthesized from either 2-(trimethysiloxyethoxy)-methyl isothiocyanate $3_{5}$ or 2-(acetoxy-ethoxy)-methyl isothiocyanate $3_{7}$ by the cycloaddition reaction (described earlier) with the potassium salt of glutaconaldehyde. Compounds $3_{5}$ and $3_{7}$ had their origin in the reactions of trimethylsilyl iodide and acetylchloride with 1,3-dioxolane respectively. The ring opening adducts were then treated with either silver or potassium thiocyanate to yield the isothiocyanates $3_{5}$ and $3_{7}$. These compounds were then subjected to the cycloaddition reaction with the potassium salt of glutaconaldehyde to yield the acyclic 1-H-pyridinethione carboxaldehydes $3_{6}$ and $3_{8}$ (see Scheme 18 and 19).
Scheme 18

\[
\text{N} - \text{C} = \text{S} \quad \xrightarrow{\text{1) TMSI, cyclohexene, } -78^\circ \text{C, 10 min.}} \quad 98\% \quad 35
\]

\[
\text{N} - \text{C} = \text{S} \quad \xrightarrow{\text{2) AgSCN, 20 min., reflux, 91\%}} \quad 36
\]

\[
\text{TMSO} - \quad \xrightarrow{\text{DMF, 25 hrs., 55°C, 48\%}} \quad \text{N} - \text{C} = \text{S} \quad \text{36}
\]

Scheme 19

\[
\text{N} - \text{C} = \text{S} \quad \xrightarrow{\text{1) AcCl, reflux, 9 hrs.}} \quad 88\% \quad 37
\]

\[
\text{N} - \text{C} = \text{S} \quad \xrightarrow{\text{2) KSCN, PhCH}_3, \text{10 hrs., reflux, 76\%}} \quad 38
\]

\[
\text{DMF, 36 hrs., 72°C, 42\%}
\]

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
CHAPTER V

CONCLUSIONS AND RECOMMENDATIONS

The syntheses just described have resulted in the production of a novel series of N and C-nucleosides which may have chemotherapeutic value for the treatment of AIDS (acquired immunodeficiency syndrome) or as anticancer agents. Compounds such as 19 1-(2',3'-didehydro-β-D-ribofuranosyl)-2-thiono-3-pyridine carboxaldehyde possessing the structural feature of the 2',3' double bond may be capable of blocking one or more steps of the replicative cycle of the AIDS virus. This process occurs because compounds blocked in the 3' and or 5' positions can serve as chain terminators during DNA elongation.

The methodology developed in this research project will have powerful ramifications in regard to construction of other N and C-nucleosides. 1,3-Dipolar cycloaddition reactions utilizing the N-methylnitroso of 2,5-anhydro-β-D-allose can be extended by using unsymmetrical dipolarophiles as well as electron rich dipolarophiles. Since this reaction is concerted and occurs through syn addition of the nitroso dipole to the multiple bond of the dipolarophile, a high level of diastereoselection may be achieved.

Lastly, the compounds prepared in this work will be submitted to the National Cancer Institute and similar testing labs for anticancer and anti AIDS evaluation.
REFERENCES


APPENDIX

I. FT-IR Spectra
II. FT $^{13}$C NMR Spectra
III. FT $^1$H NMR Spectra
I. FT-IR Spectra
II. FT 13C NMR Spectra
III. FT 1H NMR Spectra