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Cousineau, Thomas Joseph
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The Ohio State University, Ph.D., 1979
THE PREPARATION OF CERTAIN THIAZOLE AND FUSED-RING
β-D-RIBOFURANOSYL C-NUCLEOSIDES

DISSERTATION

Presented in Partial Fulfillment of the Requirements for
the Degree Doctor of Philosophy in the Graduate
School of The Ohio State University

By

Thomas J. Cousineau B.S.

* * * * * * * * *

The Ohio State University

1979

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To my parents, who provided encouragement and support throughout my graduate career, and to Barbara, whose assistance and compassion aided immensely in this effort.
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FIELD OF STUDY

Major Field: Organic Chemistry
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GENERAL STATEMENT OF
THE PROBLEM

The C-nucleosides are a group of compounds which possess significant biological properties, in particular, antiviral and antitumor activity. As a consequence, the chemistry of these molecules has recently received considerable attention. Numerous C-nucleosides have been prepared, using a wide variety of approaches. Many of these routes are not selective, however, and lead to anomeric mixtures.

A study was initiated to explore potential stereocontrolled syntheses of C-nucleosides. The results presented here describe an investigation of the reaction of a suitably protected ribosyl bromo aldehyde, prepared in a stereospecific manner, with a series of thioamides and related sulfur compounds to afford, after deblocking, thiazole C-nucleosides. In addition, the condensation of this bromo aldehyde with aminopyrimidines and other nitrogen heterocycles led to the formation of fused-ring C-nucleosides closely resembling the purine nucleosides and the formycins.
Nucleosides

Of all the molecules found in living systems, nucleosides are perhaps the most versatile. Certainly the most prominent function of these compounds is to serve as building blocks of the nucleic acids and thus to participate in the molecular mechanisms by which genetic information is stored, replicated, and transcribed. Nucleosides also play a number of other vital roles in the cell, particularly in intermediary metabolism and in energy-transforming reactions. In addition, there exists a group of compounds known as the nucleoside antibiotics, which possess a wide variety of significant biological properties.

Structurally, most nucleosides are composed of two characteristic components, a pentofuranose ring (usually D-ribose or 2-deoxy-D-ribose) and a nitrogen heterocycle (either a purine or a pyrimidine),
joined through the normal carbon-nitrogen bond. Generally, the glycosidic linkage of natural nucleosides is in the \( \beta \) configuration.

Hydrolysis of RNA yields mainly adenosine, guanosine, cytidine, and uridine, while hydrolysis of DNA affords principally 2'-deoxyadenosine, 2'-deoxyguanosine, 2'-deoxycytidine, and thymidine. These compounds, which are known collectively as the major nucleosides (see Figure 1), are also involved in other cellular activities.

Along with the major nucleosides, over forty additional minor or modified nucleosides, components altered by the addition or substitution of a variety of groups to either the glycone or aglycone, have been isolated from both RNA and DNA (see Figure 2 for a few representative examples). The sole function of the modified nucleosides is to take part in the processing of genetic information.

The nucleoside antibiotics,\(^2\),\(^3\) on the other hand, represent a diverse group of biological compounds. Individual compounds may possess antibacterial, antifungal, antiviral, or antitumor activity. Currently, this class numbers about sixty-five members, several of which are shown in Figure 3.

The largest subset of molecules within the nucleoside antibiotics is the C-nucleosides, a class of compounds in which the anomeric carbon of ribose is attached to any one of several heterocycles by a carbon-carbon glycosidic linkage.\(^2\)\^-\(^6\) The thirteen known naturally occurring C-nucleosides are shown in Figure 4. Since the C–C bond,
Figure 1. The major nucleosides
Figure 2. Selected modified nucleosides
Figure 3. Selected nucleoside antibiotics
Figure 4. The naturally occurring C-nucleosides
Figure 4. (continued)

Pyrazofurin

Showdomycin

Formycin B

Formycin

Oxofomycin B
the salient feature of these molecules, is hydrolytically stable, one important catabolic pathway--cleavage of the heterocyclic base from the sugar--is therefore inoperative. As a consequence, this class of compounds has tremendous biochemical and pharmaceutical potential. Thus, much effort has been directed in recent years toward the synthesis of the naturally occurring C-nucleosides, their analogs, and functionalized C-glycosyl precursors.6,7

Biological Significance of the C-Nucleoside Antibiotics

During fractionation of RNA hydrolysates, a "fifth nucleoside,"18 later identified as 5-β-D-ribofuranosyluridine (pseudouridine, 1),9-11 was isolated.12,13 Pseudouridine, identified symbolically as \( \Psi \), is the most predominant of the modified nucleosides, and has been detected in all tRNA species active in protein synthesis, occurring at a specific site in the T-Ψ-C arm (see Figure 5).4 Furthermore, 1 is found in the anticodon arm of several tRNA's and in the second position of the anticodon of yeast tRNA\(^{\text{Tyr}}\). Of equal importance, pseudouridine is recognized as uridine at the nucleotide14 and polynucleotide15 levels and closely resembles uridine in dimeric16 and polymeric17 form. However, 1 possesses no known antibiotic activity. For further information, reviews on the chemistry18 and biochemistry19 of pseudouridine should be consulted.
Figure 5. The base sequence in a yeast serine tRNA
The natural derivatives of pseudouridine are of only minor importance biologically. Investigators isolated 2'-O-methylpseudouridine (2) from both tRNA\(^{20-22}\) and rRNA,\(^{23}\) while 1-methyl-3-(3-amino-3-carboxypropyl)pseudouridine (4) was obtained from rRNA.\(^{24}\) The C-nucleoside 1-methylpseudouridine (4) was discovered in the fermentation broth of *Streptomyces platensis* var. *clarensis*.\(^{25}\) No biological activity was reported for this compound. Finally, the hypermodified pseudouridine derivative 5 was detected in germinating pea seedlings.\(^{26}\) This structure assignment is not convincing, however.

Oxazinomycin (6), elaborated by two *Streptomyces* strains,\(^{27,28}\) is effective against both Gram-positive and Gram-negative bacteria. Antiyeast, antifungal, and antitumor activity has also been reported for this compound.

Indochrome BII (7) is one of the main components of the indochromes, a group of water-soluble blue compounds that are released into the culture broth by bacteria that produce the pigment indigindine.\(^{29,30}\)

The most promising C-nucleoside antibiotic is pyrazofurin (8), which was isolated from *Streptomyces candidus*.\(^{31}\) This compound inhibits the growth of certain viruses\(^{32}\) and tumors\(^{32-34}\) and is currently in clinical trials as an anticancer agent. The biological effects of 8 are reversed by uridine.
Pyrazofurin B (9), the α anom er of pyrazofurin, was isolated along with 8 from the identical strain of *Streptomyces*. In aqueous solutions, 8 readily anomerizes to 9. Pyrazofurin B exhibits no antitumor activity and only marginal antiviral activity.

The nucleoside antibiotic showdomycin (10) is elaborated by *Streptomyces showdoensis*. A number of biochemical properties of 10, particularly those involving enzyme inhibition, have been described. In addition, showdomycin is a broad spectrum antibiotic, active against both Gram-positive and Gram-negative bacteria. It also exhibits remarkable activity against tumor cells.

The formycins, all of which possess the pyrazolopyrimidine ring system, were originally isolated from culture filtrates of *Nocardia interforma*. Formycin (11) is structurally related to adenosine and replaces it in a number of enzymatic reactions. This compound also exhibits activity against certain tumor cells and viruses. Formycin B (12) has shown significant antiviral activity, while oxoformycin B (13) has no known antibiotic properties.

For a more detailed discussion of the biological activity of the C-nucleosides, consult the excellent comprehensive works of Suhadolnik and Daves and Cheng.
Biological Significance of Synthetic C-Nucleosides

In addition to the natural C-nucleosides, numerous synthetic C-nucleosides have been prepared, many of which show antibiotic properties (see Figure 6). Unfortunately, a majority of these compounds have not undergone any biological screening tests, but most of those that do possess activity will be listed here. Synthetic approaches to these molecules will be discussed later.

The dibenzyl derivative of dideazapseudouridine and pseudoisocytidine have both exhibited significant antitumor activity. Also, a series of 7-substituted formycin derivatives (16), in which R = NHNH₂, NHOH, H, Cl, Br, SH, and SCH₃, among others, were prepared and tested. While several of these compounds proved inhibitory in certain test systems, no impressive biological activities were found. In an attempt to enhance the antiviral activity of pyrazofurin, several acetyl and butyryl derivatives of this antibiotic (17) were synthesized. In general, however, test results showed these compounds to possess properties comparable to 8. In addition to the compounds mentioned above, many other synthetic C-nucleosides have been prepared but have exhibited little or no biological activity.
Figure 6. Selected synthetic C-nucleosides
**Synthetic Approaches to the C-Nucleosides**

As synthetic targets, the C-nucleosides possess deceptively simple structures. The design of synthetic routes to these molecules must take two important factors into account. First, since the majority of C-nucleosides are \( \alpha-D \)-glycosyl compounds, the methods selected for C–C bond formation at the anomeric center should be stereocontrolled. Second, the carbon side-chain attached to the carbohydrate in a C-nucleoside precursor should either be appropriately functionalized or be amenable to substitution, in order to allow the further elaboration of the heterocyclic portion of the molecule.

An enormous number of C-nucleoside analogs have been synthesized, including acyclic, spirocyclic, and fused-ring compounds. In addition, many C-glycosides substituted by heterocycles at positions other than the anomeric carbon have been described. Thus, it is impossible to examine all the C-nucleoside analogs that have been reported. Therefore, this discussion will be restricted, for the most part, to the preparation of \( \alpha \)-ribofuranose compounds which have been anomERICALLY functionalized.

The methods employed for the synthesis of C-nucleosides can be classified into four general types. The first involves the conversion of an available C-nucleoside into a new one. The second approach utilizes direct condensation of suitably blocked carbohydrate derivatives with
heterocyclic bases (usually as metalated species). The third and most fruitful approach is the multistep elaboration of the desired heterocycle from a functionalized C-glycosyl precursor. The fourth approach is that of total synthesis from non-carbohydrate substrates.

While a few examples have been reported on the transformation of a readily available C-nucleoside into a different one, this approach is of limited scope. For instance, treatment of oxazinomycin (6) with methanolic ammonium hydroxide at room temperature afforded pseudouridine (1).\textsuperscript{50} Also, formycin (11) was prepared from formycin B (12) in three steps (see Scheme 1).\textsuperscript{48}

The preparation of 1-methylpseudouridine (4) from pseudouridine (1) has been reported by two independent research groups. Fox and coworkers\textsuperscript{51} trimethylsilylated 1 with hexamethyldisilazane to afford compound 18. Selective methylation at N\textsuperscript{1} with methyl iodide presumably gave the quaternary ammonium salt 19\textsubscript{a}, which spontaneously eliminated trimethylsilyl iodide via nucleophilic attack of iodide ion on
Scheme 1
silicon to yield 20a. Hydrolytic deprotection afforded 4. Earl and Townsend used a similar approach.\(^{52}\) Thus, successive treatment of 2', 3', 5'-tri-O-acetylpseudouridine (21) with bis-trimethylsilylaceta-mide and methyl iodide gave a colorless foam, from which 4 was obtained by reaction with ammonia. These authors speculated that compounds 19b and 20b were intermediates in this synthesis.

Townsend and coworkers prepared, albeit in low yield, the pyrazofurin analog 22a from formycin (11) via the hydrazide 22b.\(^{53}\)

Formycin has also been modified to give anhydro derivatives (e.g., 23)\(^{54}\) and to afford the unsaturated compound 24.\(^{55}\) Finally,
two C-nucleoside analogs (25a and 25b) were synthesized from pseudouridine (1) as outlined below. Ozonolytic degradation of triacetyl-

![Chemical structure of 25a and 25b]

two C-nucleoside analogs (25a and 25b) were synthesized from pseudouridine (1) as outlined below. Ozonolytic degradation of triacetyl-

![Chemical structure of 26]

two C-nucleoside analogs (25a and 25b) were synthesized from pseudouridine (1) as outlined below. Ozonolytic degradation of triacetyl-

![Chemical structure of 27a, 27b, 27c, and 27d]

pseudouridine (21) gave the ureido derivative 26. Subsequent treatment with thiosemicarbazide followed by ring closure with sodium hydroxide afforded the thiono compound 25a. The oxygen analog 25b was readily prepared from 25a by the action of methyl iodide and aqueous acid.

The direct condensation of an appropriately blocked sugar derivative with a metalated heterocycle is certainly the simplest method
devised for the preparation of C-nucleosides but also is of limited scope and often leads to anomeric mixtures. The first synthesis of pseudouridine was achieved in very low yield via reaction of the ribosyl chloride 27a with the lithio pyrimidine 28a to afford the coupled product 29 as a mixture of anomers. Subsequent acid hydrolysis gave 1 plus its α anomer and two pyranose C-nucleosides.57

By employing a pyrimidine derivative with the more hydrolyzable tert-butyl ether groups (28b), Brown and coworkers improved substantially on this approach.58 Thus, condensation of 28b with the aldehydo-D-ribose 30 gave the epimeric mixture 31, which, upon acid treatment, cyclized with simultaneous deprotection to afford 1 plus its α anomer. This procedure was subsequently studied in detail, and the yields increased, by Moffatt and coworkers.59 2'-Deoxypseudouridine was similarly prepared.58
Asbun and Binkley reported a synthesis of pseudouridine from the ribonolactone \(32\). Thus, condensation of \(32\) with the dibenzyl pyrimidine derivative \(28c\) afforded the hemiketal \(33\), which was subsequently reduced with sodium borohydride to give the triol \(34\). Catalytic hydrogenolysis, followed by acid catalyzed hydrolysis and cyclization, gave pseudouridine. Other D-aldonolactones were also treated with \(28c\) to give the corresponding 5-\(\text{R}\)-D-alditol-1-yluracils. Additionally,
these authors reacted the pyrimidine derivative 28c with a series of open-chain aldehydo sugars. For example, condensation of 28c with diisopropylidene-aldehydo-D-xylose (35) afforded compounds 36. Hydrogenolysis followed by acid treatment gave the xylo pseudouridine analog 37.

Similarly, the reaction of ribosyl chloride 27a with the organo-cadmium compound 38, led, after removal of the protecting groups, to the deazapseudouridine 39, isolated as an anomic mixture. The 2'-deoxy analog was likewise prepared. Unfortunately, both C-nucleosides were unstable and underwent rapid decomposition.

Finally, pseudocytidine (40) was prepared via condensation of the aldehydo-D-ribose 30 with the dilithio derivative 41 followed by
deblooming and cyclization with acid, analogous to a procedure used to prepare pseudouridine.\textsuperscript{58,59}

Numerous examples of the third approach, the multistep elaboration of the desired heterocycle from a functionalized C-glycosyl precursor, have been reported. In order to review these syntheses, however, preparation of the various C-\(\beta\)-D-pentofuranosyl derivatives must be discussed.

The preparation of 2,5-anhydroaldoses and 2,5-anhydroaldonic acids from the deamination of 2-amino-2-deoxyaldoses and the corresponding acids, respectively, is a well known reaction in the carbohydrate field.\textsuperscript{64,65} Pertinent examples include the reaction of the glucose derivative 42 with silver oxide to give 2,5-anhydro-D-mannose 43.\textsuperscript{66}

![Chemical structure of 42 and 43](image)

and the deamination of the gluconic acid 44 with nitrous acid to afford 2,5-anhydro-D-gluconic acid 45.\textsuperscript{67}

![Chemical structure of 44 and 45](image)
Attempted synthesis of 2, 5-anhydro-D-allose (46) or its derivatives from the requisite altropyranoside 47a via nitrous acid deamination led to the formation of pyranose compounds, due to the conformational mobility of the system. This problem was overcome, however, by the preparation of the conformationally rigid amino-sugar 48 obtained via acid catalyzed intramolecular cyclization of 47b followed by azide reduction. Nitrous acid deamination of 48 in acetic acid afforded quantitatively the ring contracted product 49. This material was subsequently transformed into several protected anhydroallose derivatives.

Intramolecular acid catalyzed dehydration of an alditol can in principle yield a 2, 5-anhydroalditol. For instance, when the mannitol
derivative \( 50 \) was heated with \( p \)-toluenesulfonic acid, 2,5-anhydro-1,6-di-O-benzoyl-D-glucitol (51) was obtained along with two other products.\(^{69-71}\)

![Chemical Structure of 50 and 51]

Intramolecular cyclization via displacement of a sulfonate group has also been used to prepare 2,5-anhydroaldoses. Thus, treatment of the mannitol derivative \( 52 \) with concentrated hydrochloric acid afforded the dibromide \( 53 \) as shown in Scheme 2.\(^{72}\)

![Scheme 2]

Numerous examples of electrophilic substitution reactions with glycosyl halides have been reported. Friedel-Crafts reaction of ribosyl chloride 27a with 1,3,5-trimethoxybenzene gave the corresponding
aromatic derivative 54. Neighboring group participation was given as the reason why only the β anomer was obtained. Examples of C-glycosides prepared in this way include the antitumor compound 55 and the thiophene 56.

Olefinic substrates have also been used in electrophilic substitution reactions. Thus, treatment of 27a with the trimethylsilyl enol ether derived from cyclohexanone led to the formation of 57, presumably through the 1,2-benzoxonium ion 58. Similarly, the malonate 59 and the hexene derivatives 60 were prepared from the ketene acetal 61 and hexene, respectively.
One of the most versatile C-glycosyl precursors is the nitrile 62, synthesized by reaction of the ribosyl bromide 27b with mercuric cyanide in nitromethane. Participation by the 2-O-benzoyl group accounts for the formation of only the β-isomer. Many other nitriles, such as the arabinosyl derivative 63 and the 2-deoxyriboosyl compound 64, have been prepared in an analogous manner. In these cases, however, both anomers were formed, since no neighboring group participation was possible.
From the nitrile 62 several functionalized derivatives have been prepared, including the acid 65a, the amine 65b, the diazo compound 

\[
\begin{align*}
\text{ROH}_2 & \quad X \quad \text{g}, X = \text{CO}_2\text{H}, R = \text{H} \\
\text{b}, X = \text{CH}_2\text{NH}_2, R = \text{H} \\
\text{e}, X = \text{CHNH}_2, R = \text{Bn} \\
\text{d}, X = \text{CHO}, R = \text{Bn} \\
\text{f}, X = \text{CHO}, R = \text{Bz} \\
\text{g}, X = \text{CSNH}_2, R = \text{Bz}
\end{align*}
\]

65c (prepared from 65b via the urea and the N-nitroso urea derivative), the aldehydes 65d and 65e (obtained by reductive hydrolysis of 62 and isolated as the diphenylimidazolidine derivative, followed by protecting group modification), the thioimidate 65f (via a modified Pinner reaction on 62), and the thioamide 65g. From these intermediates numerous C-nucleosides have been elaborated, as will be discussed later.

Organometallic reagents have been used extensively to prepare C-glycosyl derivatives. For example, treatment of the xylosyl chloride 66 with allylmagnesium bromide afforded the propenes 67, as a

\[
\begin{align*}
\text{AcOH}_2 & \quad \text{Cl} \\
\text{66} \\
\text{AcOH}_2 & \quad \text{CH=CHCH}_3 \\
\text{67}
\end{align*}
\]
mixture of anomers. Fox and coworkers reacted the ribosyl chloride 27a with diphenyl cadmium to give the $\delta$ anomer 68 along with other products. Further elaboration led to the nitro compound 69, a cyclic analog of chloramphenicol (70), which is a protein synthesis inhibitor.

In a series of papers, Buchanan and coworkers have described the synthesis of several acetylene derivatives. Thus, condensation of 27c with ethynylmagnesium bromide afforded 71a along with
its α anomer. Treatment of 71a with palladium chloride, mercuric chloride, and carbon monoxide in methanol gave the maleic ester 72. Additional acetylenes prepared by Buchanan and others include the propargyl alcohol 71b and the phenyl derivative 71c. Employing the silver salt of methyl propiolate, both 73a and 73b (from the crystalline ribosyl chloride 74a) have been obtained.

The condensation of carbonionic reagents with appropriate carbohydrate derivatives has been thoroughly examined. In the ribo series, reaction of 27c with diethyl sodio malonate afforded 75a, along with its α anomer. Ohrui and Fox condensed 74a with malonate anion and with ethyl acetoacetate anion to give the diester 75b and the keto ester 76, respectively, along with their α anomers. Other anions, such as those derived from nitromethane and ethyl isocyanoacetate have also been reacted with carbohydrate derivatives. Finally,
DeBernardo and Weigele condensed 74b with the potassium salt of diethyl acetonedicarboxylate to afford the α anomer 77 as the major product, along with other compounds. Under these conditions, the major pathway appeared to be a simple S$_N^2$ reaction.

The Wittig reaction has been studied extensively in the carbohydrate field. The condensation of a carbohydrate aldehyde with a stabilized phosphorane leads initially to a chain extended, unsaturated product, which may undergo intramolecular cyclization (Michael-type addition), perhaps catalyzed by excess ylide, to give anomerically functionalized C-glycosides (see Scheme 3). In this way, D-ribose and
D-xylose were treated with acetylmethylenetriphenylphosphorane (78a) to give the ketones 79 and 80 as anomeric mixtures. Subsequently, numerous other protected anhydro derivatives were prepared.

Hanessian and coworkers condensed 2, 3-O-isopropylidene-D-ribofuranose (81a) with ethoxycarbonylmethylenetriphenylphosphorane (78b) in refluxing toluene to give the crystalline ethyl 2-C-(2, 3-O-isopropylidene-β-D-ribofuranosyl)acetate 82a, and treated 2, 3, 5-tri-O-benzoyl-D-ribofuranose (83a) with the same ylide in DMF to afford the β-C-glycosyl compound 84a. These reactions proceed with remarkable stereocontrol, the reasons for which are as yet undetermined. At
about the same time, Buchanan et al., \cite{89} starting from \(83b\), obtained in a similar manner the \(\beta\) ester (\(84b\)), as well as the \(\alpha\) ester. Interestingly, these researchers were able to isolate the intermediate acyclic \(E\) and \(Z\) unsaturated esters.

\[ ROH_{2}C \quad H_{3}C \quad CH_{3} \quad ROH_{2}C \quad CH_{3} \]

\(81\)

\[ ROH_{2}C \quad CH_{2}R' \quad ROH_{2}C \quad CH_{2}R' \]

\(g, R = H, R' = \text{CO}_2C_2H_5 \)
\(b, R = H, R' = \text{CO}_2CH_3 \)
\(c, R = \text{Tr}, R' = \text{CO}_2CH_3 \)
\(c, R = \text{Tr}, R' = \text{CN} \)
\(e, R = \text{Tr}, R' = \text{CN} \)

\(82\)

\[ RO_{2}C \quad OR \quad RO_{2}C \quad OR \]

\(g, R = \text{Bz} \)
\(b, R = \text{Bz} \)
\(b, R = \text{Bn} \)
\(b, R = \text{Bn} \)

\(83\)

\[ RO_{2}C \quad CH_2CO_2C_2H_5 \]

\[ g, R = \text{Bz} \]
\(b, R = \text{Bz} \)
\(b, R = \text{Bn} \)

\(84\)

Moffatt and coworkers\cite{102} undertook a detailed investigation of the Wittig reaction of \(81a\) and \(81b\) with stabilized ylides. Thus, treatment of \(81a\) with methoxycarbonylmethylenetriphenylphosphorane (\(78c\)) in refluxing acetonitrile afforded the \(\beta\) ester \(82b\) and the \(\alpha\) anomer in a ratio of 22 to 1, while the analogous reaction of \(81b\) gave the \(\beta\) anomer \(82c\) along with the \(\alpha\) anomer in a ratio of 3 to 1. By employing \(78d\), the
corresponding nitriles 82d and 82e and their α anomers were also prepared. These workers demonstrated that the β compound is the kinetic product, while the α anomer is the thermodynamic product, by treating 82b with sodium methoxide in refluxing methanol (see Scheme 4).

\[
\begin{align*}
\text{HOH}_2C & \quad \text{HOH}_2C & \quad \text{HOH}_2C \\
\text{CHCO}_2CH_3 & \quad \text{CHCO}_2CH_3 & \quad \text{CHCO}_2CH_3
\end{align*}
\]

\text{SCHEME 4}

Under these conditions, the two esters are equilibrated via an unsaturated acyclic intermediate. GLC analysis showed that the equilibrium ratio of β ester to α ester was 1 to 3. This unexpected behavior has recently been explained by Ohrui and Emoto, who showed by a combination of \(^1\)H NMR and X-ray analysis that the α anomer existed in the oxygen atom envelope down form, and the β anomer existed in a twisted

\[
\begin{align*}
\text{TrOH}_2C & \quad \text{TrOH}_2C \\
\text{H} & \quad \text{H} \\
\text{CH}_2R & \quad \text{CH}_2R \\
\text{H}_3C \quad \text{CH}_3 & \quad \text{H}_3C \quad \text{CH}_3
\end{align*}
\]

\text{α ANOMER} \quad \text{β ANOMER}

\text{Figure 7. The conformations of ribofuranose derivatives}
oxygen atom envelope up conformation (see Figure 7). In this way, the α anomer has fewer diaxial interactions than the β anomer and consequently is more stable. Moffatt has also shown that the isopropylidene group helps to promote intramolecular cyclization of the intermediate olefin, by forcing the hydroxyl group at C-6 (see Scheme 4) into close proximity with the terminal end of the double bond. Other protecting groups, such as benzoyl or benzyl, do not have so great an effect.

Russian workers have recently reported the preparation of the highly functionalized iodo esters 85a and 85b from the unsaturated esters 86a and 86b, respectively. These acyclic compounds were isolated from the Wittig reaction of ylide 78b with ribofuranose derivatives 81b and 83b (no solvent given). Subsequent treatment with CF₃COOI in acetonitrile afforded the iodo esters (configuration at C-2 unspecified). Interestingly, the E-isomer of 86b afforded the β anomer 85b, while the Z-isomer of 86b gave the corresponding α anomer.
The reaction of the aldehydo-D-ribose 30 with a series of stabilized ylides, including the ester 78b, the nitrile 78d, the amide 78e, and the succinimide 87, afforded the corresponding chain extended compounds 88. Unfortunately, the subsequent intramolecular cyclization of the C-glycosyl succinimide to give a compound analogous to showdomycin (10) was never reported.

A novel approach to the synthesis of C-nucleosides involves the photochemical rearrangement of S-nucleosides. Thus, treatment of 27d with 4-mercapto-2-methylthiopyrimidine gave compound 89 as pure
Irradiation of $^89$ followed by methylation afforded the blocked C-nucleoside $^90$. The rearrangement occurs with retention of configuration at C-1', as evidenced by the subsequent transformation of $^90$ into pseudouridine (1). An intramolecular process is presumed.

The utilization of several of these C-glycosyl precursors in the synthesis of C-nucleosides or their analogs will now be presented. Showdomycin has been prepared in three ways. Following protecting group modification of phloroglucinol derivative $^54a$ to give $^54b$, degradation of the aromatic ring with ozone gave the keto ester $^91a$. Wittig reaction of $^91a$ with the stabilized ylide $^78b$ afforded maleate $^91b$ as an $E/Z$ mixture which was hydrolyzed and dehydrated to give anhydride $^92$. Successive treatment with ammonia, ethyl polyphosphate, and acid led to the formation of showdomycin. C-Nucleoside $^93$ was also obtained by the action of hydrazine on the corresponding maleic acid derivative.
Trummlitz and Moffatt, using an analogous approach, obtained showdomycin from aldehyde \( \text{65d} \).\(^{107} \) Thus, reaction of \( \text{65d} \) with sodium cyanide and hydrogen peroxide gave a mixture of hydroxy amides \( \text{94a} \),

![Diagram](image1)

which were then converted to their corresponding hydroxy esters \( \text{94b} \). Oxidation with DCC-DMSO afforded the keto ester \( \text{95} \), similar to \( \text{90a} \). Condensation of \( \text{94} \) with the phosphorane \( \text{78e} \) gave the maleimide directly, presumably via spontaneous cyclization of an intermediate cis-oriented maleamic acid ester. Deprotection completed the synthesis. In an extension of this procedure, 3-methylshowdomycin \( \text{96} \) was prepared via condensation of \( \text{95} \) with ylide \( \text{97} \), followed by deblocking.\(^{108} \)

![Diagram](image2)
Kalvoda has subsequently discovered a simple, shorter route to showdomycin.\textsuperscript{109}

Pyrazofurin (8) was also synthesized by the Czech workers.\textsuperscript{110}

Keto ester 91a was converted to hydrazone 98 by the action of (1-benzylhydrazino)acetic acid. Cyclization (sodium acetate/acetic anhydride) followed by simultaneous esterification and base-catalyzed methanolysis afforded 99a. Pyrazofurin was obtained by transformation of ester 99a to amide 99b and subsequent hydrogenolysis of the benzyl group.

DeBernardo and Weigele have synthesized both pyrazofurin (8) and pyrazofurin B (9).\textsuperscript{99} Thus, the sodium salt of diester 77 was subjected to diazotization with \textit{p}-toluenesulfonyl azide to yield the \textit{a} pyrazolinone 100. Reaction of 100 with sodium ethoxide in ethanol resulted in the selective removal of the quaternary ethoxycarbonyl group and concurrent solvolysis of the benzoate ester to give 101a. Treatment of
101a with ammonia for short periods resulted in the isolation of 101b along with minor amounts of 8 anomer 102. Prolonged exposure of 101a to ammonia, however, gave 102 as the sole product. This epimerization presumably involves an acyclic intermediate (for an analogy, see Scheme 4). At this point the two anomers were separated and each compound deblocked to give the two antibiotics 8 and 9.
The researchers at Hoffmann-LaRoche have also prepared oxazinomycin (6). In this synthesis, the intermediates were not anomerically stable, however, so mixtures had to be used. A 2-to-1 mixture of nitrile 82e and its α anomer, respectively (prepared by a Wittig-Horner reaction of 81b), was formylated with bis-(dimethylamino)-tert-butylloxymethane (103) to give enamines 104 as an anomeric mixture (see Scheme 5). Treatment of 104 with hydroxylamine afforded a mixture of aminoisoxazoles 105a and 105b, which were separated and hydrogenated individually to give α and β enaminoamides 106a and 106b, respectively. Unfortunately, hydrolysis of either of these compounds gave a mixture of aldehyde/enol tautomers, as well as C-1' anomers (107). Condensation of 107 with N,N'-carbonyldiimidazole afforded oxazines 108a and 108b, which were separated and subsequently deprotected to give oxazinomycin (6) and its α anomer, respectively.

Fox and coworkers have developed non-stereocontrolled methodology for the preparation of several pseudouridine analogs. Formylation of a mixture of ester 82b and its α anomer afforded 109a as an
Scheme 5
α/β mixture in low yield.\textsuperscript{112} This material could be methylated to yield \textsuperscript{109b}. Condensation of either \textsuperscript{109a} or \textsuperscript{109b} with guanidine gave the protected C-nucleosides \textsuperscript{110} in very low yield as an anomeric mixture. After separation of the anomers, individual acid treatment afforded pseudoisocytidine (\textsuperscript{15}) and its α anomer. These two compounds were found to equilibrate under acidic conditions, with β predominating. Similar reaction with thiourea and with urea led to the formation of \textsuperscript{111a} (β anomer only!) and \textsuperscript{112}, respectively. Deprotection of \textsuperscript{111a}

![Diagram](attachment:image.png)

gave 2-thiopseudouridine (\textsuperscript{111b}), while separation of the two anomers of \textsuperscript{112} followed by individual deblocking afforded pseudouridine (\textsuperscript{1}) and its α anomer. Analogously, by use of nitriles \textsuperscript{109c} and \textsuperscript{109d} in this sequence, the pyrimidine C-nucleosides \textsuperscript{113a} and \textsuperscript{113b} and their α anomers were obtained.\textsuperscript{113} The synthesis of pseudocytidine (\textsuperscript{40}) by this route failed, however. Arabinosyl C-nucleosides were also prepared in this manner.\textsuperscript{114} Finally, in a closely related synthesis, Ohrui and
Fox condensed the malonate derivative 75b with urea to yield the protected barbituric acid salt 114.  

Utilizing a 1,3-dipolar cycloaddition reaction, Czech workers synthesized oxoformycin B (13). Thus, treatment of the diazo compound 65c with dimethyl acetylenedicarboxylate afforded pyrazole 115a, which was converted selectively into a monoamide 115b by the action of
Fox condensed the malonate derivative $7_{5b}$ with urea to yield the protected barbituric acid salt $114$.\textsuperscript{96}

Utilizing a 1,3-dipolar cycloaddition reaction, Czech workers synthesized oxoformycin B ($13$).\textsuperscript{81} Thus, treatment of the diazo compound $6_{5c}$ with dimethyl acetylenedicarboxylate afforded pyrazole $115a$, which was converted selectively into a monoamide $115b$ by the action of
ammonia. Successive treatment of 115b with hydrazine and nitrous acid afforded azide 115c. Cyclization to compound 116a (presumably via the intermediate isocyanate) occurred with heating. Cleavage of the benzyl groups completed the synthesis. The pyridazine C-nucleoside 117 was also prepared from 115a.

Acton and coworkers synthesized formycin B (12) in an analogous manner.\textsuperscript{115,116} In order to avoid the formation of the oxoformycin nucleus, acid 115d was prepared. Curtius rearrangement of 115d gave anhydride 116b, which, when treated with methanol, underwent simultaneous esterification and decarboxylation to afford 118. Cyclization with formamide yielded compound 119, which was debenzylated to give formycin B.

Moffatt and coworkers have prepared several C-nucleosides via elaboration of aldehyde 65e. Thus, 65e was condensed with phosphorane 78c to yield unsaturated ester 120.\textsuperscript{117} 1,3-Dipolar addition with diazomethane followed by dehydrogenation with chlorine gave pyrazole 121a. Further manipulation gave compounds 121b-d. The diamide 122
was also synthesized from 65e using ethyl diazoacetate as the 1, 3-dipole.

In a closely related approach, isoxazole 123 was obtained from aldehyde 65e. Wittig reaction with ylide 78a afforded enone 124a,

which was subsequently converted to its oxime (124b). Treatment of 124b with iodine and base to effect both ring closure and dehydrogenation,
followed by debenzoylation, gave C-nucleoside 123. Similar condensation of 65e with phosphorane 125 led to the formation of compound 126, which upon treatment with hydrazine gave 127a, presumably via initial hydrazone formation followed by intramolecular cyclization and dehydrohalogenation. Deblocking gave the free pyrazole C-nucleoside 127b.

These Syntex researchers also demonstrated a 1,3-dipolar cycloaddition with a carbohydrate 1,3-dipole. First, aldehyde 65e was converted to oxime 128. Successive treatment of 128 with chlorine and
triethylamine gave the intermediate nitrile oxide 129, which was reacted immediately with ethyl propiolate to afford oxazole 130a. Ammonia treatment effected amide formation and deprotection to yield 130b directly (see Scheme 6).

Moffatt and coworkers also prepared a 1,2,4-oxadiazole from the oxime 128. Thus, successive treatment of 128 with chlorine and ammonia gave amidoxime 131. Condensation with acetic anhydride followed by deblocking afforded C-nucleoside 132.

Finally, these workers investigated the preparation of purine-like C-nucleosides. Starting from the tribenzyl compound 121e, Curtius rearrangement followed by acid treatment led to the formation of
aminopyrazole 133. Ring annelation with phenoxy carbonyl isocyanate afforded compound 134a, which was deblocked to yield the free C-nucleoside 134b.

Several groups have used acetylenic carbohydrate precursors to prepare C-nucleosides. Fox and coworkers condensed guanidine with ester 73c to yield compound 135. Michael addition of ammonia or pyrrolidine to 73c gave the enamine derivatives 136a and 136b, respectively. Reaction of 136a with ethoxycarbonyl isothiocyanate led to the formation of protected C-nucleosides 137 as an α/β mixture. Hydrolysis
of 136b to the corresponding keto ester followed by condensation with thiourea afforded compound 138. None of these products were deprotected, however.

The Sloan-Kettering group also explored 1,3-dipolar cycloaddition reactions with acetylenic C-glycosyl precursors. Treatment of 73b with trimethylsilyl azide gave the free triazole C-nucleoside 139a directly. Presumably the deprotection reactions were catalyzed by traces of hydrazoic acid. Ester 139a was subsequently converted to amide 139b. Similarly, pyrazole 140a was prepared via reaction of 73b with diazomethane. Ammonia treatment gave amide 140b, which was deblocked to yield the known pyrazole C-nucleoside 121d.

Condensation of 121d with ethyl N-cyano- or ethyl N-carboethoxyformimidates (141a and 141b) gave, after deprotection, compounds 142 (an isostere of adenosine and formycin) and 143 (an isostere of inosine and formycin B), respectively.
Finally, Buchanan and coworkers\textsuperscript{88,91} have synthesized a series of C-nucleosides from acetylenic precursors, including pyrazoles \textsuperscript{121b}, \textsuperscript{144}, and \textsuperscript{145}, as well as several triazoles.

Research has also been directed toward the preparation of thiazole C-nucleosides. Earlier syntheses of some acyclic 2- and 4-C-glycosyl thiazoles from suitable aldonic acid thioamides\textsuperscript{123-125} or α-haloketoses,\textsuperscript{126} respectively, have been extended recently to include ribofuranosyl thiazole C-nucleosides. Specifically, Spanish workers have condensed thioamide \textsuperscript{65g} with chloroacetone, ethyl
oxalochloroacetate and ethyl bromopyruvate to give thioazoles 146a, 147a, and 148a, respectively. The major side products of these reactions were the corresponding furan derivatives of type 149,

resulting from benzoate elimination. Ammonia treatment of the protected C-nucleosides led to the formation of the free compounds 146b, 147b, and 148b. Srivastava and coworkers have also prepared compounds 148a and 148b, and in addition, have condensed thioamide with methyl formylchloroacetate to yield the thiazole 150a. Reaction with ammonia gave the amide 150b. The amide 148b was also converted to the thioamide 148c via the corresponding nitrile. Biochemical
evaluation of these C-nucleosides determined that the amide \( \text{amide} \) possessed significant antiviral activity and also inhibited guanine nucleotide biosynthesis.

French workers, in a series of papers, have utilized the thioformimidate \( \text{65f} \) to prepare several C-nucleosides.\(^{127-129}\) For example, benzoylated imidazole C-nucleosides \( \text{151a-c} \) were synthesized by the reaction of \( \text{65f} \) with the appropriate 2-amino-2-cyanoacetic acid derivatives.\(^{83}\) Other carbohydrate analogs were also prepared.\(^{127}\) Further
manipulation of 151a, namely, condensation with formamidine acetate, followed by deprotection, gave C-nucleoside 152. Similarly, condensation of 65f with 5-amino-4-cyanopyrazole and with 5-amino-4-cyanoimidazole led, after deblocking, to the formation of compounds 153 and 154 respectively.

The preparation of homo-C-nucleosides has also been investigated. Bobek and Farkas treated amine 65b successively with nitrourea and benzyl chloride to yield the urea 155a. Reaction of 155a with β-ethoxyacryloyl chloride gave compound 155b, which was cyclized in acid to afford uracil derivative 156a. "Homouridine" (156b) was obtained upon hydrogenolysis of the benzyl groups. Sequential reaction of 156a with thionyl chloride and ammonia gave cytosine derivative 157a, which was deprotected to yield "homocytidine" (157b).

Secrist has utilized β ester 82c to synthesize a series of homo-C-nucleosides. Thus, treatment of 82c with lithio-tert-butyl acetate
afforded keto ester 158 as an anomeric mixture. Condensation of 158 with thiourea, guanidine, acetamidine, or benzamidine gave the protected pyrimidine compounds 159, which were subsequently deblocked to yield homo-C-nucleosides 160.

Access to anomerically functionalized, racemic C-ribofuranosyl compounds and their analogs has also been achieved through total synthesis. In a series of papers, Just and coworkers\textsuperscript{131-135} have gained access to a wide variety of C-nucleosides using a Diels-Alder approach. Thus, reaction of furan with methyl 3-bromoacrylate led to the formation of bicyclic ester 161. Further transformation of 161...
gave cis-diol 162, which upon subsequent manipulation afforded $\text{dl}$ C-ribofuranosyl derivative 163a. From 163a and from other similarly prepared compounds, several racemic C-nucleosides, including pyrazoles, triazoles, and oxadiazoles, were elaborated.$^{132}$ In addition, carbocyclic analogs (164),$^{133}$ 2-deoxyribosyl analogs (165),$^{134}$ and nitrogen analogs (166)$^{135}$ were obtained using parallel routes.

In a closely related synthesis, the racemic keto ester 167 was obtained via Diels-Alder reaction of furan with 1, 3-diethoxycarbonylallene (168), followed by additional operations.$^{136}$ Successive treatment of 167 with benzenediazonium fluoroborate under basic conditions and sodium borohydride afforded ring-opened compound 163b.$^{137}$
Bicyclic lactone 169a has been prepared via two routes. Starting from the readily accessible tetrachloro compound 169, Gensler obtained racemic 169a via LiAlH₄ reduction, selective cis-hydroxylation, cis-diol protection, ozonolysis, reductive workup, and lactonization. Condensation of 169a with aminoguanidine bicarbonate followed by deblocking afforded d,l homo-C-nucleoside 171. Noyori and coworkers prepared optically active 169a from the bicyclic ketone 172 by sequential cis-hydroxylation, acetonide formation, Baeyer-Villiger oxidation, and optical resolution. Treatment of 169a with the DMF-derived reagent 103 afforded compound 169b, a common intermediate used for the preparation of several C-nucleosides. Thus,
pseudouridine (1), 2-thiopseudouridine (111b), and pseudoisocytidine (15) were obtained via condensation of 169b with urea, thiourea, and guanidine, respectively, and subsequent deprotection. Showdomycin (10) was also prepared by ozonolysis of 169b, followed by condensation with phosphorane 78e and deblocking. The value of this approach lies in the high degree of stereochemical control of the anomeric center that is attained.
RESULTS AND DISCUSSION

Preparation of Thiazole C-Nucleosides

The goal of this research was to prepare a series of 5'-2'-D-ribofuranosyl thiazole C-nucleosides of general structure 173. Since thiazoles are known to have various physiological effects in living systems, including inhibition of bacterial, parasitic, viral, and fungal growth, it was felt that thiazole C-nucleosides might also possess antibiotic properties. This idea was reinforced when, during the course of the work, the 2'-2'-D-ribofuranosyl thiazole C-nucleoside 148b was found to exhibit potent antiviral activity.85

Of the several synthetic procedures described in the literature for obtaining thiazoles, the condensation of thioamides and related compounds with α-halocarbonyl derivatives has been the most extensively
used.\textsuperscript{141,142} An antithetic analysis of the problem clearly shows that the best synthetic approach to these molecules involves a suitably protected ribofuranosyl $\alpha$-haloaldehyde of general structure 174. Therefore, the intent of this research was to design a synthetic route to an $\alpha$-halo aldehyde, which would employ a stereocontrolled method for carbon-carbon bond formation at the anomeric center. Furthermore, it would be highly desirable to maintain the $\beta$ configuration throughout the syntheses. Finally, with the appropriate $\alpha$-halo aldehyde in hand, conditions must be found to effect thiazole ring formation. If possible, extension of this condensation to other compounds would also be sought.

While no known examples of the condensation of a carbohydrate $\alpha$-halo aldehyde with a thioamide can be found in the literature, a precedent does exist for a similar reaction with an $\alpha$-halo ketone. Thus, penta-$O$-acetyl-1-bromo-ketoglucoheptulose (175) was reacted with
thiourea to yield 2-amino-4-(D-glucopenta-acetoxy)-pentylthiazole (176a). Subsequent deacetylation afforded the acyclic C-nucleoside 176b.

As the starting material for this project, the known methyl 3, 6-anhydro-2-deoxy-4, 5-O-isopropylidene-7-O-trityl-D-allo-heptonate (82c) was chosen. This material is prepared, along with its D-altro isomer, in three steps from D-ribose (see Scheme 7). Condensation of D-ribose with acetone under acidic conditions affords 2, 3-O-isopropylidene-D-ribose (81a) as a viscous syrup. Purification involves either an acetylation-deacetylation procedure or column chromatography. Selective reaction of the primary hydroxyl group with triphenylmethyl chloride (trityl chloride) in pyridine gives compound 81b as a stiff syrup, which can be purified by dry column chromatography on a small scale. Wittig reaction of 81b with excess phosphorane 78c in refluxing acetonitrile leads to the formation of the C ester 82c and the corresponding C ester in a ratio of 3 to 1. These compounds, which are isolated as colorless foams, can be separated by preparative layer chromatography.

Since large quantities of 82c were required, modifications of these reactions were explored that would avoid the use of chromatography and hopefully would result in crystalline compounds. Rather than utilize the classical method of Levene to prepare 81a, the more recent procedure of Hughes and Speakman was employed. This
Scheme 7

\[ \text{CHO} \quad \text{H-C-OH} \quad \text{H-C-OH} \quad \text{H-C-OH} \quad \text{H-CH}_2\text{OH} \]

\[ \text{D-ribose} \]

\[ \xrightarrow{\text{O}} \quad \text{TrOH}_2\text{C} \quad \text{TrOH}_2\text{C} \]

\[ \xrightarrow{\text{(H\textsuperscript{+}) RT}} \quad \text{H}_3\text{C-CH}_3 \quad \text{H}_3\text{C-CH}_3 \]

\[ \text{B}1\text{a} \]

\[ \xrightarrow{\text{\( (C_6\text{H}_5)\text{CCl}_3 \)} \text{pyr. RT}} \]

\[ \text{B}1\text{b} \]

\[ \xrightarrow{\text{\( (C_6\text{H}_5)\text{PO} = \text{CHCO}_2\text{CH}_3 \)} \text{CH}_3\text{CN, 80\textdegree}} \]

\[ \text{B}1\text{c} \quad \text{\( + \) \text{\( \alpha \)}-amomer} \]

\[ \text{B}2\text{c} \]

\[ \text{SCHEME 7} \]
The tritylation procedure of Fox and coworkers\textsuperscript{145} was followed exactly. The product was purified by silica gel chromatography with 2:1 petroleum ether-ether as eluent. The Wittig reaction developed by Ohru et al.\textsuperscript{102} was modified slightly. The condensation was carried out in refluxing acetonitrile with 1.5 equivalents of phosphorane 78c for eight hours. Purification was conveniently accomplished by the following procedure. After removal of solvent in vacuo, the crude product was taken up in 1:1 petroleum ether-ether and passed through a short plug of silica gel with the aid of suction. Further washing with the same solvent system followed by evaporation afforded a mixture of the $\alpha$ and $\beta$ esters in 96\% yield as a colorless foam, pure as analyzed by thin layer chromatography. The product ratio was about 3 to 1 with the $\beta$ ester predominating.

In an attempt to obtain crystalline 82c, the foam was dissolved in diethyl ether to a concentration of 0.67 M, protected from moisture, and stored for a period of several days at 3°C. From this solution the $\beta$ ester spontaneously crystallized. Filtration, followed by washing with cold ether, afforded 68\% of the $\beta$ ester as a free-flowing white solid. The mother liquors were concentrated to give a foam which consisted predominantly of the $\alpha$ ester. Compound 82c could be further purified by recrystallization from diethyl ether. Additionally, once crystalline material is available, 82c can be readily crystallized from the syrupy
mixture of anomeric esters by seeding the syrup and storing it at 0°C.

Furthermore, a procedure was developed for the preparation of large quantities of \( 82c \), without purification of the intermediates.\(^{146}\)

Thus, \( \text{D-ribose} \) was treated with acetone to afford crude \( 81a \), which was tritylated directly to give compound \( 81b \). Without purification, this syrup was used in the Wittig reaction. Evaporation of the solvent followed by plug filtration led to the isolation of a sticky solid, which was collected by filtration and washed with 1:1 petroleum ether-ether to afford crystalline \( 82c \). In this way, ca. 26 g of material could be obtained starting from 20 g of \( \text{D-ribose} \).

Before discussing synthetic schemes, structural characterization methods should be mentioned. Gross structure for these compounds can usually be determined by \( ^1\text{H} \) NMR analysis. In some cases, anomeric configuration can also be established by \( ^1\text{H} \) NMR. Imbach has developed a simple, general method for the determination of anomeric configuration of \( 2',3'\)-O-isopropylidene-\( \text{D-ribofuranosyl nucleosides} \).\(^{147}\)

He observed that the differences (\( \Delta\delta \)) in the chemical shifts of the isopropylidene methyl groups were not the same for anomeric pairs.

Thus, the \( \Delta\delta \) for \( \beta \) anomers was always greater than 0.21 ppm, while the \( \Delta\delta \) for \( \alpha \) anomers was always less than 0.10 ppm. This criterion can also be extended to C-nucleosides, but unfortunately, it may be unreliable when the 5' hydroxyl group is substituted.
It has also been found\textsuperscript{148} that the peak assigned to the anomeric proton of a $\beta$-D-ribofuranosyl nucleoside (including C-nucleosides and C-glycosyl derivatives\textsuperscript{113}) appears at higher field (usually ca. 0.5 ppm) than the peak observed for the anomeric proton of the corresponding $\alpha$-D anomer. Usually both anomers are required, however, before a definitive assignment can be made.

MacCoss et al.\textsuperscript{149} have examined a series of 2,3-O-isopropylidene-D-ribonucleosides and have observed that $\beta$ anomers display an "apparent triplet" resonance peak for H-4$, while $\bar{\beta}$ anomers exhibit a higher multiplet for H-4$.

The anomeric configuration can also be determined on the basis of $^{13}$C NMR data. Moffatt and coworkers have noted that in C-glycosides derived from 2,3-O-isopropylidene-D-ribose and 2,3:5,6-di-O-isopropylidene-D-allose, the isopropylidene methyl groups appear at 25.5 + 0.2 and 27.5 + 0.2 ppm for $\beta$ anomers and 24.9 + 0.3 and 26.3 + 0.2 ppm for $\alpha$ anomers.\textsuperscript{102} This correlation has been refined and expanded by studies conducted in this laboratory (see Appendix). Compilation of $^{13}$C NMR data for over sixty C-glycosides and C-nucleosides derived from 2,3-O-isopropylidene-D-ribose only, prepared here and elsewhere, showed that in the $\beta$ series, the isopropylidene methyl signals appear at 25.6 ± 0.2 and 27.5 ± 0.2 ppm, while in the $\alpha$ series, the methyl resonances occur at 25.0 ± 0.3 and 26.3 ± 0.2 ppm. In addition, closer examination of these data revealed that in the vast majority of
cases, the difference in chemical shifts of the two isopropylidene methyl carbons ($\Delta\delta$) is $1.90 \pm 0.2$ for the $\beta$ anomers and $1.25 \pm 0.2$ for the $\alpha$ anomers. Furthermore, the central or quaternary carbon of the isopropylidene group appeared at $114.5 \pm 0.6$ ppm for the $\beta$ anomers and $112.7 \pm 0.6$ ppm for the $\alpha$ anomers.

Several synthetic routes can be envisioned for the transformation of an ester into an $\alpha$-halo aldehyde. The methods employed for the elaboration of ester $82c$ into the corresponding $\alpha$-halo aldehyde must be relatively mild, however, for strong acid conditions will hydrolyze the protecting groups, and strong base will epimerize the $\beta$ anomer to the $\alpha$ anomer (see Scheme 4). The synthetic plan that was chosen is outlined in Scheme 8. The aldehyde $177$ should be available either via initial reduction of $82c$ to the corresponding alcohol followed by oxidation.
to 177 or by direct reduction of the ester to the aldehyde. Any one of several methods could then be employed to transform aldehyde 177 into the bromo aldehyde 178.

The ester 82c was cleanly reduced to the primary alcohol 179 in 96% yield by treatment with lithium aluminum hydride in tetrahydrofuran at 0°C (see Scheme 9). Attempted oxidation of 179 to the aldehyde 177, using either Collins reagent or pyridinium chlorochromate\textsuperscript{150} led, however, to the formation of the corresponding aldehyde as an anomeric mixture, as determined by thin layer chromatography. Apparently, the medium is basic enough to cause anomerization.

Another oxidation method, N-chlorosuccinimide/dimethyl sulfide,\textsuperscript{151} was unsuccessful, effecting detritylation instead. The direct reduction of the ester 82c to the aldehyde 177 was examined next. A solution of 82c in dry toluene was cooled to -78°C and treated with 1.1 equivalents of diisobutylaluminum hydride (DIBAL-H). The aldehyde was isolated from this reaction mixture in 90% yield as a colorless foam. The product was clearly one isomer and was assigned the β configuration on the
basis of $^{13}$C NMR data (methyl signals at 25.60 and 27.49 ppm, $\Delta \delta = 1.89$ ppm; quaternary carbon at 114.51 ppm; see Table 1). Presumably, the DIBAL-H reduction of the ester takes place before any anomerization can occur.

With the aldehyde 177 in hand, direct halogenation was attempted. Several different methods were investigated, including $\text{Br}_2$, $\text{CaCO}_3$, $\text{CH}_2\text{Cl}_2$, 0°C; NBS, $\text{CHCl}_3$, RT; $\text{CuCl}_2$·$2\text{H}_2\text{O}$, LiCl, DMF, 80°C; NBS, hv, $\text{CHCl}_3$, 40°C; and $\text{C}_6\text{H}_5\text{N}^+\text{(CH}_3)_3\text{Br}_3^-$, $\text{K}_2\text{CO}_3$, THF, RT. All procedures failed, however. The next approach involved bromination of the corresponding enamine (180). The classical procedures used to prepare enamines,$^{152}$ pyrolytic cracking of an aminal or acid-catalyzed azeotropic removal of water, were not compatible with this system, so alternative methods had to be sought. After several attempts, very mild conditions were found to effect this transformation, namely, reaction of the aldehyde 177 with 1.5 equivalents of morpholine in benzene at room temperature for fifteen minutes. Inspection of the $^1\text{H}$ NMR spectrum (see Tables 2 and 3) of the resulting colorless foam indicated complete disappearance of starting material (no CHO signal) and formation of an enamine (morpholine and vinyl peaks, $J_{1,2} = 12$ Hz). The $^{13}$C NMR spectrum of this material indicated that of the four possible products (double bond isomers as well as anomers), only the two anomers (180a, b) were present, however, in a ratio of ca. two to one, $\beta$ to $\alpha$. While the exact mechanism of this reaction was never ascertained, one of two possible
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Solvent is CDCl₃. Chemical shifts are in parts per million downfield from internal tetramethylsilane. Certain assignments could not be confirmed by decoupling experiments and may be reversed.
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*Solvent is CDCl$_3$. Chemical Shifts are in parts per million downfield from internal tetramethylsilane.*

*Certain signals for both diastereomers are distinguishable.*
Table 3. First-Order Coupling Constants of Functionalized C-Glycosides (Hz)^a

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^a Solvent is CDCl₃
^b 9.49 signal
routes can be envisioned: either morpholine anomerizes aldehyde 177 before enamine formation occurs or the enamine, once formed, equilibrates via zwitterionic intermediate 181 (see Scheme 10). In any event, since this reaction takes place without any stereocontrol and milder conditions for this reaction could not be found, other routes to the bromo aldehyde 178 had to be explored. It should be mentioned that this procedure is perhaps the mildest method known to transform an aldehyde into an enamine. Interestingly, the α/β mixture reacted readily with bromine to afford an anomeric mixture of bromo aldehydes plus some dibromo compounds.

Bromo aldehydes have been prepared in the past from enol acetates, 153 so a synthesis of enol acetates 182 was pursued. Treatment of aldehyde 177 with 4.0 equivalents each of acetic anhydride and potassium carbonate in refluxing acetonitrile led to the formation of two isomeric enol acetates (product ratio ca. 1:1) in 85\% yield. These two compounds were separated by thick layer chromatography using three developments with 4:1 petroleum ether-ether. Examination of their
\(^1H\) and \(^{13}C\) NMR spectra revealed that both products possessed the \(\text{E}\) configuration. Thus, these compounds were double bond isomers, with the less polar component assigned the \(\text{E}\) configuration \((J_{\text{trans 1,2}} = 12.0 \text{ Hz})\) and the more polar component assigned the \(\text{Z}\) configuration \((J_{\text{cis 1,2}} \approx 7.0 \text{ Hz})\).

While this method for the preparation of enol acetates \(182\text{a, b}\) proved satisfactory, milder procedures were also investigated. Since 4-dimethylaminopyridine (DMAP) is a highly active acylation catalyst for alcohols,\(^{154}\) it seemed reasonable that this amine should also serve well for enols and enolates. Treatment of aldehyde \(177\) with 3.0 equivalents of acetic anhydride, 2.0 equivalents of triethylamine, and 0.1 equivalent of DMAP in tetrahydrofuran at room temperature afforded enol acetates \(182\text{a, b}\) in 73\% yield with a product ratio of nine to one, \(\text{E:Z}\). This procedure was examined further in this laboratory, with regard to scope and limitations and was found to be quite general.
for aliphatic aldehydes. Thus, the enol acetates of butanal, pentanal, heptanal, hexadecanal, and 2-methylpropanol were all readily prepared by this procedure. With ketones, however, this method did not provide satisfactory yields of products.

Several attempts were made to brominate the enol acetates \(182a, b\), including \(\text{Br}_2, \text{CH}_2\text{Cl}_2, 0^\circ\text{C}\); \(\text{NBS, CH}_2\text{Cl}_2, \text{R.T.}\); \(\text{Br}_2, \text{K}_2\text{CO}_3, \text{CH}_2\text{Cl}_2, 0^\circ\text{C}\), and \(\text{NBS, CH}_3\text{OH, R.T.}\). These methods all proved unsatisfactory, giving low yields of bromo aldehyde or leading to a plethora of products. Extension of an earlier procedure for the preparation of bromohydrins from olefins\(^{156}\) to include enol acetates proved successful, however. Thus, reaction of the mixture \(182a, b\) with 2.0 equivalents each of NBS and water in DMSO at room temperature followed by aqueous sodium bicarbonate workup gave the bromo aldehyde \(178\) in 73\% yield. This product is a mixture of diastereomers at C-2 which could not be separated by thick layer chromatography. Both compounds were shown by their \(^1\text{H}\) and \(^{13}\text{C}\) NMR spectra to possess the \(\beta\) configuration.

Reduction of bromo aldehyde \(178\) with sodium borohydride afforded the bromohydrin \(183\) as an inseparable mixture of diastereomers. While further manipulations of \(183\) were not attempted, this highly functionalized molecule is certainly a promising C-nucleoside precursor.
Conditions were now sought to effect the condensation of bromo aldehyde 178 with thioamides. Classical procedures\textsuperscript{141,142} involve the use of ethanol, benzene, or water as solvent, or no solvent at all, with yields being highly variable. Elevated temperatures are usually required. Using the reaction of 178 with thioacetamide (184a) as the model system, numerous solvent/temperature combinations were investigated, including absolute ethanol/40° or 80°C; 95% ethanol/RT or 80°C; pyridine/60°C; acetonitrile/40° or 80°C; DMF/50°C; and DMSO/RT. All gave very low yields of product or no product. With hexamethyldiphosphoramid (HMPA), however, at either room temperature or 60°C, satisfactory yields of thiazole 185a were isolated. Thus, the optimum conditions found were to use 2.5 equivalents of thioacetamide with 1.0 equivalents of bromo aldehyde 178 in HMPA at 60°C for six hours. In this manner, the protected C-nucleoside 185a was obtained in 25% as a colorless foam. This structure assignment followed directly from spectral data. In particular, the \textsuperscript{1}H NMR spectrum (see Tables 4 and 5)
Table 4. 60 MHz ¹H NMR Chemical Shifts of Protected Thiazole C-Nucleosides (ppm)\(^a\)

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\(^a\)Solvent is CDCl₃. Chemical shifts are in parts per million downfield from internal tetramethylsilane.
Table 5. First-Order Coupling Constants of Protected Thiazole C-Nucleosides (Hz)\(^a\)

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\(^a\) Solvent is CDCl\(_3\).
exhibited a three-proton singlet at 2.59 δ and a one-proton singlet at 7.47 δ (H-4). The configurational assignment of R for 185a was determined from the 13C NMR spectrum (see Table 6), in which the isopropylidene methyl signals appear at 25.64 and 27.59 ppm, and the central isopropylidene carbon occurs at 114.85 ppm.

Following this same procedure, thiazoles 185b-d were prepared in 30-51% yield from the thioamides 184b-d. In addition, the amide 185e was obtained in high yield from the ester 185c by the action of methanolic ammonia. In all cases, the products were colorless foams.
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<th>C₄</th>
<th>C₆</th>
<th>C₈'</th>
<th>C₉'</th>
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*Solvent is CDCl₃. Chemical shifts are in parts per million downfield from internal tetramethylsilane. Certain assignments could not be confirmed by decoupling experiments and may be reversed.
obtained by purification by thick layer chromatography. Characterization was made based on spectral data. The salient feature of the \textsuperscript{1}H NMR spectra was the singlet assigned to H-4, which occurs at 7.40 to 7.90\textdgr{}. The compounds all possessed the $\beta$ configuration.

When \textit{17e} was condensed for six hours with thiourea (\textit{18e}), however, two aminothiazole C-nucleosides were isolated in 42\% combined yield. These two compounds, which were easily separated by thick layer chromatography in a product ratio of 25:73, were identified as the $\beta$ anomer \textit{185f} and the $\alpha$ anomer \textit{186}, respectively. From

\begin{center}
\includegraphics[width=0.2\textwidth]{186}
\end{center}

inspection of their spectra, it was clear that these compounds were isomers (singlets at 7.02\textdgr{} for \textit{185f} and 7.04\textdgr{} for \textit{186}, assigned to H-4). Also, both compounds had similar mass spectra, including exact mass measurements (m/e = 514). Thus, both products were clearly 2-aminothiazole C-nucleosides. Assignment of configuration was made based on several criteria. First, in the \textsuperscript{13}C NMR spectra, \textit{185f} exhibits isopropylidene methyl signals at 25.68 and 27.62 ppm and a quaternary
carbon signal at 114.77 ppm, while for 186 the methyl signals appear at 25.10 and 26.41 ppm and the quaternary carbon occurs at 112.97 ppm. Second, the anomeric protons are found at 4.945 for 185f and 5.305 for 186, indicative of $\beta$ and $\alpha$ configuration, respectively, as discussed earlier. Finally, the H-4' resonance signal for 185f appears as a multiplet at 4.08-4.326, while for 186, it appears as an "apparent triplet" at 4.218, with a coupling constant of 3.5 Hz.

As with any heterocycle that contains mobile hydrogen atoms, 2-aminothiazoles can exist in more than one tautomeric form. Spectral studies have determined that the 2-amino tautomer (187a) greatly predominates over the 2-imino form (187b, see Scheme II). In this case IR and UV spectra were not definitive enough to assign a tautomeric preference, but $^1$H NMR clearly indicated that the 2-amino form (187a) predominates. From a series of fixed tautomeric compounds, Werbel has determined that for the 2-amino derivatives, H-4 occurs at ca. 7.145, while for the 2-imino compound, H-4 appears at ca. 6.506. As mentioned earlier, the $^1$H NMR spectrum for the $\alpha$ anomer (185f)
exhibits a one-proton singlet at 7.026, assigned to H-4, while the corresponding signal for the \( \alpha \) anomer (186) occurs at 7.046. Clearly, both compounds exist predominantly in the amino tautomeric form (187a).

One mechanistic rationale for the occurrence of both anomers is that under the reaction conditions, the initially formed \( \beta \) anomer (185f)

undergoes a facile ring opening as shown in Scheme 12 to give the open-chain zwitterionic intermediate 188. Subsequent ring closure of 188 in Michael-type fashion could then occur in two ways, either to return to the \( \beta \) anomer 185f or to proceed to the \( \alpha \) anomer 186.

Some precedent for this reaction does exist in the C-nucleoside literature. Thus, Chambers et al. have proposed a similar mechanism for the anomerization of pseudouridine (1) in either acid or base (see Scheme 13).
This equilibration of the α and β aminothiazoles was studied in some detail. When the condensation reaction was interrupted after short reaction times, varying amounts of the two anomers were isolated, as outlined in Table 7. Clearly, the β anomer appears to be the kinetic product of the reaction, while the α anomer is the thermodynamic product. If pure β product is subjected to the same reaction conditions (1.5 equivalents thiourea, HMPA, 60°C, four hours), it is recovered virtually unchanged. If, however, thiourea hydrobromide is substituted
for thiourea in this reaction, both anomers are isolated in the ratio 35:65, β to α. Thus, this equilibration appears to be acid catalyzed.

<table>
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<th>reaction time (min)</th>
<th>ratio</th>
<th>total yield (%)</th>
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<td>30</td>
<td>74:26</td>
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<td>120</td>
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<tr>
<td>360</td>
<td>27:73</td>
<td>42.2</td>
</tr>
</tbody>
</table>

Condensation of bromoaldehyde 178 with O-ethyl thiocarbonate (thionourethane, 184f) afforded the 2-thiazolone compound 189a. The
keto structure was determined from $^1$H NMR data (lack of an ethyl pattern) and from mass spectral data (exact mass determined for m/e = 515). Furthermore, $^{13}$C NMR data confirmed the $\beta$ configuration.

Under these reaction conditions, the intermediate 2-ethoxy-thiazole derivative $190$ is attacked by bromide ion to give $189a$ directly.

Studies on the 2-thiazolone ring system have demonstrated the predominance of the keto tautomer ($191a$) over the hydroxy tautomer ($191b$), unlike the corresponding amino system (see Scheme 14). The IR spectrum of $189a$ indicates a strong preference for the keto tautomer, with a carbonyl stretch at 1660 cm$^{-1}$, and no hydroxyl band.

Similarly, treatment of $178$ with ammonium dithiocarbamate ($192$) led to the formation of the 2-thiazolethione $189b$. Again, the
configuration is 8 as determined from the $^{13}$C NMR spectrum. The tautomeric equilibrium for this ring system also lies heavily on the thione side (see Scheme 14).\(^{161}\) This is confirmed in the IR spectrum of 189b, which shows the lack of any SH stretch.

Finally, the reaction of bromo aldehyde 178 with either thiobenzamide (184g) or ethyl 2-thiooxamate (184h) failed to produce any identifiable thiazole products, even under forcing conditions. This is due presumably to the reduced nucleophilicity of these thioamides.

The free nucleosides 193a-f, 194, and 195a were obtained by treatment of 185a-f, 186, and 189a, respectively, with either methanolic hydrogen chloride or aqueous formic acid. Under these acidic conditions, no anomerization occurred with the exception of the

\[
\begin{align*}
\text{193a}, R &= \text{CH}_3 \\
\text{b, } R &= \text{CH}_2\text{C}_6\text{H}_5 \\
\text{c, } R &= \text{CH}_2\text{CO}_2\text{CH}_3 \\
\text{d, } R &= \text{H} \\
\text{e, } R &= \text{CH}_2\text{CONH}_2 \\
\text{f, } R &= \text{NH}_2
\end{align*}
\]
2-aminothiazoles. Prolonged treatment of 185 with methanolic hydrogen chloride resulted in considerable anomerization. Such was not the case with 186, however. This problem was circumvented by employing brief (ten minute) reaction times. NMR values are given in Tables 8 and 9.

Some difficulties were encountered when the amide 185e was deblocked. In addition to formation of the free amide nucleoside 193e in 46% yield, the free ester nucleoside 193c was isolated in 44% yield. This problem was circumvented, however, by preparing 193e from 193c using methanolic ammonia. Under these conditions, the yield of the amide 193e was 80%.

All attempts to prepare the free 2-thiazolethione C-nucleoside 196b failed. Several methods were employed, including very short reaction times and ion exchange resins, as well as those already mentioned, but in each case, the crude reaction mixture was found to be devoid of any UV activity above 300 nm, indicative of destruction of the 2-thiazolethione ring. Since this heterocyclic system is known to be acid stable, some other mechanism must be operative, such as attack of the 5' hydroxyl group either on the thione carbon or on the double bond.

The structure elucidation of both the protected and the free thiazole C-nucleosides is facilitated somewhat by the use of mass spectrometry. In the protected series, the base peak is always found at m/e 243,
Table 8. 80 MHz $^{13}$C NMR Chemical Shifts of Thiazole C-Nucleosides (ppm)$^a$

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<th>$C_5$</th>
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$^a$Solvent is DMSO-$d_6$. Chemical shifts are in parts per million downfield from internal tetramethylsilane. Certain assignments could not be confirmed by decoupling experiments and may be reversed.
Table 9. 60 MHz $^1$H NMR Chemical Shifts of Thiazole C-Nucleosides (ppm)$^a$

| Compound | $C_4^H$ | $C_1^H$ | $C_4^H$-$C_4^H$ | $C_4^H$ | OH | Other |
|----------|---------|---------|-----------------|---------|---------|
| 193a     | 7.55 (s) | 4.81 (d) | 3.70-3.95 (m) | 3.20-3.60 (m) | 4.60-5.20 (br s) | CH$_3$ 2.60 (s) |
|          |         |         | | | | |
| 193b     | 7.60 (s) | 4.90-5.05 (m) | 3.72-3.95 (m) | 3.28-3.58 (m) | 4.70-5.25 (br s) | CH$_2$ 4.28 (s) |
|          |         |         | | | | C$_6$H$_5$ 7.31 (s) |
| 193c     | 7.62 (s) | 5.18 (d) | 3.80-4.00 (m) | 3.30-3.58 (m) | 4.70-5.28 (br s) | CH$_3$ 3.66 (s) |
|          |         |         | | | | CH$_2$ 4.12 (s) |
| 193d     | 7.82 (s) | 4.89 (d) | 3.65-4.00 (m) | 3.35-3.55 (m) | 4.70-5.20 (br s) | C$_2$H 8.96 (s) |
|          |         |         | | | | |
| 193e     | 7.58 (s) | 5.20 (s) | 3.70-4.10 (m) | 3.32-3.65 (m) | 4.60-5.20 (br s) | CH$_3$ 3.83 (s) |
|          |         |         | | | | NH$_2$ 7.10 (br s) |
| 193f     | 6.80 (s) | 4.70 (d) | 3.65-4.05 (m) | 3.35-3.52 (m) | 4.90-5.50 (br s) | J = 6 Hz |
|          |         |         | | | | |
| 194      | 6.82 (s) | 5.05 (d) | 3.70-3.95 (m) | 3.35-3.60 (m) | 4.60-5.10 (br s) | J = 3 Hz |
|          |         |         | | | | |
| 195a     | 6.87 (s) | 4.46 (d) | 3.60-3.98 (m) | 3.31-3.60 (m) | 4.80-5.30 (br s) | J = 6 Hz |

$^a$Solvent is DMSO-$d_6$. Chemical shifts are in parts per million downfield from internal tetramethylsilane.
assigned to \((C_6H_5)_3C^+\), but other significant fragmentations can be seen, including \(M-CH_3\), \(M-C_3H_6O\), and \(M-C_6H_5\). As is often the case with nucleosides, it was difficult to obtain a molecular ion for many of these protected \(C\)-nucleosides. In the free series, the base peak was usually the \(B+30\) (or \(M-103\)) peak, assigned to a fragmentation of the ribosyl moiety to give a protonated formyl base residue, as depicted in Scheme 15. This phenomenon, first discovered by Townsend and Robins,\(^{161}\) is strong evidence that the carbon-carbon glycosyl linkage is not ruptured to any extent, in contrast to normal nucleosides, which usually show intense peaks at \(B+1\), \(B+2\), and \(133(D\-ribose)\). Other major peaks are \(M^+\) and \(M-\text{H}_2\text{O}\).

**Preparation of Fused-Ring \(C\)-Nucleosides**

With the utility of the bromo aldehyde 178 firmly established, other condensation reactions were investigated. Specifically, the synthesis of fused-ring nitrogen heterocycles was examined, since these
C-nucleosides would closely resemble the purine nucleosides, the formycins, and certain hypermodified nucleosides.

Initial experiments involved the preparation of the tricyclic C-nucleoside 196a. This compound should be available from the reaction of 178 with adenine, analogous to the method used by Leonard and coworkers to obtain 1, N\(^6\)-ethenoadenosine (eAdo, 197a).\(^{163}\) Treatment of 178 with adenine in HMPA, under conditions similar to those used for the preparation of the thiazole C-nucleosides, led to the formation of a compound in 36% yield that was assigned the structure 196a. Spectral data, including \(^{13}\)C NMR (\(\beta\) configuration) and mass spectrum, support this assignment. Although the exact substitution of the aglycone was not known with certainty (the other regioisomer, 198, could also have been formed), no rigorous structure proof was attempted since earlier work by Paul and coworkers had firmly established the regiospecificity of the
reaction. These researchers treated adenosine with α-chloro-n-butyraldehyde to give a crystalline product. X-ray analysis of this compound determined 197b to be the correct structure. Clearly, the 6-amino group of adenosine is attached to the carbonyl carbon atom of the aldehyde. Presuming a similar mechanistic pathway for the reaction of bromo aldehyde 178 with adenine, 196a would be formed.

The condensation of bromo aldehyde 178 with cytosine, analogous to Leonard's preparation of 3, N'-ethenocytidine (ɛ-Cyd, 199),163 was also examined. Employing typical reaction conditions, 200a was isolated in 37% yield. While spectral data supported this assignment, the exact substitution could not be confirmed. Since the regiochemistry of this reaction was not known, a structure proof of 200a was undertaken. From the examination of molecular models, it became clear that while an ether linkage could be formed between carbons 5 and 5' of 200a to
give an anhydronucleoside (201), the other potential regioisomer (202) could not possibly form an anhydronucleoside. The plan was to prepare 201 via the mesylate 200b.
The detritylation of 200a with dimethoxypropane and p-toluenesulfonic acid in acetone afforded the desired product (200c) in 47\% yield along with another compound, assigned structure 200d, also in 47\% yield. Assignments were straightforward from the spectral data. In particular, \(^{13}\)C NMR data indicated the absence of any anomerization for either C-nucleoside during the reaction. For 200d, the presence of the 2-methoxypropane moiety was demonstrated by mass spectral and \(^1\)H NMR data. The position of this group on the 5' oxygen and not on the heterocycle was confirmed by IR (carbonyl stretch at 1720 cm\(^{-1}\)) and UV data. Mesylation of 200c in pyridine at 0\(^\circ\) occurred readily to give 200b. Following a procedure developed by Secrist,\(^{165}\) 200b was cyclized with DBU in methylene chloride to give 201 in 75\% yield. Evidence in support of this assignment include the correct exact mass (m/e = 289), lack of a carbonyl stretch in the IR spectrum, and a significant change in the UV spectrum. Interestingly, the \(^{13}\)C NMR correlation between the isoproplidene group and the anomeric configuration does not hold for this compound (methyl signals at 25.10 and 26.94 ppm, quaternary carbon at 112.97 ppm). Inspection of a molecular model of 201 shows clearly that even though the molecule possesses the \(\alpha\) configuration the furan ring cannot exist in an oxygen atom envelope up configuration (see Figure 7). Rather, the ribose ring is almost planar or perhaps in a slight oxygen atom envelope down form. Consequently, the correlation fails for this
anhydronucleoside. Apparently, the confirmation of the furanose ring has a greater influence on this correlation than do electronic effects.

In addition to adenine and cytosine, other nitrogen heterocycles were examined. Thus, treatment of bromo aldehyde 178 with 2-aminopyridine afforded 203a in 57% yield, while condensation of 178 with 2-aminopyrimidine gave 204a in 46% yield. The correct structures were easily confirmed from spectral data. Both of these reaction types are well established. Treatment of an α-halo aldehyde with either 2-aminopyridine or with 2-aminopyrimidine leads to the formation of a 3-substituted imidazo[1,2-a]pyridine (205)\textsuperscript{166} or a 3-substituted imidazo[1,2-a]pyrimidine (206),\textsuperscript{167} respectively. Studies of both cases have demonstrated that the ring nitrogen displaces the halide, while the amino group condenses with the carbonyl group.
Deblocking of the protected C-nucleosides 196a, 200a, 203a, and 204a with aqueous formic acid led to the formation of 196b, 200e, 203b, and 204b, respectively. Compound 200e was also available via acid treatment of 200d. These compounds were all fully characterized by $^1$H and $^{13}$C NMR (see Tables 10-12) and mass spectral data. In addition, the fluorescent spectra of these C-nucleosides agree well with those of the parent heterocycles.

Other Attempted Preparations of C-Nucleoside Precursors

In addition to the research already described, several other reactions leading to the formation of C-nucleosides and functionalized C-glycosides were investigated. The further utilization of several key intermediates, including the ester 82c, the enamines 180, and the bromo aldehyde 178 in condensation reactions was examined. Also explored was the treatment of certain ribosyl halides with carbanionic reagents. Finally, the synthesis of homo-C-nucleoside precursors was attempted.

Initially, a synthetic route to oxazinomycin (6) was sought. An antithetic inspection of this molecule suggests that one possible route
Table 10. 80 MHz $^{13}$C NMR Chemical Shifts of Fixed-Ring C-Nucleosides (ppm)\(^a\)

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\(^a\)Chemical shifts are in parts per million downfield from internal tetramethylsilane. Certain assignments could not be confirmed by decoupling experiments and may be reversed.

\(^{b}\)C\(_{1}\) signal not observed

\(^{c}\)Signal obscured by aromatic signals
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<td>4.18-4.50 (m)</td>
<td>1.21-1.40 (m)</td>
<td>1.40 (s)</td>
</tr>
<tr>
<td>201e</td>
<td>B</td>
<td>7.74 (s)</td>
<td>9.12 (dd)</td>
<td>7.96 (dd)</td>
<td>8.57 (dd)</td>
<td>5.04 (s)</td>
<td>1.80-4.10 (m)</td>
<td>1.80-4.40 (m)</td>
<td>1.40-1.71 (m)</td>
</tr>
</tbody>
</table>

$^a$Solvents are: A, CDCl$_3$; B, DMSO-$d_6$; C, 95% CDCl$_3$, DMSO-$d_6$. Chemical shifts are in parts per million downfield from internal tetramethylsilane.

$^b$Signal obscured by aromatic protons.

$^c$C$_{6}$H

$^d$C$_{12}$H

OH 4.00-4.50 (m)
Table 12. First-Order Coupling Constants of Fused-Ring C-Nucleosides (Hz)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Solvent</th>
<th>J₃,₆</th>
<th>J₆,₇</th>
<th>J₁',₂'</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>196a</td>
<td>A</td>
<td></td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>196b</td>
<td>B</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>200a</td>
<td>A</td>
<td>7</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>200b</td>
<td>A</td>
<td>7</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>200c</td>
<td>C</td>
<td>7</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>200d</td>
<td>A</td>
<td>8</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>200e</td>
<td>B</td>
<td>8</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>200f</td>
<td>A</td>
<td>7</td>
<td>1.5</td>
<td>J₃'a,₅'b = 12.5</td>
<td></td>
</tr>
<tr>
<td>203a</td>
<td>A</td>
<td>7</td>
<td>7</td>
<td>6</td>
<td>J₇,₈ = 8</td>
</tr>
<tr>
<td>203b</td>
<td>B</td>
<td>7</td>
<td>7</td>
<td>6</td>
<td>J₇,₈ = 9</td>
</tr>
<tr>
<td>204a</td>
<td>A</td>
<td>6.5</td>
<td>4</td>
<td>5</td>
<td>J₅,₇ = 2</td>
</tr>
<tr>
<td>204b</td>
<td>B</td>
<td>7</td>
<td>4</td>
<td>6</td>
<td>J₅,₇ = 2</td>
</tr>
</tbody>
</table>

*a Solvents are: A, CDCl₃; B, DMSO-d₆; C, 9:1 CDCl₃-DMSO-d₆
could proceed via preparation of an aldehydo ester (207) or other similar compound. The simplest approach appeared to be formylation of the

\[
\begin{align*}
\text{HOH}_2C & \quad O \\
\text{HO} & \quad OH \\
\text{OH} & \quad \text{O} \\
\text{OH} & \quad \text{HOH}_2C \\
\end{align*}
\]

known ester 82c. As reported by Fox and coworkers\textsuperscript{113} and subsequently confirmed in this laboratory, this transformation is not only a very low-yield process (ca. 3\%), but anomeration occurs as well. Thus, numerous attempts to effect the conversion of ester 82c to the aldehydo ester 208a, including the use of different solvent systems and various

\[
\begin{align*}
\text{TrOH}_2C & \quad \text{CHO} \\
\text{H}_3C & \quad \text{CH}_3 \\
\end{align*}
\]

reaction temperatures, all gave poor results. Apparently, under the basic reaction conditions employed, the molecule prefers to remain in the acyclic form (see Scheme 4) and, therefore, is virtually inert toward
formylation. Interestingly, DeBernardo and Weigele\textsuperscript{111} later were able to carry out in high yield a similar reaction on the nitrile 82e, although anomerization did occur (see Scheme 5). By utilizing bis-(dimethylamino)-tert-butylxymethane (103) as the formylating agent, the reaction could be performed under neutral conditions. Thus, little of the acyclic material was formed, and the reaction proceeded as expected. Anomerization did occur, however, presumably via the zwitterionic intermediate 209.

Since the results of the formylation procedure were unsatisfactory, alternative pathways to compound 208a were investigated. The requisite aldehydo ester should in principle be available by simply reversing the order in which the functional groups are introduced. The plan devised for this approach was to treat enamines 180 with either methyl chloroformate or with an isocyanate to give after aqueous workup aldehydo ester 208a or an aldehydo amide (208b). Several reagents were examined, including methyl chloroformate, phenyl isocyanate, and
ethoxycarbonyl isocyanate. However, the elevated temperatures needed to effect these transformations led to the decomposition of the enamines. Reactions of enamines 180 with acetyl chloride and with phosgene also failed.

The preparation of imidazole C-nucleosides of type 210 was also investigated. Condensation of bromo aldehyde 178 with guanidine carbonate, formamidine acetate, and acetamidine hydrochloride in HMPA gave poor results, presumably due to the low nucleophilicity of the amidine functional group. Attempted cyclization of 178 with urea was also unsuccessful.

The reaction of ribosyl halides with various carbanions was also explored. As mentioned earlier, malonate and acetoacetate anions had been used by other research groups in the synthesis of functionalized C-glycosides. In an attempt to prepare aldehyde ester 208a, the condensation of ribosyl chloride 74a with methyl cyanoacetate anion was
examined. The synthetic plan was to transform the cyanoacetate 211 to 208a via standard methods. The condensation, carried out with sodium hydride in refluxing dimethoxymethane, gave 211 in high yield as an α/β mixture. While this approach appeared promising, it was abandoned in order to concentrate on other projects. Further manipulations of this highly functionalized molecule should certainly be explored, however.

The work of Meyers and coworkers\textsuperscript{168} on dihydro-1,3-oxazines prompted the application of these compounds in the C-nucleoside field. Thus, treatment of ribosyl chloride 74a with the anion of 2-carboethoxy-methylloxazin (212) should give adduct 213, which could then be transformed to the aldehydo ester 208c by methods developed by the Meyers
group. The initial condensation reaction failed to give satisfactory results, however, under a variety of conditions. This may be due to the fact that \( \text{212} \) only reacts well with primary halides, secondary iodides, and activated halides.

Other carbanionic reagents were investigated, including dithiane anion and the functionalized dithiane anion \( \text{214} \). Methyl phenylsulfinylacetate anion (\( \text{215} \)) was also examined. Reactions of these anions with ribosyl chloride \( \text{74a} \) under a variety of conditions all gave poor results.

![Chemical structures](image)

The condensation of aldehyde \( \text{177} \) with ylides should lead to chain-extended carbohydrates which could be further modified to give homo-\( \text{C} \)-nucleosides. Thus, reaction of \( \text{177} \) with phosphoranes \( \text{78a} \) and \( \text{78c} \) gave the enone \( \text{216a} \) and the unsaturated ester \( \text{216b} \), respectively.

![Chemical structures](image)
In principle, these molecules could be treated with various compounds, including difunctional reagents and 1,3-dipoles, to afford homo-C-nucleosides. Since all homo-C-nucleosides that had been tested were found to be inactive, however, this approach was not pursued any further.

**Summary and Suggestions for Further Work**

Methodology for the preparation of several C-nucleoside precursors (aldehyde 177, bromo aldehyde 178, alcohol 179, enamines 180, enol acetates 182, and bromo alcohol 183) has been developed. The various conditions employed for these syntheses are mild and usually afford high yields. In most cases, the $\alpha$ anomer is produced stereospecifically. All compounds were fully characterized by $^1$H and $^{13}$C NMR and mass spectral data.

Condensation of bromo aldehyde 178 with a series of thioamides led to the formation of 2-substituted 5-C-thiazole C-nucleosides (185a-d) in moderate yields. In addition, treatment of 178 with thionourethane and with ammonium dithiocarbamate afforded the corresponding 2-thiazolone (189a) and 2-thiazolethione (189b), respectively. Transformation of ester 185c to amide 185e occurred readily with methanolic ammonia. All compounds were assigned the $\beta$ configuration on the basis of their $^{13}$C NMR spectra. Deblocking was performed at room temperature with
either methanolic hydrogen chloride or 90% formic acid. All attempts to prepare the free 2-thiazolethione C-nucleoside (195b) failed, however.

The reaction of 178 with thiourea gave an α/β mixture of 2-aminothiazole C-nucleosides (185f, 186). Mechanistic studies suggest that the initially formed β anomer is equilibrated to the α anomer. Acid promotes this equilibration. Brief treatment of these compounds with methanolic hydrogen chloride afforded the free C-nucleosides (193f, 194) with no detectable equilibration.

Condensation of 178 with aminopyrimidines and other nitrogen heterocycles afforded fused-ring C-nucleosides (196a, 200a, 203a, and 204a). In the case of 200a, the exact structure was not known, so a structure proof was performed. The anhydro nucleoside 201 was prepared via the mesylate 200b, thus confirming the original assignment. Deprotection of these compounds was accomplished in the highest yield with 90% formic acid. All compounds were fully characterized by 1H and 13C NMR and mass spectral data.

Determination of anomeric configuration of the functionalized C-glycosides and of the protected C-nucleosides was greatly aided by the use of 13C NMR spectroscopy. A correlation of the isopropylidene carbon signals and the anomeric configuration was refined and expanded.

The potential of several of these C-nucleoside precursors should be explored. Preparation of homo-C-nucleosides derived from aldehyde 177 should be examined. Double-bond addition reactions of enamines
180 and enol acetates 182 should certainly be investigated, such as the Diels-Alder reaction. 1,3-Dipolar addition reactions may also be possible. Many potential candidates (nitrile ylides, nitrile oxides, azomethine ylides, azides, etc.) exist in this area. Other possibilities include carbenic additions and free radical reactions. Epoxidation reactions should be considered as well. Further transformations of the aldehyde 177, alcohol 179, and bromo alcohol 183 should be investigated. With the versatility of bromo aldehyde 178 firmly established, numerous other condensations can be envisioned. For example, furans (Feist-Benary synthesis) and pyrroles (Hantzsch synthesis) could be prepared. Additional pyrimidines should also be condensed with 178. Finally, the anhydronucleoside 201 should be amenable to nucleophilic attack at C-5, leading to other substituted imidazo[1,2-\text{c}]pyrimidines. Hopefully, any future endeavors will benefit from the chemistry and structural correlations presented here.
EXPERIMENTAL

General Methods

Melting points were determined on a Thomas-Hoover capillary melting-point apparatus and are corrected. Infrared spectra were recorded on a Perkin-Elmer 467 grating infrared spectrophotometer, and only selected absorptions are given; the spectra were calibrated against the polystyrene absorption peak at 1601 cm$^{-1}$. $^1$H NMR spectra were measured with a Varian EM-360 instrument and $^{13}$C NMR spectra with a Bruker WP-80; chemical shifts are expressed in parts per million downfield from internal tetramethylsilane. All $^{13}$C NMR assignments are supported by the splittings in off-resonance decoupling experiments. Fluorescence spectra were measured on a Perkin-Elmer MPF-3L fluorescence spectrophotometer. Ultraviolet absorption spectra were recorded on a Cary 15 ultraviolet-visible spectrophotometer. Quantitative measurements were carried out by preparing a stock solution of the compound in water and then diluting with either 0.1 N HCl, 0.1 N NaOH, or pH 7.0 phosphate buffer. Extinction coefficients ($\log \varepsilon$) are listed in parentheses. High-resolution mass spectra were obtained on an AEI-MS9 spectrometer at 70 eV, and only selected fragmentations
are given. Optical rotations were measured on a Perkin-Elmer 241 polarimeter in a 1 dm. tube; concentrations are in g/100 ml. Micro-
analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee, and Mr. William Rond, The Ohio State University. In all cases wherein analyses included solvents, the solvent protons were observed in the $^1$H NMR spectra.

Toluene was distilled from calcium hydride and stored over 4A molecular sieves. Acetonitrile was predried over 4A molecular sieves, distilled from phosphorus pentoxide, and stored over 4A molecular sieves. Dimethylsulfoxide was distilled under reduced pressure from sodium hydroxide pellets and stored over 4A molecular sieves. Hexa-
methylphosphoramidide was distilled under reduced pressure from calcium hydride and stored at -10°C.

Thin-layer chromatography was carried out on precoated glass TLC plates (silica gel F-254, 0.025-mm thickness) from EM Laboratories, Inc. Thick-layer chromatography was performed on glass plates (20 x 20 cm) coated to 0.25-mm thickness with 30 g of silica gel 60 PF-254 (EM Laboratories, Inc.) using calcium sulfate as binder. Solvent systems used (v/v) were: A, 1:1 benzene-ether; B, 4:1 petroleum ether-ether; C, 2:1 petroleum ether-ether; D, 1:1 petroleum ether-ether; E, 19:1 CH$_2$Cl$_2$-CH$_3$OH; F, 9:1 CH$_2$Cl$_2$-CH$_3$OH; G, 85:15 CH$_2$Cl$_2$-CH$_3$OH; and H, 4:1 CH$_2$Cl$_2$-CH$_3$OH.
Methyl 3, 6-Anhydro-2-deoxy-4, 5-O-isopropylidene-
7-O-trityl-D-allo-heptonate (82c)

A solution of 20.0 g (0.133 mol) of D-ribose and 5.0 mL of concentrated \( \text{H}_2\text{SO}_4 \) in 400 mL of acetone was stirred for 1 h at RT. The reaction mixture was then neutralized with an excess of solid anhydrous sodium carbonate and filtered. Washing of the solids with acetone followed by concentration of the filtrate afforded ca. 25 g of a yellow syrup, consisting mainly of 2, 3-O-isopropylidene-D-ribofuranose (81a), \( R_F = 0.50 \) (solvent A).

Without further purification, this material was dissolved in 50 mL of pyridine and reacted with 44.5 g (0.160 mol) of triphenylmethyl chloride (trityl chloride) at RT for 24 h. The mixture was then poured into 650 mL of water. After the aqueous supernatant layer was decanted, the precipitated syrup was dissolved in 400 mL of dichloromethane and treated with a solution of 50.0 g of cadmiun chloride in 500 mL of water. The resulting solids were then filtered and washed with CH\(_2\)Cl\(_2\). The organic layer was separated, dried over anhydrous magnesium sulfate, and concentrated to give ca. 60 g of crude 2, 3-O-isopropylidene-5-O-trityl-D-ribofuranose (81b) as a colorless foam, \( R_F = 0.48 \) (solvent D).
This material was then dissolved in 650 ml of acetonitrile and treated with 66.9 g (0.200 mol) of methoxycarbonylmethylenetriphenylphosphorane (78c) at reflux for 8 h. The solvent was removed in vacuo and the residue purified by plug filtration on 250 g of silica gel, using solvent D as eluant. Evaporation of the appropriate fractions afforded a sticky solid which was collected by filtration and washed with solvent B to give 26.3 g (40.5% overall) of 82c as a free-flowing crystalline solid, mp 121-22°C; R_F = 0.60 (solvent D); IR (KBr) 2860, 1773, 1602, and 1390 cm\(^{-1}\); [\(\alpha\)]\(^{25}\)_D +5.24° (c 1.11, CHCl₃); NMR values are in Tables 1-3; mass spectrum calcd m/e 488.2199; found m/e 488.2207; m/e 488 (M\(^+\)), 473 (M-CH₃), 458 (M-2CH₃), 430 (M-C₃H₆O), 411 (M-C₆H₅), 259 (TrO\(^+\)), and 243 (Tr\(^+\)).

Anal. Calcd for C\(_{30}\)H\(_{32}\)O\(_6\): C, 73.75; H, 6.60.
Found: C, 74.05; H, 6.71.

The filtrate contained the α anomer (R_F = 0.62, solvent D) and 82c as the major components in a ratio of ca. 4 to 1, as indicated by TLC analysis.

3,6-Anhydro-2-deoxy-4,5-O-isopropylidene-7-O-trityl-D-allo-heptose (177)

A solution of 244 mg (0.50 mmol) of ester 82c in 2.0 mL of toluene under a N\(_2\) atmosphere was
cooled to -78°C, and 0.60 mL (0.55 mmol) of diisobutylaluminum hydride (19% in hexane) was added via syringe. TLC analysis (solvent D) after 30 min indicated complete disappearance of starting material. The reaction mixture was quenched with 1.0 mL of CH₃OH and allowed to warm to RT during 45 min. The resulting gelatinous solid was filtered through a pad of Celite and washed with ether. Concentration of the filtrate and purification by preparative TLC (solvent D) afforded 208 mg (90.8%) of 177 as a colorless foam: Rᵋ = 0.55 (solvent D); IR (neat) 2920, 2740, 1718, 1595, and 1390 cm⁻¹; [α]D²⁵ + 6.63° (c 0.92, CHCl₃); NMR values are in Tables 1-3; mass spectrum calcd m/e 458.2093; found m/e 458.2102; m/e 458 (M⁺), 443 (M-CH₃), 400 (M-C₅H₆O), 381 (M-C₆H₅), and 243 (Tr⁺).


Found: C, 76.34; H, 6.71.

E- and Z-1-O-Acetyl-3,6-anhydro-2-deoxy-4,5-O-isopropylidene-7-O-trityl-D-allo-hept-1-enitol (182a and 182b)
Method A. A mixture of 215 mg (0.47 mmol) of aldehyde 177, 0.18 mL (1.87 mmol) of acetic anhydride, and 259 mg (1.87 mmol) of anhydrous potassium carbonate in 2.35 mL of acetonitrile was heated at reflux for 4 h. After cooling, the solids were filtered and washed with chloroform, and the filtrate was evaporated to dryness. Purification on preparative TLC (solvent D) gave 199 mg (84.7%) of a mixture (ca. 1:1) of the E and Z isomers (182a and 182b, respectively) as a colorless syrup: \( R_F = 0.65 \) (solvent D). These two compounds could be separated by preparative TLC using three developments with solvent B.

Method B. A mixture of 240 mg (0.52 mmol) of aldehyde 177, 0.15 mL (1.57 mmol) of acetic anhydride, 0.22 mL (1.57 mmol) of triethylamine, and 6 mg (0.05 mmol) of dimethylaminopyridine in 2.1 mL of dry THF was stirred at RT for 5 h. TLC analysis (solvent D) indicated greater than 95% conversion to products. After the reaction mixture was evaporated to dryness, the syrupy residue was dissolved in 25 mL of Et₂O, extracted with 10 mL of aqueous 10% NaHCO₃ solution, followed by 10 mL of water, dried over anhydrous magnesium sulfate, and concentrated. Purification on preparative TLC (solvent D) afforded 191 mg (72.9%) of 182a and 182b in a ratio of ca. 9 to 1.

182a: \( R_F = 0.40 \) (solvent B); IR (neat) 2932, 1760, 1681, 1379, and 943 cm⁻¹; \([\alpha]_D^{25} -20.9^\circ C \) (c 1.35, CHCl₃); NMR values are in Tables 1-3; mass spectrum calcd \( m/e \) (for M⁻CH₃) 485.1964; found \( m/e 485.1974 \); \( m/e 500 \) (M⁺), 485 (M⁻CH₃), 423 (M⁻C₆H₅), and 243 (T₅⁺).
182b: $R_F = 0.35$ (solvent B); IR (neat) 2932, 1762, 1679, 1600, and 1380 cm$^{-1}$; $[\alpha]_{D}^{25} = -13.7^\circ$ (c 1.50, CHCl$_3$); NMR values are in Tables 1-3; mass spectrum calcd (for M-CH$_3$) m/e 485.1964; found m/e 485.1974; m/e 500 (M$^+$), 485 (M-CH$_3$), 423 (M-C$_6$H$_5$), and 243 (Tr$^+$).

Anal. Calcd for C$_{31}$H$_{32}$O$_6$ (mixture): C, 74.38; H, 6.74.

Found: C, 74.53; H, 6.65.

**General Procedure for the Preparation of the Enol Acetates of Isobutyraldehyde, Pentanal, and Hexadecanal**

The purified aldehyde (0.20 mol) was stirred with 2.4 g (0.02 mol) of dimethylaminopyridine, 40.5 g (0.40 mol) of triethylamine, and 102.1 g (1.00 mol) of acetic anhydride at 55°C for 24 h. Upon completion of the reaction, the reddish-brown solution was poured onto 300 g of ice and stirred for 2 h. The mixture was extracted with 150 mL of Et$_2$O and the ether layer washed well with 10% aqueous NaHCO$_3$ (1 x 100 mL, 1 x 50 mL) and 100 mL of H$_2$O and then dried over Na$_2$SO$_4$. The aqueous layers were combined and back-extracted with Et$_2$O (2 x 50 mL). The extract was washed with 10% aqueous NaHCO$_3$ (1 x 60 mL, 1 x 30 mL) and 60 mL of H$_2$O and then dried over Na$_2$SO$_4$. The ether layers were combined and the solvent evaporated at reduced pressure using a RT water bath. The crude product was fractionated with a 13-cm Vigreux column and each fraction checked for purity by $^1$H NMR.
The hexadecanal enol acetate was chromatographed on silica gel, eluting with 99:1 petroleum ether-ether. The products were all 1:1 mixtures of the \( \text{E} \) and \( \text{Z} \) isomers.

**Isobutyraldehyde enol acetate:** 69.9\%; bp 125-27°C (lit bp 124-26°C\(^{169}\)); identical to the literature spectrum.\(^{169}\)

**Pentanal enol acetate:** 79.9\%; bp 146-48°C (lit bp 148-49°C\(^{170}\));

\(^1\text{H} \text{NMR} \delta 0.90 (t, 3, J = 7 \text{ Hz}, \text{CH}_2\text{CH}_3), \text{ multiplet centered at } 1.47 (m, 2, \text{CH}_2\text{CH}_3), \text{ partially hidden multiplet at } 1.92 (m, 2, \text{CH}_2\text{C=C}), 2.07 (s, 3, \text{CH}_3, \text{ E isomer}), 2.10 (s, 3, \text{CH}_3, \text{ Z isomer}), 4.81 (q, \text{ two overlapping triplets, } 1, J_{1,2} = J_{2,3} = 7 \text{ Hz}, \text{ C-CH=C, Z isomer}), 5.35 (dt, 1, \text{J}_{1,2} = 12.5 \text{ Hz}, \text{J}_{2,3} = 7 \text{ Hz}, \text{ C-CH=C, E isomer}), 6.95 (dt, 1, \text{J}_{1,2} = 12.5 \text{ Hz}, \text{J}_{2,3} = 7 \text{ Hz}, \text{ C-CH=C, Z isomer}), 7.00 (dt, 1, \text{J}_{1,2} = 12.5 \text{ Hz}, \text{J}_{2,3} = 7 \text{ Hz}, \text{ C-CH=C, Z isomer}).

**Hexadecanal enol acetate:** 47.3\%; oil; \(^1\text{H} \text{NMR} \delta 0.88 (t, 3, \text{CH}_3), 1.27 [br s, 24, (\text{CH}_2)_{12}], 1.97 (m, \text{ partially hidden, 2, } \text{CH}_2\text{-C=C}), 2.08 (s, 3, \text{CH}_3, \text{ E isomer}), 2.12 (s, \text{CH}_3, \text{ Z isomer}), 4.76 (q, \text{ two overlapping triplets, } J_{1,2} = J_{2,3} = 7 \text{ Hz}, \text{ C-CH=C, Z isomer}), 5.31 (dt, 1, \text{J}_{1,2} = 12 \text{ Hz}, \text{J}_{2,3} = 7 \text{ Hz}, \text{ C-CH=C, E isomer}), 6.93 (dt, 1, \text{J}_{1,2} = 7 \text{ Hz}, \text{J}_{1,3} = 1.5 \text{ Hz}, \text{ O-CH=C, Z isomer}), \text{ and } 7.00 (dt, 1, \text{J}_{1,2} = 12 \text{ Hz}, \text{J}_{1,3} = 1 \text{ Hz}, \text{ O-CH=C, E isomer}).
3,6-Anhydro-2-bromo-2-deoxy-4,5-O-isopropylidene-7-O-trityl-D-allo-heptose (178)

A solution of 136 mg (0.27 mmol) of 182 and 0.01 mL (0.54 mmol) of water in 1.36 mL of DMSO cooled in a water bath was treated with 97 mg (0.54 mmol) of N-bromo-succinimide. After stirring for 30 min, the reaction mixture was quenched with 2 mL of 10% aqueous NaHCO₃ solution, diluted with 5 mL of H₂O, extracted with 2 x 10 ml portions of ether, dried over anhydrous magnesium sulfate, and concentrated. Purification on preparative TLC (solvent D) gave 106 mg (72.6%) of 178 as a colorless foam: \( R_F = 0.65 \) (solvent D). These di-stereomers could not be separated. IR (neat) 2935, 2730, 1733, 1598, and 1390 cm⁻¹; \([\alpha]_D^{25} +9.10^\circ\) (c 0.78, CHCl₃); NMR values are in Tables 1-3; mass spectrum calcd \( m/e \) (for \( C_{29}H_{29}BrO_5 \)) 536.1198; found \( m/e \) 536.1207; \( m/e \) 538, 536 (M⁺); 523, 521 (M-CH₃); 461, 459 (M-C₆H₅); 457 (M-Br); and 243 (Tr⁺).

Anal. Calcd for \( C_{29}H_{29}BrO_5 \): C, 64.81; H, 5.44.

Found: C, 64.69; H, 5.55.
To a solution of 326 mg (0.67 mmol) of ester 82c in 2.67 mL of THF cooled to 0°C under a N₂ atmosphere was added 25 mg (0.67 mmol) of LiAlH₄. The reaction mixture was stirred for 30 min at 0°C then allowed to warm to RT over 2 h. TLC analysis (solvent D) indicated complete disappearance of starting material. After quenching with moist sodium sulfate, the reaction mixture was filtered through a pad of Celite. Washing the solids with THF, followed by concentration of the filtrate and purification on preparative TLC (solvent D), afforded 295 mg (96.1%) of 179 as a colorless foam: \( R_F = 0.25 \) (solvent D); IR (neat) 3450, 2922, 1592, 1388, and 1075 cm⁻¹; [\( \alpha \)]_D^25 -3.22° (c 2.45, CHCl₃); NMR values are in Tables 1-3; mass spectrum calcd \( m/e \): 460.2249; found: \( m/e \) 460.2262; \( m/e \) 460 (M⁺), 383 (M-C₆H₅), 259 (TrO⁺), and 243 (Tr⁺).

Anal. Calcd for C₂₉H₃₂O₅: C, 75.62; H, 7.00.

Found: C, 75.43; H, 6.98.
To a solution of 215 mg (0.40 mmol) of bromo aldehyde 178 in 5.0 mL of absolute EtOH cooled to 0°C was added 15 mg (0.40 mmol) of NaBH₄. TLC analysis (solvent C) after 30 min showed complete disappearance of starting material. Water (2.0 mL) was added, and the solvents were evaporated under reduced pressure. The residue was taken into CH₂Cl₂, extracted with H₂O, dried over anhydrous magnesium sulfate, and concentrated. Purification on preparative TLC (solvent C) gave 178 mg (82.4%) of 183 as a colorless foam: Rₓ = 0.35 (solvent C). These diastereomers could not be separated. IR (neat) 3460, 2922, 1593, 1388, and 1080 cm⁻¹; [α]D²⁵ = -0.97° (c 3.30, CHCl₃); NMR values are in Tables 1-3; mass spectrum calcd (for C₂₉H₃₈BrO₅) m/e 538.1355; found m/e 538.1366; m/e 540, 538 (M⁺); 525, 523 (M-CH₃); 510, 508 (M-2CH₃); 482, 480 (M-C₆H₅O); 463, 461 (M-C₆H₅); 259 (TrO⁺); and 243 (Tr⁺).

Anal. Calcd for C₂₉H₃₈BrO₅: C, 64.56; H, 5.79.

Found: C, 64.62; H, 5.97.
3,6-Anhydro-1,2-dideoxy-4,5-O-isopropylidene-1-morpholino-7-O-trityl-D-allo- and -D-altro-hept-1-enitol (180)

To a solution of 263 mg (0.57 mmol) of aldehyde 177 in 2.12 mL of benzene protected from moisture was added 75 mg (0.86 mmol, 0.02 mL) of morpholine. After stirring 15 min at RT, the volative components were removed by rotary evaporation followed by high-vacuum pumping to afford crude 180 as a colorless foam. This material was used without further purification. IR (neat) 2940, 2860, 1652, 1451, and 1370 cm⁻¹; [α]D²⁵ -24.8°, rotation measured immediately after solution preparation; -18.8°, rotation measured seven days after solution preparation (c 1.00, CHCl₃); NMR values are in Tables 1-3; mass spectrum calcd m/z 527.2671; found m/z 527.2684; m/z 527 (M⁺), 512 (M-CH₃), and 243 (Tr⁺). Product instability precluded satisfactory elemental analysis.

General Condensation Procedure

A solution of 645 mg (1.20 mmol) of bromo aldehyde 178 and 3.00 mmol of the nucleophile (thioamide, related sulfur compound, or nitrogen heterocycle) in 7.2 mL of HMPA was stirred at 60°C for 6 h. After
cooling, the reaction mixture was dissolved in 75 mL of Et₂O, extracted with 3 x 10 mL portions of H₂O, dried over anhydrous magnesium sulfate, and concentrated. Purification was accomplished by preparative TLC.

5-C-(2,3-O-Isopropylidene-5-O-trityl-β-D-ribofuranosyl)-2-methylthiazole (185a)

Thioacetamide, 225 mg; purification, solvent C; colorless foam, 154 mg (25.0%): Rᵢ = 0.35 (solvent C); IR (neat) 2920, 1597, and 1388 cm⁻¹; UV 𝜆_max (EtOH): acid, 252; pH 7.0, 257; base, 254; NMR values are in Tables 4-6; mass spectrum m/z 513 (M⁺), 498 (M-CH₃), 436 (M-C₆H₅), and 243 (Tr⁺).

2-Benzyl-5-C-(2,3-O-isopropylidene-5-O-trityl-β-D-ribofuranosyl)-thiazole (185b)

2-Phenyldithioacetamide, 453 mg; purification, solvent C; colorless foam, 365 mg (51.6%): Rᵢ = 0.28 (solvent C); IR (neat) 2930, 1600, and
1389 cm$^{-1}$; UV $\lambda_{\text{max}}$ (EtOH): acid, 248; pH 7.0, 249; base, 247; NMR values are in Tables 4-6; mass spectrum $m/e$ 589 ($M^+$), 574 ($M-\text{CH}_3$), 512 ($M-\text{C}_6\text{H}_5$), and 243 ($\text{Tr}^+$).

2-Carbomethoxymethylene-5-C-(2,3-O-isopropylidene-5-O-trityl-$\beta$-D-ribofuranosyl)-thiazole (185c)

O-Methyl 1-thiomalonamate, 400 mg; purification, solvent D; colorless foam, 209 mg (30.5%): $R_F = 0.35$ (solvent D); IR (neat) 2925, 1740, 1595, and 1388 cm$^{-1}$; UV $\lambda_{\text{max}}$ (EtOH): acid, 250; pH 7.0, 251; base, 248; NMR values are in Tables 4-6; mass spectrum $m/e$ 571 ($M^+$), 556 ($M-\text{CH}_3$), 494 ($M-\text{C}_6\text{H}_5$), and 243 ($\text{Tr}^+$).

5-C-(2,3-O-Isopropylidene-5-O-trityl-$\beta$-D-ribofuranosyl)-thiazole (185d)

Thioformamide, 183 mg; purification, solvent D; colorless foam, 276 mg (46.1%): $R_F = 0.40$ (solvent D); IR (neat) 2920, 1596, and 1386
cm⁻¹; UV λ_max (EtOH): acid, 266; pH 7.0, 261; base, 259; NMR values are in Tables 4-6; mass spectrum calcd m/e 499.1817; found m/e 499.1830; m/e 499 (M⁺), 498 (M-H), 484 (M-CH₃), 422 (M-C₆H₅), and 243 (Tr⁺).

2-Amino-5-C-(2, 3-O-isopropylidene-5-O-trityl-β-D-ribosfuranosyl)-thiazole (185f) and 2-Amino-5-C-(2, 3-O-isopropylidene-5-O-trityl-α-D-ribofuranosyl)-thiazole (186)

Thiourea, 228 mg; purification and anomer separation, ether (three elutions). Identical reaction conditions, with the exception of time, were employed to determine the kinetic and thermodynamic products. Product ratios are those of isolated compounds purified by preparative TLC (see Table 7).
185f: colorless foam, 71 mg (11.5%); \( R_F = 0.40 \) (ether); IR (neat) 3295, 2935, 1613, 1516, and 1370 cm\(^{-1}\); UV \( \lambda_{\text{max}} \) (EtOH): acid, 259; pH 7.0, 263; base, 263; NMR values are in Tables 4-6; mass spectrum calcd m/e 514.1926; found m/e 514.1936; m/e 514 (M\(^+\)), 499 (M–CH\(_3\)), 437 (M–C\(_6\)H\(_5\)), and 243 (Tr\(^+\)).

186: colorless foam, 190 mg (30.7%); \( R_F = 0.35 \) (ether); IR (neat) 3316, 2920, 1620, 1509, and 1360 cm\(^{-1}\); UV \( \lambda_{\text{max}} \) (EtOH): acid, 259; pH 7.0, 264; base, 263; NMR values are in Tables 4-6; mass spectrum calcd m/e 514.1926; found m/e 514.1941; m/e 514 (M\(^+\)), 499 (M–CH\(_3\)), and 243 (Tr\(^+\)).

Epimerization of 185f

A solution of 206 mg (0.40 mmol) of 185f and 157 mg (1.00 mmol) of thiourea hydrobromide (prepared by bubbling anhydrous hydrogen bromide into a methanolic solution of thiourea cooled to 0°C and precipitating the product out with ether, mp 64-67°C) in 2.4 ml of HMPA was heated at 60°C for 4 h. Workup as before afforded 52 mg (25.2%) of 185f and 109 mg (52.9%) of 186 (product ratio 32:68). When thiourea was substituted for thiourea in this reaction, 185f was recovered unchanged.

5-C-(2,3-O-Isopropylidene-5-O-trityl-\( \beta \)-D-ribofuranosyl)-2(3H)-thiazolone (189a)

\( \beta \)-Ethyl thiocarbamate, 315 mg; purification, ether; colorless foam, 229 mg (37.0%); \( R_F = 0.45 \) (ether); IR (neat) 3188, 2925, 1660,
1385, and 1080 cm⁻¹; UV $\lambda_{\text{max}}$

(EtOH): acid, 254; pH 7.0, 260;
base, 261; NMR values are in
Tables 4-6; mass spectrum calcd
$m/e$ 515.1766; found $m/e$ 515.1776;
$m/e$ 515 ($M^+$), 500 (M–CH₃), 457
(M–C₃H₆O), 438 (M–C₆H₅), and
243 ($Tr^+$).

5-C-(2,3-O-Isopropylidene-5-O-trityl-D-ribofuranosyl)-2(3H)-thiazolethione (189b)

Ammonium dithiocarbamate,
330 mg; purification, ether; light-
yellow foam, 243 mg (38.1%); $R_F =
0.60$ (ether); IR (neat) 3060, 2900,
1596, 1388, and 1040 cm⁻¹; UV
$\lambda_{\text{max}}$ (EtOH): acid, 321; pH 7.0,
322; base, 314; NMR values are in
Tables 4-6; mass spectrum $m/e$ 531
($M^+$) and 243 ($Tr^+$).
A solution of 236 mg (0.41 mmol) of 185c in 10 mL of saturated methanolic ammonia was allowed to stand lightly stoppered at RT for 18 h. TLC analysis (solvent E) indicated complete disappearance of starting material. After volatile materials were removed, the residue was dissolved in 20 mL of CHCl₃ and extracted with 25 mL of H₂O. The aqueous layer was back-extracted with 20 mL of CHCl₃, and the organic layers were combined, dried over anhydrous magnesium sulfate, and concentrated. Purification by preparative TLC, using solvent E, afforded 186 mg (80.9%) of 185c as a colorless foam, Rₚ = 0.20 (solvent E): IR (neat) 3318, 2925, 1681, 1597, and 1386 cm⁻¹; UV λ max (EtOH): acid, 255; pH 7.0, 261; base, 252; NMR values are in Tables 4-6; mass spectrum m/e 556 (M⁺), 541 (M—CH₃), 479 (M—C₆H₅), and 243 (Tr⁺).

General Deprotection Procedure

Method A. A 1.0-M solution of the protected C-nucleoside in 10% methanolic hydrogen chloride was allowed to stand at RT for 3 h. After
evaporation of solvent, the residue was triturated with ether to remove trityl methyl ether. The residue was dissolved in methanol and passed through an Amberlite IR-45 (OH\(^-\)) column (3 x 12 cm) with 200 mL of methanol. The solution was concentrated, and the residue was purified by preparative TLC to afford the free C-nucleoside.

Method B. A 0.1-M solution of the protected C-nucleoside in 9:1 formic acid-water was allowed to stand at RT for 18 h. Processing and purification as in Method A gave the free C-nucleoside.

\[
\text{2-Methyl-5-C-3-D-ribofuranosylthiazole (193a)}
\]

Method B; purification, solvent

F; white solid, 84.0\(^\circ\); mp 110-13\(^\circ\)C,

\[R_F = 0.25 \text{ (solvent F)}; \text{IR (neat)}\]

3335 and 2910 cm\(^{-1}\); UV \(\lambda_{\text{max}}\):

acid, 247 (3.81); pH 7.0, 240 (3.82); base, 238 (3.90); \([\alpha]_{D}^{25}\)

-60.4\(^\circ\) (c 2.02, CH\(_3\)OH); NMR

values are in Tables 8 and 9; mass spectrum calcd \(m/e\) 231.0565;

found \(m/e\) 231.0570; \(m/e\) 231 (M\(^+\)); 213 (M-H\(_2\)O), 200 (M-CH\(_2\)OH), and 128 (M-C\(_4\)H\(_7\)O\(_3\)).

Anal. Calcd for C\(_9\)H\(_{13}\)NO\(_4\)S·1.10 CH\(_3\)OH: C, 45.51; H, 6.58; N, 5.26.

Found: C, 45.12; H, 6.30; N, 5.47.
2-Benzyl-5-C-β-D-ribofuranosylthiazole (193b)

Method A; purification, solvent

G; white solid, 74.0%; mp 110-12°C; R = 0.45 (solvent G); IR (neat) 3310 and 2920 cm⁻¹; UV λ_max: acid, 254 (3.94); pH 7.0, 247 (3.97); base, 248 (4.02); [α]_D^{25} = -57.1° (c 3.26, CH₃OH); NMR values are in Tables 8 and 9; mass spectrum calcd m/z 307.0878; found m/z 307.0885; m/z 307 (M⁺), 289 (M-H₂O), 230 (M-C₆H₅), 216 (M-CH₂C₆H₅), and 204 (M-C₄H₇O₃).

Anal. Calcd for C₁₅H₁₇NO₄S: C, 58.61; H, 5.58; N, 4.56.

Found: C, 58.26; H, 5.62; N, 4.51.

2-Carbomethoxymethylene-5-C-β-D-ribofuranosylthiazole (193c)

Method A; purification, solvent

G; colorless foam, 70.9%; R = 0.50 (solvent G); IR (neat) 3330, 2910, and 1735 cm⁻¹; UV λ_max: acid, 251 (3.79), pH 7.0, 246 (3.80); base, 247 (3.87); [α]_D^{25} = -49.6° (c 3.19, CH₃OH); NMR values are in Tables 8 and 9; mass
spectrum calcd m/e 289.0620; found m/e 289.0627; m/e 289 (M⁺), 271 (M–H₂O), 258 (M–CH₂OH), and 186 (M–C₄H₇O₃).

Anal. Calcd for C₁₁H₁₃NO₆S·0.50 CH₃OH: C, 45.23; H, 5.61; N, 4.59.

Found: C, 45.19; H, 5.38; N, 4.73.

5-C-Δ-D-Ribofuranosylthiazole (193d)

Method B; purification, solvent F; colorless foam, 82.1°C; RᵢF = 0.27 (solvent F); IR (neat) 3340 and 2930 cm⁻¹; UV λmax; acid, 244 (3.70); pH 7.0, 236 (3.73); base, 236 (3.83); [α]D⁰ -53.4° (c 2.05, CH₃OH); NMR values are in Tables 8 and 9; mass spectrum calcd m/e 217.0409; found m/e 217.0413; m/e 217 (M⁺), 199 (M–H₂O), and 114 (M–C₄H₇O₃).

Anal. Calcd for C₈H₁₁NO₄S·0.25 CH₃OH: C, 43.99; H, 5.37; N, 6.22.

Found: C, 43.62; H, 5.22; N, 6.52.

2-Carbamoylmethylene-5-C-Δ-D-ribofuranosylthiazole (193e)

Method A; purification, solvent H; colorless foam, 46.0%; 44.0% of ester 193c was also isolated from this reaction.
**2-Amino-5-β-D-ribofuranosylthiazole (193f)**

Method A (ten-minute reaction time); purification, solvent H; colorless foam, 61.7%; \( R_F = 0.25 \) (solvent H); IR (neat) 3310 and 2920 cm\(^{-1}\); UV \( \lambda_{\text{max}} \): acid, 257 (3.98); pH 7.0, 259 (3.93); base, 261 (3.94); \([\alpha]_D^{25} -71.4^\circ\)

**Preparation of Amide 193e from Ester 193c**

A solution of 175 mg (0.61 mmol) of ester 193c in 10 mL of saturated methanolic ammonia was allowed to stand lightly stoppered for 24 h. TLC analysis (solvent H) showed the complete disappearance of starting material. Removal of the volatile materials, followed by purification by preparative TLC (solvent H) afforded 129 mg (77.7%) of 193e.
(c 2.97, CH₃OH); NMR values are in Tables 8 and 9; mass spectrum calcd m/e 232.0518; found m/e 232.0523; m/e 232 (M⁺), 214 (M–H₂O), 201 (M–CH₂OH), 129 (M–C₄H₇O₃).

Anal. Calcd for C₈H₁₂N₂O₄S·0.50 CH₃OH: C, 41.11; H, 5.68; N, 11.28. Found: C, 40.90; H, 5.35; N, 10.97.

2-Amino-5-α-D-ribofuranosylthiazole (194)

Method A (ten-minute reaction time); purification, solvent H; colorless foam, 63.4%; Rₐ = 0.25 (solvent H); IR (neat) 3320 and 2935 cm⁻¹; UV λ max: acid, 258 (3.98); pH 7.0, 261 (3.94); base, 261 (3.96); [α]D²⁵ ‐3.64º (c 1.10, CH₃OH); NMR values are in Tables 8 and 9; mass spectrum calcd m/e 232.0518; found m/e 232.0523; m/e 232 (M⁺), 214 (M–H₂O), 201 (M–CH₂OH), 129 (M–C₄H₇O₃).

Anal. Calcd for C₈H₁₂N₂O₄S: C, 41.37; H, 5.21; N, 12.06. Found: C, 41.52; H, 5.21; N, 11.78.

5-α-D-Ribofuranosyl-2(3H)-thiazolone (195a)

Method B; purification, solvent G; colorless foam, 82.9%; Rₐ = 0.23 (solvent G); IR (neat) 3310, 2910, 1653 cm⁻¹; UV λ max: acid, 245 (3.86); pH 7.0, 245
(3.86); base, 257 (3.87); \([\alpha]_{D}^{25} -32.7^\circ (c 1.76, \text{CH}_3\text{OH});\) NMR values are in Tables 8 and 9; mass spectrum calcd \(m/e 233.0358;\) found \(m/e 233.0366;\) \(m/e 233 (M^+), 215 (M-\text{H}_2\text{O}); 190 (M-\text{CONH}); 130 (M-\text{C}_4\text{H}_2\text{O}_2);\)

Anal. Calcd for C_{16}H_{16}NO_3S·0.50 CH_3OH: C, 40.95; H, 5.22; N, 5.62. Found: C, 40.91; H, 5.12; N, 5.28.

7-C-(2,3-O-Isopropylidene-5-O-trityl-\(\beta\)-D-ribofuranosyl)-imidazo[2,1-i]purine (196a)

Adenine, 408 mg; purification, solvent F; colorless foam, 183 mg

(36.6%): \(R_F = 0.45\) (solvent F); IR (neat) 3060, 2920, 1668, 1385 cm\(^{-1};\)

UV \(\lambda_{\text{max}}\) (EtOH): acid, 277; pH 7.0, 276; base, 284; NMR values are in Tables 10-12; mass spectrum \(m/e 573 (M^+), 243 (\text{Tr}^+).\)

7-C-\(\beta\)-D-Ribofuranosylimidazo[2,1-i]purine (196b)

Method B; purification, solvent H; colorless foam; 46.8% \(R_F = 0.30\) (solvent H); IR (neat) 3310, 2920, and 1625 cm\(^{-1};\) UV \(\lambda_{\text{max}}\): acid, 276 (4.43); pH 7.0, 276 (4.31); base, 284 (4.33); \([\alpha]_{D}^{25} -228^\circ (c 0.70, \text{CH}_3\text{OH});\) NMR
values are in Tables 10-12; mass spectrum m/e 291 (M⁺), sample decomposed; fluorescence spectrum (CH₃OH) emission maximum at 409 nm, excitation at 322 nm.


3-C-(2,3-O-Isopropylidene-5-O-trityl-β-D-ribofuranosyl)imidazo[1,2-c]pyrimidin-5(6H)one (200a)

Cytosine, 333 mg; purification, solvent E (three elutions); colorless foam, 244 mg (37.0%): Rᵢ = 0.45 (solvent D); IR (neat) 3255, 2930, 1716, 1627, 1360, and 1180 cm⁻¹; UV λₘₐₓ (EtOH): acid, 256; pH 7.0, 263; base, 264; NMR values are in Tables 10-12; mass spectrum m/e 549 (M⁺), 534 (M-CH₃), 243 (Tr⁺).

3-C-(2,3-O-Isopropylidene-β-D-ribofuranosyl)-imidazo-
[1,2-c]pyrimidin-5(6H)-one (200c) and 3-C[2,3-O-
Isopropylidene-5-O-(2-methoxy-2-propyl)-β-
D-ribofuranosyl]-imidazo[1,2-c]-
pyrimidin-5(6H)-one (200d)

A solution of 200a (538 mg, 0.94 mmol), 2,2-dimethoxypropane (22 mL) and p-toluenesulfonic acid monohydrate (925 mg, 4.86 mmol)
in acetone (30 mL) was stirred at RT for 1 h. Sodium bicarbonate (3.0 g) was then added, and the reaction mixture was stirred for an additional 30 min. The mixture was filtered and concentrated to a syrup which was purified by preparative TLC (solvent F).

**200c**: colorless syrup, 144 mg (47.8%); \( R_F = 0.30 \) (solvent F); IR (neat) 3230, 2915, 1721, 1629, and 1360 cm\(^{-1}\); UV \( \lambda_{\text{max}} \) (EtOH): acid, 248, 295; pH 7.0, 275; base, 250, 287; NMR values are in Tables 10-13; mass spectrum calcd \( m/e \) 307.1168; found \( m/e \) 307.1176; \( m/e \) 307 (M\(^+\)), 292 (M-CH\(_3\)), 277 (M-2 CH\(_3\)), 249 (M-C\(_3\)H\(_6\)O), 163 (B+29).

**200d**: colorless foam, 176 mg (47.4%); \( R_F = 0.55 \) (solvent F); IR (neat) 3225, 2930, 1720, 1621, and 1380 cm\(^{-1}\); UV \( \lambda_{\text{max}} \) (EtOH): acid, 257, 287; pH 7.0, 262; base, 263, 287; NMR values are in Tables 10-12; mass spectrum \( m/e \) 347 (M-CH\(_3\)OH), 307 (M-C\(_4\)H\(_8\)O).
3-C-(2,3-O-Isopropylidene-5-O-methylsulfonyl-β-D-ribofuranosyl)-imidazo[1,2-c]pyrimidin-5(6H)-one (200b)

To a solution of 80 mg (0.26 mmol) of compound 200c in 3.0 mL of pyridine cooled to 0°C was added 0.02 mL (0.32 mmol) of methanesulfonyl chloride. After stirring at 0°C for 3 h, TLC analysis (solvent F) showed the appearance of a faster moving spot and almost complete disappearance of starting material. The reaction mixture was poured into 10 g of ice, and the resulting solution was extracted with CHCl₃, dried over anhydrous magnesium sulfate, and concentrated. Purification on preparative TLC using solvent F gave 82 mg (82.0%) of 200b as a colorless foam: \( R_F = 0.60 \) (solvent F); IR (neat) 3255, 2930, 1716, 1627, 1360, and 1180 cm\(^{-1}\); UV \( \lambda_{\text{max}} \) (EtOH): acid, 252, 294; pH 7.0, 275; base, 251, 287; NMR values are in Tables 10-12; mass spectrum \( m/e 289 \) (M-CH₃SO₃H).

3-C-β-D-Ribofuranosylimidazo[1,2-c]pyrimidin-5(6H)one (200e)

Method B (from either 200a or 200d); purification, solvent H; colorless foam, 59.1% (from 200a), 57.3% (from 200d); \( R_F = 0.28 \).

\( \text{MsOHpC} \)
(solvent H); IR (neat) 3305, 2935, 1716, and 1630 cm\(^{-1}\); UV \(\lambda_{\text{max}}\) : acid, 288 (3.97); pH 7.0, 272 (4.03); base, 284 (4.02); \([\alpha]_{D}^{25}\) +27.4 (c 0.86, CH\(_3\)OH); NMR values are in Tables 10-12; mass spectrum calcd m/e 267.0855; found m/e 267.0863; m/e 267 (M\(^{+}\)), 249 (M–H\(_2\)O), 164 (M–C\(_4\)H\(_7\)O\(_3\)); fluorescence spectrum (CH\(_3\)OH), emission maximum at 375 nm, excitation at 316 nm.

Anal. Calcd for C\(_{11}\)H\(_{13}\)N\(_3\)O\(_5\): C, 49.44; H, 4.90; N, 15.72.

Found: C, 49.77, H, 5.01; N, 13.64.

\(\overset{5',5'}{-\text{Anhydro-3-C-(2,3-O-isopropylidene-\(\text{\textbeta}\)-D-ribofuranosyl)-imidazo[1,2-\text{c}]pyrimidin-5-ol}}\)\(^{171}\)

A solution of 160 mg (0.41 mmol) of mesylate 200b and 0.07 mL (0.46 mmol) of 1,5-diazabicyclo-[5.4.0]undec-5-ene (DBU) in 4.10 mL of CH\(_2\)Cl\(_2\) was stirred at RT for 12 h. TLC analysis (solvent F) indicated the formation of a faster-moving, fluorescent spot. The reaction mixture was purified directly on preparative TLC (solvent F) to give 90 mg (75.0%) of 201 as a colorless syrup: \(R_{F} = 0.75\) (solvent
F); IR (neat) 2970, 1626, and 1385 cm\(^{-1}\); UV \(\lambda_{\text{max}}\) (CH\(_3\)OH stock solution): acid, 273 (3.97); pH 7.0, 269 (3.90); base, 277 (4.03); \([\alpha]_D^{25}\) -105° (c 1.48, CHCl\(_3\)); NMR values are in Tables 10-12; mass spectrum calcd \(m/e\) 289.1062; found \(m/e\) 289.1068; \(m/e\) 289 (M\(^+\)), 274 (M−CH\(_3\)), 231 (M−C\(_3\)H\(_6\)O); fluorescence spectrum (CH\(_3\)OH), emission maximum at 404 nm, excitation at 335 nm.

\[3-C-(2, 3-O-Isopropylidene-5-O-trityl-F-D-ribofuranosyl)-imidazo[1, 2-a]pyridine (203a)\]

2-Aminopyridine, 282 mg;
purification, ether; colorless foam,
363 mg (56.8%); \(R_F = 0.20\) (ether);
IR (neat): 2935, 1637, 1597, and 1385 cm\(^{-1}\); UV \(\lambda_{\text{max}}\) (EtOH): acid, 280; pH 7.0, 281, 301; base, 279; NMR values are in Tables 10-12; mass spectrum calcd \(m/e\) 532.2362; found \(m/e\) 232.2375; \(m/e\) 532 (M\(^+\)), 517 (M−CH\(_3\)), 243 (Tr\(^+\)).

\[3-C-\beta-D-Ribofuranosylimidazo[1, 2-a]pyridine (203b)\]

Method B; purification, solvent G; white crystals, mp = 188-190°C;
65.7%; \(R_F = 0.25\) (solvent G); IR (neat) 3345, 2935, 1633, and 1504
cm\(^{-1}\); UV \(\lambda_{\max}\): acid, 276 (3.88); pH 7.0, 279 (3.75); base, 280 (3.75); 
\([\alpha]_D^{25}\) -129° (c 1.02, CH\(_3\)OH); NMR values are in Tables 10-12; mass spectrum 
calcd m/e 250.0953; found m/e 250.0958; m/e 250 (M\(^+\)), 232 
(M-H\(_2\)O), 219 (M-CH\(_2\)OH), and 147 (M-C\(_4\)H\(_7\)O\(_3\)); fluorescence spectrum 
(CH\(_3\)OH) emission maximum at 376 nm, excitation at 338 nm.

Anal. Calcd for C\(_{12}\)H\(_{14}\)N\(_2\)O\(_4\): 0.25 CH\(_3\)OH: C, 56.97; H, 5.85; N, 
10.85. Found: C, 56.83; H, 5.61; N, 10.63.

3-\(\text{C-(2, 3-O-Isopropylidene-5-O-trityl-\(\beta\)-D-ribofuranosyl)}\)-imidazo[1, 2-a]pyrimidine (204a)

2-Aminopyrimidine, 285 mg;
purification, solvent E; colorless foam, 298 mg (46.6%): \(R_F = 0.35\) (solvent E); 
IR (neat) 2930, 1620, and 1381 cm\(^{-1}\); 
UV \(\lambda_{\max}\) (EtOH): acid, 267; pH 7.0, 264, 326; base, 266; NMR values are 
in Tables 10-12; mass spectrum, 243 
(Tr\(^+\)), sample decomposed.

3-\(\text{C-\(\beta\)-D-Ribofuranosylimidazo[1, 2-a]pyrimidine (204b)}\)

Method B; purification, 
solvent G; colorless foam, 63.9%; 
\(R_F = 0.23\) (solvent G); IR (neat) 
3310, 2940, 1619, and 1502 cm\(^{-1}\);
UV $\lambda_{\text{max}}$: acid, 278 (3.59); pH 7.0, 276 (3.44), 319 (3.43); base, 276 (3.46), 319 (3.45); $[\alpha]_D^{25} -108^\circ$ (c 1.04, CH$_3$OH); NMR values are in Tables 10-12; mass spectrum m/e 222 (M−CH$_2$OH), 149 (M−C$_4$H$_8$O$_2$); fluorescence spectrum (CH$_3$OH), emission maximum at 440 nm, excitation at 316 nm.

Anal. Calcd for C$_{11}$H$_{13}$N$_3$O$_4$: C, 52.58; H, 5.21; N, 16.73.

Found: C, 52.86; H, 5.49; N, 13.98.
Table 13. Compilation of the $^{13}$C NMR Values of the Isopropyldene Carbons of C-Glycosides and C-Nucleosides (ppm)$^a$

<table>
<thead>
<tr>
<th>α Anomers</th>
<th>CH$_3$</th>
<th>CH$_3$</th>
<th>$\Delta$δ</th>
<th>C$_Q$</th>
<th>Ref.</th>
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<td>27.60</td>
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<tr>
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<td>27.57</td>
<td>1.89</td>
<td>114.21</td>
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<tr>
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<td>27.47</td>
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<tr>
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<td>R = C-Br</td>
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<tr>
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<td>27.49</td>
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Table 13 (continued)

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<td>1.90</td>
<td>114.43</td>
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Table 13 (continued)

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Average Values 25.60 27.50 1.90 114.50

$\pm0.2$ $\pm0.2$ $\pm0.2$ $\pm0.6$
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Table 13 (continued)

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<th>CH₃</th>
<th>Δδ</th>
<th>CQ</th>
<th>Ref.</th>
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<td>R = NH₂</td>
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Average Values 25.00 26.30 1.25 112.70

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- Solvent is CDCl₃, Chemical shifts are in parts per million downfield from internal tetramethylsilane
- Reference 102
- This signal is well outside of the value range
- This work
- M. C. Clingerman, unpublished results
- Reference 130
- J.A. Secrist III, unpublished results
- Solvent is 9:1 CDCl₃–DMSO–d₆
- These values were not used to compute the average


11. In a strict sense designation of the C-nucleosides or of the C-glycosyl precursors isomeric at C-1 of the carbohydrate moiety as α and β anomers is incorrect; however, this designation is more readily understood than the systematic notation and will be used throughout the text. Also, for ease of discussion, trivial names rather than systematic ones will be used.


160. See Reference 157, p. 361.


171. Although this nomenclature is acceptable, the current *Chemical Abstracts* index name for this compound is 

\[8R-(8\alpha, 8a\beta, 11a\beta, 12a)]-8, 8a, 11a, 12-Tetrahydro-10, 10-dimethyl-8, 12-epoxy-7H, 10H-6, 9, 11-trioxa-2, 5, 12b-triazacyclopenta[7, 8]-cyclonon[1, 2, 3-cd]indene.\]