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The development of a synthetically useful penal dic acid equivalent and its application to the asymmetric synthesis of polyoxin J

Park, Jung Min, Ph.D.
Case Western Reserve University, 1990
THE DEVELOPMENT OF A SYNTHETICALLY USEFUL PENTADECIC ACID
EQUIVALENT AND ITS APPLICATION TO THE ASYMMETRIC SYNTHESIS OF
POLYOXIN J

by

JUNG MIN PARK

submitted in partial fulfillment of the requirements
for the degree of Doctor of Philosophy

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May 1990
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Jung Min Park
THE DEVELOPMENT OF A SYNTHETICALLY USEFUL PENALDIC ACID EQUIVALENT AND ITS APPLICATION TO THE ASYMMETRIC SYNTHESIS OF POLYOXIN J

Abstract

by

JUNG MIN PARK

This thesis describes the development of a synthetically useful penaldic acid equivalent, 1,1-dimethylcylthyl (R)-4-formyl-2,2-dimethyl-3-oxazolidine carboxylate (5b). This differentially protected β-hydroxy α-aminoaldehyde was obtained in 60-70% distilled yield over 4 steps from commercially available D-serine and shown to be 94-96% enantiomerically pure by $^1$H NMR, $^{19}$F NMR, and HPLC analyses of its diastereomeric Mosher ester derivatives. The aldehyde can serve as a chiral nonracemic synthon as well as a penaldic acid equivalent for the asymmetric synthesis of complex nucleoside antibiotics such as the polyoxins, amipurimycin, and the miharamycins.

Chapter 3 of this thesis describes the application of the penaldic acid equivalent 5b to the asymmetric synthesis of polyoxin J, an agricultural antibiotic exhibiting marked selectivity against certain phytopathogenic fungi. The asymmetric synthesis of a protected form of polyoxin J was achieved by the peptide coupling of suitably protected forms of its acyclic and cyclic components.
The acyclic component, 5-O-carbamoylpolyoxamic acid (9), is obtained in 11% yield over 8 steps from the penaldic acid equivalent 5b, all chirality being derived from the existing stereogenic center in 5b. During the synthesis of 9, conditions for cis-hydroxylation of N-protected allylic amine systems such as 29 have been found. When CO$_2$-buffered KMnO$_4$ was used as a reagent, the 2,3-syn, 3,4-syn dihydroxylated products was obtained with a (2.5:1) diastereofacial selectivity. When the chiral ligand, hydroquinidine p-chlorobenzoate was used with OsO$_4$, the 2,3-anti, 3,4-syn dihydroxylated product was obtained with a (6:1) stereoselectivity.

The cyclic nucleoside component, thymine polyoxin C (10), is obtained in 5% yield over 11 steps from penaldic acid equivalent 5b wherein all chirality was again derived from the existing stereogenic center in 5b. The synthesis of 10 involved four distinct phases: (1) the diastereoselective nucelophilic addition to penaldic acid equivalent 5b, (2) the stereocontrolled elaboration of furanose via cis-hydroxylation, (3) a release of the latent α-aminoacid moiety in a suitably protected form, and (4) a stereo- and regioselective nucleoside formation using Vorbrüggen's methodology.

Finally, an efficient peptide coupling of γ-hydroxy acid and amine has been found by using a silylation protection sequence without any relactonization and/or racemization problems.
To my mother
Duk Sun Kam
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LIST OF ABBREVIATIONS

Bn  benzyl
BOC  tert-butyloxy carbonyl
(BOC)$_2$O  di-tert-butyl-dicarbonate
Cbz  benzyloxy carbonyl
DOC  dicyclohexyl carbodiimide
de  diastereomeric excess
DIBAL  diisobutylaluminum hydride
DMAP  2-dimethylaminopyridine
DMP  2,2-dimethoxypropane

ee  enantiomeric excess

FAB  fast atom bombardment

HMDS  hexamethyldisilane
HMPA  hexamethylphosphoramide
HOBT  1-hydroxybenzotriazole
HPLC  high performance liquid chromatography
HRMS  high resolution mass spectrometry

IR  infrared

LRMS  low resolution mass spectrometry

MTPA  $\alpha$-methoxy-$\alpha$-(trifluoromethyl)-phenylacetic acid

NMR  nuclear magnetic resonance
NMO  N-methyl N-morpholine oxide
NOE  nuclear Overhauser effect

-xi-
Ph  phenyl
PPTS pyridinium para-toluenesulfonate
TBS tert-butyldimethylsilyl
TBSCI tert-butyldimethylsilyl chloride
TFA trifluoroacetic acid
THF tetrahydrofuran
TLC thin layer chromatography
TMNO trimethyl N-oxide
TMS tetramethylsilane
TMSCI trimethylchlorosilane
TMSOTf trimethylsilyl trifluoromethanesulfonate
TsOH para-toluene sulfonic acid
WSC 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
INTRODUCTION

Over the past fifty years, a number of unusual amino acids have been isolated from natural sources. The antibiotic activity demonstrated by some of these compounds themselves or as components of larger systems makes them attractive synthetic targets. A recurring subunit in some of these amino acids is the $\beta$-hydroxy- (or alkoxy-) $\alpha$-amino acid group as shown in Figure 1.

**Figure 1.** Representative Examples of Nucleoside Antibiotics Containing the $\beta$-Hydroxy- (or Alkoxy-) $\alpha$-Amino Acid Subunit.
One approach to compounds of this type involves stereocontrolled buildup of a chiral building block which, after further manipulation, yields desired the β-hydroxy- (or alkoxy-) α-amino acid group. Although penadic acid has the structure required for this approach (Figure 2), it both racemizes and undergoes decarboxylation easily. A protected form of penadic acid (hence, a penadic acid equivalent) is therefore needed. One route to a stable penadic acid equivalent could involve the conversion of commercially available serine to a differentially protected serinal (not shown).

Figure 2. General Approach to β-Hydroxy- (or Alkoxy-) α-Amino Acids.

Several requirements must be met in order to make this approach useful: the building block must be (1) prepared in a configurationally pure form in high yield, (2) able to exert diastereocontrol during addition reactions, and (3) amenable to eventual release of the α-amino acid group. Three differentially protected serinals had been prepared prior to this work, however, it was determined that these would not be suitable penadic acid equivalents because of either the poor yields and dubious enantiomeric
purities, or the low diastereoselectivity obtained during their addition reactions.

In this thesis, the synthesis and configurational purity of a new and synthetically useful penaldic acid equivalent derived from serine is presented and the application of this penaldic acid equivalent based strategy to the asymmetric synthesis of the complex peptidyl nucleoside antibiotic, polyoxin J is described.
Chapter 2

DEVELOPMENT OF A SYNTHETICALLY USEFUL PENALDIC ACID EQUIVALENT

SYNTHESIS OF THE PENALDIC ACID EQUIVALENT

The synthesis of the chiral penaldic acid equivalent 5 is outlined in Scheme I starting from either L-serine (a-series) or D-serine (b-series). Generally, this required (1) protection of the amine and acid functional groups, (2) formation of the oxazolidine ring system, and (3) semi-reduction of the ester to an aldehyde.\(^4\)

Scheme I. Preparation of the Penaldic Acid Equivalent 5.

\[ \text{HO-} \text{CH}_2 \text{CH}_2 \text{COOH} \rightarrow \text{HO-} \text{CH}_2 \text{CH}_2 \text{COOR} \]

(i) (BOC)\(_2\)O, 1N NaOH
(ii) CH\(_2\)_N\(_2\) or CH\(_3\)_I + K\(_2\)CO\(_3\) \(\rightarrow\) 90%

a-series from L-serine
b-series from D-serine

\[ \text{HO-} \text{CH}_2 \text{CH}_2 \text{COH} \rightarrow \text{HO-} \text{CH}_2 \text{CH}_2 \text{CONHBOC} \]

DMP, TsOH (-MeOH) \(\rightarrow\) 80%

\[ \text{HO-} \text{CH}_2 \text{CH}_2 \text{CONHBOC} \rightarrow \text{HO-} \text{CH}_2 \text{CH}_2 \text{CONHBOC} \]

DIBAL, toluene, -78 °C \(\rightarrow\) 85%
In the first step, the amine was protected selectively with a tert-butyloxy carbonyl (BOC) group using a modification of Wünsh's procedure (treatment of serine 1 with di-tert-butyl dicarbonate (BOC₂O) in 1 N NaOH solution, pH > 10)⁵ to produce N-BOC serine 2. Protection of the crude acid 2 was accomplished by a modification of Arndt's procedure⁶a using ethereal diazomethane solution to give the N-BOC serine methyl ester 3 in two steps (91% crude yield). An alternative esterification method that avoids the use of toxic diazomethane involved a treatment of acid 2 with methyl iodide and potassium carbonate in dimethylformamide (DMF)⁶b to give the ester 3 in two steps (90% crude yield). The enantiomeric purity of 3 (obtained from both esterification methods) was not determined although polarimetry revealed low and variable rotations (see Experimental Section).⁷ Furthermore no literature value for the maximum rotation could be found for comparison. However, the configurational purity and stability were subsequently confirmed by transformation of 3 to the penaldic acid equivalent 5 which was shown to be 94-96% enantiomerically pure (vide infra).

A precedent for the formation of the 2,2-dimethyloxazolidine ring system using 2,2-dimethoxypropane (DMP) under acid-catalyzed conditions was provided by the reaction of 2-acetamido-2-deoxy-D-mannose with DMP to give 2-acetamido-2-deoxy-2,3-N,O-isopropylidene-5,6-O-isopropylidene-D-mannofuranose as shown in next page (eq. 1).⁸
It was found that slow distillation of a solution made up of N-BOC serine methyl ester 3, DMP, and a catalytic amount of p-toluenesulfonic acid (TsOH) in benzene resulted in the clean formation of the oxazolidine methyl ester 4. This was isolated in 70-80% yield after either vacuum distillation or flash chromatography. Although the infrared and mass spectra obtained for 4 were consistent with the proposed structure, the $^1$H NMR spectrum showed two sets of signals at ambient temperature which coalesced upon raising the probe temperature to 75 °C. Cooling the sample restored the original spectrum. These results showed a dynamic equilibrium of two conformers owing to the restricted rotation of the carbamate (Figure 3).

\[ \text{E-conformer} \quad \leftrightarrow \quad \text{Z-conformer} \]

**Figure 3.** Two Possible Conformers of Oxazolidine Ester 4.
The observed energy barrier for 4 was ca. 28 kcal/mol as determined by a complete band shape analysis of the diastereotopic methyl groups at C-2.\textsuperscript{9a} This value is about 10 kcal/mol higher than normally observed for carbamates and may reflect the superposition of additional conformational changes associated with the substituted 5-membered ring.\textsuperscript{9b}

In the third step, semi-reduction of the ester 4 to the corresponding aldehyde 5, was achieved by treatment with diisobutylaluminum hydride (DIBAL)\textsuperscript{10a} in toluene at -78 °C, followed by quenching with cold MeOH at this same temperature. This led to the clean formation of oxazolidine aldehyde 5 uncontaminated by the over-reduction product (alcohol). The mechanism of this reaction is believed to involve a strong coordination at low temperature (-70 °C) between the intermediate hemiacetal and an aluminum species\textsuperscript{10b} (Figure 4).

![Figure 4. Mechanism of Semi-Reduction of Ester 4 Using DIBAL.](image-url)
The aldehydes (5a from L-serine and 5b from D-serine) were obtained in 75-85% yield after vacuum distillation. The distilled products contained ca. 5% of the starting ester 4 as judged by their TLC and $^1$H NMR spectra but were suitable for use without further purification. Pure 5a and 5b were obtained after flash chromatography and showed a maximum optical rotation of $\pm 105^\circ\text{I}$ with no evidence of decomposition after storage at 5 °C for nine months. Even though compound 5 seemed configurationally stable to the above purification conditions, a more sensitive assay that would leave no doubt about this point was desired (vide infra).

**DETERMINATION OF THE CONFIGURATIONAL PURITY OF THE PENALDIC ACID EQUIVALENT VIA MOSHER ESTER DERIVATIVES**

In order to determine the configurational purities of the aldehydes (5a and 5b), they were deliberately converted to their respective alcohols (6a and 6b) and condensed with (S)-(−)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (MTPA) according to Mosher's procedure$^{11}$ giving (S,S)-7a and (R,S)-7b respectively (Scheme II).

**Scheme II. Preparation of Mosher Ester Derivatives of 5.**

(5a from L-serine, (R,S)-7b from D-serine)
Later, the enantiomeric excesses (ee) of the chiral aldehydes was calculated by extrapolation from the respective diastereomeric ratios determined by $^1\text{H}$ NMR, $^{19}\text{F}$ NMR, and HPLC analyses of the derivatives 7.

**Preparation of Mosher Ester Derivatives of Penaldic Acid Equivalent 5**

Aldehyde 5a derived from L-serine was reduced with sodium borohydride to give the alcohol 6a, which was then condensed with (S)-(MTPA) in the presence of dicyclohexylcarbodiimide (DCC) and a catalytic amount of 4-dimethylaminopyridine (DMAP)\textsuperscript{12} to give the Mosher ester (S,S)-7a in 75% overall yield. This method (DCC + DMAP) is highly recommended for the formation of MTPA esters because it is amenable to small-scale reactions and does not involve the more expensive MTPA chloride. The same sequence was applied to the aldehyde 5b obtained from D-serine yielding a diastereomer (R,S)-7b.

**Determination of Configurational Purity of the Mosher Ester Derivatives**

As stated above $^1\text{H}$ NMR, $^{19}\text{F}$ NMR, and HPLC methods were used to determine the enantiomeric excess of aldehydes 5a and 5b based on the analysis of their corresponding Mosher ester derivatives 7. It was found by $^1\text{H}$ NMR that the diastereotopic protons (H-1'a and H-1'b)\textsuperscript{13} of (S,S)-7a displayed a different chemical shift from the analogous protons of (R,S)-7b (Figure 5). Integration of these proton signals provided the presumptive evidence that there was at least 93-95% ee in the precursor
$^1$H NMR Conditions: (200 MHz, C$_6$D$_6$, 60 °C)

(S,S:R,S) = (3:2)

Figure 5. Partial Proton NMR Spectra of MTPA Ester 7a and 7b.
aldehydes 5a and 5b. It was also found by $^{19}$F NMR that the fluorine resonances of the CF$_3$ group in the diastereomers have different chemical shifts at ambient temperature (not at 60 °C) and this provided another measure of the enantiomeric purity - indicating a 93-95% ee for the precursor aldehydes. It was also shown by HPLC (SiO$_2$ column; 20:1 hexanes-EtOAc) that the diastereomers (S,S)-7a and (R,S)-7b were separable and indicated a limit for 93-95% ee of the precursor aldehydes. Since HPLC analysis of the starting L- and D-serines (Diacel chiral column; 0.25 M CuSO$_4$ solution) each indicated 1% cross contamination, the overall enantiomeric purity of the syntheses of 5a and 5b was set at 94-96%.

Table I. HPLC Assay of Enantiomeric Purity of MTPA Esters of 7a and 7b.

<table>
<thead>
<tr>
<th>compound</th>
<th>method</th>
<th>$t_R$, min</th>
<th>ee/de, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-serine</td>
<td>a</td>
<td>17</td>
<td>98</td>
</tr>
<tr>
<td>D-serine</td>
<td>a</td>
<td>13</td>
<td>98</td>
</tr>
<tr>
<td>(S,S)-7a</td>
<td>b</td>
<td>20</td>
<td>93</td>
</tr>
<tr>
<td>(R,S)-7b</td>
<td>b</td>
<td>17</td>
<td>95</td>
</tr>
</tbody>
</table>

Method (a): Diacel Chiralpak WH column at 50 °C eluting with 0.25 mM aqueous CuSO$_4$ at 2.0 mL/min and employing UV detection at 254 nm. Method (b): 10 μm SiO$_2$ (25cm x 4.5 mm) at 25 °C eluting with (20:1) hexanes-EtOAc at 2.0 mL/min and employing UV detection at 254 nm.
CONCLUSION

The oxazolidine aldehydes 5a and 5b were shown to be conveniently prepared and easily purified on a synthetically useful scale (30-60 g) from commercially available L- and D-serines. The configurational purity of these N-protected α-amino aldehydes was shown to be 94-96% ee. Compounds 5a and 5b appear ideally suited as chiral, nonracemic synthons for the asymmetric synthesis of complex nucleoside antibiotics, unusual amino acids, and other nitrogen-containing targets.
Chapter 3

SYNTHETIC APPLICATION OF PENALDIC ACID EQUIVALENT TO THE ASYMMETRIC SYNTHESIS OF POLYOXIN J

BACKGROUND ON THE POLYOXINS

The polyoxins comprise a family of agricultural antibiotics isolated from Streptomyces cacaoi var. asoensis that exhibit marked selectivity against phytopathogenic fungi.\textsuperscript{14} They function by inhibiting chitin synthetase, presumably by mimicking the natural substrate, uridine diphosphate N-acetylglucosamine (UDP-GlcNAc) (Figure 6). Recent studies suggest that these compounds (or analogues thereof) may also be therapeutically useful against Candida albicans, a fungal pathogen which commonly affects humans.\textsuperscript{15}

Thirteen polyoxins are known of which the gross structure for eight of these is shown in Figure 6. As can be seen in the figure, they incorporate an unusual α-aminoaldonic acid fragment and an α-aminoaruronic acid fragment that are connected by a peptide linkage. Mild acid hydrolysis of the peptide linkage in these polyoxins leads to the isolation of 5-O-carbamolypolyoxamic acid (9) and a pyrimidine nucleoside (10). The stereochemistry of these two segments was firmly established by Isono using a combination of chemical, spectral, and X-ray based techniques.\textsuperscript{1b}
Previous Synthesis of Polyoxin J

The only existing total synthesis of polyoxin J (8, \( R_1 = \text{Me}, R_2 = \text{OH}, \) and \( R_3 = \text{OH} \)) was achieved by Kuzuhara and coworkers.\(^{16a} \) This involved the peptide coupling reaction of activated ester of 5-O-carbamoyl-
polyoxamic acid and thymine polyoxin C \((10, R_1 = \text{Me}, R_2 = \text{OH})\) which were synthesized from corresponding carbohydrate starting materials (Figure 7, vide infra).

![Diagram of polyoxin J synthesis]

Figure 7. Kuzuhara’s Synthesis of Polyoxin J.

**Previous Syntheses of 5-O-Carbamoylpolyoxamic Acid (9)**

There have been three independent syntheses of 5-O-carbamoylpolyoxamic acid. Kuzuhara modified the existing stereocenters of 1,2-O-isopropyldene-\(\alpha\)-L-sorbopyranose 11 that contained the appropriate carbon backbone (Figure 8).\(^{16}\)\(^b\) The inversion of stereocenters was achieved by mesylation of 11 followed by azide displacement to give azidodiol dimesylates which were treated with KOH followed by its protection to provide the azidodiol dibenzyl ether 12 with all necessary stereocenters in 5-O-carbamoylpolyoxamic acid (9). Multiple protections and deprotections were used for the generation of 5-O-carbamoyl and \(\alpha\)-
amino acid functionalities. Because of this, the method was tedious and the overall yield quite low.

![Chemical Structures](image)

**Figure 8.** Kuzuhara's Synthesis of 5-O-Carbamoylpolyoxamic Acid 9.

More recent efforts directed toward the synthesis of 5-O-carbamoylpolyoxamic acid 9 have been developed by Mukaiyama using a tartarate-derived aldehyde 13 as a four-carbon chiral building block (Figure 9). The same starting material was also utilized in a synthesis of thymine polyoxin C (10) (vide infra). This unified approach required that the additional chiral centers be introduced with some degree of stereocontrol. Thus, the stereocontrolled addition of lithium acetylide to 13 proceeded with excellent erythro-selectivity (49:1) to give propargylic alcohol 14. After the nitrogen function was introduced by an azide displacement via tosylate, the standard transformations were used to give
a protected 5-O-carbamoylpolyoxamic acid 15, but its conversion to, and comparision with 5-O-carbamoylpolyoxamic acid itself was not completed.

![Chemical Reaction Diagram]

Figure 9. Mukaiyama's Approach to 5-O-Carbamoylpolyoxamic Acid (9).

An alternative synthesis of 5-O-carbamoylpolyoxamic acid using the same aldehyde 13 as Mukaiyama has recently been reported by workers at Schering-Plough (Figure 10). Their route began with a Wadsworth-Horner-Emmons reaction of 13 to give the (E)-α,β-unsaturated ester. This compound was reduced to an allylic alcohol and then converted to the trichloromethyl imidate derivative 16. The amine group was introduced somewhat differently using a facile [3,3] sigmatropic rearrangement of 16 which gave a (1:1) mixture of the diastereomeric trichloroacetamides
17 and "iso"-17. Each compound was separately transformed to the final product, 5-O-carbamoylpolyoxamic acid 9 and its (2R) epimer "iso"-9 using standard transformations. Even though neither of their intermediates (18 and "iso"-18) matched Mukaiyama's intermediate 15, product 9 was shown to possess the correct stereochemistry by an X-ray analysis of a crystalline γ-lactone derivative of 18. Although this route provided a short synthesis of 9, it is inefficient because of the low stereoselectivity obtained during the rearrangement of 16.

Figure 10. The Schering-Plough Synthesis of 5-O-Carbamoylpolyoxamic Acid (9).
Previous Syntheses of Thymine Polyoxin C

A highly efficient approach to uracil polyoxin C was achieved by Moffatt using Strecker methodology (Figure 11). This involved a treatment of 2',3'-O-cyclohexylylideneuridine-derived aldehyde 19 with sodium cyanide to provide a (1:1) epimeric mixture of stable hydroxyamides 20. After separation of this mixture, each diastereomer was aminated and deprotected using standard procedures to obtain the uracil polyoxin C. It is believed that this might be a convenient approach to thymine polyoxin C where the 2',3'-O-cyclohexylylideneuridine-derived aldehyde is replaced with 2',3'-O-cyclohexyldenethymidine-derived aldehyde. Even though this synthesis was concise, it involves a readily available starting material. It would not be applicable to the synthesis of unusual branched aminosugars such as the one contained as a fragment in amipurmycin (see Figure 1) since the corresponding starting aldehyde is not readily available.

Figure 11. Moffatt’s Synthesis of Uracil Polyoxin C.

Kuzuhara's approach to thymine polyoxin C began with the carbohydrate 3-O-benzyl-1,2-O-isopropyridene-5,6-di-O-methanesulfonyl
α-D-allofuranose (21), a starting material which contains the desired carbon skeleton and stereochemistry (Figure 12). Functional groups such as the amino group at C-5 and the thymine group at C-1 were then added.

Figure 12. Kuzuhara's Synthesis of Thymine Polyoxin C.

It was necessary to differentiate between the primary alcohol (C-6) and the secondary alcohol (C-5) using a protection and deprotection sequence in order to introduce the azide group at the C-5 position to give 22. Transformation of 22 to anomeric acetates 23 was again achieved via multiple protection and deprotection protocols. Pyrimidine moiety was successfully introduced using Vorbüggen's nucleosidation methodology giving 24. Finally, oxidation of the primary alcohol to an acid and
reduction of the azide gave thymine polyoxin C 10. Again, this approach is inefficient because of the necessity for multiple protection and deprotection sequences.

Mukaiyama's approach\textsuperscript{17} (Figure 13) utilized a solvent dependent, (Z)-selective Wittig reaction with aldehyde 13 to assemble the butenolide 25.

\begin{align*}
\text{Me} \quad \text{Me} \\
\text{BnO} \quad \text{CHO} \\
\text{13}
\end{align*}

\begin{align*}
i) \text{KmNO}_4, \text{dicyclichexano-} \\
18\text{-crown-6} \\
\text{ii}) \text{DMP, cat. TsOH} \\
\text{iii}) \text{KF, Bu}_4\text{NHSO}_4 \\
75\% \text{ yield over 3 steps}
\end{align*}

\begin{align*}
\text{BnO} \\
\text{HO} \\
\text{Me} \quad \text{Me} \\
\text{26}
\end{align*}

\begin{align*}
i) \text{1-methyl-2-fluoro-pyrimidinylsulate, Et}_3\text{N} \\
\text{ii}) \text{LiN}_3, \text{HMPT} \\
71\% \text{ yield over 2 steps}
\end{align*}

\begin{align*}
\text{HO} \\
\text{Me} \\
\text{N} \quad \text{N} \\
\text{N} \\
\text{27}
\end{align*}

\begin{align*}
\text{i}) \text{DIBAL, -78}\degree\text{C} \\
\text{ii}) 70\% \text{ HOAc, 80}\degree\text{C} \\
\text{iii}) \text{Ac}_2\text{O, pyridine}
\end{align*}

\begin{align*}
\text{iv}) 2,4\text{-bis(trimethylsiloxy)}- \\
5\text{-methylpyrimidine, TMSOTf} \\
\text{v}) \text{BBr}_3, -42\degree\text{C} \\
92\% \text{ yield over 4 steps}
\end{align*}

\begin{align*}
\text{Me} \\
\text{H} \quad \text{O} \\
\text{N} \quad \text{N} \\
\text{28}
\end{align*}

\begin{align*}
i) \text{NH}_3, \text{MeOH} \\
\text{ii}) \text{DMP, cat. TsOH} \\
95\% \text{ yield over 2 steps}
\end{align*}

\begin{align*}
\text{HO} \\
\text{Me} \\
\text{N} \quad \text{N} \\
\text{N} \\
\text{Me} \\
\text{24}
\end{align*}

\begin{align*}
\text{see Figure 12}
\end{align*}

\begin{align*}
\text{Me} \\
\text{H} \quad \text{O} \\
\text{N} \quad \text{N} \\
\text{OH} \\
\text{HO} \\
\text{N} \quad \text{N} \\
\text{25}
\end{align*}

\begin{align*}
i) \text{NH}_3, \text{MeOH} \\
\text{ii}) \text{DMP, cat. TsOH} \\
95\% \text{ yield over 2 steps}
\end{align*}

\begin{align*}
\text{Me} \\
\text{CO}_2\text{H} \\
\text{H}_2\text{N} \quad \text{OH} \\
\text{Me} \\
\text{10}
\end{align*}

Figure 13. Mukaiyama's Formal Synthesis of Thymine Polyoxin C.
Cis-hydroxylation of this compound using KMnO₄ proceeded exclusively from the less hindered α-face, as required, leading to 26 after acetonide formation and desilylation. The nitrogen functionality was then introduced at C-5 via azide displacement of a 2-pyridinium alkoide (generated in situ) and yielded compound 27. After lactone reduction and formation of the anomeric acetates, nucleoside formation was effected using Vorbrüggen's nucleosidation to give 28. Deacetylation followed by acetonide formation led to the intermediate 24 which had previously been converted to thymine polyoxin C 10 by Kuzuhara (see Figure 12) and thus constituted a formal synthesis of this compound.

Retrosynthesis of Polyoxin J

It was felt that polyoxin J (8) could be obtained by the peptide coupling reaction of suitably protected forms of two segments, 5-O-carbamoylpoloxamic acid (9) and thymine polyoxin C (10) (Scheme III). These two segments 9 and 10 could arise from the stereocontrolled oxidation of the N-protected allylic amino alcohol 29 and homoallylic amino alcohol 30 respectively. These intermediates 29 and 30 could be derived from the homologation (C-C bond formation) of penaldic acid equivalent 5b (derived from D-serine), thus making the approach highly convergent.

The use of the penaldic acid equivalent 5b prepared in chapter 2, as a chiral, nonracemic starting material for the asymmetric construction
Scheme III. Retrosynthetic Analysis of Polyoxin J (8).

**Coupling reaction**

**Oxidation**

**Homologation**

D-serine
of the polyoxins contrasts with previous work in the area, which had relied primarily on carbohydrates as chiral building blocks (vide supra). This approach should be superior to the previous methods since the penal dic acid equivalent 5b already contains a three carbon skeleton, chiral center, and amine functional group with the correct configuration which would serve to minimize the need for multiple protection and deprotection steps.

Herein reported is a stereocontrolled and asymmetric synthesis of polyoxin J described in three sections: (1) synthesis of the acyclic component, 5-O-carbamoyl polyoxamic acid (9), (2) synthesis of the nucleoside component, thymine polyoxin C (10), and (3) the peptide coupling of 9 and 10.
SYNTHESIS OF 5-O-CARBAMOYLPOLYOXAMIC ACID (9)

The synthesis of polyoxin J begins with the synthesis of the fragment 5-O-carbamoylpolyoxamic acid (9). As is seen in Scheme IV, this is accomplished by homologation (C-C bond formation) of penaldic acid equivalent 5b (derived from D-serine) with a 2-carbon unit to generate the N-BOC allylic amino alcohol 29 followed by subsequent stereoselective oxidation to the desired product.\textsuperscript{20} Since diastereoselective cis-hydroxylations of homochiral allylic amine systems such as 29 are not well established,\textsuperscript{21} the stereoselectivity of the reactions used are of great interest in order to give the syn (to amide group) diols in 5-O-carbamoylpolyoxamic acid (9).

Scheme IV. Synthetic Strategy of 5-O-Carbamoylpolyoxamic Acid (9).

Two Carbon Homologation

 Attempted Wittig Route. The most obvious homologation of oxazolidine aldehyde 5b with a 2-carbon unit involves Wittig
olefination as outlined in Scheme V. Wittig Reaction of aldehyde 5b with the stabilized ylide, ethyl (triphenylphosphoranylidene)acetate, in CH₂Cl₂ afforded a (19:1) mixture of (E)- and (Z)-isomers 31 and 32 respectively in 80% combined yield. Separation of the desired (E)-isomer 31 from the (Z)-isomer 32 was achieved by fractional recrystallization.

Scheme V. Wittig Homologation Route of Penaldic Acid Equivalent 5b.

The stereochemistry of 31 and 32 was ascertained using ¹H NMR spectroscopy by comparison of their olefinic proton coupling constants (J = 15.6 Hz, 31; J = 11.3 Hz, 32) and by observation of the chemical shift differences between the H-4 protons in each isomer (4.08 ppm in 31; 5.64 ppm in 32). Such a large difference in chemical shift is believed to be due to the deshielding effect of the carbonyl group on the proximal H-4 proton of the (Z)-isomer 32.
The selective reduction of the α,β-unsaturated ester 31 obtained from the Wittig reaction to the desired allylic alcohol 33 proved to be difficult. A list of the reducing agents and conditions tried is given in Table II. As is seen from the table, reduction of unsaturated ester 31 with DIBAL not only gave the desired allylic alcohol 33 but also a variety of undesired products (i.e., saturated alcohol 34, saturated ester 35, unsaturated aldehyde 36, and an unknown product 37). Reduction using LiAl(1Bu)2(1Bu)H, a reagent known to suppress overreduction (entry 5),\textsuperscript{23} still gave a mixture of the desired allylic alcohol 33 and the saturated alcohol 34 in 44% yield. Attempts to purify the allylic alcohol 33 however failed since it decomposes on silica gel by air-oxidation to the unsaturated aldehyde 36. It should be noted that the reduction of unsaturated ester 31 using LiAl(1Bu)2(1Bu)H (entry 6) did give a moderate yield (51%) of unsaturated aldehyde 36. This rather selective reduction to 36 may be due to steric hinderance created by the bulky reducing agent. Because a satisfactory reduction protocol was not found at this point, the homologation of aldehyde 5b beginning with a Wittig reaction was abandoned in favor of a Grignard based route (vide infra).

Recently, Moriiwake and coworkers\textsuperscript{24} claimed that the non-selective reduction of α,β-unsaturated esters having a γ-nitrogen system may be due to an unfavorable coordination of the γ-nitrogen with DIBAL (Figure 14). With an α,β-unsaturated ester similar to ours, they found that prior coordination of the γ-nitrogen with BF3·Et2O followed by DIBAL addition improves the selective reduction to the allylic alcohol significantly.
Table II. Nonselective Reduction of α,β-Unsaturated Ester 31.

\[
\begin{align*}
&\text{EtO} \quad \text{HO} \\
&\text{BOC} \quad \text{BOC} \\
&\text{N} \quad \text{N} \\
&\text{O} \quad \text{O} \\
\text{31} &\xrightarrow{\text{"H"}^\text{+}} \text{HO} \quad \text{HO} \\
&\text{BOC} \quad \text{BOC} \\
&\text{N} \quad \text{N} \\
&\text{O} \quad \text{O} \\
\text{33} &\quad \text{34} \\
&\text{EtO} \quad \text{H} \quad \text{BOC} \quad \text{BOC} \quad \text{Unknown} \\
&\text{N} \quad \text{N} \\
&\text{O} \quad \text{O} \\
\text{35} &\quad \text{36} &\quad \text{37}
\end{align*}
\]

<table>
<thead>
<tr>
<th>entry</th>
<th>reducing agent (eq)</th>
<th>conditions (solvent; T; h)</th>
<th>product ratio (^a) (33 &amp; 34 : 35 : 36)</th>
<th>purified yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DIBAL (4.3)</td>
<td>CH(_2)Cl(_2); 0 °C; 3(^b)</td>
<td>4.7 : 1.0 : 2.7 33 &amp; 34 (21)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>DIBAL (4.0)</td>
<td>toluene; 0 °C; 2(^c)</td>
<td>4.5 : 0.9 : 2.5 33 &amp; 34 (20)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>DIBAL (4.6)</td>
<td>CH(_2)Cl(_2); -78 °C; 4(^b)</td>
<td>2.1 : 0.1 : 1.0 33 &amp; 34 (40)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Vitride (1.0)</td>
<td>toluene; 0 °C; 1(^b)</td>
<td>3.0 : 1.1 : 0 33 &amp; 34 (44)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>LiAl((^1\text{Bu})_2(^3\text{Bu})\text{H})</td>
<td>THF; -78 °C → -20 °C; 3(^d)</td>
<td>1.3 : 1.0 : 0 33 &amp; 34 (44)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>LiAl((^1\text{Bu})_2(^3\text{Bu})\text{H})</td>
<td>THF; -78; 2(^b)</td>
<td>0 : 0.5 : 1.0 36 (51)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) determined by proton NMR of each purified product.
\(^b\) acidic work-up (cold MeOH, cold 1N HCl)
\(^c\) basic work-up (3 eq of H\(_2\)O, 4 eq of NaF per equiv. DIBAL)
\(^d\) acidic work-up (Na\(_2\)SO\(_4\)-10H\(_2\)O at -78 °C, 0.5 M KHSO\(_4\) solution)
Their allylic alcohol was surprisingly more stable than ours. Even though this example suggests that the selective reduction of our \(\alpha,\beta\)-unsaturated ester 31 is possible, the observed instability of our allylic alcohol 33 precludes reinvestigation.

![Chemical structure](image)

Figure 14. Moriwake's Selective Reduction of an \(\alpha,\beta\)-Unsaturated \(\gamma\)-Nitrogen Containing System.

**Grignard Homologation Route.** As mentioned above, the instability and low yield of the allylic alcohol 33 obtained from the reduction of unsaturated ester 31 prompted an alternative strategy based on a Grignard route for the homologation of oxazolidine aldehyde 5b (Scheme VI). Thus, treatment of aldehyde 5b with vinylmagnesium bromide in THF gave a (6:1) mixture of diastereomeric secondary allylic alcohols 38 and 39 in 80\% yield. Though inconsequential for the remainder of the synthesis of the N-BOC allylic amino alcohol 29, the configuration of the major product 38 was identified as erythro\(^{25}\) using the well-known dioxolane derivatization sequence (see Table IV, page 39).
Scheme VI. Grignard Homologation Route of Penaldic Acid Equivalent 5b.

The mixture of secondary allylic alcohols 38 and 39 obtained above was then converted to the secondary allylic urethane(s) 41 using a standard two-step sequence. This involved treatment of 38/39 with p-nitrophenyl chloroformate to form the activated carbonate(s) 40 followed by ammonolysis to give secondary urethane(s) 41 in 68% overall yield. An Overmann rearrangement of secondary urethanes 41 mediated PdCl₂(CH₃CN)₂ resulted in a clean allylic transposition to the desired primary allylic urethane 42 in 86% yield.

The oxazolidine moiety of 42 was selectively cleaved in the presence of the acid-sensitive BOC group by treatment of this compound with methanolic p-toluenesulfonic acid. Competitive removal of the BOC group
was observed when the reaction was allowed to proceed to completion but
the optimal conditions (see Experimental Section) afforded a crystalline
N-BOC allylic amino alcohol 29 in 80% yield after one recycle of
unreacted 42. This (recrystallized) compound was shown to be
configurationally pure (98-99% ee) via $^{19}$F NMR analysis of the
diastereomeric Mosher esters 43 and 44 which were derived from (R)-
MTPA and (S)-MTPA respectively (Figure 15).\textsuperscript{11}

Oxidation

Now that the homologation of penaldic acid equivalent 5b to N-BOC
allylic amino alcohol (29) had been completed, we were ready for the key
oxidation sequence which would involve both a stereoselective cis-
hydroxylation of the double bond and oxidation of the primary alcohol to
carboxylic acid.

Cis-Hydroxylation of the N-BOC Allylic Amino Alcohol 29
Using OsO\textsubscript{4}. Several attempts were made to optimize the stereoselectivity
of the cis-hydroxylation of N-BOC allylic amino alcohol (29) using various
osmylation conditions (Table III, page 32). In one attempt (entry 1), 29
was treated with a catalytic amount of OsO\textsubscript{4} and N-methylmorpholine-N-
oxide (NMO)\textsuperscript{28} which resulted in the formation of an inseperable mixture
of diastereomers in 80% combined yield. The ratio of diastereomers
formed was determined to be (1:1) by $^1$H NMR analysis of the
corresponding acetates. It was also found that osmylation of the
Figure 15. $^{19}$F NMR of Mosher Ester Derivative of 29.
oxazolidine derivative 42 also gave a (1:1) mixture of diastereomers (entry 2). The lack of diastereofacial selectivity observed in these reactions agreed with previous observations by Hauser\textsuperscript{21a} and Dyong\textsuperscript{21b} on osmylation reactions involving similar N-protected allylic amine systems.

The recently discovered Sharpless asymmetric cis-hydroxylation\textsuperscript{29} was also examined in an attempt to prepare the dihydroxylated derivatives of 29 or 42. In one experiment, treatment of 42 with OsO\textsubscript{4} and hydroquinidine p-chlorobenzoate produced the undesired 2,3-anti product in six fold excess over the desired 2,3-syn product (Table III, entry 3). Although not the appropriate stereochemistry for 5-O-carbamoylpolyoxamic acid (9), the methodology used here to obtain the lyxo-configuration (i.e. in the 2,3 - anti product) may be useful in cis-hydroxylations of other N-protected allylic amine systems that require such a configuration (cf ref. 22). In experiments similar to the one above, when hydroquinidine p-chlorobenzoate was replaced with hydroquinine p-chlorobenzoate, the diastereoselectivity shifted in favor of the desired 2,3-syn product over the anti by (3:2) (entries 4 and 5). Although reasons for the difference in selectivity are not clear, it may be due to diastereomeric transition state energy differences between the homochiral substrate (42 or 29) and the two OsO\textsubscript{4}-coordinated chiral ligands. During this kind of double asymmetric induction,\textsuperscript{30} steric effects are believed to be the major cause of this energy difference. Perhaps improved syn diastereoselectivity could be obtained through the use of a different chiral ligand.
Table III. Cis-Hydroxylation of N-BOC Allylic Amine Systems Using OsO₄.

\[
\begin{align*}
&\begin{array}{lll}
 & & \text{(syn)} \\
 & & \text{(anti)} \\
\end{array} \\
&\begin{array}{l}
\text{H}_2\text{NCO}_2\text{CH} \cdots \text{R} \quad \text{BOC} \quad \text{N} \quad \text{R} \\
\text{H}_2\text{NCO}_2\text{CH} \cdots \text{R} \quad \text{BOC} \quad \text{N} \quad \text{R}
\end{array}
\end{align*}
\]

| entry | starting amine | R         | reagent                             | yield (%) | ratio | (syn:anti)
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>29</td>
<td>H</td>
<td>OsO₄, NMO</td>
<td>80</td>
<td></td>
<td>(1 : 1)</td>
</tr>
<tr>
<td>2</td>
<td>42</td>
<td>(Me₂C)₁/₂</td>
<td>OsO₄, NMO</td>
<td>62</td>
<td></td>
<td>(1 : 1)</td>
</tr>
<tr>
<td>3</td>
<td>42</td>
<td>(Me₂C)₁/₂</td>
<td>OsO₄, NMO, dihydroquinidine p-chlorobenzoate</td>
<td>80</td>
<td></td>
<td>(1 : 6)</td>
</tr>
<tr>
<td>4</td>
<td>42</td>
<td>(Me₂C)₁/₂</td>
<td>OsO₄, NMO, dihydroquinine p-chlorobenzoate</td>
<td>80</td>
<td></td>
<td>(3 : 2)</td>
</tr>
<tr>
<td>5</td>
<td>29</td>
<td>H</td>
<td>OsO₄, NMO, dihydroquinine p-chlorobenzoate</td>
<td>80</td>
<td></td>
<td>(3 : 2)</td>
</tr>
</tbody>
</table>

*Ratio determined by \(^1\text{H} \text{NMR after derivatization of diols to corresponding acetates.}*)

\[
\begin{align*}
\text{dihydroquinidin p-chlorobenzoate} \\
\text{dihydroquinine p-chlorobenzoate}
\end{align*}
\]
Steroselective Oxidation of the Homochiral Allylic Amino Alcohol 29 Using KMnO₄. In view of the low stereoselectivity for syn hydroxylation obtained with the osmylations, KMnO₄ oxidation was tried. This reagent is known to give cis-hydroxylation of alkenes and to selectively oxidize primary alcohols in the presence of secondary alcohols. The N-BOC allylic amino alcohol (29) was treated with KMnO₄ under carefully controlled CO₂-buffered conditions (pH 6-7) to give an inseparable mixture of lactols 47 and 48 in 97% crude yield (Scheme VII).

Scheme VII. Oxidation of N-BOC Allylic Amino Alcohol 29 Using KMnO₄.
Apparently, the first formed hydroxylaldehydes 45 and 46 undergo spontaneous lactol formation, and further oxidation of the aldehyde is precluded at this pH. When the basicity of the reaction was increased to pH = 10 (a condition usually necessary for permanganate oxidation of 1° alcohols to carboxylic acids), the urethane group was cleaved, and the resulting primary alcohol underwent oxidation as well.

Oxidation of the lactol mixtures 47 and 48 with N-bromourea (prepared in situ with Br₂ + H₂NCONH₂ + BaCO₃)³²a gave a (2.5:1) mixture of lactones 49 and 50 in 40% purified yield. In spite of the modest yield, this procedure was found to be superior to other known methods³² for the chemical oxidation of lactols to lactones (i.e., Br₂/aqueous buffer or BaCO₃; NBS/CH₂Cl₂; DMSO-Ac₂O; Ag₂CO₃/Celite, reflux; CrO₃-pyridine). When the purified lactones 49 and 50 were submitted to the conditions of their formation (i.e., bromourea oxidation conditions) they gave no indication of epimerization at the C-2 position. Therefore it was concluded that the observed 2.5:1 ratio was due to a diastereofacial preference during the cis-hydroxylation step with KMnO₄. At this point it was postulated that the major lactone 49 should have the desired 2S, 3S, 4R configuration based on a (presumed) bicyclic transition state which places the NHBOC substituent at C-2 in a less sterically hindered equatorial position (Figure 16).

A preliminary assignment of the stereochemistry of these lactones was obtained by the NOE difference spectra³³ of their corresponding trifluoroacetic acid salts 51 and 52.
It was found that irradiation of the H-2 proton of the minor product 52 resulted in an enhancement of its H-4 proton (see Scheme VII). This suggested that the minor product is the undesired anti-dihydroxylated compound since such an NOE enhancement would not be expected for the H-2 and H-4 protons of the syn-dihydroxylated compound 51 because of the larger interatomic distance. Proof that the major lactone did indeed possess the 2,3-syn, 3,4-syn stereochemistry was obtained by successful conversion to the final compound, 5-O-carbamoylpolyoxamic acid (vide infra).

**Hydrolysis of Lactone 49 to 5-O-Carbamoylpolyoxamic Acid** (9). For final comparison, the major lactone 49 was deprotected and hydrolyzed with 1 N HCl at 95 °C to give a (4:1) mixture of 5-O-carbamoylpolyoxamic acid hydrochloride salt 53 and the lactone hydrochloride salt 54 (eq. 2). Prolonged reaction times at this temperature did not drive the reaction to completion suggesting the existence of an equilibrium between 53 and 54. Similar behavior had been reported for the analogous acyclic γ-hydroxy-α-amino acid component of the nikkomycins as well.33
The stereochemistry of 53 was confirmed by its 400 MHz $^1$H NMR spectrum (DCl in D$_2$O) which was superimposable with one obtained for the authentic sample of 5-O-carbamoyl polyoxamic acid (9). In the event that a purified 5-O-carbamoylpolyoxamic acid becomes necessary, it is believed that the mixture of 53 and 54 could be separated by Isono's method for the purification of polyoxin J.$^{14b}$

**Conclusion**

A strategy for the synthesis of 5-O-carbamoylpolyoxamic acid was developed wherein all chirality was derived from D-serine. Conditions were also found for stereoselective syn and anti cis-hydroxylations of the N-protected allylic amine system. When CO$_2$-buffered KMnO$_4$ was used as the oxidant, the 2,3-syn dihydroxylated product was obtained with moderate stereoselectivity. When the chiral ligand dihydroquinidine p-chlorobenzoate was used with OsO$_4$ as the oxidant, the 2,3-anti dihydroxylated product was obtained stereoselectively as a result of (matched) double asymmetric induction.
SYNTHESIS OF THYMINE POLYOXIN C (10)

Thymine polyoxin C (10) was prepared using an approach similar to the one used in the synthesis of 5-O-carbamoylpolyoxamic acid (9). As is seen in Scheme VIII, this is accomplished by the 3-carbon homologation of penaldic acid equivalent 5b (derived from D-serine) to form the propargyl alcohol derivative 55 followed by furanose elaboration to 56. The α-amino acid is obtained by the deprotection of the oxazolidine ring system in 56 to form the N-protected primary amino alcohol followed by its oxidation to the amino acid. Finally, attachment of the nucleoside base to the sugar moiety to form thymine polyoxin C is accomplished using Vorbrüggen's nucleosidation protocol.

Scheme VIII. Synthetic Strategy of Thymine Polyoxin C (10).
Three-Carbon Homologation

The 3-carbon homologation of penaldic acid equivalent 5b to form the propargyl alcohol 55 begins with the stereoselective nucleophilic addition of a lithioalkyne to form the required erythro configurational relationship between H-4 and H-1'. Lithio propiolaldehyde dimethyl acetal 57 and lithio ethyl propiolate 58 were chosen for this purpose since they are suitably functionalized for furanose formation and are easily prepared in situ by treatment of known alkynes with n-butyl lithium.

\[
\text{LiC}==\text{CCH(OMe)}_2 \quad \text{LiC}==\text{CCO}_2\text{Et}
\]

57 \hspace{1cm} 58

Homologation Using Lithio Propiolaldehyde Dimethyl Acetal 57. Addition of lithio propiolaldehyde dimethyl acetal 57 to penaldic acid equivalent 5b proceeds at -78 °C in THF to give propargylic alcohol 59 as the major product with an (8:1) erythro selectivity over 60 in 75% purified yield (Scheme IX). The configurational relationship between H-4 and H-1' was determined by first converting 59 to the conformationally well-defined dioxolane 62 via a 2-step sequence ((i) TsOH in methanol (ii) TsOH in DMP). The \(^1\)H NMR coupling constant between H-4 and H-5 of dioxolane 62 was 8 Hz which is indicative of a trans-diaxial relationship between these protons in the chair conformation (Table IV, entry 1).\(^3\)\(^6\)
Scheme IX. Nucleophilic Addition of Lithio Propiolaldehyde
Dimethyl Acetal 57 to Oxazolidine Aldehyde 5b.

\[
\begin{align*}
&\text{5b} & \xrightarrow{\text{LiC} = \text{CCH(OMe)}_2} & \text{57} & \xrightarrow{\text{THF, -78°C}} & \text{59} & (8:1) & \text{60} \\
& & & & & \text{TsOH, MeOH} & \text{R.T.} & \text{61} & \xrightarrow{\text{TsOH,DMP}} & \text{62} \\
& & & & & & & & & \text{trans-(dialxial)} & \text{cis-(gauch)}
\end{align*}
\]

Table IV. \(^{3}J_{4,5}\) Coupling Constant of Dioxolane Derivatives.

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>(^{3}J_{4,5}) Coupling Constant</th>
<th>reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>trans</td>
<td>cis</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>C=CH(OMe)_2</td>
<td>8 Hz</td>
<td>this work</td>
</tr>
<tr>
<td>2</td>
<td>CH=CH_2</td>
<td>10 Hz</td>
<td>1-2 Hz</td>
</tr>
<tr>
<td>3</td>
<td>CH_2CO_2Me</td>
<td>10 Hz</td>
<td>1-2 Hz</td>
</tr>
</tbody>
</table>
Conversely, as seen in Table IV, related dioxolanes which possess the threo stereochemistry tend to exhibit 1-2 Hz vicinal coupling between H-4 and H-5 which indicates their cis-(gauch) relationship (entries 2, 3).

The erythro selectivity may be ascribed to a Felkin-Anh-Houk transition state model\(^ {37} \) (conformer A in Figure 17) such that carbon-carbon bond formation occurs from the least hindered si-face (anti) to the polar amino group. This observation is consistent with the observations of others when non-chelating conditions were employed for nucleophilic additions to aldehyde 5\(^ {38} \). Interestingly, under chelating conditions using Lewis acid additives such as ZnCl\(_2\), the stereoselectivity was reversed to give the threo-configuration by a chelation-controlled addition to conformer B (where, in this case, the nucleophile attacks from the least hindered re-face).\(^ {39} \)

![Felkin-Anh-Houk Transition State Model](image1.png)

![Chelation-Controlled Transition State Model](image2.png)

**Figure 17.** Proposed Transition State for Nucleophilic Addition to Oxazolidine Aldehyde 5b.
Homologation Using Lithio Ethylpropiolate 58. The analogous addition of 58 was also investigated. Since the erythro selectivity is apparently obtained from a non-chelated nucleophilic addition, it could be improved even further by elimination of chelation effects involving the lithium cation (see also ref. 36b). Thus, in the presence of HMPA, which sequesters the lithio cation, lithio ethylpropiolate 58 reacted with aldehyde 5b to give the adduct 63 in 75% purified yield with a (13:1) erythro selectivity over adduct 64 (Scheme X).

Scheme X. Nucleophilic Addition of Lithio Ethylpropiolate 58 to Oxazolidine Aldehyde 5b.

Initially, the presumption of erythro stereochemistry was based strictly on extrapolation from the result obtained from the addition of
lithio propiolaldehyde dimethyl acetal, but stereoselectivity was later proven by correlation of 63 with thymine polyoxin C 10 (vide infra).

The enantiomeric purity of 63 was determined by analysis of its diastereomeric Mosher esters. In separate experiments, 63 was condensed with (R)-MTPA and (S)-MTPA (DCC-DMAP conditions) to give the corresponding diastereomers (R,R)-65 and (R,S)-66 respectively. Proton NMR analysis of the esters indicated a 98-99% de, and therefore a 98-99% ee of compound 67 by inference. Both adducts 59 and 63 obtained from the two lithioalkyne additions to aldehyde 5b were used for the synthesis of thymine polyoxin C.

**Furanose Elaboration**

The formation of the furanose structure from the two adducts 59 and 63 was accomplished using standard procedures. Generally, this required (1) the semi-hydrogenation of the triple bond to a cis double bond, (2) an acid-catalyzed cyclization to an unsaturated furanose or butyrolactone, and (3) stereoselective dihydroxylation of the double bond (the order of steps (2) and (3) can be interchanged).

**Dihydrofuran Formation Starting with Adduct 59.** The semi-hydrogenation of the propargylic alcohol 59 proceeded cleanly using the Pd/BaSO₄/quinoline (Lindlar-type catalyst system) to give the (Z)-allylic alcohol 67 in 98% purified yield (Scheme XI). The (Z)-olefin stereochemistry in compound 67 was not obvious by ¹H NMR because of
the broadness of the two olefinic proton resonances (H-3' and H-4'). However, cyclization of the (Z)-allylic alcohol 67 was readily accomplished using pyridinium p-toluenesulfonate (PPTS)\textsuperscript{42} as a mild acid catalyst in benzene. This reaction gave a (1:1) mixture of anomeric dihydrofurans 68 and 69 in 97% yield. From the high combined yield of these two steps, it was concluded that the geometry at the double bond must be (Z), otherwise it would not have cyclized. The use of the stronger TsOH instead of PPTS resulted in both premature oxazolidine methanolysis and elimination of methanol to give undesired furans as judged by \textsuperscript{1}H NMR.

**Scheme XI. Dihydrofuran Formation 68/69 with Adduct 59.**

![Chemical structure](image)

**Formation of Butenolide 72 from Adduct 63.** The ester 63 was saponified with ethanolic-KOH solution and the resulting propiolate salt 70 was then dissolved in water and submitted to Lindlar semi-
hydrogenation to give a (Z)-hydroxycrotonate 71 which, upon acidic workup, spontaneously lactonized to afford the butenolide 72 in 69% overall yield after flash chromatography. The need for prior ester saponification in this case was arrived at after it was found that attempted semi-hydrogenation of 63 (or its corresponding free acid 70)\textsuperscript{43a} resulted in an unacceptable amount of overreduction. Conversion of the ester substituent to a negatively-charged carboxylate apparently makes the substrate behave like an electron-rich alkyne, which is known to be more resistant to such overreduction (cf. the successful semi-reduction of 59 to 67).

Scheme XII. Formation of Butenolide 72 from Adduct 63.

Cis-Hydroxylations of Dihydrofurans 68/69 and (Z)-Allylic Alcohol 67. Since the anomerich mixture of dihydrofurans 68 and 69
was not separable by column chromatography, it was submitted directly to cis-hydroxylation using standard catalytic osmium tetroxide conditions with N-methyl morpholine N-oxide (NMO) as a carrier oxidant\textsuperscript{28} (Scheme XIII). Two isomeric diols 73 and 74 were isolated from this reaction in 32\% and 44\% yield respectively after chromatographic separation. The structural assignment of these two compounds was not clear at this point but was later verified after completion of the synthesis and correlation with naturally-derived thymine polyoxin C (vide infra). Eventually, it was shown that only one of the diols, 74, possessed the required allo-configuration, the other, 73, being of the manno-configuration.

Scheme XIII. Cis-Hydroxylations of Dihydrofuran 68/69 and (Z)-Allylic Alcohol 67.
These results suggested that the anomeric methoxy group might control the facial selectivity of this osmylation reaction. Since the configuration of the anomeric methoxy group was established during the cyclization of 67 to 68/69, it was concluded that the ratio of these products probably could not be improved significantly.

An alternative route to the desired allo-stereochemistry using the precuror of dihydrofurans 68/69, (Z)-allylic alcohol 67, was investigated as well since the directing effect of each prochiral methoxy group at the pre-anomeric center should cancel. It was expected that stereoselective cis-hydroxylation of the (Z)-allylic alcohol 67 would occur based on Kishi's empirical osmylation rule for chiral allylic alcohols\textsuperscript{44} - i.e., anti addition (to the hydroxy group) to give a triol possessing the desired allo-configuration (Figure 18).

![Diagram of osmylation reaction](image)

Figure 18. Application of Kishi's Empirical Rule to (Z)-Allylic Alcohol 67.

Subjection of (Z)-allylic alcohol 67 to the usual osmylation conditions resulted in the formation of what appeared to be a single triol as judged by TLC analysis. Because of the nondescript nature of its \textsuperscript{1}H NMR spectrum, this material was not further characterized at this stage,
but cyclized directly by heating in the presence of PPTS (Scheme XIII). Two isomeric furanose products were obtained in 17 and 51% yield after flash chromatography which were identified as the previously isolated β-methyl allo-furanoside 74 and a new compound which was subsequently identified as the β-methyl manno-furanoside 75 (again, the absolute stereochemistry of 75 was assigned later by correlation with thymine polyoxin C). Since the manno-furanoside 75 could only have come from a triol having the manno-configuration, it was concluded that osmylation of 67 must have occurred primarily syn to the hydroxyl group, presuming the conformation depicted in Figure 18. In this case, Kishi's empirical rule does not hold.

Even before the final structural correlations with thymine polyoxin C were made, it was felt that the relative stereochemical relationship between C-4' and C-5' in compounds 73 and 74 was trans based on their $^{13}$C NMR chemical shift similarities with known trans furanosides (Table V, entries 1 & 2, 3 & 4). It was also felt that the relative stereochemistry in compound 75 was cis based on its chemical shift similarities with known cis furanosides (Table V, entries 5, 6, and 7). In order to complete the synthesis to polyoxin C it was first necessary to convert diols 73, 74, and 75 to their protected diacetates. This was accomplished using acetic anhydride and pyridine to provide compounds 76, 78, and 77 in quantitative yield (Scheme XIII).
Table V. $^{13}$C Chemical Shifts of Methyl Glycofuranosides.

<table>
<thead>
<tr>
<th>entry</th>
<th>methyl glycofuranoside</th>
<th>C-5(^{a})</th>
<th>C-4(^{a})</th>
<th>C-3(^{a})</th>
<th>C-2(^{a})</th>
<th>C-5(^{a})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>α-D-manno</td>
<td>109.7</td>
<td>77.9</td>
<td>72.5</td>
<td>80.5</td>
<td>64.5</td>
</tr>
<tr>
<td>2</td>
<td>73</td>
<td>110.7</td>
<td>78.9</td>
<td>70.9</td>
<td>80.7</td>
<td>65.3</td>
</tr>
<tr>
<td>3</td>
<td>β-Dallo</td>
<td>109.0</td>
<td>75.6</td>
<td>72.7</td>
<td>83.4</td>
<td>63.9</td>
</tr>
<tr>
<td>4</td>
<td>74</td>
<td>108.5</td>
<td>76.5</td>
<td>74.4</td>
<td>83.6</td>
<td>65.2</td>
</tr>
<tr>
<td>5</td>
<td>β-D-manno</td>
<td>103.6</td>
<td>73.1</td>
<td>71.2</td>
<td>80.7</td>
<td>64.4</td>
</tr>
<tr>
<td>6</td>
<td>α-D allo</td>
<td>103.8</td>
<td>72.3</td>
<td>69.9</td>
<td>85.9</td>
<td>63.5</td>
</tr>
<tr>
<td>7</td>
<td>75</td>
<td>100.9</td>
<td>72.0</td>
<td>70.0</td>
<td>79.4</td>
<td>64.1</td>
</tr>
</tbody>
</table>

\(^{a}\)Numbering system of the known glycofuranosides was converted to our system for easier comparison.

**Cis-Hydroxylation of Butenolide 72.** The butenolide 72 derived from ethyl propiolate adduct 63 was subjected to standard osmium-catalyzed cis-hydroxylation conditions (Scheme XIV). Under these conditions, the reaction took three days. When NMO was replaced with TMNO (trimethyl N-oxide),\(^{46}\) the reaction took eight hours and gave a single diol 79 which was isolated in 58% yield after flash chromatography along with 12% of unreacted 72. The high facial selectivity obtained above is consistent with the observation of Stork\(^{47}^{a}\)
and Lukes\textsuperscript{47b} on systems similar to ours where cis hydroxylation occurs from the less hindered α-face of butyrolactone 72.

The structural assignment of 79 was initially supported by its \textsuperscript{1}H NMR coupling constant which showed \textsuperscript{3}J_{2',3'} = 0 Hz (a value consistent with a 90° dihedral angle between H-2' and H-3'). Such an angle is possible only when these protons are trans to each other. The absolute stereochemical assignment of 79 was later verified after completion of the synthesis and correlation with thymine polyoxin C (vide infra).

**Scheme XIV.** Cis-Hydroxylation of Butenolide 72.

The anomeric center was created by semi-reduction of lactone 79 using diisobutylaluminum hydride. The resulting crude anomeric triol
mixture 80 was peracylated to give a (4:1) mixture of anomeric acetates 81 in 80% combined yield after flash chromatography. The major component was identified as the β-anomer based on 1H NMR similarities between it and the previously synthesized β-methyl allo-furanoside 78.

Formation of the α-Amino Acid.

At this point, all four furanose acetates 76, 77, 78, and 81 were carried on separately to gain more definitive evidence regarding their stereochemistry. The next stage involved the generation of α-amino acid moieties from their oxazolidine precursors. This required the deketalization to deliver N-protected primary amino alcohols followed by the oxidation of the alcohols to the N-protected amino acids.

Deketalization of the Oxazolidine Derivatives. Deketalization of compounds 76, 77, and 78 using TsOH in MeOH afforded the N-protected amino alcohols 82, 83, and 84, in moderate to good yield (Scheme XV). In the case of compound 81, different deprotection conditions (AcOH, 40 °C) were used since TsOH-MeOH gave complex mixtures. As had been previously observed (see Section 2.1), removal of the (acid sensitive) BOC group was competitive with the desired cleavage of the oxazolidine ring system. Therefore, these reactions were terminated when aminoalcohol formation (i.e. N-BOC deprotection) was first detected as a highly ninhydrin-active polar TLC spot. After extractive work up, the unreacted starting material was easily separated from the desired product by chromatography and then recycled. Interestingly, in the case of
deprotection of 81, both product 85 and recovered starting material 81 were found to be further enriched in their β-anomers with the ratio improving from (4:1) to (6:1).

**Scheme XV. Formation of the α-Amino Acid.**

\[
\begin{align*}
\text{BOC Sugar} & \xrightarrow{\text{For 76-78}} \text{TsOH, MeOH} \\
& \quad \xrightarrow{\text{For 81, AcOH, 40°C}} \\
\text{HN-} & \xrightarrow{\text{H}^+} \text{CF}_3\text{CO}_2^- \\
\text{Sugar} & \xrightarrow{\text{TFA, CH}_2\text{Cl}_2, 0°C} \\
& \quad \xrightarrow{\text{Ac}_2\text{O, pyridine, NaHCO}_3} \\
\text{CO}_2\text{Me} & \xrightarrow{\text{by CbzCl}} \\
\text{HN-} & \xrightarrow{\text{H}^+} \text{CF}_3\text{CO}_2^- \\
\text{Sugar} & \xrightarrow{\text{OAc}} \\
\text{CO}_2\text{Me} & \xrightarrow{\text{R}} \\
\end{align*}
\]

**Oxidation of N-Protected Amino Alcohols.** The N-BOC aminoalcohols 82-85 were then oxidized to carboxylic acids using a catalytic amount of RuO\(_2\)·H\(_2\)O in the presence of excess NaIO\(_4\) as a carrier.
oxidant (Scheme XV).\textsuperscript{48} Without further purification, the crude carboxylic acids were esterified with diazomethane to give the corresponding methyl esters 86 - 89 in good overall yield after flash chromatography.

Because the nucleosidation conditions (vide infra) utilize strong Lewis acid catalysts, it was necessary to replace the acid-sensitive N-BOC group with either N-acetyl or N-Cbz protecting groups.\textsuperscript{49} Treatment of 86 - 89 with trifluoroacetic acid gave the corresponding ammonium salts 90 - 93 which were then treated with Ac\textsubscript{2}O in pyridine to give the N-acetyl derivatives 94 - 97 respectively. Ammonium salts 91 and 93 were treated with benzyl chloroformate in NaHCO\textsubscript{3} to give the N-Cbz derivatives 98 and 99 respectively.

\textbf{Nucleosidation}

The silyl-Hilbert-Johnson approach to pyrimidine nucleoside synthesis has been well developed by Vorbrüggen.\textsuperscript{50} This methodology has already been successfully applied to previous syntheses of thymine polyoxin C (10).\textsuperscript{16c,17} It generally involves the nucleophilic addition of a silylated base to peracetylated sugars in the presence of Friedel-Crafts catalysts (Figure 19).
Figure 19. Vorbrüggen's Nucleosidation Methodology.

The synthesis of thymine polyoxin C (10) began with the preparation of bis-silylated thymine 101 in 85% distilled yield from the silylation of commercially available thymine (100) using HMDS (eq 3). Use of either TMSCl or pyridine as catalyst enhanced the rate of this reaction.

Nucleosidation of Methyl Mannofuranosides 94, 95, and 98.

Nucleosidation using bis-silylated thymine 101 was first applied to the methyl mannofuranosides 94, 95, and 98. It was first necessary to convert the methoxy groups to acetoxy groups using a modification of Hudson's acetolysis conditions. This was necessary because methyl glycofuranosides such as these require anomeric activation due to the
poor leaving ability of the methoxy group as a result of its lower reactivity.\textsuperscript{50}

In separate experiments, acetolysis of 94 and 95 using (20:1:1) $\text{Ac}_2\text{O}$-$\text{H}_2\text{SO}_4$-$\text{AcOH}$ at -40 °C produced a single common product 102 as judged by TLC and $^1$H NMR in 91% and 97% crude yields respectively (eq. 4). These results proved that compounds 94 and 95 differ only in their anomeric configurations. Milder acetolysis conditions (Hudson’s solution diluted in CH$_2$Cl$_2$ at -40 °C) were used with compound 98 because of the instability of its N-Cbz group. This provided a single compound 103 in 43% crude yield (eq. 4). The acetolysis products were submitted to nucleosidation without additional purification.

![Diagram](image)

Optimized nucleosidation conditions are tabulated in Table VI. The first set of conditions tried was one that Kuzuhara had used for his thymine polyoxin C synthesis.\textsuperscript{16c} Treatment of tetraacetate 102 with bis-silylated thymine 101 in the presence of SnCl$_4$ at ambient temperature gave a (3:1) mixture of $N^1$- and $N^3$-nucleosides 104 and 105 in 60%
Table VI. Nucleosidation of 102 and 103.

<table>
<thead>
<tr>
<th>substrate</th>
<th>lewis acid</th>
<th>T (°C)</th>
<th>product</th>
<th>ratio</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>102</td>
<td>SnCl₄</td>
<td>RT</td>
<td>104 105</td>
<td>(3:1)</td>
<td>60</td>
</tr>
<tr>
<td>103</td>
<td>SnCl₄</td>
<td>RT</td>
<td>106 107</td>
<td>(4:1)</td>
<td>55</td>
</tr>
<tr>
<td>102</td>
<td>SnCl₄</td>
<td>95</td>
<td>104 105</td>
<td>(12:1)</td>
<td>60</td>
</tr>
<tr>
<td>102</td>
<td>TMSOTf</td>
<td>95</td>
<td>104 105</td>
<td>(1:0)</td>
<td>79</td>
</tr>
</tbody>
</table>

combined yield (entry 1). The regiochemistry of the N¹- and N³-nucleosides was unambiguously ascertained from their ¹H NMR spectra since only the N³-nucleoside 105 exhibits coupling (J = 4.8 Hz) between N¹-H and H-6. The 1',2'-trans stereochemistry of compound 104 was deduced from a series of NOE difference experiments that resulted in enhancements of H-1', H-3' (overlapping signals), and H-2' upon irradiation of the H-6 signal and a reciprocal enhancement of H-6 upon irradiation of H-2'. The stereoselective generation of the 1',2'-trans isomer obtained above is known to be due to neighboring group participation of the C-2' acetoxy group to form a bridged bicyclic
acetoxonium ion which undergoes nucleophilic addition so as to produce
the 1',2'-trans stereochemistry as shown in Figure 19 (page 52). In a
similar manner, the nucleosidation of N-Cbz derivative 103 afforded a
(4:1) mixture of N1- and N3-nucleosides 106 and 107 in 55% yield (entry
2). Because of the moderate regioselectivities and yields obtained above,
other reaction conditions for nucleosidation were also examined.
Application of the conditions cited above but at 95 °C with the tetraacetate
102 (Table VI, entry 3) provided a much more acceptable (12:1) mixture of
N1- and N3-nucleosides even though the overall yield remained about the
same (55 - 60%). However, substitution of TMSOTf for SnCl4 at 95 °C (entry
4) provided only the N1-nucleoside 104 in 79% after chromatographic
purification. This observation is consistent with Voßbrüggen's result with
similar systems which led him to conclude that the less acidic Lewis acid
(TMSOTf) gives higher regioselectivity (i.e. predominant N1-isomer).
This is presumably because conditions are just acidic enough to form a
bridged bicyclic acetoxonium ion, but not too acidic to form a σ-complex
with the silylated base.50b,c The higher yield of these reactions was
attributed to the ease of work-up as well (SnCl4 forms emulsions).50b,c

The synthetic acetate 104 and the authentic acetate 121 (vide infra)
were compared by TLC and 1H NMR spectroscopy (see Experimental
Section). The results showed that they were different compounds.
Further evidence of their nonidentity was provided by the N-acetylated
product 108 prepared from a treatment of acetate 104 with sodium
hydroxide solution (eq 5). Even though NaCl was not removed from the N-
acetyl derivative 108, its TLC and $^1$H NMR spectrum were clearly different from the authentic N-acetyl derivative 120 (vide infra, also see Experimental Section).

Finally, the deprotected compound 109 was prepared by the saponification of the N-Cbz aminoester 106 followed by hydrogenation (R-NH-Cbz $\rightarrow$ R-NH$_2$) (eq 6). This sequence afforded pure compound 109 whose NMR data did not match that of thymine polyoxin C (10) even though their TLC behavior was identical. Therefore, taken all together, it was concluded that compounds 94, 95, and 98 possess the manno-configuration since none of them led to nucleosides that matched the authentic polyoxin standards.
Nucleosidation of Methyl Allofuranoside 96. The above results suggest that the remaining β-methyl glycoside 96 should possess the allo-configuration as required for the polyoxins. However, when the β-methyl glycoside 96 was subjected to modified Hudson acetalysis conditions, and the resulting crude product submitted to the nucleosidation conditions described above, a (1:1) mixture of undesired diastereomeric acyclic nucleosides 112 and 113 was obtained in 62% combined yield (at 64% conversion of starting material 96) (Scheme XVI).

Scheme XVI. Acetolysis and Nucleosidation of Methyl Allofuranose 96.

These unusual acyclic nucleoside products\textsuperscript{53} were separately characterized by both $^1$H NMR spectroscopy and high resolution FAB mass spectrometry. Obviously, they arise from the aberrant acetolysis products 110 and 111 which are themselves generated from unexpected endocyclic cleavage during the acetolysis. The reason for the endocyclic
opening in compound 96 is not clear but it is postulated that intramolecular proton transfer from the protonated amide species to the ring oxygen may cause faster dissociation of the endocyclic C--O bond than the exocyclic C--OMe bond.\textsuperscript{54}

**Nucleosidation of Peracetylated Allofuranoses 97 and 99.**
Since the compounds 97 and 99 derived from the cis-hydroxylation of butenolide 72 (page 51) already have an acetoxyl group at the anomic center, acetolysis is not necessary for the nucleosidation. Thus nucleosidation of compound 97 with bis-silylated thymine 101 in the presence of TMSOTf gave a (1:2.4) mixture of N\textsuperscript{1}-nucleoside 114 and the bicyclic 1,5-anhydro derivative 115 (eq. 7).

The minor product 114 had the same R\textsubscript{f} and \textsuperscript{1}H NMR spectrum as an authentic polyoxin C derivative (vide infra). The structure of 115 was determined by its measured mass, lack of an N-H stretch in the IR spectrum, a simplified \textsuperscript{1}H NMR spectrum in which the signals for H-1, H-4, and H-5 appeared as singlets, and a \textsuperscript{13}C chemical shift for C-1 that was consistent with an O-C-N substitution pattern. This kind of bridged cyclic
compound has also been observed by Rosenthal in similar nucleosidations.\textsuperscript{55}

On the other hand, the N-Cbz derivative 99 did not suffer competitive intramolecular attack by nitrogen as did 97 and was found to produce the protected nucleoside 116 in 85% isolated yield after flash chromatography (eq. 8). This may be due to a lower nucleophilicity of the carbamate versus the acetamide. Under these conditions, N-deprotected nucleoside 117 was also isolated in 14% yield.

\begin{equation}
\begin{align*}
\text{99} &\xrightarrow{101\ \text{TMSOTI}} \text{101} \\
\text{116} & + \text{117}
\end{align*}
\end{equation}

Compound 116 was transformed to compound 118 by the standard deprotection sequence (eq. 9). A full comparison of 118 with authentic polyoxin C (10) showed them to be identical in all respects.

\begin{equation}
\begin{align*}
\text{116} &\xrightarrow{(i) \ 0.1 \ N \ \text{LiOH}} \text{118} \quad \text{then 0.1 \ N \ HCl} \\
&\xrightarrow{(ii) \ H_2, \ Pd/C} \text{118}
\end{align*}
\end{equation}
Authentic Sample Preparation and Derivatization

For our comparisons, authentic polyoxin C (119) was transformed into three different compounds: thymine polyoxin C (10), the N-acetyl derivative 120 of thymine polyoxin C, and the fully protected derivative 121 of thymine polyoxin C. The methodology used for the synthesis of authentic thymine polyoxin C (10) and N-acetylated derivative 120 from 119 was identical to that reported by Isono in his original paper\textsuperscript{14}\textsuperscript{b} - that is, hydrogenolysis of polyoxin C with PtO\textsubscript{2} catalyst and selective N-acetylation of thymine polyoxin C (10) using Ac\textsubscript{2}O + NaOAc (Scheme XVII).

Scheme XVII. Authentic Sample Preparation and Derivatization.
The protections of acid and diol groups to give the N-acetyl derivative 121 were achieved by (i) mild esterification of the acid using MeOH with amberlyst-15 as an acid-catalyst\textsuperscript{56} and (ii) standard acetylation of the diol to provide the fully protected derivative 121 of thymine polyoxin C. With these samples in hand, three different comparisons of the synthetic nucleosides with the authentically-derived material were possible.

**Conclusion**

Thymine polyoxin C (10) has thus been prepared in 5% overall yield via a 15 step sequence starting from the serine-derived penaldic acid equivalent 5b. The overall synthetic strategy involved four distinct phases: (1) diastereoselective addition of a 3-carbon nucleophile (lithio ethyl propiolate 58) to the protected serinal derivative (5b → 63), (2) stereocontrolled elaboration of the 5-amino-5-deoxy-allofuranose moiety via cis-hydroxylation of a 4-substituted butenolide (63 → 81), (3) release of the latent α-amino acid moiety in a suitably protected form (81 → 99), and (4) stereo- and regioselective nucleoside formation using Vorbrüggen’s glycosylation methodology followed by deprotection (99 → 10).

This asymmetric synthesis of thymine polyoxin C (10) from the penaldic acid equivalent 5b illustrates the viability and efficacy of our general approach to glycosyl α-aminoacids and sets the stage for the application of this strategy to more complex peptidyl nucleoside targets such as the amipurimycin.
PEPTIDE COUPLING AND SYNTHESIS OF A PROTECTED DERIVATIVE OF POLYOXIN J

The remaining task for the total synthesis of polyoxin J (8) is the coupling of optically pure lactone 49 and free amine 117 which have been successfully prepared as described in the previous sections. Two different coupling approaches were tried (Scheme XVIII). One involved the direct coupling of an available intermediate (lactone 49) while the other approach relied on traditional peptide chemistry, i.e. condensation of the corresponding carboxylic acid 122 (derived from lactone 49) and free amine 117.

Scheme XVIII. Synthetic Approach to Polyoxin J (8).
Direct Coupling via γ-Lactone

The direct coupling of different types of γ-lactones with various amines to form an amide linkage has been documented. Thus, Metternich\textsuperscript{57a} showed that the coupling reaction of the protected α-hydroxy γ-lactone shown in equation 10 with n-butyl amine produces the corresponding amide linkage.

\[
\begin{align*}
\text{BOCHN} & \quad \text{BOCHN} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{OH} \\
\text{O} & \quad \text{OH}
\end{align*}
\]

\text{n-BuNH}_{2}, \text{ R.T.}

\[
\begin{align*}
\text{BOCHN} & \quad \text{BOCHN} \\
\text{OH} & \quad \text{OH} \\
\text{OH} & \quad \text{OH} \\
\text{OH} & \quad \text{OH}
\end{align*}
\]

(10)

Helmchen\textsuperscript{57b} also showed that the direct coupling of racemic α-substituted γ-lactones with a chiral amine in the presence of 2-hydroxyquinidine in toluene at 110 °C afforded a mixture of separable diastereomeric amides thus providing a method for the resolution of the starting racemic α-hydroxy lactones (eq. 11).

\[
\begin{align*}
\text{R} & \quad \text{R} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H}
\end{align*}
\]

\text{2-hydroxy-}
\text{quinidine}
\text{110\textdegree C}

\[
\begin{align*}
\text{R}^2 & \quad \text{R}^2 \\
\text{R}^1 & \quad \text{R}^1 \\
\text{R}^1 & \quad \text{R}^1 \\
\text{R}^1 & \quad \text{R}^1
\end{align*}
\]

(11)

**Model Study.** In order to examine the feasibility of this plan it was decided to first use a simple amine partner. Thus, benzylamine (10 eq) reacted with lactone 49 in the presence of HOBT in methanol at 80 °C to
produce a (2:1) mixture of diastereomeric amides 123 and 124 in 56% combined yield (eq. 12). The relative ratio of diastereomers was determined after chromatographic purification. In view of the resulting diastereomeric mixture, it was that epimerization at the C-2 position had occurred during the reaction.

![Chemical Reaction Diagram]

The structures of these compounds were confirmed by their $^1$H NMR, IR, and mass spectra but the absolute configuration at the C-2 position of each diastereomer was not unambiguously determined. Even though epimerization had occurred, this reaction provided a concise synthesis of the expected amide linkage.

**Attempted Direct Coupling Reaction of Lactone 49 with Amine 4.** Similarly, the direct coupling reaction of lactone 49 with free amine 117 was attempted (eq. 13). It was found that amine 117 was not stable under these conditions and the isolated products of the reaction were the unreacted starting lactone 49 (41% yield) along with the N-acetylated thymine polyoxin C 114 (29% yield). Presumably, the latter product 114 resulted from facile intermolecular O- to N-transacetylation. Therefore, this direct coupling protocol was abandoned and efforts were focused on an alternative approach using a traditional peptide coupling reaction.
Traditional Peptide Coupling

Owing to the instability of amine 117 during the direct coupling reaction, a milder set of conditions had to be established for the total synthesis of polyoxin J. The use of well-established peptide chemistry was undertaken to form the desired peptide (amide) linkage between the two differentially protected amino acids. In order to use this approach, the lactone 49 was first converted to the N-protected amino acid 122 (eq. 14) by saponification with lithium hydroxide (pH 7-8). Under these mild saponification conditions, the crude yield of γ-hydroxy acid was 99% with the base-sensitive urethane (5-O-carbamoyl) group remaining intact.

![Chemical structures](image)

Model Study Using L-Phenylalanine Methyl Ester.

Attempted peptide coupling of the γ-hydroxy acid 122 with L-phenylalanine methyl ester under the usual peptide coupling conditions (DCC, HOBT) resulted in intramolecular cyclization (i.e. relactonization) of the carboxyl-activated γ-hydroxy acid to afford starting lactone 49 in
72% crude yield (eq. 15). Thus, it was realized that the γ-hydroxyl group in compound 122 needed to be protected in order to avoid this ester lactonization problem.60

Because of the multifunctionality of this γ-hydroxy acid 122, it was necessary to differentiate between the hydroxyl functional groups and the acid functional group in order for the peptide coupling reaction to proceed. In this case, the use of a silyl group for protection is attractive since silylester (-CO₂-Si-) bond is weaker than the silyl ether (-O-Si-) bond and this will allow the corresponding acid to be released while the β and γ silyl ethers remain intact. In order to examine this multiple protection and the differentiation of these functional groups, N-BOC L-serine was chosen as a model compound.

**Model Study Using N-BOC L-Serine.** Treatment of N-BOC L-serine 2a with tert-butyldimethylsilyl chloride (TBSCI) and imidazole in DMF61a produced the bis-silylated derivative 126 in 97% yield (Scheme XIX). Selective deprotection of the silyl ester 126 by the action of K₂CO₃ in (3:1) MeOH-THF₆₂b produced the free acid 127 in 100% yield (Scheme
XIX). The condensation (DCC, DMAP, CH₂Cl₂)¹² of carboxylic acid 127 and free amine 117 produced dipeptide 128 in 65% isolated yield.

**Scheme XIX. Model Peptide Coupling Reaction with Silylated N-BOC L-Serine 126.**

At this point, we considered the possibility that the condensation might proceed with 126 itself, since silyl esters are labile under even mildly acidic conditions. Thus, the acidic peptide coupling conditions using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (known as "water-soluble" carbodiimide, WSC)⁶² were chosen. The peptide coupling reaction of the protected silyl ester 126 with amine 117 in the presence of HOBT afforded the same dipeptide 128 directly in 87% isolated yield (Scheme XIX).
Coupling Amine 117 with Lactone 50 Derived Acid 130. In order to extend the above model study, lactone 50 was treated with lithium hydroxide solution to provide the γ-hydroxy acid 129 in 79% yield (eq. 16).

This acid was treated with TBSCI and imidazole in DMF at 40 °C for 19 h to produce the silyl ester 130 in 93% crude yield (Scheme XX). The lability of the silyl ester on silica gel (a mild acid) made it difficult to judge the completion of this reaction by TLC, although no relactonization was detected. The condensation (HOBT, WSC) of the crude product 130 with free amine 117 produced the protected dipeptide 131 (40% yield based on 117) and the recovered starting material 130 in 60% yield which could be recycled to produce 30% more of dipeptide 131 based on recovered starting material 130. These results demonstrated that the coupling reaction could be achieved using the protected silyl ester under acidic peptide coupling conditions (HOBT, WSC) without incurring relactonization or racemization.

Synthesis of Fully Protected Polyoxin J. The γ-hydroxy acid 122 was treated with TBSCI and imidazole in DMF at 40 °C for 16 h to produce the silyl ester 132 in 93% crude yield (Scheme XX).
Scheme XX. Synthesis of the Protected Polyoxin J and Its Diastereomer.

Again, the lability of the silyl ester on silica gel (a mild acid) made it difficult to judge the completion of this reaction by TLC, although no relactonization was detected. The condensation (HOBT, WSC) of the crude product 132 and free amine 117, however, produced a (1:1:1:2) mixture of three products in 48% combined yield along with 44% of recovered 132. One of the three products was bis-silylated dipeptide 133 and the others were two monosilylated dipeptides 134 and 135. The structures of these compounds were confirmed by IH NMR, IR and FAB-MS data. However, the position of TBS group was not established in monosilylated compounds.
134 and 135 (Scheme XX). Acid hydrolysis (deprotection) of these three compounds, 133-135 should provide the final compound, polyoxin J (8)

**Conclusion**

These studies illustrate a way to prepare the peptidyl nucleoside polyoxin J (8) from the synthetic intermediates 122 and 117. An approach to efficient peptide coupling of γ-hydroxy acids and amines employing a silylation protection sequence was developed to overcome the relactonization of activated γ-hydroxy carboxylic acids. This work should permit the ready synthesis of homoserine-containing peptide analogues\(^6^3\) and related peptides or their analogues,\(^6^4\) which exhibit this same propensity for relactonization during their protection and/or activated ester formation.
Chapter 4

EXPERIMENTAL

GENERAL EXPERIMENTAL

Instrumentation. Melting points were determined on a Mel-Temp Capillary melting point apparatus. Melting and boiling points are uncorrected. Optical rotations were determined at ambient temperature with a Perkin-Elmer 142 (or 141) polarimeter and are average of at least four measurements. IR spectra were recorded on a Perkin-Elmer 1420 spectrometer. $^1$H NMR spectra were recorded on Varian XL-200 spectrometer at 200 MHz or on a Bruker MSL 400 NMR spectrometer at 400 MHz and reported in parts per million ppm on the $\delta$ scale relative to residual CHCl$_3$ ($\delta$ 7.24), C$_6$H$_6$ ($\delta$ 7.16), DMSO ($\delta$, 2.49), acetone ($\delta$, 2.04), and HDO ($\delta$, 4.67). Coupling constants ($J$) are reported in cycles per second (Hz). NOE difference data were obtained on a Bruker MSL 400 NMR spectrometer. $^{13}$C NMR spectra were recorded on Varian XL-200 spectrometer at 50.3 Hz and are reported in parts per million ppm on the $\delta$ scale relative to residual CDCl$_3$ ($\delta$ 77.0), C$_6$D$_6$ ($\delta$ 128.0), acetone-d$_6$ ($\delta$, 29.8), DMSO-d$_6$ ($\delta$, 39.5), pyridine-d$_5$ ($\delta$, 135.5), and TMS ($\delta$, 0.0). The $^{13}$C assignments were based on both APT (attached proton test)$^{65}$ and $^1$H-coupled spectra. The APT results are indicated as "+" or "-" depending on the phase of the signal, where carbon atoms having one or three
appended protons are indicated with a minus sign (-), whereas carbon atoms bearing two or no attached protons are denoted by a plus sign (+). $^{19}$F NMR were recorded on Varian XL-200 spectrometer at 188 MHz and reported in parts per million ppm on the $\delta$ scale relative to trifluoroacetic acid ($\delta$, 0.00), as an external reference. High resolution mass spectra (exact mass) were obtained with a Kratos MS 30 mass spectrometer and reported in units of $m/e$. For the volatile organic molecules, the ionizing beam was set at 20 eV (EI mode) and all samples were directly probe injected. For the non-volatile organic molecules, FAB (fast atom bombardment-positive mode) was applied using glycerol matrix. Combustion analyses were performed on TLC homogeneous and in some case recrystallized samples by Galbraith Labs, Inc., Knoxville, Tennessee.

**Chromatography.** Thin layer chromatography (TLC) analysis was performed on 0.25 mm thick Merck Silica Gel 60 F-254 plates and visualized by UV illumination and/or charring with (A) 0.3% ninhydrin in (97:3) n-BuOH-AcOH, or (B) 5% anisaldehyde in (95:5:1) EtOH-AcOH-\(H_2\)SO\(_4\), or (C) 0.5% phosphomolybdic acid in 95% EtOH. Flash column chromatography was performed on 230-400 mesh silica gel 60 supplied by E. Merck. High performance liquid chromatography (HPLC) was performed on a system consisting of Waters M590 solvent delivery systems, a Waters U6K injector and a BAS LC-22A temperature controller. Column eluents were monitored with a Kratos Spectroflow 757 UV detector and/or a Waters model R401 Differential Refractometer. Data was
recorded on a Shimadzu C-R34 data processor. The solvent mixtures for all chromatographies were prepared on a volume/volume (v/v) basis.

**Solvents and Reagents.** Reagent grade solvents were used for all extraction and chromatography except for ethyl acetate and hexanes which were distilled to remove higher boiling contaminants. The following solvents and reagents, to be used in reactions, were purified and dried beyond commercial reagent grade as follows: 6,7 tetrahydrofuran, toluene, and benzene were distilled from sodium-benzophenone ketyl under nitrogen in a recycling still. Dichloromethane and 1,2-dichloroethane were distilled from P₂O₅ and stored over 4Å molecular sieves. Pyridine and HMDS were distilled over CaH₂ and stored over 4Å molecular sieves. Trimethylsilyl triflate and tin tetrachloride were distilled under N₂ atmosphere just prior to use. Dry ethereal diazomethane solutions (approximately 0.6 M) were prepared by the following modification of Arndt's procedure: 6a N-nitroso-N-methyl urea (1 g) was added slowly in portions to a cold solution of potassium hydroxide (2 g) in 10 mL of Et₂O and 10 mL of tap water with swirling in an ice bath; the Et₂O layer was decanted and the aqueous layer was extracted with 10 mL of fresh diethyl ether which was then decanted; the combined Et₂O layers were dried over sodium hydroxide pellets in an ice bath prior to use.

**Apparatus and Reaction Conditions.** Glassware and teflon coated stirring bars were oven dried at approximately 130 °C before use. Air sensitive reactions were performed under dry, inert atmospheres of
argon or nitrogen using a ballon adaptor. Air sensitive liquids were added via syringe or cannula through a rubber septum. Cooling was achieved with the following baths: ice/water (0 °C), dry ice/carbon tetrachloride (-23 °C), dry ice/xylene (-45 °C), and dry ice/acetone (-78 °C). Heating was achieved with silicon oil baths or heating mantles. Solvents were evaporated with a Büchi rotary evaporator at 30 °C and then final traces of solvent were removed at room temperature under a vacuum of < 0.5 mm.

SYNTHESIS OF THE PENALDIC ACID EQUIVALENT 5

\[
\text{N-[(1,1-Dimethylethoxy)carbonyl]-D-(or-L-)-serine Methyl Ester (3). A solution of (BOC)_{2}O (78.4 g, 0.359 mol) in dioxane (280 mL) was added to an ice-cold solution of D-serine (31.73 g, 0.3019 mol) in 1 N NaOH solution (620 mL) over a period of 0.5 h. The reaction mixture was stirred at 5 °C for 30 min, then allowed to warm to room temperature and stirred for 3.5 h at which time the TLC in (8:1:1) n-BuOH-H_{2}O-AcOH showed the clean formation of a product, } R_f \text{ 0.65 at the expense of starting amino acid at the origin (char A). The mixture was concentrated to half its original volume by rotary evaporation at 35 °C, cooled in an ice bath, and acidified to pH 2-3 by slow addition of cold 1 N KHSO}_{4} \text{ solution (620 mL) and then extracted with EtOAc (3 x 1000 mL). The combined extracts were dried with MgSO}_{4}, filtered, and concentrated } \text{in vacuo to give N-BOC D-serine 2b as a colorless, sticky foam. This material}
\]
was dissolved in Et₂O (600 mL), cooled in an ice-bath, and treated with ten 50 mL aliquots of cold 0.6 M ethereal diazomethane prepared according to Arndt's procedure.⁶ After stirring for 30 min at 0° C, the TLC in (1:1) EtOAc-hexanes showed the clean formation of ester, R₉ 0.38, at the expense of starting material at the origin (char A). Excess diazomethane was destroyed with acetic acid, and the resulting solution was extracted with half-saturated NaHCO₃ solution (300 mL), then washed with brine (200 mL), dried with MgSO₄, filtered, and concentrated in vacuo to give N-BOC methyl ester 3b (60.1 g, 91% crude yield), as a colorless, sticky foam, which was used without further purification. The overall yield for these two steps was consistently between 80% and 90%. This procedure was applied to L-serine as well, giving an ample supply of material 3a.¹⁴ Optical measurements on this material were not useful since rotations were generally in low and variable. Furthermore, no literature data could be found for comparison. For 3b: [α]D -10.2° (c 1.02, CHCl₃), -5.9° (c 2.61, CHCl₃), -0.81 (c 2.48, CHCl₃); IR (neat): 3400, 1720 cm⁻¹; ¹H NMR (200 MHz, C₆D₆, 17 °C): δ 1.41 (s, 9 H, C(CH₃)₃), 2.5 (br s, OH, exchanged with D₂O), 3.26 (s, 3 H, CO₂CH₃), 3.66 (dd, J = 11 and 4 Hz, H-3a), 3.76 (dd, J = 11 and 4 Hz, H-3b), 4.4 (m, H-2), 5.6 (br s, NH, exchanged with D₂O). An alternative esterification method⁶ that avoids the use of toxic diazomethane involves the following procedure: To a cold solution of N-BOC L-serine 2a (32.4 g, 0.158 mol) in dimethylformamide (150 mL) was added solid K₂CO₃ (24.3 g, 0.176 mol) with ice-bath cooling, followed by addition of methyl iodide (20.3 mL, 46.28 g, 0.326 mol). The mixture was allowed to come to ambient temperature overnight with continued
stirring. The resulting mixture was suction-filtered, and partitioned between EtOAc (300 mL) and water (300 mL). The combined organic layers were washed with half-saturated brine (2 x 300 mL), water, and then brine once more. The organic layer was then dried over MgSO₄, filtered and concentrated in vacuo to give N-BOC L-serine methyl ester 3a (29.8 g, 0.136 mmol, 86% yield) as an amber oil. This material has an identical ¹H NMR spectrum as that of 3a prepared by diazomethane esterification.

![Chemical Structure](attachment:image)

3-(1,1-Dimethylethyl) 4-Methyl *(S)*-2,2-Dimethyl-3,4-oxazolidinedicarboxylate (4). A solution of N-BOC L-serine methyl ester 3a (48.5 g, 0.221 mol), DMP (55 mL, 0.45 mol), and TsOH·H₂O (0.593 g, 3.12 mmol) in benzene (770 mL) was heated under reflux for 30 min then slowly distilled until a volume of 660 mL had been collected. The TLC of the cooled reaction mixture in (1:1) hexanes-EtOAc showed the clean formation of product. *Rᶠ* 0.78, though some starting material still remained at *Rᶠ* 0.23 (char A). Additional DMP (14 mL, 0.11 mol) and fresh benzene (310 mL) were added, and the procedure was repeated, collecting 250 mL of distillate, at which time the TLC showed the reaction to be complete. The cooled amber solution was partitioned between saturated NaHCO₃ solution (200 mL) followed by brine (120 mL), then dried with MgSO₄, filtered, and concentrated in vacuo to give the crude product 4a, as an amber oil. This material was vacuum-distilled through a 10-cm Vigreaux column to give 40.3 g (70% yield) of 4a as a pale yellow liquid,
bp 101-102 °C (2 mm), [α]D -46.7° (c 1.30, CHCl₃). An essentially identical procedure emanating from D-serine gave 4b in 80% yield with a rotation of +53.0° (c 1.22, CHCl₃). In either case further purification could be achieved with flash chromatography to give product with a maximum rotation of 157° though we have found the distilled material to be entirely satisfactory for our purposes: IR (neat): 1760, 1704 cm⁻¹; ¹H NMR (200 MHz, C₆D₆ 75°C): δ 1.41 (s, 9 H, C(CH₃)₃), 1.53, 1.81 (2 s, 3 H, C(CH₃)₂), 3.35 (s, 3 H, CO₂CH₃), 3.75 (dd, J = 8.5 and 8.1 Hz, H-5a), 3.81 (dd, J = 8.5 and 3.5 Hz, H-5b), 4.26 (m, H-4); LRMS (% relative intensity, m/e): 244 (7.2, M⁺ - CH₃), 144 (52), 57 (100), 43 (10), 41 (18); Anal. Calcd. for C₁₂H₂₁N₀₅: C, 55.57; H, 8.18; N, 5.40. Found: C, 55.64; H, 8.46; N, 5.47.

1,1-Dimethylethyl (S)-4-Formyl-2,2-dimethyl-3-oxazolidinecarboxylate (5). To a stirred -78 °C solution of oxazolidine ester 4a (40.2 g, 0.155 mol) in dry toluene (300 mL) was added a -78 °C solution of DIBAL (1.5 M in toluene, 175 mL) via cannula (using positive N₂ pressure). The rate of addition was adjusted so as to keep the internal temperature below -65 °C and took ca. 1 h to complete. The reaction mixture was stirred for an additional 2 h at -78 °C (under an N₂ atmosphere) when the TLC in (4:1) hexanes-EtOAc showed the clean formation of product, Rf 0.33, with only a trace of starting material remaining at Rf 0.41 (char A). The reaction was quenched by slowly adding 60 mL of cold (-78 °C) MeOH (Caution, H₂ evolution!) again so as to keep the internal temperature below -65°C. The resulting white emulsion was slowly poured into 1000
mL of ice-cold 1 N HCl with swirling over 15 min, and the aqueous mixture was then extracted with EtOAc (3 x 1000 mL). The combined organic layers were washed with brine (1000 mL), dried with MgSO₄, filtered, and concentrated in vacuo to give a crude product 5a (33.6 g), as a colorless oil. This material was vacuum distilled through a 10 cm Vigreaux column to give 26.86 g (76% yield) of oxazolidine aldehyde 5a, as a colorless liquid, bp 83-88 °C (1.0-1.4 mm), [α]D -91.7° (c 1.34, CHCl₃). An identical procedure emanating from D-serine gave 5b in 85% yield having a rotation of +95°. These distilled products contained ca. 5% of the starting ester 4 as judged by their NMR spectra but were suitable for use without further purification. Pure samples could be obtained in either case by flash chromatography and showed a maximum optical rotation of 1105°: IR (neat): 1735, 1705 cm⁻¹; ¹H NMR (200 MHz, C₆D₆, 60°C): δ 1.34 (s, 9 H, C(CH₃)₃), 1.40, 1.59 (2 s, 2 x 3 H, C(CH₃)₂), 3.52 (dd, J = 8.7 and 8.3 Hz, H-5a), 3.65 (dd, J = 8.7 and 2.9 Hz, H-5b), 3.90 (m, H-4), 9.34 (br s, CHO); LRMS (% relative intensity, m/e): 200 (10, M⁺ - CHO), 144 (10), 100 (35), 83 (10), 58 (12), 57 (100), 43 (15), 29 (15); Anal. Calcd for C₁₁H₁₉N₀₄: C, 57.61; H, 8.37; N, 6.11. Found: C, 57.82; H, 8.59; N, 6.26.

Reduction of Penaldic Acid Equivalent 5a and 5b.

To an ice-cold solution of 5a (125 mg, 0.546 mmol) in 7 mL of (1:1) isopropyl alcohol-THF was added solid NaBH₄ (61 mg, 1.7 mmol). After the mixture was stirred for 30 min at this temperature, the TLC in (3:2) hexanes-EtOAc showed the clean formation of alcohol 6a, Rf 0.46 (char A), at the expense of
starting material at \( R_f \) 0.68. This cold solution was (carefully) partitioned between 1 N HCl (10 mL) and EtOAc (4 x 20 mL). The combined organic layers were washed with brine (10 mL), dried with MgSO\(_4\), filtered, and concentrated \textit{in vacuo} to give 108 mg of crude product 6a. Further purification was accomplished via flash chromatography on silica gel eluting with (3:2) hexanes-EtOAc and gave 90 mg (71\% yield) of pure alcohol 6a as a colorless oil, \([\alpha]_D -24.0^\circ \) (c 1.61, CHCl\(_3\)). An essentially identical procedure was applied to 5b and gave the antipode 6b. \([\alpha]_D + 23.6^\circ \) (c 1.44. CHCl\(_3\)), in 64\% yield: IR (neat): 3400, 1690, 1665 cm\(^{-1}\); \(^1\)H NMR (200 MHz, C\(_6\)D\(_6\) + D\(_2\)O, 60 °C): \( \delta \) 1.37 (s, 9 H, C(CH\(_3\))\(_3\)), 1.43, 1.56 (2 s, 2 x 3 H, C(CH\(_3\))\(_2\)), 3.51 (m, H), 3.62 (m, 3 H), 3.59 (m, H). Upon cold storage, a sample of 6b crystallized as prisms, mp 38-39 °C. Anal. Calcd for C\(_{11}\)H\(_{21}\)NO\(_4\): C, 57.11; H, 9.17; N, 6.06 Found: C, 56.96; H, 9.21; N, 6.10.

![Preparation of MTPA Derivatives](image)

\((S,S)-7a\) and \((R,S)-7b\). To a solution of alcohol 6a (59 mg, 0.26 mmol), DCC (60 mg, 0.28 mmol), and DMAP (3 mg, 0.03 mmol) in dry CH\(_2\)Cl\(_2\) (1.0 mL) was added 0.77 mL of a 0.38 M stock solution of \((S)\)-MTPA in CH\(_2\)Cl\(_2\). After the mixture was stirred at ambient temperature for 4.5 h. the TLC in (3:2) hexanes-EtOAc showed the clean formation of product, \( R_f 0.75 \) (char A), at the expense of starting material at \( R_f 0.43 \). The resulting white suspension was filtered to remove the N,N-dicyclohexylurea and then partitioned between EtOAc (20 mL) and H\(_2\)O (10 mL). The organic layer was washed with 10 mL each
of 1 N HCl, H₂O, saturated NaHCO₃ solution, and brine then dried with MgSO₄, filtered and concentrated in vacuo to give 129 mg of crude product as an oily solid. Flash chromatography on silica gel eluting with (1:1) hexanes-EtOAc yielded 119 mg (104% yield) of material (S,S)-7a, [α]D -48° (c 1.87, CHCl₃), that was analyzed directly. IR (neat): 1760, 1705 cm⁻¹; ¹H NMR (200 MHz, C₆D₆, 75° C): δ 1.39 (s, 9 H, C(CH₃)₃), 1.41, 1.53 (2 s, 2 x 3 H, C(CH₃)₂), 3.39 (d, J = 1 Hz, 3 H, OCH₃), 3.54 (dd, J = 9.2 and 5.8 Hz, H-5a), 3.62 (dd, J = 9.2 and 1.9 Hz, H-5b), 3.95 (m, H-4), 4.17 (m, H-1'a), 4.54 (dd, J = 10.4 and 3.2 Hz, H-1'b), 7.0-7.4 (m, 3 H), 7.61 (br d, J = 7.9 Hz, 2 H); ¹⁹F NMR (CDCl₃, 20°C) δ 4.92 (s). An essentially identical procedure was performed with 6b and resulted in the isolation of (R,S)-7b, [α]D -9.7° (c 1.06, CHCl₃); IR (neat): 1750, 1700 cm⁻¹; ¹H NMR (200 MHz, C₆D₆, 75°C): δ 1.41 (br s, 12 H), 1.55 (br s, 3 H, 0.5 C(CH₃)₂), 3.38 (s, 3 H, OCH₃), 3.49 (dd, J = 9.3 and 5.6 Hz, H-5a), 3.62 (dd, J = 9.3 and 1.9 Hz, H-5b), 3.91 (m, H-4), 4.10 (m, H-1'a), 4.58 (dd, J = 10.3 and 3.4 Hz, H-1'b), 7.0-7.4 (m, 3 H), 7.60 (br d, J = 7.3 Hz, 2 H); ¹⁹F NMR (CDCl₃, 19 °C) δ 4.84 (s), 4.99 (s).

SYNTHESIS OF 5-O-CARBAMOYL-POLYOXAMIC ACID

![Synthesis of 5-O-Carbamoyl-Polyoxamic Acid](image_url)  

1,1-Dimethylethyl [S-(R*,S*)]-4-(1-hydroxy-2-propenyl)-2,2-dimethyl-3-oxazolidinecarboxylate (38) and 1,1-Dimethylethyl [S-(R*,R*)]-4-(1-hydroxy-2-propenyl)-2,2-dimethyl-3-oxazolidinecarboxylate (39). To a -78 °C solution of oxazolidine aldehyde 5b (12.02 g, 52.42 mmol) in dry THF (350 mL) under
an N₂ atmosphere was added vinlymagnesium bromide (1 M in THF, 175 mL) over a 30 min period. The yellow solution was stirred for 2 h at -78 °C after which the TLC in (2:1) hexanes-EtOAc showed the clean formation of product, \( R_f 0.33 \), at the expense of starting aldehyde, \( R_f 0.43 \) (char A). The solution was warmed to 0 °C and washed with saturated NH₄Cl solution (120 mL) and then extracted with Et₂O (2 x 1 L). The combined organic layers were washed with brine (300 mL), dried with MgSO₄, filtered, and concentrated in vacuo to give a crude product (14.48 g). The \(^1\text{H} \) NMR spectrum (vide infra) of this material indicated a (6:1) mixture of diastereomers 38 and 39. Fractional vacuum distillation using a 10 cm Vigreux column yield 10.80 g (80% yield) of a (4:1) mixture of 38 and 39, as a colorless oil, bp 102 °C (0.6-0.7 mm), [\( \alpha \)]\(_D\) +26.6° (c 1.03, CHCl₃), which was used directly for the next transformation. For characterization purposes, pure samples of 38 and 39 were obtained by careful flash chromatography using (5:1) hexanes-EtOAc. Compound 38: [\( \alpha \)]\(_D\) +55.0° (c 1.47 CHCl₃); IR (neat): 3450, 3080, 1700 cm\(^{-1}\); \(^1\text{H} \) NMR (200 MHz, C₆D₆, 60 °C): δ 1.36 (s, 9 H, C(CH₃)₃), 1.42, 1.60 (2 s, 2 x 3 H, C(CH₃)₂), 3.54 (dd, \( J = 7.7 \) and 4.3 Hz, H-5a), 3.69 (br s, H-5b), 3.82 (br s, OH, exchanged with D₂O), 3.92 (br s, H-4), 4.30 (br s, H-1'), 5.08 (dd, \( J = 10.5 \) and 1.4 Hz, H-3' cis), 5.36 (dd, \( J = 17.5 \) and 1.2 Hz, H-3' trans), 5.84 (ddd, \( J = 17.5 \), 10.7, and 6.4 Hz, H-2'); \(^{13}\text{C} \) NMR (C₆D₆, 60 °C): δ 23.9, 26.4 (2 q, - C(CH₃)₂), 28.0 (q, - C(CH₃)₃), 61.9 (d, - C-4), 64.3 (t, +, C-5), 73.5 (d, - C-1'), 79.9 (s, +, C(CH₃)₃), 94.2 (s, +, C(CH₃)₂), 115 (t, +, C-3'), 138 (d, - C-2'), 153.2 (s, +, NCO₂); Anal. calcd for C₁₃H₂₃NO₄: C, 60.08; H, 9.01; N, 5.44. Found: C, 60.11; H, 9.19; N, 5.75. Compound 39: \(^1\text{H} \) NMR (200 MHz, C₆D₆, 60 °C): δ 1.38 (s, 9 H, C(CH₃)₃), 1.42,
1.62 (2 s, 2 x 3 H, C(CH₃)₂), 3.63 (dd, J = 9.4 and 6.3 Hz, H-5a), 3.70 (br s, OH, exchanged with D₂O), 3.82 (dd, J = 9.4 and 2.0 Hz, H-5b), 3.91 (dd, J = 6.7 and 6.3 Hz, H-4), 4.40 (t, J = 6.7 Hz, H-1'), 5.04 (dd, J = 10.3 and 1.5 Hz, H-3' cis), 5.26 (dd, J = 17.2 and 1.5 Hz, H-3' trans), 5.83 (ddd, J = 17.0, 10.0, and 6.7 Hz, H-2').

**1,1-Dimethylethyl** [(S - (R⁺, S⁺) - 4 - [1 - [(Aminocarbonyl)-oxy]-2-propenyl]-2,2-dimethyl-3-oxazolidinecarboxylate (41). To a solution of secondary allylic alcohols 38/39 (5.80 g, 22.50 mmol) in dry pyridine (550 mL) was added para-nitrophenyl chloroformate (11.46 g, 22.53 mmol). The resulting suspension was stirred at room temperature for 24 h under an N₂ atmosphere, during which time it became a clear yellow solution. The TLC in (2:1) hexanes-EtOAc showed the clean formation of product, Rₚ 0.65, at the expense of the starting material at Rₚ 0.35 (char A). The reaction mixture was diluted with benzene (1 L) and extracted with 0.5 M H₂SO₄ (5 x 1 L), saturated NaHCO₃ solution (5 x 1 L), and water (2 x 1 L). The organic layer was dried with MgSO₄, filtered, and concentrated in vacuo to give a crude product 40 (18.07 g) as a pale yellow solid, which was dissolved in CH₂Cl₂ (150 mL) and treated with saturated NH₃/MeOH (300 mL) at ambient temperature for 1 h until the TLC in (2:1) hexanes-EtOAc showed clean formation of product 41, Rₚ 0.22, at the expense of carbonate 40, Rₚ 0.62 (char A). After concentration of this mixture in vacuo, the resulting yellow solid was dissolved in CH₂Cl₂ (1
L) and washed with 0.5 M NaHCO₃ solution (3 x 1 L) followed by water (2 x 1 L). The organic layer was dried with MgSO₄, filtered, and concentrated in vacuo to give a crude product (6.86 g) as a yellow oil. Flash chromatography on silica gel eluting with (1:1) hexane-EtOAc gave a pure secondary urethane (4.61 g, 68% over two steps) as a (4:1) mixture of erythro/threo diastereomers 41: [α]D +38.4° (c 4.06, CHCl₃); IR (neat): 3350, 3100, 1730, 1700, 1600 cm⁻¹; ¹H NMR (200 MHz, C₆D₆, 60 °C, major isomer): δ 1.46 (s, 9 H, C(CH₃)₃), 1.51, 1.70 (2 s, 2 x 3H, C(CH₃)₂), 3.72 (dd, J = 6.7 and 1.8 Hz, H-5a), 3.85 (dd, J = 8.8 and 1.8 Hz, H-5b), 4.17 (br s, 3 H, H-4 and OCONH₂, 2H was slowly exchanged with D₂O), 5.02 (dd, J = 10.5 and 1.3 Hz, H-3’cis), 5.25 (dd, J = 17.2 and 1.4 Hz, H-3’trans), 5.60-5.71 (br s, H-2’), 5.89 (br s, H-1’); ¹³C NMR (C₆D₆, 60 °C) δ 26.8 (q, −, C(CH₃)₂), 29.2 (q, −, C(CH₃)₃), 62.8 (d, −, C-4), 63.7 (t, +, H-5), 74.9 (d, −, H-1’), 79.5 (s, +, C(CH₃)₃), 94.2 (s, +, C(CH₃)₂), 119.1 (t, +, C-3’), 136.0 (d, −, C-2’), 155.8 (s, +, NCO₂), 156.1 (s, +, OCONH₂); Anal. calcd for C₁₄H₂₄N₂O₅: C, 55.97; H, 8.07; Found: C, 56.04; H, 8.17.

1,1-Dimethylethyl [S-(E)]-4-[3-((Amino-carbonyl)oxy]-1-propenyl]-2,2-dimethyl-3-oxazolidinecarboxylate (42). To a solution of the secondary urethanes 41 (4.50 g, 14.9 mmol) in dry THF (150 mL) was added PdCl₂(CH₃CN)₂ (77.2 mg, 0.257 mmol). The resulting yellow solution was stirred at room temperature under an N₂ atmosphere for 8 h until no further reaction was apparent by TLC in (1:1) hexanes-EtOAc (three developments). The reaction mixture showed the
formation of a new product at $R_f$ 0.23 as well as some unreacted starting material at $R_f$ 0.31 (char A). The reaction mixture was partitioned between water (500 mL) and EtOAc (3 x 500 mL). The combined organic layers were washed with brine (500 mL), dried with MgSO$_4$, filtered, and concentrated in vacuo to give a crude product (4.27 g) as a yellow oil. Flash chromatography on silica gel eluting with (6:1) hexanes-EtOAc gave pure primary urethane 42 (3.01g, 86% yield based on recovered starting material 41): [α]$_D$ +10.0° (c 1.06, CHCl$_3$); IR (neat): 3350, 1730, 1700, 1600 cm$^{-1}$; $^1$H NMR (200 MHz, C$_6$D$_6$, 60 °C): δ 1.43 (s, 9 H, C(CH$_3$)$_3$), 1.53, 1.69 (2 s, 2 x 3 H, C(CH$_3$)$_2$), 3.50 (dd, $J$ = 9.3 and 6.2 Hz, H-5a), 3.60 (dd, $J$ = 9.3 and 2.5 Hz, H-5b), 4.10 (m, 3 H, H-4 and OCONH$_2$). 2H was slowly exchanged with D$_2$O, 4.46 (d, $J$ = 4.2 Hz, 2 H, H-3'), 5.64 (br s, 2 H, H-1' and H-2'); $^{13}$C NMR (C$_6$D$_6$, 60 °C): δ 26.85, 27.02 (2 q, - C(CH$_3$)$_2$), 28.42 (q, - C(CH$_3$)$_3$), 60.02 (d, -, C-4), 64.52 (t, - C-5), 68.04 (t, - C-3'), 79.52 (s, +, C(CH$_3$)$_3$), 94.05 (s, +, C(CH$_3$)$_2$), 126.98 (d, -, C-2'), 133.34 (d, -, C-1'), 154.96 (s, +, NCO$_2$), 157.12 (s, +, OCONH$_2$); Anal. calc'd for C$_{14}$H$_{24}$N$_2$O$_5$: C, 55.97; H, 8.07. Found: C, 56.00; H, 8.20.

\[
\begin{align*}
\text{H}_2\text{NCO}_2 & \quad \text{H} \quad \text{N} \quad \text{O} \\
\text{BOC} & \quad \text{O} \\
\text{29} & \quad \text{1,1-Dimethyl ethyl} \quad [S-(E)]-4-[(\text{Amino carbonyl})oxy]-1-(\text{hydroxymethyl})-2\text{-butenyl}] \text{ carbamate (29). A solution of 4.2} \\
\text{(2.86 g, 9.51 mmol) and TsOH-H}_2\text{O} & \text{(144 mg, 0.760 mmol) in MeOH (170 mL) was stirred at ambient temperature for 14 h whenupon TLC in EtOAc showed the partial formation of a product at } R_f \text{ 0.46 along with starting material at } R_f \text{ 0.77. Prolonged reaction times}
\end{align*}
\]
resulted in cleavage of the BOC moiety as evidenced by increasing amounts of intensely ninhydrin active material near the origin so the reaction was worked up after 14 h. The mixture was partitioned between saturated NaHCO₃ solution (450 mL) and EtOAc (3 x 500 mL). The combined organic layer was washed with brine (450 mL), dried with MgSO₄, filtered, and concentrated in vacuo to give a crude mixture (2.7 g) as an oil. Flash chromatography on silica gel eluting with (1:1) hexanes-EtOAc afforded alcohol 29 (1.02 g, 80% yield based on 52% conversion of starting material) as a white solid, which was recrystallized from hot EtOAc as needles, mp 107-108 °C; [α]D +11.4° (c 0.94, MeOH); IR (KBr) 3350, 1690, 1605 cm⁻¹; ¹H NMR (200 MHz, acetone-d₆, RT): δ 1.39 (s, 9 H, C(CH₃)₃), 2.70 (br s, OH, exchanged with D₂O), 3.59 (pseudo t, J = 5.8 Hz, H-1’a and H-1’b), 4.07 (br s, H-1), 4.47 (d, J = 3.5 Hz, H-4a and H-4b), 5.67 (br s, H-2 and H-3), 5.73-5.90 (br s, 3 H, NH and OCONH₂, slowly exchanged with D₂O); ¹³C NMR (acetone-d₆, RT): δ 28.6 (q, - C(CH₃)₃), 54.8 (d, - C-1), 64.8 (t, +, C-1’), 65.1 (t, +, C-4), 127.0 (d, - C-3), 133.0 (d, - C-2), 156.23 (s, +, NCO₂), 157.47 (s, +, OCONH₂); HRMS (% relative intensity, m/z): 261.1495 (26.7, M + 1, calc'd for C₁₁H₂₀NO₅ 261.1450), 205 (16.5), 173 (12.6), 161 (41.7), 144 (20.6), 129, 113 (28.6), 69, 68 (52.6), 57 (100); Anal. calc'd for C₁₁H₂₀NO₅: C, 50.75; H, 7.76.

Found: C, 50.92; H, 7.79.

\[ \text{H}_2\text{NCO}_2 \underset{\text{OMTPA}}{\text{S}} \underset{\text{BOC}}{\text{N}} \underset{\text{H}}{\text{H}} \] (S,R)-43 from (R)-MTPA (S,S)-44 from (S)-MTPA

\[ \text{[R-[R^*,S^*-(E)]-5-((Aminocarbonyl)-oxy)-2-[(1,1-dimethylethoxy)-carbonyl]amino]-3-pentenyl} \alpha-\text{Methoxy-}\alpha-(\text{trifluoromethyl}) \]
benzeneacetate (43) and \([S-[R^*,R^*-](E)]]-5-[(Aminocarbonyl)oxy]-2-[(1,1-dimethylethoxy)carbonyl] amino]-3-pentenyl \(\alpha\)-methoxy-\(\alpha\)-(trifluoromethyl)benzene- acetate (44). To a solution of 29 (3.8 mg, 0.015 mmol), 1,3-dicyclohexylcarbodiimide (3.6 mg, 0.017 mmol), and 4-(dimethylamino)-pyridine (0.5 mg, 0.004 mmol) in dry CH\(_2\)Cl\(_2\) (1.0 mL) was added a stock solution of (R)-(+)MTPA (0.09 M in dry CH\(_2\)Cl\(_2\), 0.17 mL). This solution was stirred at room temperature overnight whenupon TLC in EtOAc showed the formation of product, \(R_f\) 0.77, at the expense of starting material, \(R_f\) 0.43 (char A). The reaction mixture was filtered through cotton and concentrated in vacuo to give a crude product (16.1 mg). Preparative TLC on a 0.5 mm thick plate eluting with ethyl acetate gave a pure compound (S,R)-43 (5.2 mg, 75% yield) as a colorless oil: \(^1\)H NMR (200 MHz, C\(_6\)D\(_6\), RT): \(\delta\) 1.38 (s, 9 H, C(CH\(_3\))\(_3\)), 3.39 (s, 3 H, OCH\(_3\)), 3.68-3.79 (br s, 2 H, OCONH\(_2\), slowly exchanged with D\(_2\)O), 3.87 (dd, \(J\) = 11.0 and 6.1 Hz, H-1′a), 3.98 (dd, \(J\) = 13.0 and 4.7 Hz, H-1′b), 4.25 (br s, NCO\(_2\), exchanged with D\(_2\)O), 4.28 (d, \(J\) = 5.6 Hz, 2 H, H-4), 4.32-4.42 (br s, H-1), 5.16 (dd, \(J\) = 15.7 and 5.44 Hz, H-2), 5.40 (dt, \(J\) = 16.0 and 5.6 Hz, H-3), 7.12 (m, 3 H), 7.67 (d, \(J\) = 7.5 Hz, 2 H); \(^{19}\)F NMR (C\(_6\)D\(_6\), RT): \(\delta\) 5.26. The diastereomeric product (S,S)-44 was prepared from 29 in 78% yield as described above but by using (S)-(−)-MTPA: \(^1\)H NMR (200 MHz, C\(_6\)D\(_6\), RT): \(\delta\) 1.38 (s, 9 H, C(CH\(_3\))\(_3\)), 3.42 (s, 3 H, OCH\(_3\)), 3.77-3.84 (br s, 2 H, OCONH\(_2\), slowly exchanged with D\(_2\)O), 3.91 (m, 2 H, H-1′), 4.27 (br s, NHCO\(_2\), slowly exchanged with D\(_2\)O), 4.28 (d, \(J\) = 5.34 Hz, 2 H, H-4), 4.34-4.39 (m, H-1), 5.16 (dd, \(J\) = 15.6 and 5.2 Hz, H-2), 5.38 (dt, \(J\) = 15.8 and 5.4 Hz, H-3), 7.12 (m, 3 H), 7.67 (d, \(J\) = 7.6 Hz, 2 H); \(^{19}\)F NMR (C\(_6\)D\(_6\), RT): \(\delta\) 5.44.
2-Deoxy-2-[[[(1,1-Dimethylethoxy)carbonyl]amino]L-lyxofuranose 5-carbamate (47) and 2-Deoxy-2-[[[(1,1-Dimethylethoxy)carbonyl]amino]L-lyxofuranose 5-carbamate (48). A solution of KMnO₄ (1.0667 g, 6.75 mmol) in 10% aqueous acetone (48 mL) was added dropwise over 30 min to an ice-cold solution of homoallylic alcohol 29 (1.1991 g, 4.61 mmol) in 10% aqueous acetone (14 mL). During this reaction, CO₂ was continuously bubbled through the reaction mixture. The TLC in EtOAc indicated the clean formation of product(s), Rₙ 0.32, at the expense of starting material, Rₙ 0.42. Water (20 mL) was added, and SO₂ gas was passed through the cooled reaction mixture for 5 - 10 s, during which time the pH changed from 6 - 7 to 1 - 2 and the dark brown suspension became a clear solution. This solution was extracted with EtOAc (3 x 200 mL) and the combined organic layers were dried over MgSO₄, filtered, and concentrated in vacuo to give lactols 47/48 (1.301 g, 96% yield) as a white foam, mp 42-44 °C: IR (neat): 3500, 1700, 1600 cm⁻¹; ¹³C NMR (DMSO-d₆, RT, mixture of isomers): δ 14.04, 20.69, 28.16, 55.41, 58.97, 59.34, 59.69, 60.43, 60.72, 60.88, 61.20, 63.45, 63.97, 64.42, 64.69, 64.98, 68.99, 70.11, 73.04, 73.28, 74.13, 74.32, 75.28, 77.91, 78.32, 93.96, 94.88, 99.82, 100.76, 155.07, 155.29, 156.53, 156.70, 208.19 (aldehyde); HRMS (% relative intensity, m/z): 290.1159 (0.1, M - 2 H, calcd for C₁₁H₂₀N₂O₇ 290.1114), 160 (8.7), 146 (8.2), 133 (22.9), 104 (11.8), 101 (8.2), 88 (10.7), 69 (13.5), 60 (36.2), 59 (12.5), 58 (6.2), 57 (100).
Lactone, 5-Carbamate (49) and 2-Deoxy-2-[[1,1-Dimethylethoxy]carbonyl]amino]-L-lyxonic Acid, γ-Lactone, 5-Carbamate (50). A mixture of urea (15.0 g, 0.250 mol) and CaCO₃ (14.3 g, 0.143 mol) in H₂O (45 mL) was stirred at room temperature for 2 h, whereupon molecular bromine (10.0 mL, 31.0 g, 0.194 mol) was added over a period of 1 h, and then the mixture was stirred at room temperature for an additional hour. A solution of lactols 47/48 (1.71 g, 5.8441 mmol) in EtOAc (20 mL) was added to the resultant brown-yellow suspension over 15 min. The brown suspension was stirred at room temperature for 8 h until TLC in EtOAc showed the formation of the desired lactone products, *R*ₚ (major) 0.51 and *R*ₚ (minor) 0.57, at the expense of starting material at *R*ₚ 0.12 (char A). The reaction mixture was partitioned between EtOAc (50 mL) and water (20 mL). The aqueous phase was extracted further with EtOAc (3 x 30 mL) and, the combined organic layers were washed with 20% NaHSO₃ solution (40 mL), saturated NaHCO₃ solution (40 mL), and water (20 mL). The organic phase was then dried with MgSO₄, filtered, and concentrated *in vacuo* to give crude product (1.24 g) as a white solid. ¹H NMR analysis (vide infra) at this point revealed a (2.5:1) mixture of lactones 49 and 50 in the crude mixture. Trituration of this material with EtOAc (2 x 10 mL) left 342 mg (20% yield) of the major lactone 49 as a white solid, mp 204-206 °C. Recrystallization from hot MeOH gave 289 mg
of analytically pure 49, mp 215-216 °C. Flash chromatography of the EtOAc soluble material (604 mg) eluting with (2:1) EtOAc-hexanes afforded 190 mg (11% yield) of the minor lactone 50 as a white solid, mp 122-124 °C, more of the major lactone 49 (60 mg, 4% yield) and 50 mg of recovered starting material. Spectral data for the major lactone 49: [α]D -78° (c 0.35 DMF); IR (KBr): 3500, 3300, 1770, 1720, 1680, 1600 cm-1; 1H NMR (400 MHz, DMSO-d6, RT): δ 1.39 (s, 9 H, C(CH3)3), 4.05 (t, J = 8.0 Hz, 1 H), 4.13 (dd, J = 7.0 and 6.1 Hz, 1 H), 4.24 (dd, J = 12.5 and 1.9 Hz, 1 H), 4.48 (dd, J = 7.0 and 6.1 Hz, 1 H), 4.66 (ddd, J = 7.0, 6.3, and 1.9 Hz, 1 H), 5.91 (d, J = 5.2 Hz, OH, exchanged with D2O), 6.59 (br s, OCONH2, slowly exchanged with D2O), 7.52 (d, J = 8.1 Hz, NHCO2, slowly exchanged with D2O); 13C NMR (pyridine-d5, RT): δ 28.38 (q, -, C(CH3)3), 58.61 (d, -, C-2), 63.12 (t, +, C-5), 71.95 (d, -, C-4), 79.10 (d, -, C-3), 79.34 (s, +, C(CH3)3), 156.90 (s, +, NCO2), 157.74 (s, +, OCONH2), 174.04 (s, +, CO2); Anal. calcd for C11H28N2O7: C, 45.51; H, 6.25; N, 9.65. Found: C, 45.41; H, 6.09; N, 9.61. Spectral data for the minor lactone 50: [α]D +48° (c 0.77 DMF); IR (KBr): 3500, 3300, 1770, 1720, 1680, 1600 cm-1; 1H NMR (400 MHz, DMSO-d6, RT) δ 1.40 (s, 9 H, C(CH3)3), 4.03 (dd, J = 12.3 and 8.8 Hz, 1 H), 4.20 (dd, J = 12.3 and 4.2 Hz, 1 H), 4.26 (dd, J = 4.5 and 3.2 Hz, 1 H), 4.64 (dt, J = 8.8 and 2.8 Hz, 1 H), 4.72 (dd, J = 9.2 and 4.8 Hz, 1 H), 5.72 (d, J = 5.7 Hz, OH, exchanged with D2O), 6.54-6.71 (br s, OCONH2, slowly exchanged with D2O), 6.66 (d, J = 9.2 Hz, NHCO2, slowly exchanged with D2O); 13C NMR (pyridine-d5, RT): δ 28.40 (q, -, C(CH3)3), 56.88 (d, -, C-2), 63.74 (t, +, C-5), 69.61 (d, -, C-4), 79.18 (d, -, C-3), 80.36 (s, +, C(CH3)3), 156.93 (s, +, OCONH2), 157.99 (s, +, NCO2), 175.20 (s, +, CO2); Anal. calcd for C11H18N2O7: C, 45.51; H, 6.25; N, 9.65. Found: C, 45.41; H, 6.09; N, 9.61.
Mono(trifluoroacetate) (salt) (51) and 2-Amino-2-deoxy-L-lyxonic Acid, γ-Lactone, 5-Carbamate, Mono(trifluoroacetate) (Salt) (52). A mixture of lactone 49 (6.0 mg, 0.021 mmol) in 4% trifluoroacetic acid/CH₂Cl₂ was stirred at room temperature for 3-4 h after which TLC in EtOAc showed the clean formation of product, Rf 0.06, at the expense of starting material, Rf 0.42 (char A). The solvent was evaporated to leave 6.9 mg of 51 as a white solid, mp 138-140 °C: IR (KBr): 3440, 3300, 1790, 1700, 1650, 1580 cm⁻¹; ¹H NMR (400 MHz, D₂O, RT): δ 4.35 (dd, J = 12.7 and 2.6 Hz, H-5a), 4.38 (dd, J = 12.7 and 2.8 Hz, H-5b), 4.42 (d, J = 9.5 Hz, H-2), 4.86 (dd, J = 9.5 and 8.1 Hz, H-3), 4.94 (ddd, J = 8.1, 2.8, and 2.6 Hz, H-4); Anal. Calcd for C₈H₁₁N₂O₇F₃: C, 31.59; H, 3.65; N, 9.21. Found: C, 31.55; H, 3.51; N, 8.86. In a similar manner, treatment of 50 with trifluoroacetic acid afforded 6.9 mg of the diastereomeric trifluoroacetate salt 52 as a white solid, mp 140-141 °C: IR (KBr): 3430, 3300, 1800, 1660, 1600 cm⁻¹; ¹H NMR (400 MHz, D₂O, RT): δ 4.32 (dd, J = 12.3 and 7.7 Hz, H-5a), 4.33 (dd, J = 12.3 and 3.9 Hz, H-5b), 4.54 (d, J = 5.0 Hz, H-2), 4.78 (dd, J = 5.0 and 2.8 Hz, H-3), 4.83 (ddd, J = 7.7, 3.9, and 2.8 Hz, H-4).
2-Amino-2-deoxy-L-xylonic Acid, 5-Carbamate (5-O-Carbamoylpolyoxamic Acid), Hydrochloride (53). A stirred suspension of lactone 49 (49.7 mg, 0.170 mmol) in 1 N HCl (5.0 mL) was heated at 95 °C for 1 h when the suspension turned into the homogeneous solution and the TLC in (3.6:3.6:2.1:0.7) pyridine-EtOAc-H2O-HOAc showed the clean formation of a product that corresponded to 5-O-carbamoylpolyoxamic acid hydrochloride salt (53), Rf 0.30. A small amount of an intermediate lactone salt corresponding to 54, Rf 0.76, was also detected. The reaction mixture was cooled, and the solvent was removed in vacuo to afford 45.3 mg of product as a crystalline foam, which decomposed at 150 °C, [α]D -6.2°, [α]365 -23° (c 0.76 H2O). IR (KBr) 3700-2300, 1780 (due to minor lactone salt), 1720, 1590 cm⁻¹; ¹H NMR of 53 (400 MHz, D₂O + DCl, pD = 2.0, RT): δ 4.06 (br s, 3 H, H-3, H-5a, and H-5b), 4.08 (d, J = 3.4 Hz, 1 H, H-2), 4.24 (ddd, J = 3.4, 1.5, and 0.6 Hz, H-4). This spectrum also showed the presence of a small amount of lactone salt 54 whose signals matched those reported for 52 (vide supra). The overall ratio of 53 to 54 was determined to be (4:1) by integration. The major proton resonances of the (4:1) mixture of 53 and 54 were identical with those obtained with an authentic sample of 5-O-carbamoylpolyoxamic acid (9) in D₂O + DCl.
SYNTHESIS OF THYMINE POLYOXIN C

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\begin{align*}
1,1\text{-Dimethylethyl} & \quad [S\text{-}(R^*, S^*)]-4-(1\text{-Hydroxy-4,4-dimethoxy-2-butynyl})-2,2\text{-dimethyl-3-oxazolidinecarboxylate} \ (59). \quad \text{To a stirred } -78 \ ^\circ\text{C} & \\
\text{a solution of propiolaldehyde dimethylacetal} \ 57 & \ (13.0 \text{ g, 0.13 mol})^35 \text{ in dry THF (225 mL)} & \\
\text{was added slowly n-BuLi} & \ (2.3 \text{ M in hexanes, 47 mL, 0.11 mol}) & \\
\text{under an N}_2 \text{ atmosphere. The slightly yellow suspension was stirred for 1 h at } -78 \ ^\circ\text{C} & \\
\text{and then to this solution was added slowly a } -78 \ ^\circ\text{C} & \\
\text{solution of oxazolidine aldehyde} \ 5b & \ (13.54 \text{ g, 0.0591 mol}) & \\
\text{in dry THF (75 mL)} & \text{over 15 min. After stirring for 2 h at } -78 \ ^\circ\text{C} & \\
\text{the TLC in (4:1) hexanes-EtOAc} & \\
& \text{showed the formation of product, } R_f \ 0.11, \text{ at the expense of starting} & \\
\text{aldehyde, } R_f \ 0.30 \text{ (char B). The resulting solution was slowly poured into} & \\
\text{ice-cold 1 M NaH}_2\text{PO}_4 \ (2 \text{ L, pH 7)} & \\
& \text{with swirling. The mixture was extracted with Et}_2\text{O} \ (3 \times 1 \text{ L}), & \\
& \text{washed with brine} \ (1 \text{ L}), \text{ dried over MgSO}_4, & \\
& \text{filtered and concentrated in vacuo to give a pale yellow oil} \ (19.5 \text{ g}). & \\
\text{The } ^1\text{H NMR spectrum showed an (8:1) mixture of 59 and 60 by the comparison of} & \\
\text{their respective H-1' signals (vide infra). Flash chromatography on} & \\
\text{silica gel, eluting with (12:1) hexanes-EtOAc gave the pure erythro} & \\
\text{product 59 (14.5 g, 75%) followed by threo product 60 (2.38 g, 12%). For} & \\
59: \ [\alpha]_D \ ^{+52.0} \ ^\circ \text{ (c 1.2, CHCl}_3); \text{ IR (neat)}: 3450, 1700 \text{ cm}^{-1}; & \\
^1\text{H NMR (200 MHz, C}_6\text{D}_6, \text{ 60 }^\circ\text{C): } & \\
& \delta \ 0.92 \text{ (br s, 1 H, OH), 1.39 (s, 9 H, C(CH}_3)_3), 1.46, 1.71 (2 s, 2 \times 3 & \\
& \text{H, C(CH}_3)_2), 3.22 \text{ (s, 6 H, 2 x OCH}_3), 3.69 \text{ (m, 2 H, H-5a and 5b), 3.98 (br s, 1 H,} & \\
& \text{H-4), 4.61 (br s, 1 H, H-1'), 5.13 (d, } J = 1.2 \text{ Hz, 1 H, H-4'}); & \\
& ^13\text{C NMR (C}_6\text{D}_6, \text{ 60 & 
\]
°C): δ 26.1 (q, −, C(CH$_3$)$_2$), 28.2 (q, −, C(CH$_3$)$_3$), 52.1 (q, −, OCH$_3$), 60.1 (s, +, C(CH$_3$)$_3$), 63.2 (d, −, C-5), 64.3 (d, −, C-1'), 65.2 (t, +, C-5), 81.0 (s, +, C-2' or C-3'), 84.9 (s, +, C-3' or C-2'), 93.5 (d, −, C-4'), 95.1 (s, +, C-2), 154.5 (s, +, NCO$_2$); MS (% relative intensity, m/e): 298.1575 (1.6, M - CH$_3$O, 298.1654 calc'd for C$_{15}$H$_{24}$NO$_5$), 242 (21.0), 200 (23.4), 144 (47.7), 101 (12.8), 100 (100). For 60: $^1$H NMR (200 MHz, C$_6$D$_6$, 60 °C): δ 1.35 (s, 9 H, C(CH$_3$)$_3$), 1.42, 1.68 (2 s, 3 H, C(CH$_3$)$_2$), 3.19 (s, 6 H, 2 x OCH$_3$), 3.72 (dd + br s, J = 9.8 and 6.9 Hz, 2 H, H-5a and OH), 4.02 (br s, 1 H, H-4), 4.09 (d, J = 8.2 Hz, 1 H, H-5b), 4.81 (br s, 1 H, H-1'), 5.13 (d, J = 1.2 Hz, 1 H, H-4'); HRMS (% relative intensity, m/e): 330.1931 (0.1, M + 1, 330.1917 calc'd for C$_{16}$H$_{28}$NO$_6$), 242 (21.6), 200 (26.6), 143 (45.8), 101 (12.2), 100 (100.0).

1,1-Dimethylethyl (4S-trans)-[4-(3,3-Dimethoxy-1-propynyl)]-2,2-dimethyl-1,3-dioxan-5-yl]carbamate (62). A solution of propargylic alcohol 59 (580 mg, 1.76 mmol) and TsOH·H$_2$O (54.3 mg, 0.29 mmol) in MeOH (15 mL) was stirred at room temperature for 7.5 h at which time the TLC in (1:1) hexanes-EtOAc showed the formation of product, Rf 0.16, at the expense of starting material, Rf 0.60 (char A). The reaction mixture was poured into half saturated NaHCO$_3$ solution (80 mL) and extracted with EtOAc (2 x 100 mL). The combined organic layer was washed with brine (100 mL), dried over MgSO$_4$, filtered and concentrated in vacuo to give an amber oil (509 mg). Flash chromatography on silica gel, eluting with (1:1) hexanes-EtOAc gave the pure diol 61 (400 mg, 79% yield), as a slightly yellow oil
which was submitted directly to the next step. A solution of 61 (50 mg, 0.173 mmol) and TsOH·H₂O (2.5 mg) in 2,2-dimethoxypropane (2 mL) was stirred at room temperature for 1 h, at which time the TLC in (1:1) hexanes-EtOAc showed the formation of product 62, *Rf* 0.76, along with reformed 59, *Rf* 0.67, at the expense of starting diol 61, *Rf* 0.16 (char A). The reaction mixture was partitioned between saturated NaHCO₃ (30 mL) and EtOAc (2 x 50 mL). The combined organic layers were washed with brine (30 mL), dried over MgSO₄, filtered and concentrated *in vacuo* to give an amber oil (54.4 mg). Flash chromatography on silica gel, eluting with (4:1) hexanes-EtOAc gave pure product 62 (15.9 mg) along with recovered 61 and 59 (16 mg each). 62: ¹H NMR (200 MHz, C₆D₆ + D₂O, 60 °C): δ 1.21 (s, 3 H, 0.5 x C(CH₃)₂), 1.41 (s, 9 H, C(CH₃)₃), 1.46 (s, 3 H, 0.5 x C(CH₃)₂), 3.19, 3.20 (2 s, 2 x 3 H, CH(OCH₃)₂), 3.40 (dd, *J* = 11.2 and 7.2 Hz, H-6a), 3.75 (m, 1 H, H-5), 3.89 (dd, *J* = 11.5 and 4.3 Hz, 1 H, H-6b), 4.53 (br d, *J* = 7.2 Hz, 1H, H-4, when CH(OCH₃)₂ was irradiated, the measured coupling constant was 7.7 Hz), 5.08 (d, *J* = 1.3 Hz, CH(OCH₃)₂).

![1,1-Dimethylethyl [(S-(R*,S*)]-4-(4-Ethoxy-1-hydroxy-4-oxo-2-butynyl)-2,2-dimethyl-3-oxazolidinecarboxylate (63).](image)

To a stirred -78 °C solution of ethyl propiolate 58 (3.1 mL, 3.00 g, 30.6 mmol) in dry THF (170 mL) was added slowly n-BuLi (2.3 M in hexane, 12.8 mL, 29.3 mmol) under an Ar atmosphere. The resulting solution was stirred at -78 °C for 1 h. Then, dry HMPA (6.8 mL, 7.00 g, 39.1 mmol) was added to the above solution and, after 10 min stirring at -78 °C, a cold -78
°C solution of 5b (4.74 g, 20.7 mmol) in dry THF (17 mL) was added via cannula using a positive Ar pressure. The resulting solution was stirred at -78 °C for 1 h at which time the TLC in (2:1) hexanes-EtOAc showed the clean formation of products 63 (erythro), $R_f$ 0.55 and 64 (threo) $R_f$ 0.50 (char B), at the expense of starting aldehyde, $R_f$ 0.65. The reaction mixture was poured into an ice cold 1 M NaH$_2$PO$_4$ solution (500 mL, pH 6) and extracted with Et$_2$O (3 x 300 mL). The combined organic layers were washed with brine (500 mL), dried over MgSO$_4$, filtered, and concentrated in vacuo to give an amber oil (7.03 g. $^1$H NMR of crude product indicated (13:1) mixture of erythro and threo products). Flash chromatography on silica gel, eluting with (3:1) hexanes-EtOAc gave pure 63 (4.96 g, 75% yield after purification), as a colorless oil. $[\alpha]_D^\circ$ +46.8° (c 2.53, CHCl$_3$); IR (neat) 3420, 2230, 1710, 1670 cm$^{-1}$; $^1$H NMR (200 MHz, C$_6$D$_6$, 60 °C): δ 0.88 (t, $J$ = 7.0 Hz, 3 H, CH$_2$CH$_3$), 1.36 (s, 9 H, C(CH$_3$)$_3$), 1.40, 1.67 (2 s, 2 x 3 H, C(CH$_3$)$_2$), 3.56 (br t, $J$ = 7.0 Hz, 2 H, H-5a and H-5b), 3.88 (q + br s, $J$ = 6.8 Hz, 3 H, CH$_2$CH$_3$ and H-4), 4.43 (br s, 1 H, H-1'), 5.44 (br s, 1 H, OH); $^{13}$C NMR(C$_6$D$_6$, 60 °C): δ 13.8 (q, -, CH$_2$CH$_3$), 26.2 (q, -, C(CH$_3$)$_2$), 28.3 (q, -, C(CH$_3$)$_3$), 61.7 (t, +, CH$_2$CH$_3$), 62.6 (d, -, C-4), 64.1 (d, -, C-1'), 65.1 (t, -, C-5), 78.0 (s, +, C(CH$_3$)$_3$), 81.2 (s, +, C-3'), 86.2 (s, +, C-2'), 95.2 (s, +, C-2), 153.2 (s, +, NCO$_2$), 164.4 (s, +, CO$_2$Et); MS (% relative intensity, m/e): 254.1031 (4.4, M - CO$_2$Et, 254.1392 calcld for C$_{13}$H$_{20}$NO$_4$), 212 (12.0), 144 (20.2), 128 (34.2), 100 (100). For the threo product 64: $^1$H NMR (200 MHz, C$_6$D$_6$, 60 °C): δ 0.88 (t, $J$ = 7.1 Hz, 3 H, CH$_2$CH$_3$), 1.32 (s, 9 H, C(CH$_3$)$_3$), 1.33 (br s, 1 H, OH), 1.42, 1.66 (2 s, 2 x 3 H, C(CH$_3$)$_2$), 3.62 (dd, $J$ = 9.8 and 6.4 Hz, 1 H, H-5a), 3.88 (q, $J$ = 7.1 Hz, 2 H,
CH$_2$CH$_3$), 3.95 (dd + br s, J = 7.8 and 1.8 Hz, H-5b and H-4), 4.72 (dd, J = 6.9 and 4.3 Hz, H-1').

1,1-Dimethylethyl [S-[(R$^*$,S$^*$),4R]-1-[α-Methoxy-α-(trifluoromethyl)-α-benzeneacetyl]-4-[4,4-dimethoxy-2-butylnyl]-2,2-dimethyl-3-oxazolidinecarboxylate (65) and 1,1-Dimethylethyl [S-[(R$^*$,R$^*$),4R]-1-[α-Methoxy-α-(trifluoromethyl)-α-benzeneacetyl]-4-[4,4-dimethoxy-2-butylnyl]-2,2-dimethyl-3-oxazolidinecarboxylate (66). To a solution of propargylic alcohol 63 (32.8 mg, 0.10 mmol) in distilled CH$_2$Cl$_2$ under an Ar atmosphere was added the stock solution of DCC (0.35 M in CH$_2$Cl$_2$, 0.35 mL, 0.123 mmol) and a stock solution of DMAP (0.097 M in CH$_2$Cl$_2$, 0.1 mL, 0.001 mmol). To this yellow solution was added a stock solution of (R)-MTPA (0.171 M in CH$_2$Cl$_2$, 0.8 mL, 0.137 mmol) and the resulting suspension was stirred at room temperature for 12 h at which time the TLC in (2:1) hexanes-EtOAc showed the formation of product, $R_f$ 0.67, at the expense of starting alcohol $R_f$ 0.46. The suspension was filtered through a cotton plug and the clear filtrate was concentrated in vacuo to give the crude product (63.5 mg). Flash chromatography on silica gel, eluting with (6:1) hexanes-EtOAc gave the pure product (R,S)-65 (39.6 mg, 81% yield). $[α]_D$ +17.7° (c 2.46, CHCl$_3$); IR (neat): 2240, 1760, 1710, 1700, 1690 cm$^{-1}$; $^1$H NMR (200 MHz, C$_6$D$_6$, 60 °C): δ 0.84 (t, J = 7.2 Hz, CH$_2$CH$_3$), 1.39 (s, 12 H, 0.5 × C(CH$_3$)$_2$ and C(CH$_3$)$_3$), 1.59 (s, 3 H, 0.5 × C(CH$_3$)$_2$), 3.42 (s, 3 H, OCH$_3$), 3.63 (dd, J = 9.5 Hz
and 7.1 Hz, H-5a), 3.84 (q, J = 7.1 Hz, 2 H, CH₂CH₃), 3.92 (dd + br s, J = 9.4 and 2.7 Hz, H-5b and H-4 respectively), 6.38 (br s, 1 H, H-1'), 7.10 (m, 3 H, Ph), 7.68 (d, J = 6.9 Hz, 2 H, Ph); ¹⁹F NMR (C₆D₆, 60 °C): δ 5.08. An essentially identical procedure was performed with (S)-MTFA to give (R,S)-66 (47.3 mg, 87% yield). [α]D +60.7° (c 2.68, CHCl₃); IR (neat): 2240, 1760, 1710, 1690 cm⁻¹; ¹H NMR (200 MHz, C₆D₆, 60 °C): δ 0.84 (t, J = 7.2 Hz, CH₂CH₃), 1.29, 1.35 (2 s, 2 x 3H, C(CH₃)₂), 1.39 (s, 9 H, C(CH₃)₃), 3.53 (s, 3 H, OCH₃), 3.60 (dd, J = 9.4 Hz and 6.7 Hz, H-5a), 3.84 (q, J = 7.1 Hz, 2 H, CH₂CH₃), 3.91 (dd, J = 9.4 and 2.7 Hz, H-5b), 3.98 (br s, 1 H, H-4), 6.30 (br s, 1 H, H-1'), 7.09 (m, 3 H, Ph), 7.67 (d, J = 6.9 Hz, 2 H, Ph); ¹⁹F NMR (C₆D₆, 60 °C) δ 5.60.

![1,1-Dimethylethyl](image)

To a solution of propargyl alcohol 59 (8.38 g, 25.47 mmol) in dry benzene (180 mL) was added synthetic quinoline (1.05 mL, 1.5 g, 8.89 mmol) and reduced 5% Pd/BaSO₄ (2.68 g, 134 mg of Pd, 1.26 mmol). The black suspension was stirred under an H₂ atmosphere for a period of 2 h at room temperature at which time the TLC in (1:1) hexanes-EtOAc showed the formation of product, Rf 0.59, at the expense of the starting material, Rf 0.67 (char B). The catalyst was filtered off through Celite washing with benzene and the yellow filtrate (350 mL) was concentrated in vacuo to give a dark brown oil (9.1 g) containing a residual amount of quinoline. Flash chromatography on silica gel, eluting with (4:1) hexanes-EtOAc gave the pure product 67 (8.29
g, 98%), as a colorless oil. $[\alpha]_D^{+34.2^\circ} \text{ (c 0.86, CHCl}_3)$; IR (CHCl$_3$): 3350, 1690 cm$^{-1}$; $^1$H NMR (200 MHz, C$_6$D$_6$, 60 °C): $\delta$ 0.89 (br s, 1 H, OH, exchanged with D$_2$O), 1.39 (s, 9 H, C(CH$_3$)$_3$), 1.46, 1.65 (2 s, 2 x 3 H, C(CH$_3$)$_2$), 3.18, 3.20 (2 s, 2 x 3 H, OCH$_3$), 3.67 (dd, $J = 9.1$ and 6.7 Hz, 1 H, H-5a), 3.96 (d, $J = 9.3$ Hz, 1 H, H-5b), 4.01 (br s, 1 H, H-4), 4.79 (br s, 1 H, H-1'), 5.29 (d, $J = 4.1$ Hz, 1 H, H-4'), 5.69 (m, 2 H, H-2' and H-3'); HRMS (% relative intensity, m/e): 300.1869 (0.3, M - OCH$_3$, 300.1811 calcld for C$_{15}$H$_{26}$NO$_5$), 212 (32.7), 201 (15.5), 200 (63.1), 144 (44.0), 101 (12.8), 100 (100.0).

1,1-Dimethylethyl [2S-[2\alpha(R*)],5\alpha]4-(2,5-Dihydro-5-methoxy-2-furanyl)-2,2-dimethyl-3-oxazolidinecarboxylate (68) and 1,1-Dimethylethyl [2S-[2\alpha(R*)],5\beta]4-(2,5-Dihydro-5-methoxy-2-furanyl)-2,2-dimethyl-3-oxazolidinecarboxylate (69). To a solution of 2° allylic alcohol dimethyl acetal 67 (4.2 g, 12.7 mmol) in methanol (180 mL) was added solid PPTS (326 mg, 1.30 mmol). The clear solution was stirred at room temperature for 2.5 h, at which time the TLC in (2:1) hexanes-EtOAc showed the formation of product $R_f0.64$, at the expense of the starting material, $R_f0.38$ (char B). The reaction was poured into a half-saturated NaHCO$_3$ solution (500 mL) and extracted with CH$_2$Cl$_2$ (500 mL) and washed with brine (500 mL). Each aqueous layer was re-extracted with CH$_2$Cl$_2$ (2 x 500 mL) and all organic layers were combined, dried over MgSO$_4$, filtered and concentrated in vacuo to obtain an amber oil (4.2 g). The $^1$H NMR spectrum of crude product showed a (1:1) mixture of $\alpha$- and $\beta$-
anomers (vide infra). Flash chromatography on silica gel, eluting with (4:1) hexanes-EtOAc gave a (1:1) mixture of 68/69 (3.70 g, 97%), as a colorless oil. [\( \alpha \)]\(_D\) -12.2° (c 0.96, CHCl\(_3\)); IR (neat): 3080, 1700, 1685, 1620 cm\(^{-1}\); \(^1\)H NMR (200 MHz, C\(_6\)D\(_6\), 60 °C): \( \delta \) 1.39, 1.41 (2 s, 9 H, C(CH\(_3\))\(_3\)), 1.53 (s, 3 H, 0.5 x C(CH\(_3\))\(_2\)), 1.68, 1.73 (2 s, 3 H, 0.5 x C(CH\(_3\))\(_2\)), 3.20, 3.30 (2 s, 3 H, OCH\(_3\)), 3.65 (dd, \( J = 8.9 \) and 6.0 Hz, 1 H, H-5a), 3.80 (br s, 1 H, H-4), 4.02 (d, \( J = 8.8 \) Hz, 0.5 H, H-5b), 4.21 (d, \( J = 8.9 \) Hz, 0.5 H, H-5b), 5.07 (br s, 1 H, H-2'), 5.54 (m, 1 H, H-4'), 5.58 (s, 0.5 H, H-5'), 5.71 (d, \( J = 4.4 \) Hz, 0.5 H, H-3'), 5.92 (d, \( J = 6.4 \) Hz, 0.5 H, H-5'), 6.04 (d, \( J = 5.9 \) Hz, 0.5 H, H-3'); \(^{13}\)C NMR (C\(_6\)D\(_6\), 60 °C): \( \delta \) 24.8 (q, - C(CH\(_3\))\(_2\)), 28.4 (q, - C(CH\(_3\))\(_3\)), 53.4, 54.7 (q, - OCH\(_3\), \( \alpha \) and \( \beta \)), 61.1, 61.3 (d, - C-4, \( \alpha \) and \( \beta \)), 65.0 (t, +, C-5), 79.7 (s, +, \( \in\) (CH\(_3\))\(_3\)), 85.8 (d, - C-2'), 94.3 (s, +, C-2), 109.5, 109.8 (d, - C-5', \( \alpha \) and \( \beta \)), 126.9, 127.2 (d, - C-3' or C-4', \( \alpha \) and \( \beta \)), 133.7, 134.5 (d, - C-4' or C-3', \( \alpha \) and \( \beta \)). 155.5 (s, +, NCO\(_2\)).

![1,1-Dimethyl ethyl][S-(R*,S*)]-4-(2,5-Dihydro-5-oxo-2-furanyl)-2,2-dimethyl-3-oxazolidine carboxylate (72). A solution of 63 (1.06 g, 3.23 mmol) in EtOH (8 mL) was cooled to 0 °C and to this cold solution was added dropwise a 5% KOH solution (11 mL, 9.79 mmol). The resulting brown solution was stirred at 0 °C for 10 min and then at room temperature for 50 min whenupon the TLC in (2:1) hexanes-EtOAc showed the disappearance of starting ester, \( R_f \) 0.65 (char B) and the formation of a new product 70 at the origin. The ethyl alcohol was removed on a rotary evaporator and then quinoline (0.1 mL, 0.846 mmol), water (30 mL) + reduced 5%
Pd/BaSO₄ (160 mg, 0.075 mmol) were added to the basic (pH 12) aqueous solution. The black suspension was stirred under H₂ atmospheric pressure for 5 h when a sample was withdrawn and treated with (1:1) H₂O-AcOH to induce lactonization prior to the TLC analysis. The TLC in (1:1) MeOH-EtOAc + 1 drop of HOAc showed the clean formation of unsaturated lactone, Rₚ 0.92, at the expense of starting alkyne, Rₚ 0.70 (char B). The catalyst was filtered off through a Celite pad eluting with water (50 mL) and Et₂O (50 mL). The resulting 2-phase mixture was extracted with Et₂O (2 x 50 ml) to remove the neutral byproducts, and then acidified to pH 1-2 with a cold 1N HCl, and extracted with CH₂Cl₂ (5 x 100 mL). The extracts were washed with brine (100 mL), dried with MgSO₄, filtered and concentrated in vacuo to give an amber oil (713 mg). The ¹H NMR spectrum of this material showed a (4:1) ratio of butenolide and its corresponding free acid. When the amber oil was kept under vacuum (0.5 torr) over 12 h at room temperature, it spontaneously cyclized to the desired butenolide which was then chromatographed on silica gel, eluting with (1:1) hexanes-EtOAc to afford pure 72 (633 mg, 69 % yield), as a colorless oil. [α]D - 41.3° (c 1.19, CHCl₃): IR (neat): 3100, 1760, 1695, 1600 cm⁻¹; ¹H NMR (200 MHz, C₆D₆, 60 °C): δ 1.32 (s, 9 H, C(CH₃)₃), 1.37, 1.53 (2 s, 2 x 3 H, C(CH₃)₂), 3.41 (dd, J = 9.34 and 5.56 Hz, 1 H, H-5a), 3.52 (br s, 1 H, H-4), 3.70 (d, J = 9.3 Hz, 1 H, H-5b), 4.80 (br s, 1 H, H-1') 5.59 (dd, J = 5.76 and 1.92 Hz, 1 H, H-3'), 6.80 (dd, J = 5.77 and 1.47 Hz, 1 H, H-2'); ¹³C NMR (C₆D₆, 60 °C): δ 27.4 (q, - , C(CH₃)₂), 28.3 (q, - , C(CH₃)₃), 59.8 (d, -, C-4), 64.8 (t, +, C-5), 80.6 (s, +, C(CH₃)₃), 82.4 (d, - , C-1'), 94.6 (s, +, C-2), 121.3 (d, -, C-3'), 154.6 (d, -, C-2'), 156.7(s, +, NCO₂), 171.4 (s, +, CO₂); HRMS (% relative intensity,
m/e: 227.0805 (0.6, M - H₂C=C(CH₃)₂, 227.0794 calcd for C₁₀H₁₃NO₅), 210 (11.9), 200 (12.4), 168 (22.0), 144 (20.0), 100 (100.0).

1,1-Dimethylethyl [2R-[2α(R*),3α,4α,5β]-4-[3,4-Dihydroxytetrahydro-5-methoxy-2-furanyl]-2,2-dimethyl-3-oxazolidine-carboxylate (73) and 1,1-Dimethylethyl [2R-[2α(R*),3β,4β,5α]-4-[3,4-bis(hydroxy)tetrahydro-5-methoxy-2-furanyl]-2,2-dimethyl-3-oxazolidine-carboxylate (74). To a solution of 2,5-dihydrofurans 68/69 (3.65 g, 12.2 mmol) in acetone (80 mL) was added a stock solution of OsO₄ and NMO in water (90 mL, 0.008 M in OsO₄, 1.20 M in NMO). The yellow solution was stirred at room temperature for 12 h whenupon TLC in (1:1) hexane-EtOAc showed the formation of two products, Rf 0.40 and Rf 0.16, at the expense of the starting material, Rf 0.67 (char A). The reaction mixture was poured into saturated Na₂SO₃ solution (500 mL) and extracted with EtOAc (500 mL). The organic layer was washed with pH 4 buffer solution (500 mL) and brine (500 mL). Each aqueous layer was re-extracted with EtOAc (2 x 500 mL) and all organic layers were combined, dried over MgSO₄, filtered and concentrated in vacuo to give a slightly yellow solid (3.91 g). Flash chromatography on silica gel, eluting with (1:1) hexanes-EtOAc gave α-methyl mannofuranoside 73 (Rf 0.40, 1.8 g, 44%) as a colorless oil and β-methyl allofuranoside 74 (Rf 0.16, 1.3 g, 32%).
as a white solid (mp 120-121 °C). For β-methyl mannofuranose 73, [α]D +97.8° (c 1.13, CHCl₃); IR (neat): 3400, 1670 cm⁻¹; ¹H NMR (200 MHz, C₆D₆, 60 °C): δ 1.25 (s, 9 H, C(CH₃)₃), 1.28, 1.39 (2 s, 2 x 3 H, C(CH₃)₂), 3.23 (s, 3 H, OCH₃), 3.40 (d, J = 9.5 Hz, 1 H, OH), 3.63 (dd, J = 9.1 and 5.4 Hz, 1 H), 3.95 (br s, 2 H), 4.17 (dd, J = 9.9 and 5.5 Hz, 1 H), 4.24 (d, J = 9.2 Hz, 1 H), 4.34 (m, 1 H), 5.03 (d, J = 3.42 Hz, 1 H, H-5'), 6.03 (br s, 1 H, OH); ¹³C NMR (C₆D₆, 60 °C): δ 27.7 (q, - , C(CH₃)₂), 28.2 (q, - , C(CH₃)₃), 55.6 (q, - , OCH₃), 60.0 (d, - , C-4), 65.3 (t, +, C-5), 70.9 (d, - , C-3'), 79.0 (d, - , C-4'), 80.7 (d, - , C-2'), 81.6 (s, +, C(CH₃)₃), 94.2 (s, +, C-2), 110.7 (d, - , C-5'), 154.4 (s, +, NCO₂); MS (% relative intensity, m/e ): 318.1565 (11.8, M - CH₃, 318.1552 calcld for C₁₄H₂₄NO₇). 218 (14.3), 204 (11.0), 200 (37.7), 186 (13.6), 116 (38.4), 101 (12.8), 100 (100). For ¹β-methyl allofuranoside 74, [α]D -55° (c 1.47, CHCl₃); IR (KBr): 3460, 1660 cm⁻¹; ¹H NMR (200 MHz C₆D₆, 60 °C): δ 1.36 (s, 9 H, C(CH₃)₃), 1.46, 1.62 (2 s, 2 x 3 H, C(CH₃)₂), 2.31 ( br s, 1 H, OH, exchanged with D₂O), 3.10 (s, 3 H, OCH₃), 3.67 (dd, J = 8.9 and 5.8 Hz, 1 H), 3.95 (t, J = 6.0 Hz, 1 H), 4.0 (br d, J = 4.4 Hz, 1 H), 4.18 (q + br s, J = 7.1 Hz, 2 H), 4.44 (br s, 1 H), 4.77 (s, 1 H, H-5'); ¹³C NMR (C₆D₆, 60 °C) δ 27.3 (q, - , C(CH₃)₂), 28.4 (q, - , C(CH₃)₃), 54.9 (q, - , OCH₃), 60.7 (d, - , C-4), 65.2 (t, +, C-5), 74.4 (d, - , C-3'), 76.5 (d, - , C-4'), 80.4 (s, +, C(CH₃)₃), 83.6 (d, - , C-2'), 94.4 (s, +, C-2), 108.5 (d, - , C-5'), 153.4 (s, +, NCO₂); Anal. Calcld for C₁₅H₂₇NO₇: C, 54.04; H, 8.16; N, 4.20. Found: C, 53.88; H, 8.17; N, 4.27.
oxazolidinecarboxylate (74) and 1,1-Dimethylethyl [2R-
[2α(R*)],3α,4α,5α]-4-[3,4-Dihydroxytetrahydro-5-methoxy-2-
 furyl]-2,2-dimethyl-3-oxazolidinecarboxylate (75). To a
solution of 2° allylic alcohol 67 (8.29 g, 25.1 mmol) in acetone (140 mL)
was added a stock solution of OsO4 and NMO (140 mL, 0.003 M in OsO4, 1.20 M
in NMO). The brown solution was stirred for 24 h at room temperature.
The TLC in EtOAc showed the formation of product, Rf 0.38, at the expense
of the starting material, R f 0.78 (char A). The reaction was poured into
saturated Na2SO3 solution (1 L) and stirred for 30 min at room
temperature. After removing the acetone by rotary evaporation, the
reaction mixture was extracted with EtOAc (1 L), then the organic layer
was washed with 0.5 N HCl (1 L) and brine (1 L). The aqueous layers were
each re-extracted with EtOAc (2 x 1 L) respectively and the combined
organic extracts were dried with MgSO4, filtered and concentrated in vacuo
to give an amber oil (5.87 g). Flash chromatography on silica gel,
eluting with (4:1) hexanes-EtOAc gave the (inseparable) triol mixture
(5.24 g, 57%) as a white solid. This material was submitted directly to the
following cyclization conditions: To a solution of triol (4.62 g, 12.7 mmol)
in benzene (1.4 L) was added PPTS (340 mg, 1.33 mmol). The clear solution
was refluxed for 1 h, at which time the TLC in EtOAc showed the
disappearance of the starting triols, Rf 0.50, and the formation of two
products, R f minor 0.79 and R f major 0.59 (char A). The reaction was
cooled to room temperature and poured into half-saturated NaHCO3
solution (1 L). The mixture was extracted with benzene and washed with
brine (1 L). Each aqueous layer was re-extracted with EtOAc (2 x 1 L) and
the combined organic layers were dried over MgSO₄, filtered and dried \textit{in vacuo} to give a yellow gum (3.39 g). Flash chromatography on silica gel, eluting with (5:1) hexanes-EtOAc gave the minor β-methyl allofuranoside 74 (0.70 g, 17% yield) as a white solid, mp 120-122 °C, which was identical to one of the products from the cyclic route, and the major α-methyl mannofuranoside 75 (2.14 g, 51% yield) as a white solid (mp 72-78 °C). For 75: [α]₀D -65° (c 1.21, CHCl₃); IR (KBr): 3450, 1675 cm⁻¹; \textsuperscript{1}H NMR (200 MHz, C₆D₆, 60 °C): δ 1.29 (s, 9 H, C(CH₃)₃), 1.35, 1.51 (2 s, 2 x 3 H, C(CH₃)₂), 3.21 (s, 3 H, OCH₃), 3.67 (dd, J = 9.0 and 5.7 Hz), 3.78 (br s, 1 H), 3.93 (br s, 2 H), 4.25 (t, J = 5.8 Hz, 1 H), 4.34 (dd, J = 9.0 and 1.2 Hz, 1 H), 4.60 (d, J = 4.98 Hz, 1 H, H-5'), 5.27 (br s, 2 H, 2 x OH); \textsuperscript{13}C NMR (C₆D₆, 60 °C): δ 27.7 (q, C(CH₃)₂), 28.0 (q, C(CH₃)₃), 55.8 (q, OCH₃), 57.0 (d, C-4), 65.0 (t, +, C-5), 69.9 (d, C-3'), 74.2 (d, C-4'), 80.8 (d, C-3'), 81.1 (s, C(CH₃)₃), 94.1 (s, +, C-2), 102.9 (d, C-5'), 151.6 (s, +, NCO₂); MS (% relative intensity, m/e): 334.1866 (1.3, M + 1, 334.1866 calcd for C₁₅H₂₈NO₇), 318 (28.0), 246 (15.3), 228 (14.9), 218 (32.6) 203 (14.6), 200 (96.5), 186 (61.0), 146 (10.0), 144 (100.0), 143 (11.0), 116 (39.1), 100 (19.2).

**General Procedure for Acetylation:** To a 0.21 M solution of dihydroxy furanose in (1:1) Ac₂O-pyridine was added 0.02 equiv of DMAP. The homogeneous solution was stirred at room temperature for 24 h, at which time the TLC in (1:1) hexanes-EtOAc indicated the disappearance of starting material and the clean formation of product (char A). The reaction mixture was diluted with EtOAc (200 mL) and organic layer was washed with 1 N HCl (100 mL), saturated NaHCO₃ solution (100 mL) and
brine (100 ml). The aqueous layers were each re-extracted with EtOAc (2 x 200 mL) respectively and all organic layers were combined, dried over MgSO₄, filtered and concentrated in vacuo to give an amber oil. Each product was chromatographed on silica gel, eluting with (1:1) hexanes-EtOAc to obtain the pure diacetate (90-93% yield).

1,1-Dimethylethyl [2R-(2α(R*),3α,4α,5β)]-4-[3,4-Bis(acetyloxy)tetrahydro-5-methoxy-2-furanyl]-2,2-dimethyl-3-oxazolidine-carboxylate (76). The starting diol 73 (44.1 mg, 0.132 mmol, Rf 0.39) gave diacetate 76 (51.1 mg, 93% yield, Rf 0.53) as a white solid, mp 114-115 °C. [α]D +80.4° (c 0.99, CHCl₃); IR (CHCl₃): 1750, 1700 cm⁻¹; ¹H NMR (200 MHz, CDCl₃, 55 °C): δ 1.44 (s, 9 H, C(CH₃)₃), 1.48, 1.56 (2 s, 2 x 3 H, C(CH₃)₂), 2.01, 2.06 ( 2 s, 2 x 3 H, OCOCH₃), 3.36(s, 3 H, OCH₃), 3.92 (dd, J = 8.8 and 6.2 Hz, 1 H, H-5a), 4.23 (d + br s, J = 10.0 Hz, 2 H, H-5b and H-4), 4.45 (t, J = 3.6 Hz, 1 H, H-2'), 4.99 (d, J = 2.9 Hz, 1 H, H-3'), 5.22 (dd, J = 5.1 and 2.9 Hz, 1 H, H-4'), 5.40 (t, J = 4.6 Hz, 1 H, H-3''); HRMS (% relative intensity, m/e): 417.1975 (0.1, M⁺), 417.1999 calcd for C₁₉H₃₁NO₉, 302 (63.2), 200 (28.9), 126 (25.9),100 (100.0).

1,1-Dimethylethyl [2R-(2α(R*),3β,4β,5α)]-4-[3,4-Bis(acetyloxy)tetrahydro-5-methoxy-2-furanyl]-2,2-dimethyl-3-oxazolidine-carboxylate (78). The starting diol 74 (487 mg, 1.46 mmol, Rf 0.23) gave diacetate 78 (553 mg, 91%
yield, \( R_f \) 0.74), as a colorless oil. [\( \alpha \)]\(_D\) 0°, [\( \alpha \)]\(_{578}\) -3.1° (c 1.00, CHCl\(_3\)); IR (CHCl\(_3\)): 1750, 1690 cm\(^{-1}\); \(^1\)H NMR (200 MHz, CDCl\(_3\), 55 °C): \( \delta \) 1.45 (s, 9 H, C(CH\(_3\))\(_3\)), 1.48, 1.55 (2 s, 2 x 3 H, C(CH\(_3\))\(_2\)), 1.97, 2.05 (2 s, 2 x 3 H, OCOCH\(_3\)), 3.35 (s, 3 H, OCH\(_3\)), 3.91 (dd, \( J = 8.6 \) and 5.6 Hz, 1 H, H-5a), 4.04 (d + br s, \( J = 8.7 \) Hz, 2 H, H-5b + H-4), 4.25 (t, \( J = 6.0 \) Hz, 1 H, H-2'), 4.83 (s, 1 H, H-5'), 5.25 (d, \( J = 4.8 \) Hz, 1 H, H-4'), 5.45 (t, \( J = 5.8 \) Hz, 1 H, H-3'); \(^1\)C NMR (C\(_6\)D\(_6\), 60 °C): \( \delta \) 19.6 (q, - , OCOCH\(_3\)), 26.9 (q, - , C(CH\(_3\))\(_2\)), 27.9 (q, - , C(CH\(_3\))\(_3\)), 54.7 (q, - , OCH\(_3\)), 59.4 (d, - , C-4), 64.7 (t, + , C-5), 72.9 (d, - , C-3'), 75.5 (d, - , C-4'), 79.9 (s, +, C(CH\(_3\))\(_3\)), 81.1 (d, - , C-2'), 94.1 (s, +, C-2), 106.4 (d, - , C-5'), 151.6 (s, +, NCO\(_2\)), 168.6 (s, +, OCOCH\(_3\)); HRMS (% relative intensity, m/e): 402.1675 (2.1, M - CH\(_3\), 402.1764 calcld for C\(_{18}\)H\(_{28}\)NO\(_9\)), 200 (16.1), 168 (14.0), 144 (26.1), 126 (26.9), 115 (34.0), 100 (100).

\[ \text{1,1-Dimethylethyl} \quad [2R-(2\alpha(R^*),3\alpha,4\alpha,5\alpha)-4-[3,4-Bis(acetyloxy)tetrahydro-5-methoxy-2-furanyl]-2,2-dimethyl-3-oxazolidine-carboxylate (77). The starting diol 75 (1.40 g, 4.21 mmol, \( R_f \) 0.15) gave diacetate 77 (1.62 g, 93% yield, \( R_f \) 0.61) as a colorless oil. [\( \alpha \)]\(_D\) -28.7° (c 0.90, CHCl\(_3\)); IR (CHCl\(_3\)): 1750, 1690 cm\(^{-1}\); \(^1\)H NMR (200 MHz, CDCl\(_3\), 55 °C): \( \delta \) 1.46 (s, 9 H, C(CH\(_3\))\(_3\)), 1.48, 1.58 (2 s, 2 x 3 H, C(CH\(_3\))\(_2\)), 2.05, 2.07 (2 s, 2 x 3 H, CO\(_2\)CH\(_3\)), 3.45 (s, 3 H, OCH\(_3\)), 3.93 (dd, \( J = 8.6 \) and 6.8 Hz, 1 H, H-5a), 3.99 (br s, 1 H, H-4), 4.37 (dd, \( J = 8.7 \) and 1.9 Hz, 1 H, H-5b), 4.64 (dd, \( J = 5.0 \) and 2.0 Hz, 1 H, H-2'), 5.01 (br s, 2 H, H-2' + H-5'), 5.52 (m, 1 H, H-3'); \(^1\)C NMR (C\(_6\)D\(_6\), 60 °C): \( \delta \) 19.6 (q, - , OCOCH\(_3\)), 26.5 (q, - , C(CH\(_3\))\(_2\)), 28.0 (q, - , C(CH\(_3\))\(_3\)), 55.3 (q, - , OCH\(_3\)), 57.2 (d, - ,
C-4), 64.1 (t, +, C-5), 69.8 (d, -, C-3'), 72.0 (d, -, C-4'), 79.0 (s, +, C(CH$_3$)$_3$), 79.4 (d, -, C-2'), 93.3 (s, +, C-2), 100.9 (d, -, C-5'). 151.8 (s, +, NCO$_2$), 168.7 (s, +, OCOCH$_3$); HRMS (% relative intensity, m/e): 419.2149 (0.7, M + 2, 419.2155 calc'd for C$_{19}$H$_{33}$NO$_9$), 362 (11.1), 330 (24.8), 318 (11.2), 303 (13.8), 302 (67.2), 270 (24.4), 200 (55.2), 168 (11.7), 158 (14.0), 143 (66.2), 140 (15.9), 127 (10.8), 126 (69.7), 108 (13.8), 101 (27.8), 100 (100.0).

1,1-Dimethylethyl  [2R-[2α(R*),3β,4β]]-2,2-
Dimethyl-4-(tetrahydro-3,4-dihydroxy-5-
oxo-2-furanyl)-3-oxazolidinecarboxylate

(79). To a solution of alkene 72 (4.21 g, 14.8 mmol)
in acetone (100 mL) + water (40 mL) was added trimethyl amine N-oxide (3.24 g, 29.2 mmol) and OsO$_4$ solution (8 x 10$^{-3}$ M in (3:1) $^1$BuOH-CCl$_4$, 36 mL, 0.29 mmol). The resulting homogeneous solution was stirred at room temperature for 22 h whenupon TLC in (2:1) EtOAc-hexanes showed the formation of diol, $R_f$ 0.27 (char A) along with residual starting alkene 72, $R_f$ 0.55. To this was added 10% NaHSO$_3$
 solution (40 mL) and the resulting solution was stirred for 30 min to decompose excess oxidant. After removing the acetone on the rotary evaporator, the aqueous mixture was extracted with EtOAc (6 x 150 mL), washed with brine (100 mL), dried over MgSO$_4$, filtered and concentrated in vacuo to give a slightly dark foam (2.96 g). Flash chromatography on silica gel, eluting with (2:1) hexanes-EtOAc first gave unreacted alkene 72 (250 mg) followed by pure diol 79 (2.15 g, 49% yield based on recovered starting material), as a white foam. [α]$_D$ +31.8° (c 0.87, CHCl$_3$); IR (CHCl$_3$):
3550, 1790, 1695, 1675 cm⁻¹; ¹H NMR (400 MHz, C₆D₆, 60 °C, 4.4 mg in 0.4 mL of C₆D₆): δ 1.30 (s, 9 H, C(CH₃)₃), 1.33, 1.45 (2 s, 2 x 3 H, C(CH₃)₂), 2.20, 2.28 (2 br s, 2 x 1 H, 2 x OH, exchanged with D₂O), 3.40 (dd, J = 9.4 and 5.3 Hz, 1 H, H-5a), 3.48 (dd, J = 9.1 and 5.4 Hz, 1 H, H-4), 3.67 (d, J = 9.5 Hz, 1 H, H-5b), 4.27 (d, J = 9.5 Hz, 1 H, H-2'), 4.35 (br s, 2 H, H-3' and H-4'); ¹³C NMR (C₆D₆, 60 °C): δ 27.8 (q, -, C(CH₃)₂), 28.4 (q, -, C(CH₃)₃), 57.7 (d, -, C-4), 65.6 (t, +, C-5), 69.4 (d, -, C-4' or C-3'), 69.8 (d, -, C-3' or C-4'), 81.3 (s, +, C(CH₃)₃), 84.9 (d, -, C-2'), 94.8 (s, +, C-2), 153.2 (s, +, NCO₂), 175.5 (s, +, CO₂); HRMS (% relative intensity, m/e): 302.1246 (8.7, M - CH₃, 302.1240 calcld for C₁₃H₂₀NO₇), 244 (11.9), 203 (12.7), 202 (100), 144 (12.5), 100 (55.7).

![1,1-Dimethylethyl](attachment:image.png)

1,1-Dimethylethyl [2R-[(2α(R*),3β,4β,5α)]]-
2,2-Dimethyl-4-[(3,4,5-tris-(acetoxy)tetrahydro-2-furanyl)-3-
oxazolidine-carboxylate (81). To a stirred -78 °C solution of dihydroxy lactone 79 (2.0 g, 6.3 mmol) in dry CH₂Cl₂ (14 mL, -78 °C) was added DIBAL (1.5 M in toluene, 14 mL, 21.0 mmol) over a 15 min period under an Ar atmosphere. After stirring for 1 h at -78 °C, the TLC in EtOAc showed the formation of lactol 80, *Rf* 0.40, at the expense of starting lactone, *Rf* 0.74 (char A). Cold MeOH (7.7 mL) was slowly added to this solution at -78 °C and this was poured into ice-cold 1 N HCl (300 mL). The resulting mixture was extracted with EtOAc (3 x 300 mL), washed with brine (200 mL), dried over MgSO₄, filtered and concentrated *in vacuo* to give a slightly yellow foam (1.40 g). Flash chromatography on silica gel, eluting with EtOAc gave the starting
lactone 79 (211.3 mg) followed by the lactol 80 (1.15 g, 64% yield based on recovered the starting material), as a white foam. This lactol (1.14 g, 3.60 mmol) was dissolved in pyridine (3.0 mL) and acetic anhydride (3.0 mL) and the slightly yellow solution was stirred for 5 h at room temperature when the TLC in (1:1) hexanes-EtOAc showed the complete formation of triacetate 81, Rf 0.62, at the expense of starting lactol 80, Rf 0.09 (char A). The solvent was removed in vacuo to give an amber oil (1.57 g). Flash chromatography on silica gel, eluting with (1:1) hexanes-EtOAc gave the triacetate 81 (1.53 g, 96% yield, 1H NMR of product showed (4:1) ratio of β- and α- anomers) as a colorless oil. [α]D -1.82° (c 0.88, CHCl3); IR (CHCl3): 1750, 1690 cm⁻¹; 1H NMR (200 MHz, CDCl3, 55 °C): δ 1.49 (s, 9 H, C(CH3)3), 1.50, 1.51 (2 s, 2 x 3 H, C(CH3)2), 2.02 (s, 0.75 x 3 H), 2.04 (s, 0.25 x 3 H), 2.08 (s, 0.75 x 3 H), 2.09 (s, 0.25 x 3 H), 2.10 (s, 3 H), 3.92 (dd, J = 9.2 and 5.2 Hz, 1 H, H-5a), 4.04 (d, J = 8.3 Hz, 1 H, H-5b), 4.05 (br s, 1 H, H-4), 4.28 (t, J = 7.5 Hz, 1 H, H-2'), 5.29 (dd, J = 6.6 and 4.5 Hz, 0.25 H, H-4'α), 5.42 (d, J = 4.8 Hz, 0.75 H, H-4'β), 5.62 (m, 1 H, H-3'), 6.14 (s, 0.75 H, H-5'β), 6.38 (d, J = 4.8 Hz, 0.25 H, H-5'α); 13C NMR (CD6, 60 °C): δ 19.8, 20.0, 20.4 (q, -3 x COCH3), 27.4, 27.6 (q, -C(CH3)2), 28.4 (q, -C(CH3)3) 58.9, 59.9 (d, - C-4 α and β), 65.5 (t, +, C-5), 70.5, 72.7 (d, - C-3' α and β), 70.5, 75.5 (d, - C-4'), 80.6 (s, +, C(CH3)3), 82.1, 84.2 (d, - C-2' α and β), 94.5 (s, +, C-2), 94.0, 98.8 (d, - C-5' α and β), 152.3 (s, +, NCO2), 168.9 (s, +, COCH3); HRMS (% relative intensity, m/e): 430.1712 (2.8, M - CH3, 430.1713 calcd for C19H28NO10), 200 (17.0), 168 (18.5), 144 (22.9), 143 (10.7), 100 (100).
General Procedure for Oxazolidine Methanolysis: To a 0.038 M solution of each oxazolidine (76, 77, or 78) in MeOH was added 0.16 equiv of TsOH-H₂O. The resulting homogeneous solution was stirred at room temperature for 12 h at which time the TLC showed the partial formation of product along with the starting material (char A). With substrates 77 & 78 it was noted that prolonged reaction times resulted in the cleavage of the BOC group as indicated by increasing amounts of ninhydrin active material at the TLC origin. The reaction mixture was poured into a saturated NaHCO₃ solution (80 mL) and the resulting mixture was extracted with EtOAc (3 x 250 mL). The combined organics were washed with brine (80 mL), dried over MgSO₄, filtered and concentrated in vacuo to give the crude product. Flash chromatography on silica gel, eluting with (1:1) hexanes-EtOAc, gave the pure product along with the recovered starting material.

![Chemical Structure](image)

**Methyl 5-Deoxy-5-[[1,1-dimethylethoxy]carbonyl]amino]-α-D-mannofuranoside, 2,3-Diacetate (82).** The starting material 76 (315 mg, 0.755 mmol, Rf 0.72) gave 82 (159 mg, 56% yield with 100% conversion of starting material) as a colorless oil, Rf 0.37 in (2:1) EtOAc-hexanes. [α]D +69.9° (c 1.64, CHCl₃); IR (neat): 3450, 1750, 1710 cm⁻¹; ¹H NMR (200 MHz, CDCl₃, RT): δ 1.38 (s, 9 H, C(CH₃)₃), 2.03, 2.09 (2 s, 2 x 3 H, OCOCH₃), 3.38 (s, 3 H, OCH₃), 3.71 (dd, J = 11.2 and 3.2 Hz, 1 H, H-6a), 3.93 (dd, J = 11.3 and 3.4 Hz, 1 H, H-6b), 4.04 (m, 1 H, H-5), 4.27 (dd, J = 8.6 and 3.9 Hz, 1 H, H-4), 4.99 (d, J = 3.5 Hz, 1 H, H-1), 5.18 (dd, J = 5.0
and 3.3 Hz, 1 H, H-3), 5.51 (t, J = 3.9 Hz, 1 H, H-2); HRMS (% relative intensity, m/e): 346.1513 (3.9, M - OCH₃, 346.1502 calc'd for C₁₅H₂₄NO₈), 290 (12.6), 217 (15.4), 188 (13.8), 186 (11.0), 159 (10.8), 158 (34.4), 141 (15.8), 129 (16.1), 127 (15.6), 126 (100.0), 116 (18.4), 115 (66.1), 112 (17.7), 104 (19.8), 103 (12.4), 102 (23.3), 100 (13.5).

Methyl 5-Deoxy-5-[(1,1-dimethylethoxy) carbonyl]amino]-β-D-mannofuranoside, 2,3-Diacetate (83). The starting material 77 (640.4 mg, 1.535 mmol, Rᶠ 0.50) gave the product 83 (331.6 mg, 73% yield with 78% conversion of starting material) as a white solid, mp 50-53 °C, Rᶠ 0.16 in (1:1) EtOAc-hexanes. [α]D -84° (c 1.17, CHCl₃); IR (CHCl₃): 3440, 1740, 1710 cm⁻¹; ¹H NMR (200 MHz, CDCl₃ + D₂O, RT): δ 1.38 (s, 9 H, C(CH₃)₃), 2.06, 2.12 (2 s, 2 x 3 H, OCOCH₃), 3.37 (s, 3 H, OCH₃), 3.69 (dd, J = 12.3 & 3.0 Hz, 1 H, H-6a), 3.90 (dd, J = 11.1 and 3.0 Hz, 1 H, H-6b), 4.03 (br s, 1 H, H-5), 4.19 (dd, J = 9.0 and 4.6 Hz, 1 H, H-4), 5.02 (br s, 2 H, H-1 and H-2), 5.60 (t, J = 4.5 Hz, 1 H, H-3); ¹³C NMR (C₆D₆, RT): δ 19.8, 20.7 (2 q, -, 2 x OCOCH₃), 28.1 (q, - C(CH₃)₃), 51.1 (d, - C-5), 55.5 (q, - OCH₃), 62.2 (t, +, C-6), 68.9 (d, -, C-3), 72.2 (d, -, C-2), 76.6 (d, -, C-4), 78.9 (s, +, C(CH₃)₃), 101.2 (d, -, C-1), 155.2 (s, +, NCO₂), 169.5 (s, +, OCOCH₃), 169.8 (s, +, OCOCH₃); Anal. Calc'd for C₁₆H₂₇NO₉: C, 50.92; H, 7.21; N, 3.71. Found: C, 50.97; H, 7.40; N, 3.80.
Methyl 5-Deoxy-5-[[((1,1-dimethylethoxy)-carbonyl]amino]-β-D-allofuranoside, 2,3-Diacetate (84). The starting material 78 (244 mg, 0.585 mmol, \( R_f 0.74 \)) gave 84 (84.6 mg, 50% yield after 77% conversion of starting material, as a white solid, \( R_f 0.21 \) in (1:1) EtOAc-hexanes. \([\alpha]_D -17.3^\circ \) (c 0.99, CHCl₃); IR (CHCl₃): 3450, 1750, 1710 cm⁻¹; \(^1\)H NMR (200 MHz, CDCl₃, RT): δ 1.43 (s, 9 H, C(CH₃)₃), 2.03, 2.09 (2 s, 2 x 3 H, OCOCH₃), 2.57 (br s, 1 H, OH), 3.39 (s, 3 H, OCH₃), 3.78 (m, 3 H, H-6a, H-6b and H-5), 4.25 (t, \( J = 6.5 \) Hz, 1 H, H-4), 4.88 (s, 1 H, H-1), 5.12 (d, \( J = 6.5 \) Hz, 1 H, NH), 5.23 (d, \( J = 5.2 \) Hz, 1 H, H-2), 5.43 (dd, \( J = 7.0 \) and 4.9 Hz, 1 H, H-3).

5-Deoxy-5-[[((1,1-dimethylethoxy)-carbonyl]amino]-β-D-allofuranoside, 1,2,3-Triacetate (85). A solution of 81 (1.56 g, 3.52 mmol) in 70% HOAc (100 mL) was heated to 45 °C and stirred for 4 h at this temperature. The TLC in (1:1) hexanes-EtOAc showed the partial formation of N-BOC amino alcohol 85, \( R_f 0.24 \) (char A) along with the starting material, \( R_f 0.60 \). Prolonged reaction times resulted in cleavage of the BOC group. Therefore, the reaction was cooled to room temperature at this point and carefully poured into cold saturated NaHCO₃ solution (200 mL). The resulting mixture was extracted with EtOAc (3 x 200 mL), washed with brine (100 mL), dried over MgSO₄, filtered, and concentrated in vacuo to give a white
foam (0.770 g). Flash chromatography on silica gel, eluting with (1:1) hexanes-EtOAc gave starting material 81 (0.791 g) followed by N-BOC amino alcohol 85 (0.504 g, 71% yield based on recovered starting material 81; ¹H NMR of product showed (7:1) ratio of β- to α- anomers) as a colorless oil. [α]D -9.5° (c 0.96, CHCl₃); IR (CHCl₃): 3400, 1750, 1700 cm⁻¹; ¹H NMR (200 MHz, CDCl₃, RT): δ 1.32 (s, 9 H, C(CH₃)₃), 1.93, 1.99, 2.00 (3 s, 3 x 3 H, 3 x OCOCH₃), 2.07 (br s, 1 H, OH, exchanged with D₂O), 3.65 (m, 3 H, H-5, H-6a and H-6b), 4.16 (t, J = 6.9 Hz, 1 H, H-4), 4.96 (br d, J = 7.3 Hz, 1 H, NH, slowly exchanged with D₂O), 5.10 (dd, J = 6.6 and 4.6 Hz, 0.12 H, H-2α), 5.23 (d, J = 4.8 Hz, 0.88 H, H-2β), 5.32 (dd, J = 6.6 and 5.3 Hz, 0.12 H, H-3α), 5.38 (dd, J = 6.7 and 5.3 Hz, 0.88 H, H-3β), 6.02 (s, 0.88 H, H-1β), 6.29 (d, J = 4.5 Hz, 0.12 H, H-1α); ¹³C NMR (C₆D₆, for β-anomer): δ 19.6, 19.8, 20.1 (q, -3 x OCOCH₃), 28.5 (q, - C(CH₃)₃), 54.4 (d, - C-5), 61.3 (t, +, C-6), 72.4 (d, -, C-3 or C-4), 74.8 (d, -, C-4 or C-3), 79.2 (s, +, C(CH₃)₃), 80.6 (d, -, C-2), 98.4 (d,-, C-1), 155.7 (s, +, NCO₂), 168.9 (s, +, OCOCH₃); HRMS (% relative intensity, m/e): 374.1421 (6.3, M - OCH₃, 374.1451 calcd for C₁₆H₂₄NO₉), 272 (21.1), 258 (12.2), 230 (13.7), 214 (25.9), 202 (16.7), 187 (15.2), 186 (16.6), 170 (18.8), 160 (27.9), 158 (17.7), 154 (13.9), 146 (26.8), 144 (13.8), 143 (56.0), 142 (12.6), 128 (15.6), 126 (100), 116 (21.9), 115 (59.1), 102 (96.6).

General Procedure for Alcohol Oxidation: To a 0.038 M solution of N-BOC amino alcohol (82, 83, or 84) in 60% aqueous acetone was added 10 equiv of solid NaIO₄ followed by 0.08 equiv of RuO₂·H₂O. The greenish suspension was stirred for 24 h at room temperature at which time the TLC in EtOAc showed the disappearance of starting alcohol and
the formation of acid at the origin (char A). Isopropanol (6 mL) was added to the reaction mixture and it was stirred for an additional 30 min to consume excess oxidant. The resulting suspension was filtered thru Celite to remove catalyst and NaIO₂ and the yellow filtrate was concentrated \textit{in vacuo} to give a brown foam. The brown foam was dissolved in Et₂O (10 mL) at 0 °C and treated directly with diazomethane solution (5 mL) at which point the TLC in (1:1) EtOAc-hexanes or in EtOAc showed the clean transformation of acid to an ester (char A). Excess diazomethane was quenched by dropwise addition of HOAc. The mixture was diluted with Et₂O (50 mL), then washed with saturated NaHCO₃ solution (20 mL) and brine (20 mL). The resulting saturated NaHCO₃ layer and brine layer were re-extracted with Et₂O (2 x 20 mL), respectively and organic layers were combined, dried over MgSO₄, filtered and concentrated \textit{in vacuo} to give a brown foam. Flash chromatography on silica gel, eluting with (1:1) hexanes-EtOAc gave the pure N-BOC amino ester (72-75% yield).

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\text{Methyl } [\text{methyl-5-deoxy-5-}\{(\text{1,1-dimethyl-ethoxy})\text{carbonyl}\} \text{ amino-} \alpha\text{-D-mannofuranosid}j\text{uronate}, 2,3-Diacetate (86).} \text{ The alcohol } 82 \text{ (150 mg, 0.399 mmol) gave acid 86 (121 mg, 75% yield) as a colorless oil, } R_f 0.48 \text{ in (1:1) EtOAc-hexanes. } [\alpha]_D^\text{+83.7°} \text{ (c 1.17, CHCl₃); IR (neat): 3350, 1750, 1715 cm}^{-1}; ^1\text{H NMR (200 MHz, CDCl₃, RT): } \delta \text{ 1.43 (s, 9 H, C(CH₃)₃), 2.04, 2.11 (2 s, 2 x 3 H, OCOCH₃), 3.34 (s, 3 H, OCH₃), 3.71 (s, 3 H, CO₂CH₃), 4.66 (t, } J = 6.2 \text{ Hz, 1 H, H-4), 4.81 (dd, } J = 9.8 \text{ and 6.3 Hz, 1 H, H-5), 4.96 (d, } J = 1.2 \text{ Hz, 1 H, H-1), 5.07 (br s, 1 H, NH), 5.12}
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(dd, J = 5.43 and 1.4 Hz, 1 H, H-2), 5.64 (t, J = 5.9 Hz, 1 H, H-3); HRMS (% relative intensity, m/e): 406.1722 (0.1, M + 1, 406.1713 calcd for C_{17}H_{28}NO_{10}, 217 (80.4), 126 (19.3), 116 (17.3), 115 (100.0).

**Methyl [methyl-5-deoxy-5-[(1,1-dimethyl-ethoxy)carbonyl] amino]-β-D-mannofuranosiduronate, 2,3-Diacetate (87).** The alcohol 83 (440 mg, 1.167 mmol) gave acid 87 (340 mg, 72% yield), as a white solid, mp 42-45 °C, Rf 0.39 in (1:1) EtOAc-hexanes. [α]_D^-42.5° (c 1.17, CHCl₃); IR (CHCl₃): 3450, 1750, 1710 cm⁻¹; ¹H NMR (400 MHz, CDCl₃, RT): δ 1.41 (s, 9 H, C(CH₃)₃), 2.07, 2.13 (2 s, 2 x 3 H, OCOCH₃), 3.42 (s, 3 H, OCH₃), 3.67 (s, 3 H, CO₂CH₃), 4.69 (dd, J = 8.3 and 4.2 Hz, 1 H, H-5), 4.84 (t, J = 5.0 Hz, 1 H, H-4), 4.98 (t, J = 5.2 Hz, 1 H, H-2), 5.04 (d, J = 4.58 Hz, 1 H, H-1), 5.32 (d, J = 8.7 Hz, 1 H, NH), 5.66 (t, J = 5.8 Hz, 1 H, H-3); ¹³C NMR (C₆D₆, RT) δ 19.8, 20.1 (2 q, -, OCOCH₃), 28.0 (q, -, C(CH₃)₃), 51.5 (q, -, OCH₃), 53.5 (q, -, CO₂CH₃), 55.4 (d, -, C-5), 68.7 (d, -, C-4), 71.3 (d, -, C-3), 77.7 (d, -, C-2), 79.2 (s, +), 101.3 (d, -, C-1), 155.0 (s, +, NCO₂), 168.9, 169.2 (2 s, +, OCOCH₃), 170.6 (s, +, CO₂CH₃); Anal. Calcd for C_{17}H_{27}NO_{10}: C, 50.35; H, 6.72; N, 3.46. Found: C, 50.43; H, 6.77; N, 3.52.

**Methyl [methyl-5-deoxy-5-[(1,1-dimethyl-ethoxy)carbonyl] amino]-β-D-allofuranosiduronate, 2,3-Diacetate (88).** The alcohol 84 (58 mg, 0.154 mmol) gave acid 88 (45.5 mg, 73% yield) as a colorless oil, Rf 0.39 in EtOAc. IR (CHCl₃): 3400, 1750, 1710 cm⁻¹; ¹H NMR (200 MHz, CDCl₃, RT): δ 1.42 (s, 9 H, C(CH₃)₃), 2.01,
2.08 (2 s, 2 x 3 H, OCOCH₃), 3.32 (s, 3 H, OCH₃), 3.74 (s, 3 H, CO₂CH₃), 4.40 (dd, J = 7.9 and 4.1 Hz, 1 H, H-4), 4.56 (dd, J = 8.3 and 4.2 Hz, 1 H, H-5), 4.81 (s, 1 H, H-1), 5.18 (d, J = 4.8 Hz, 1 H, H-2), 5.42 (d, J = 8.3 Hz, 1 H, NH), 5.53 (dd, J = 7.8 and 4.8 Hz, 1 H, H-3); HRMS (% relative intensity, m/e): 406.1708 (0.1, M + 1, 406.1713 calcd for C₁₇H₂₈NO₁₀). 217 (86.2), 157 (30.8), 126 (14.5), 116 (11.1), 115 (100.0).

![Methyl 5-Deoxy-5-[[1,1-dimethylethoxy]carbonyl]amino]-β-D-allofuranuronate, 1,2,3-Triacetate (89). The alcohol 85 (460 mg, 1.14 mmol) gave acid 89 (340 mg, 68% yield) as a colorless oil, Rf 0.57 in (1:1) hexanes-EtOAc (char A). The ¹H NMR spectrum of the product showed a (7:1) ratio of β- and α-anomers, as a white foam. [α]D +16.1° (c 0.84, CHCl₃); IR (CHCl₃): 3350, 1750, 1710 cm⁻¹; ¹H NMR (200 MHz, CDCl₃, RT): 8 1.42 (s, 9 H, C(CH₃)₃), 2.03, 2.08, 2.09 (3 s, 3 x 3 H, 3 x OCOCH₃), 3.74 (s, 3 H, CO₂CH₃), 4.41 (dd, J = 7.5 and 4.8 Hz, 1 H, H-4), 4.57 (dd, J = 8.7 and 4.8 Hz, 1 H, H-5), 5.30 (d, J = 5.0 Hz, 1 H, H-2), 5.37 (d, J = 7.5 Hz, 1 H, NH), 5.53 (t, J = 6.2 Hz, 1 H, H-3), 6.1 (s, 0.88 H, H-1), 6.38 (d, J = 4.5 Hz, 0.12 H, H-1α); ¹³C NMR (CD₆D₆, RT): 19.5, 20.1 (q, –, 3 x OCOCH₃), 27.9 (q, –, C(CH₃)₃), 51.6 (q, –, CO₂CH₃), 55.5 (d, –, C-5), 70.9 (d, –, C-3 or C-4), 74.2 (d, –, C-4 or C-3), 79.7 (s, +, C(CH₃)₃), 81.9 (d, –, C-2), 98.0 (d, –, C-1), 155.0 (s, +, NCO₂), 168.6, 168.8, 169.4 (s, +, 3 x OCOCH₃); HRMS (% relative intensity, m/e): 318.0852 (5.0, M - OAc - H₂C=C(CH₃)₂, 318.0825 calcd for C₁₂H₁₆NO₉). 246 (10.7), 245 (84.2), 203 (32.4), 197 (24.2), 155 (12.8), 144 (100), 133 (54.1), 126 (10.9).
General Procedure for N-BOC Group Removal and N-Acetylation. To a 0.12 M solution of N-BOC methyl ester in CH₂Cl₂ was added 10 equiv of TFA. The slightly yellow solution was stirred for 1 h at room temperature at which time the TLC in (1:1) hexanes-EtOAc showed the disappearance of starting alcohol and the formation of amine at the origin (char A). The solvent was evaporated in vacuo to give a yellow liquid. This crude amine salt was treated with (1:1) Ac₂O-pyridine (0.18 M in amine salt) and the homogeneous solution was stirred at room temperature for 2 h. The TLC in EtOAc showed the clean formation of product, at the expense of the starting amine (char A). All solvents were removed in vacuo to give an amber oil which was chromatographed on silica gel, eluting with (2:1) hexanes-EtOAc to give the pure N-acetyl amino ester (ca 93 % yield).

Methyl [Methyl 5-(acetylamino)-5-deoxy-α-D-manno-furanosiduronate, 2,3-Diacetate (94). The starting material 86 (55.5 mg, 0.137 mmol) gave 94 (40.0 mg, 84 % yield, Rf 0.60), as a colorless oil. ¹H NMR (200 MHz, CDCl₃, RT): δ 2.02, 2.05, 2.06 (3 s, 3 x 3 H, 2 x OCOCH₃, NCOCH₃ ), 3.34 (s, 3 H, OCH₃), 3.71 (s, 3 H, CO₂CH₃), 4.63 (t, J = 6.4 Hz, 1 H, H-4), 4.96 (d, J = 1.6 Hz, 1 H, H-1), 5.15 (m, 2 H, H-2 and H-5), 5.62 (t, J = 5.7 Hz, 1 H, H-3), 5.95 (d, J = 9.4 Hz, 1 H, NH); HRMS (% relative intensity, m/e): 348.1332 (3.4, M + 1, 348.1294 calcd for C₁₄H₂₂NO₉), 316 (10.9), 218 (12.7), 217 (100.0), 186 (15.6), 157 (35.9), 154 (17.9).
Methyl [Methyl 5-(acetylamino)-5-deoxy-β-D-mannofuranosid]uronate, 2,3-Diacetate (95).

The starting material 87 (291 mg, 0.721 mmol) gave the product 95 (242 mg, 97% yield, Rf 0.30), as a colorless oil. [α]D -55.0° (c 1.47, CHCl3); IR (CHCl3): 3450, 1750, 1685 cm⁻¹; ¹H NMR (400 MHz, CDCl₃, RT): δ 2.06, 2.09, 2.14 (3 s, 3 x 3 H, 2 x OCOCH₃ and NCOCH₃), 3.43 (s, 3 H, OCH₃), 3.70 (s, 3 H, CO₂CH₃), 4.74 (t, J = 6.4 Hz, 1 H, H-4), 4.98 (t, J = 5.4 Hz, 1 H, H-2), 5.04 (d, J = 4.8 Hz, 1 H, H-1), 5.14 (dd, J = 8.9 and 7.2 Hz, 1 H, H-5), 5.67 (t, J = 5.8 Hz, 1 H, H-3), 6.28 (d, J = 8.8 Hz, 1 H, NH); ¹³C NMR (CD₃D₆, RT): δ 19.6, 20.2, 22.4 (3 q, -2 x OCOCH₃ and NCOCH₃), 51.6 (q, - OCH₃), 52.1 (d, - C-5), 55.3 (q, - CO₂CH₃), 68.6 (d, - C-4), 71.4 (d, - C-3), 77.6 (d, - C-2), 101.4 (d, - C-1), 169.0 (s, + NCO₂), 169.3 (s, + 2 x OCOCH₃), 170.5 (s, + CO₂CH₃); HRMS (% relative intensity, m/e): 348.1292 (1.3, M + 1, calcd for C₁₄H₂₂NO₉ 348.1294), 217 (90.0), 186 (14.1), 157 (31.0), 154 (15.0), 131 (14.5), 126 (26.5), 115 (100.0).

Methyl [Methyl 5-(Acetylamino)-5-deoxy-β-D-allofuranosid]uronate, 2,3-Diacetate (96).

The starting material 88 (220 mg, 0.543 mmol) gave 96 (150 mg, 80% yield, Rf 0.49), as a colorless oil. ¹H NMR (200 MHz, CDCl₃, RT): δ 2.02, 2.04, 2.08 (3 s, 3 x 3 H, 2 x OCOCH₃, NCOCH₃), 3.32 (s, 3 H, OCH₃), 3.75 (s, 3 H, CO₂CH₃), 4.42 (dd, J = 8.0 and 3.6 Hz, 1 H, H-4), 4.81 (s, 1 H, H-1), 4.87 (dd, J = 8.0 and 4.8 Hz, 1 H, H-5), 5.18 (d, J = 4.8 Hz, 1 H, H-2), 5.56 (dd, J = 8.0 and 4.6 Hz, 1 H, H-3), 6.35 (d, J
= 7.8 Hz, 1 H, NH); HRMS (% relative intensity, m/e): 316.1039 (2.7, M -
OCH₃, 316.1032 calcd for C₁₃H₁₈NO₈), 217 (42.1), 157 (12.9), 115 (100.0).

**Methyl 5-(Acetylamino)-5-deoxy-β-D-allofuranuronate, 1,2,3-Triacetate (97).** The
starting material 89 (77 mg, 0.18 mmol) gave 97 (55
mg, 95% yield based on 87% conversion of 89) as a
colorless oil, R_f 0.56 in EtOAc. ^1^H NMR of this product
showed a (7:1) ratio of β- and α- anomers - see below), as a white foam.
[α]_D +33.8° (c 0.83, CHCl₃); IR (CHCl₃): 3350, 1750, 1675 cm⁻¹; ^1^H NMR (200
MHz, CDCl₃, RT): δ 1.93, 1.97, 2.00, 2.10 (4 s, 4 x 3 H, 3 x OCOCH₃, NCOCH₃), 3.66
(s, 3 H, CO₂CH₃), 4.33 (dd, J = 7.4 and 4.2 Hz, 1 H, H-4), 4.81 (dd, J = 8.4 and 4.3
Hz, 1 H, H-5), 5.20 (d, J = 4.9 Hz, 1 H, H-2), 5.46 (dd, J = 7.4 and 5.0 Hz, 1 H, H-
3), 5.98 (s, 0.88 H, H-1β), 6.24 (d, J = 4.5 Hz, 0.12 H, H-1α), 6.48 (d, J = 8.5 Hz, 1
H, NH); ^13^C NMR (CD₃D₅, RT): δ 19.6, 19.8, 20.1, 21.9 (q, -, 3 x OCOCH₃, NCOCH₃),
51.7 (q, -, CO₂CH₃), 53.7 (d, -, C-5), 70.7 (d, -, C-3 or C-4), 74.3 (d, -, C-4 or C-
3), 82.1 (d, -, C-2), 98.0 (d, -, C-1), 168.1, 168.7, 169.0, 169.2 (s, +, OCOCH₃,
NCOCH₃, CO₂CH₃).

**Methyl [Methyl 5-deoxy-5-[(phenyl-methoxy)carbonyl] amino]-α-D-
mannofuranosyluronate, 2,3-Diacetate (98).** To a 0 °C solution of the TFA amine salt 91
(301
mg) in dioxane (11 ml) was added 7% NaHCO₃ solution
(3 mL) followed by benzyl chloroformate (0.15 mL, 1.00 mmol). The
resulting suspension was stirred for 10 min at room temperature at which time the TLC in (1:1) hexanes-EtOAc showed the clean formation of N-Cbz amino ester 98, \( R_f 0.25 \), at the expense of starting amine at the origin (char A). The reaction mixture was diluted with tap water (100 mL) and extracted with \( \text{CH}_2\text{Cl}_2 \) (3 x 150 mL). The combined organic layers were washed with brine (100 mL), dried over \( \text{Na}_2\text{SO}_4 \), filtered and concentrated \textit{in vacuo} to give a colorless oil (359 mg). Flash chromatography on silica gel, eluting with (1:1) hexanes-EtOAc gave the pure N-Cbz aminoester 98 (228 mg, 83% yield over 2 steps), as a colorless oil. \( [\alpha]_D -43.2^\circ \) (c 0.87 CHCl₃); IR (CHCl₃): 3340, 1750, 1725 cm⁻¹; \(^1\)H NMR (200 MHz, CDCl₃, RT): \( \delta \) 2.05, 2.08 (2 s, 2 x H), 2 x OCOCH₃), 3.28 (s, 3 H, OCH₃), 3.69 (s, 3 H, CO₂CH₃), 4.76 (t, \( J = 6.5 \text{ Hz} \), 1 H, H-4), 4.87 - 4.98 (m, 2 H, H-2 & H-5), 5.02 (d, \( J = 4.6 \text{ Hz} \), 1 H, H-1), 5.07 (d, \( J = 12.1 \text{ Hz} \), 1 H, CH₂Ph), 5.16 (d, \( J = 12.0 \text{ Hz} \), 1 H, CH₂Ph), 5.61 (d, \( J = 7.3 \text{ Hz} \), 1 H, NH), 5.66 (t, \( J = 5.8 \text{ Hz} \), 1 H, H-3), 7.33 (s, 5 H, C₅H₅).

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\text{Methyl 5-Deoxy-5-[(phenylmethoxy)-carbonyl]amino-\beta-D-allofuranuronate, 1,2,3-Triacetate (99). Using the above procedure, the starting amine TFA salt 93 (540 mg) gave N-Cbz aminoester 99 (310 mg, 82%), } R_f 0.93 \text{ in EtOAc. The } \]

1H NMR spectrum of this product showed a (7:1) ratio of \( \beta \)- and \( \alpha \)-anomers-see below), as a white foam. \( [\alpha]_D +16.8^\circ \) (c 0.62, CHCl₃); IR (CHCl₃): 3420, 1750, 1720, 1715 cm⁻¹; \(^1\)H NMR (200 MHz, CDCl₃, RT): \( \delta \) 2.01 (s, 6 H, 2 x OCOCH₃), 2.10 (s, 3 H, OCOCH₃), 3.75 (s, 3 H, CO₂CH₃), 4.45 (dd, \( J = 7.6 \) and 4.4 Hz, 1 H, H-4), 4.67 (dd, \( J = 8.7 \) and 4.3 Hz, 1 H, H-5), 5.11 (s, 2 H,
CH₂Ph), 5.28 (d, J = 4.7 Hz, 1 H, H-2), 5.54 (m, 2 H, H-3 and NH), 6.08 (s, 0.88 H, H-1β), 6.36 (d, J = 4.3 Hz, 0.12 H, H-1α), 7.33 (s, 5 H, C₆H₅); ¹³C NMR (C₅D₆, RT): 25.2, 24.6, 24.7 (q, - , 3 x COOCH₃), 56.9 (q, - , CO₂CH₃), 61.1 (d, - , C-5), 71.4 (t, +, CH₂Ph), 76.0 (d, - , C-3), 79.0 (d, - , C-2), 86.2 (d, - , C-4), 103.1 (d, - , C-1), 133.0, 122.5 (d, - , Ph), 142.1 (d, - , Ph), 162.2 (s, +, COOCH₃, NCO₂), 174 (s, +, CO₂CH₃); HRMS (% relative intensity, m/e): 407.1223 (2.6, M - HOAc, calcld for C₁₉H₂₁NO₉ 407.1216), 245 (68.9), 203 (19.5), 197 (12.9), 162 (16.9), 155 (15.0), 143 (100), 127 (10.4).

2,4-Bis(trimethylsiloxy)-5-methylpyrimidine

(101). To a dried flask containing a solid thymine 100 (2.5 g, 0.020 mol) under an Ar atmosphere was added sequentially distilled dichloroethane (130 mL), distilled HMDS (30 mL, 0.143 mol), and distilled TMSCI (6 mL, 0.047 mmol). The stirred white suspension was refluxed at 120 °C (bath temperature) for 1 h at which time the suspension had become a homogeneous solution. All solvents were removed by short path distillation under an Ar atmosphere. The residual yellow oil was transferred to a smaller flask (25 mL) via cannula using a positive Ar pressure, and a dried short path distillation apparatus was quickly attached. Vacuum distillation of crude material gave a colorless oil (4.5 g, 84% yield, bp 78-80 °C/0.5 mm). During vacuum distillation, cold water was not circulated through the condenser since the product tended to solidify. ¹H NMR (200 MHz, CDCl₃, RT): δ 0.34, 0.36 (2 s, 2 x 9 H), 2.00 (s, 3 H, 5-CH₃), 8.01 (s, 1 H, H-6).
General Procedure for Modified Hudson Acetolysis. A cold 7 x 10^{-3} M solution of N-acetyl amino ester in (20:1:1) Ac₂O-AcOH-H₂SO₄ was stirred between -25 ° and -20 °C for 1.5 h after which a sample was withdrawn and quenched with MeOH to consume excess Ac₂O prior to TLC analysis. The TLC in EtOAc showed the disappearance of starting material and the formation of product (char A). Cold MeOH was slowly added to the reaction mixture over 0.5 h, then the resulting solution was carefully added in ten portions to an ice-cold saturated NaHCO₃ solution. The product was extracted with CH₂Cl₂ (3 x 500 mL) and the combined organic extracts were washed with brine (500 mL), dried over Na₂SO₄, filtered and concentrated in vacuo to give the crude anomeric acetates as yellow foams.

Methyl 5-[(Acetylamino)-5-deoxy-α-D-manno-furanuronate, 1,2,3-Triacetate (102). The methyl α-mannofuranoside 94 (40 mg, 0.1152 mmol, Rf 0.90) gave the tetraacetate 102 (41.9 mg, 97% crude yield, Rf 0.45), as a red solid which was recrystallized from (5:1) EtOAc-hexanes to give a white solid, mp 77-79 °C. [α]₁D +111.6° (c 1.26, CHCl₃); ^1H NMR (200 MHz, CDCl₃, RT): δ 2.00, 2.06, 2.07, 2.09 (4 s, 4 x 3 H, 3 x OCOCH₃ and NCOCH₃), 3.71 (s, 3 H, CO₂CH₃), 4.71 (t, J = 6.3 Hz, 1 H, H-4), 5.13 (dd, J = 9.4 and 7.0 Hz, 1 H, H-5), 5.31 (dd, J = 5.4 and 2.7 Hz, 1 H, H-2), 5.65 (t, J = 5.6 Hz, 1 H, H-3), 5.99 (d, J = 9.4 Hz, 1 H, NH), 6.22 (d, J = 2.0 Hz, 1 H, H-1). The identical tetraacetate 102 (79.3 mg, 91% crude yield, Rf 0.45) was
obtained from the methyl β-mannofuranoside 95 (80 mg, 0.231 mmol, \( R_f \) 0.30).

\[ \text{Methyl 5-[(phenylmethoxy)carbonyl]amino}- \]
\[ 5\text{-deoxy-\( \alpha \text{-D-mannofuranuronate, 1,2,3-} \]
\[ \text{Triacetate (103). To a cold (-25 °C) solution of N-Cbz} \]
\[ \text{amino ester 95 (91 mg, 0.207 mmol) in CH}_2\text{Cl}_2 \] (5 mL) was
\[ \text{added (20:1:1) Ac}_2\text{O}-\text{AcOH-H}_2\text{SO}_4 \] (0.5 mL). The clear
solution was stirred between -25° and -20 °C for 1 h whereupon a sample
was withdrawn and treated with MeOH to quench the excess Ac_2O. The
TLC in (1:1) hexanes-EtOAc showed the clean conversion of starting
material, \( R_f \) 0.33 to product, \( R_f \) 0.43 (char A). Cold MeOH (1 mL) was slowly
added to the reaction mixture over 0.5 h, then it was diluted with CH_2Cl_2
(50 mL) and the solution was carefully added to an ice-cold saturated
NaHCO_3 solution (50 mL) with swirling. The product was extracted into
CH_2Cl_2 (3 x 50 mL). The extracts was washed with brine (50 mL), dried
over Na_2SO_4, filtered and concentrated \textit{in vacuo} to give a red oil (41.7 mg,
43% crude yield). For N-Cbz triacetate 103: \(^1\text{H NMR (200 MHz, CDCl}_3\text{, RT):} \)
\( \delta \)
\[ 1.95, \ 2.01, \ 2.06 \text{ (3 s, 3 x 3 H, 3 x OCOCH}_3\text{),} \ 3.71 \text{ (s, 3 H, CO}_2\text{CH}_3\text{),} \]
\[ 4.83 - 4.95 \text{ (m, 2 H, H-4 & H-5),} \ 5.08 \text{ (d, } J = 12.2 \text{ Hz, CH}_2\text{Ph),} \]
\[ 5.20 \text{ (d, } J = 12.0 \text{ Hz, 1 H, CH}_2\text{Ph),} \]
\[ 5.23 \text{ (dd, } J = 5.53 \text{ & } 1.24 \text{ Hz, 1 H, H-2),} \ 5.34 \text{ (d, } J = 9.1 \text{ Hz, 1 H, NH),} \]
\[ 5.69 \text{ (t, } J = 6.0 \text{ Hz, 1 H, H-3),} \ 6.20 \text{ (s, 1 H, H-1),} \ 7.35 \text{ (s, 5 H, C}_6\text{H}_5\text{).} \]
This crude product
was submitted to the nucleoside reaction without further purification.
Methyl 5-(Acetylamino)-1,5-dideoxy-1-(3,4-dihydro-5-methyl-2,4-dioxo-1(2H)-pyrimidinyl)-β-D-mannofuranuronate, 2,3-Diacetate (104). To a solution of 102 (32 mg, 0.086 mmol) in dry dichloroethane (3.5 mL) was added sequentially bis-silylated thymine 101 (94 mg, 0.347 mmol) and TMSOTf (0.10 mL, 0.134 g, 0.637 mmol) under an Ar atmosphere. The yellow solution was refluxed at 95 °C for 30 min when the TLC in (9:1) CHCl3-MeOH showed the formation of a UV-active product, Rf 0.52, at the expense of starting material 102 at Rf 0.56. The reaction was cooled to room temperature and diluted with CH2Cl2 (30 mL) then washed with saturated NaHCO3 solution (20 mL) and brine (20 mL). The resulting two aqueous layers were each re-extracted with CH2Cl2 (2 x 30 mL) respectively and all organic layers were combined, dried over Na2SO4, filtered and concentrated in vacuo to give a slightly yellow foam (42 mg). Flash chromatography on silica gel, eluting with (15:1) CHCl3-MeOH gave pure 104 (30 mg, 79% yield), as a white foam. [α]D +70.1° (c 0.84, CHCl3); IR (CHCl3): 3380, 1750, 1680 cm⁻¹; ¹H NMR (400 MHz, CDCl3, RT): δ 1.90 (s, 3 H, 5-CH3), 1.99, 2.18 (2 s, 9 H , 2 x OCOCH₃, NCOCH₃), 3.76 (s, 3 H, CO₂CH₃), 4.92 (dd, J =9.1 and 3.4 Hz, 1 H, H-4'), 5.10 (t, J = 9.4 Hz, 1 H, H-5'), 5.73 (m, 2 H, H-1' and H-3'), 5.86 (dd, J = 6.6 and 4.9 Hz, 1 H, H-2'), 6.50 (d, J = 9.5 Hz, 1 H, NH), 6.98 (d, J = 1.2 Hz, 1 H, H-6), 8.7 (br s, 1H, N³H); ¹³C NMR (acetone-d₆, RT) δ 10.6 (q, -5-CH₃), 18.6, 18.9, 20.9 ( 3q, - , 2 x OCOCH₃ and NCOCH₃), 50.0 (d, - C-5'), 50.8 (q, - CO₂CH₃), 69.6 (d, - C-4'), 72.1 (d, - C-3'),
78.9 (d, -, C-2'), 88.4 (d, -, C-1'), 108.0(d, -, C-5), 136 (s, +, C-6), 151.4 (s, +, C-2), 164.4 (s, +, C-4), 168.3, 169.5 (s, +, OCOCH₃), 176.1 (s, +, CO₂CH₃); HRMS (FAB/glycerol matrix): m/e 442.1468, M, 442.1462 calcd for C₁₈H₂₃N₃O₁₀.

For comparison, a sample of the regioisomeric N³-nucleoside 105 was obtained from the corresponding SnCl₄-catalyzed reaction (see page 63): ¹H NMR (400 MHz, CDCl₃, RT): δ 1.86 (s, 3 H, 5-CH₃), 2.00, 2.01, 2.15 (3 s, 3 x 3 H, 2 x OCOCH₃, NCOCH₃), 3.72 (s, 3 H, CO₂CH₃), 5.12 (m, 2 H, H-4' and H-5'), 5.80 (dd, J = 5.3 and 2.9 Hz, 1 H, H-3'), 6.17 (t, J = 5.5 Hz, 1 H, H-2'), 6.65 (d, J = 6.7 Hz, 1 H, H-1'), 6.75 (br s, 1 H, NH), 6.96 (d, J = 5.3 Hz, 1 H, H-6), 8.92 (d, J = 4.8 Hz, 1 H, N¹H); HRMS (FAB/glycerol matrix): m/e 442.1460, M, 442.1462 calcd for C₁₈H₂₃N₃O₁₀.

Methyl 1,5-Dideoxy-1-(3,4-dihydro-5-methyl-2,4-dioxo-1(2H)-pyrimidinyl)-5-[(phenylmethoxy)carbonyl]amino]-α-D-mannofuranuronate, 2,3-Diacetate (106) and Methyl 1,5-Dideoxy-3-(3,4-dihydro-5-methyl)-2,4-dioxo-1(2H)-pyrimidinyl)-5-[(phenylmethoxy)carbonyl]amino]-α-D-mannofuranuronate, 2,3-Diacetate (107).

To a solution of 103 (40 mg, 0.086 mmol) in dry dichloroethane (2 mL)
was added sequentially bis-silylated thymine 101 (81 mg, 0.30 mmol) and SnCl4 (0.07 mL, 156 mg, 0.598 mmol) under an Ar atmosphere. The slightly yellow solution was stirred at room temperature for 30 min when the TLC in EtOAc showed the formation of 106, Rf 0.80, and 107, Rf 0.63, respectively at the expense of starting 103, Rf 0.88 (char A). The reaction mixture was diluted with CH2Cl2 (50 mL) and washed with saturated NaHCO3 solution (30 mL) and brine (30 mL). These resulting two aqueous layers were re-extracted with CH2Cl2 (2 x 50 mL) and all organic layers were combined, dried over Na2SO4, filtered and concentrated in vacuo to give a dark brown oil (38.6 mg. 1H NMR of crude product showed a 4:1 mixture of N1 and N3 nucleosides). Flash chromatography on silica gel, eluting with (2:1) hexanes-EtOAc gave pure 106 (20.2 mg, 44% yield) and 107 (4.8 mg, 11% yield). For 106: 1H NMR (200 MHz, CDCl3, RT): δ 1.89 (s, 3 H, 5-CH3), 2.01, 2.09 (2 s, 2 x 3 H, 2 x OCOCH3), 3.72 (s, 3 H, CO2CH3), 4.84 (t, J = 8.8 Hz, 1 H, H-5'), 4.97 (dd, J = 7.8 & 4.1 Hz, 1 H, H-4'), 5.08 (d, J = 12.2 Hz, 1 H, CH2Ph), 5.12 (d, J = 11.9 Hz, 1 H, CH2Ph), 5.53 (d, J = 9.6 Hz, NH), 5.66 -5.70 (m, 2 H, H-1' & H-2'), 5.74 (t, J = 4.4 Hz, 1 H, H-3'), 6.90 (s, 1 H, H-6), 7.33 (s, 5 H, C6H5), 8.77 (s, 1 H, N3H); HRMS (FAB/glycerol matrix): m/e 534.1723, M + 1, 534.1724 calcd for C24H28N3O11. For 107: 1H NMR (200 MHz, CDCl3, RT): δ 1.86 (s, 3 H, 5-CH3), 1.93, 2.09 (s, 2 x 3 H, 2 x OCOCH3), 3.69 (s, 3 H, CO2CH3), 4.87 (t, J = 9.1 Hz, 1 H, H-5'), 5.03 (m, 1 H, H-4'), 5.10 (apparent d, J = 6.0 Hz, 2 H, CH2Ph), 5.52 (d, J = 9.9 Hz, 1 H, NH), 5.80 (t, J = 5.3 Hz, 1 H, H-3'), 5.97 (t, J = 5.3 Hz, 1 H, H-2'), 6.54 (d, J = 4.6 Hz, 1 H, H-1'), 6.85 (s, 1 H, H-6), 7.34 (s, 5 H, C6H5), 8.28 (s, 1 H, N1H); HRMS (FAB/glycerol matrix): m/e 534.1731, M + 1, 534.1724 calcd for C24H28N3O11.
5-(Acetylamino)-1,5-dideoxy-1-(3,4-dihydro-5-methyl-2,4-dioxo-1(2H)-pyrimidinyl)-\(\alpha\)-D-mannofuranuronic Acid (108). To a flask containing 104 (22 mg, 0.050 mmol) was added cold 0.1 N NaOH solution (1.5 mL, 0.15 mmol) at 0 °C. The slightly yellow solution was stirred at 0 °C for 3 h, whereupon TLC in (2:1:1) n-BuOH-H\(_2\)O-\(\text{AcOH}\) showed the formation of product, \(R_f\) 0.48 (authentic \(N\)-acetyl thymine poloxin C (121): \(R_f\) 0.52), at the expense of the starting material, \(R_f\) 0.84 (char A). The basic mixture was extracted with EtOAc (6 x 10 mL) and the aqueous layer was then acidified to \(pH = 1\) with 0.1 N HCl. The water was removed \textit{in vacuo} to give crude 108 as a yellow solid (15.9 mg) that contained NaCl. The NMR sample (2.5 mg) was treated with D\(_2\)O (0.5 mL), then HDO and excess D\(_2\)O was removed \textit{in vacuo} prior to taking the \(^1\)H NMR spectrum. \(^1\)H NMR (400 MHz, DMSO-\(d_6\), 2.5 mg/0.5 mL, RT): \(8\) 1.76 (s, 3 H, 5-CH\(_3\)), 1.85 (s, 3 H, NCOCH\(_3\)), 4.04 (br s, 1 H), 4.32 (br s, 1 H), 4.35 (t, \(J = 6.8\) Hz, 1 H, H-2'), 4.53 (dd, \(J = 6.5\) and 3.1 Hz, 1 H, H-3'), 5.76 (d, \(J = 7.78\) Hz, 1 H, H-1'), 7.62 (s, 1 H, H-6).

5-Amino-1,5-dideoxy-1-(3,4-dihydro-5-methyl-2,4-dioxo-1(2H)-pyrimidinyl)-\(\alpha\)-D-mannofuranuronic Acid (109). To a flask containing 106 (9.0 mg, 0.017 mmol) was added 0.1 N NaOH solution (0.5 mL, 0.05 mmol) at 0 °C. The yellow solution was stirred at 0 °C for 2 h at which
time the TLC in EtOAc showed the disappearance of starting material, \( R_f \) 0.69, and the formation of polar product (acid) at the origin (char A). The basic mixture was extracted with EtOAc (2 x 3 mL) and aqueous layer containing product was acidified to pH = 1 with 0.1 N HCl. The product was extracted with EtOAc (3 x 3 mL) and the combined wet organic layer was filtered through a short Na\(_2\)SO\(_4\) column and the filtrate was concentrated \textit{in vacuo} to give a crude N-Cbz nucleoside (4.4 mg, 60% crude yield). To a solution of this crude N-Cbz nucleoside (4.4 mg, 0.010 mmol) in MeOH (0.5 mL) was added 5% Pd/C (4 mg). The black suspension was stirred under hydrogen atmosphere for 1.5 h at which time the TLC in (5:4:1) CHCl\(_3\)-MeOH-H\(_2\)O showed the formation of product 109, \( R_f \) 0.29, at the expense of starting material, \( R_f \) 0.57 (char A). The TLC in (2:1:1) \( ^n\)BuOH-MeOH-H\(_2\)O showed the product to have the same \( R_f \) value as authentic thymine polyoxin C (10), \( R_f \) 0.32 (char A). The catalyst was removed by filtration through a Celite and carbon pad, eluting with (1:1) MeOH-H\(_2\)O, and the filtrate (10 mL) was concentrated \textit{in vacuo} to give 109 as a yellow solid (2 mg). Chromatography on sephadex G25 SF, eluting with (1:1) MeOH-H\(_2\)O gave pure 109 (1.3 mg, 44% yield) as a white solid. \(^1\)H NMR (400 MHz, D\(_2\)O + DCl, pD 1-2, RT): \( \delta \) 1.81 (s, 3 H, 5-CH\(_3\)), 4.37 (d, \( J = 5.7 \) Hz, 1 H, H-5'), 4.44 (t, \( J = 3.6 \) Hz, 1 H, H-4'), 4.53 (dd, \( J = 7.2 \) and 4.4 Hz, 1 H, H-2'), 4.95 (dd, \( J = 5.4 \) and 3.6 Hz, 1 H, H-3''), 5.88 (d, \( J = 7.2 \) Hz, 1 H, H-1''), 7.48 (s, 1 H, 6-H). This \(^1\)H NMR spectrum did not match that of an authentic sample of thymine polyoxin C (10). HRMS (FAB/glycerol matrix): m/e 302.0984, M + 1, 302.0988 calcd for C\(_{11}\)H\(_{16}\)N\(_3\)O\(_7\).
Methyl 5-(Acetylamino)-1,5-dideoxy-1-(3,4-dihydro-5-methyl-2,4-dioxo-1(2H)-pyrimidinyl)-1(RS)-methoxy-D-allo-hexuronate, 2,3,4-Triacetate (112) and (113). Application of the modified Hudson acetylosis conditions to methyl furanoside 96 (35 mg, 0.101 mmol, \( R_f 0.43 \)) gave what turned out to be the acyclic pentaacetates 110/111 as a chromatographically homogeneous red oil (36.5 mg, 97% yield, \( R_f 0.50 \)) which was directly submitted to the nucleosidation without further characterization. To a solution of crude acetylosis products 110/111 (54.9 mg, 0.118 mmol) in dry dichloroethane (2.5 mL) was added sequentially bis-silylated thymine 101 (98.6 mg, 0.364 mmol) and SnCl\(_4\) (0.07 mL, 0.599 mmol) under an Ar atmosphere. The slightly yellow solution was refluxed at 95 °C for 1 h when the TLC in (13:1) CHCl\(_3\)-MeOH showed the formation of two product at \( R_f 0.32 \) and \( R_f 0.26 \) along with the starting material, \( R_f 0.36 \) (char A). The reaction was cooled to room temperature and diluted with CH\(_2\)Cl\(_2\) (70 mL) and washed with saturated NaHCO\(_3\) solution (30 mL) then brine (30 mL). The resulting aqueous layers were each re-extracted with CH\(_2\)Cl\(_2\) (2 x 70 mL) respectively and all organic layers were combined, dried over Na\(_2\)SO\(_4\), filtered and concentrated in vacuo to give a yellow oil (47.4 mg, 67% crude yield. \(^1\)H NMR of crude product showed a 1:1 mixture of diastereomers 112/113). Flash chromatography on silica gel, eluting with (30:1) CHCl\(_3\)-MeOH gave starting material (19.6 mg) and two new products, 112 (12.3 mg, \( R_f 0.32 \)) and 113 (11.5 mg, \( R_f 0.26 \)). For 112: \(^1\)H
NMR (200 MHz, CDCl₃, RT): δ 1.91 (s, 3 H, 5-CH₃), 1.96, 2.05, 2.07, 2.16 (4 s, 4 x 3 H, 3 x OCOCH₃ and NCOCH₃ ), 3.37 (s, 3 H, OCH₃), 3.79 (s, 3 H, CO₂CH₃). 5.15 (d, J = 8.6 Hz, 2 H, H-4' and H-5'), 5.49 (br s, 2 H, H-2' and H-3’). 5.87 (d, J = 8.7 Hz, 1 H, H-1’), 6.17(d, J = 8.7 Hz 1 H, NH), 7.02 (s, 1 H, H-6), 8.08 (br s, 1H, N₃H); HRMS (FAB/glycerol matrix): m/e 516.1822, M + 1, 516.1829 calcd for C₂₁H₃₀N₃O₁₂. For 113: ¹H NMR (200 MHz, CDCl₃, RT): δ 1.95 (s, 3 H, 5-CH₃), 2.01, 2.06, 2.08, 2.10 (4 s, 4 x 3 H, 3 x OCOCH₃ and NCOCH₃), 3.31 (s, 3 H, OCH₃), 3.74 (s, 3 H, CO₂CH₃), 5.00 (dd, J = 8.3 and 3.7 Hz, 1 H, H-5’), 5.30 (m, 3 H, H-2’, H-3’ and H-4’), 5.63 (d, J = 5.0 Hz, 1 H, H-1’), 6.24 (d, J = 8.2 Hz 1 H), 7.04 (br s, 1 H, H-6), 8.30 (br s, 1H, N₃H); HRMS (FAB/glycerol matrix): m/e 516.1834, M + 1, 516.1829 calcd for C₂₁H₃₀N₃O₁₂.

Methyl 5-(Acetylamino)-1,5-dideoxy-1-(3,4-dihydro-5-methyl-2,4-dioxo-1(2H)-pyrimidinyl)]-β-D-allofuranuronate, 2,3-Diacetate (114). To a solution of 97 (31 mg, 0.084 mmol) in dry dichloroethane (3.0 mL) was added sequentially bis-silylated thymine 101 (78 mg, 0.289 mmol) and TMSOTf (0.10 mL, 0.118 g, 0.531 mmol) under an Ar atmosphere. The yellow solution was refluxed at 95 °C for 30 min when the TLC in (13:1) CHCl₃-MeOH showed the formation of a product at Rf 0.29 (which matched an authentic sample of tetraacetate 121) and a UV-inactive product at Rf 0.45, at the expense of starting material at Rf 0.36 (char A). The reaction
was cooled to room temperature and diluted with CH₂Cl₂ (30 mL) then washed with saturated NaHCO₃ solution (20 mL) and brine (20 mL). The resulting two aqueous layers were re-extracted with CH₂Cl₂ (2 x 30 mL) respectively and all organic layers were combined, dried over Na₂SO₄, filtered and concentrated in vacuo to give a slightly yellow foam (33 mg). Flash chromatography on silica gel, eluting with (30:1) CHCl₃-MeOH resulted in the isolation of a compound identified as 115 (14.6 mg, 55% yield) followed by pure 114 (8.6 mg, 23% yield), both as white foams. The ¹H NMR spectrum of 114 matched that of authentic N-acetyl thymine polyoxin C 121 (vide infra). For 114: [α]D +35.6° (c 0.83, CHCl₃); IR (CHCl₃): 3380, 1740, 1685 cm⁻¹; For the bicyclic compound 115: [α]D -57.7° (c 1.16, CHCl₃); IR (CHCl₃): 1750, 1670 cm⁻¹; ¹H NMR (200 MHz, CDCl₃, RT): δ 2.10, 2.18 (2 s, 6 H and 3 H, 2 x OCOCH₃, NCOCH₃), 3.80 (s, 3 H, CO₂CH₃), 4.37 (d, J = 4.7, 1 H), 4.92 (d, J = 4.6 Hz, 1 H), 5.14 (s, 2 H), 5.63 (s, 1 H, H-1); ¹³C NMR (C₆D₆, RT): δ 19.5, 21.0 (OCOCH₃, NCOCH₃), 52.0, 58.7, 71.7, 75.2, 80.9, 89.4 (C-1), 168.9; MS (% relative intensity, m/e): 316.1029 (12.2, M⁺ + 1, 316.1032 calcd for C₁₃H₁₈N₈O₈), 272 (30.1), 256 (41.4), 228 (52.3), 214 (73.4), 186 (79.1), 182 (43.6), 172 (89.9), 171 (56.0), 157 (95.5), 154 (37.3), 144 (63.4), 142 (49.9), 140 (31.6), 126 (100), and 115 (76.1).

![Synthetic N-Acetyl Thymine Polyoxin C](image)

**Synthetic N-Acetyl Thymine Polyoxin C** (120). To a solution of synthetic 114 (3.6 mg, 0.0082 mmol) in (1:1) H₂O-THF (5 mL) in ice bath was added the stock solution of LiOH·H₂O (0.27 M, 0.1 mL, 0.027 mmol). The slightly yellow solution was stirred at 0
°C for 1 h when the TLC in (2:1:1) nBuOH-H₂O-HOAc showed the formation of a product at Rf 0.52 at the expense of starting material. The reaction mixture was acidified with 0.1N HCl to a pH of 1-2 and then all solvents were removed in vacuo to give a white solid containing LiCl (7.0 mg). The ¹H NMR spectrum of this sample matched that of authentic N-acetyl thymine polyoxin C (120) contaminated with NaCl (vide infra).

![Methyl 1,5-Dideoxy-1-(3,4-dihydro-5-methyl-2,4-dioxo-1(2H)-pyrimidinyl)-5-[(phenylmethoxy)-carbonyl]amino]-β-D-allofuranuronate, 2,3-Diacetate (116) and Methyl 5-Amino-1,5-dideoxy-1-(3,4-dihydro-5-methyl-2,4-dioxo-1(2H)-pyrimidinyl)-β-D-allofuranuronate, 2,3-Diacetate (117). To a solution of 99 (299 mg, 0.640 mmol) in dry dichloroethane (27 mL) was added sequentially bis-silylated thymine 101 (583 mg, 2.15 mmol) and TMSOTf (0.76 mL, 0.871 g, 3.92 mmol) under an Ar atmosphere. The slightly yellow solution was refluxed at 100 °C for 30 min when the TLC in (13:1) CHCl₃-MeOH showed the formation of two UV-active products, Rf 0.58 (N-Cbz nucleoside 116) and Rf 0.49 (N-deprotected nucleoside 117), at the expense of starting material at Rf 0.64. The reaction was cooled to room temperature and diluted with CH₂Cl₂ (200 mL) then washed with saturated NaHCO₃ solution (150 mL) and brine (100 mL). The resulting two aqueous layers were
reextracted with CH$_2$Cl$_2$ (2 x 100 mL) respectively and all organic layers were combined, dried over Na$_2$SO$_4$, filtered and concentrated in vacuo to give a slightly yellow foam (320 mg). Flash chromatography on silica gel, eluting with (30:1) CHCl$_3$-MeOH gave pure 116 (272 mg, mp 80-82 °C, 85% yield), as a white foam along with 117 (34.6 mg, 14 % yield), as a white foam. For 116: [α]$_D$ +19.8° (c 0.56, CHCl$_3$); IR (CHCl$_3$): 3380, 1750, 1715, 1690 cm$^{-1}$; $^1$H NMR (200 MHz, CDCl$_3$, RT): $\delta$ 1.87 (d, $J = 0.7$ Hz, 3 H, 5-CH$_3$), 2.06 (s, 6 H, 2 x OCOCH$_3$), 3.78 (s, 3 H, CO$_2$CH$_3$), 4.37 (dd, $J = 4.7$ and 3.5 Hz, 1 H, H-4'), 4.81 (dd, $J = 8.5$ and 3.7 Hz, 1 H, H-5'), 5.11 (s, 2 H, CH$_2$Ph), 5.24 (t, $J = 6.0$ Hz, 1 H, H-2'), 5.50 (t, $J = 5.9$ Hz, 1 H, H-3'), 5.79 (d, $J = 8.1$ Hz, 1 H, NH), 5.92 (d, $J = 5.6$ Hz, 1 H, H-1'), 7.03 (d, $J = 0.6$ Hz, 1 H, H-6), 7.32 (br s, 5 H, C$_6$H$_5$), 8.55 (br s, 1 H, N$_3$H, exchanged with D$_2$O); $^{13}$C NMR (acetone-d$_6$, RT): $\delta$ 10.8 (q, -, 5-CH$_3$), 18.7 (q, -, OCOCH$_3$), 51.2 (q, -, CO$_2$CH$_3$), 54.5 (d, -, C-5), 65.5 (t, +, CH$_2$Ph), 69.0 (d, -, C-3' or C-4'), 71.3 (d, -, C-4' or C-3'), 80.2 (d, -, C-2'), 87.6 (d, -, C-1'), 110 (s, +, C-5), 126.9, 127.1, 127.5 (d, -, Ph), 135.8 (d, -, C-6), 136.0 (s, +, Ph), 149.0 (s, +, C-2), 155.4 (s, +, NCO$_2$), 162.5 (s, +, C-4), 168.3, 168.4 (s, +, OCOCH$_3$), 168.5 (s, +, CO$_2$CH$_3$); MS (FAB/glycerol, m/e): 534.1715, M + 1, 534.1724 calcd for C$_{24}$H$_{28}$N$_3$O$_{11}$). For 117: IR (CHCl$_3$): 3380, 3020, 1740, 1690 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-d$_6$, RT): $\delta$ 1.78 (s, 3 H, 5-CH$_3$), 2.00, 2.07 (2 s, 2 x 3 H, OCOCH$_3$), 3.63 (s, 3 H, CO$_2$CH$_3$), 3.74 (d, $J = 5.0$ Hz, 1 H, H-5'), 4.18 (t, $J = 4.12$ Hz, 1 H, H-4'), 5.37 (dd, $J = 5.89$ and 3.24 Hz, 1 H, H-3'), 5.44 (t, $J = 6.3$ Hz, 1 H, H-2'), 5.95 (d, $J = 6.3$ Hz, 1 H, H-1'), 7.83 (s, 1 H, H-6); $^{13}$C NMR (acetone-d$_6$, RT): $\delta$ 11.0 (q, -, 5-CH$_3$), 18.6, 18.9 (q, -, OCOCH$_3$), 50.9 (q, -, CO$_2$CH$_3$), 63.2 (d, -, C-5'), 70.2 (d, -, C-3' or C-4'), 71.4 (d, -, C-4' or C-2'), 82.8 (d, -, C-2'), 84.2 (d, -, C-1'), 109.8 (s, +, C-5), 134.3 (d, -, C-6), 149.8
(s, +, C-2), 162.2 (s, +, C-4), 167.7, 168.3 (s, +, 2 O\text{COCH}_3), 170.9 (s, +, C\text{O}_2\text{CH}_3); 
HRMS (FAB/glycerol): m/e 400.1346, M + 1, 400.1356 calcd for C\text{16H}_{22}\text{N}_3\text{O}_9.

![Chemical Structure](Image)

5-Amino-1,5-dideoxy-1-(3,4-dihydro-5-methyl-2,4-dioxo-1(2H)-pyrimidinyl)-\beta-D-allofuranuronic Acid (Synthetic Thymine Polyoxin C) (118). To a 0 °C solution of N-Cbz nucleoside 116 (88.7 mg, 0.166 mmol) in THF (8 mL) and H\text{2O} (1.5 mL) was added solid LiOH·H\text{2O} (24 mg, 0.57 mmol). The resulting yellow solution was stirred at 0 °C for 1 h at which time the TLC in (5:4:1) CHCl\text{3}-MeOH-H\text{2O} showed the formation of N-Cbz thymine polyoxin C, $R_f$ 0.59, at the expense of starting material, $R_f$ 0.96 (char A). The reaction was diluted with H\text{2O} (10 mL) and extracted with CH\text{2Cl}_2 (3 x 20 mL) to remove any non-acidic material and the resulting basic solution was cooled to 0 °C and acidified to pH = 2-3 with 1N HCl. This mixture was extracted with EtOAc (6 x 20 mL) and all organic layers were combined, dried over Na\text{2SO}_4, filtered and concentrated in vacuo to give N-Cbz thymine polyoxin C a yellow solid (49 mg). To a slightly yellow solution of this material (42.1 mg, 0.10 mmol) in MeOH (4.5 mL) was added 5% Pd/C (33 mg). The black suspension was stirred under H\text{2} atmospheric pressure for 4 h when the TLC in (5:4:1) CHCl\text{3}-MeOH-H\text{2O} showed the formation of thymine polyoxin C 118 (=10), $R_f$ 0.21 (char A), at the expense of starting material at $R_f$ 0.51. The reaction mixture was filtered through a pad of Celite and activated carbon with eluting hot H\text{2O} (3 x 10 mL) and the filtrate was concentrated in


vacuo to give synthetic 118 (=10) as a yellow solid (20.8 mg, 54% yield); mp 182-185 °C, (shr 145 °C); [authentic 10: mp 190-194 °C (shr at 170°C), lit.\textsuperscript{1b} mp 240-244 °C, lit.\textsuperscript{17c} mp 242-244 °C]. [α]_D +8.0° (c 0.37, H\textsubscript{2}O) [lit.\textsuperscript{1b} [α]_D +8.7° (c 0.208, H\textsubscript{2}O), lit.\textsuperscript{17c} [α]_D +8.2° (c 0.7, H\textsubscript{2}O); \textsuperscript{1}H NMR (400 MHz, D\textsubscript{2}O + DC\textsubscript{l}, pD = 0.68, RT): δ 1.72 (s, 3 H, 5-CH\textsubscript{3}), 4.20 (dd, J = 6.9 and 2.6 Hz, 1 H, H-4'), 4.27 (dd, J = 6.1 and 4.0 Hz, 1 H, H-2'), 4.40 (d, J = 2.6 Hz, 1 H, H-5'), 4.53 (t, J = 6.5 Hz, 1 H, H-3'), 5.60 (d, J = 3.9 Hz, 1 H, H-1'), 7.17 (s, 1 H, H-6). This \textsuperscript{1}H NMR spectrum was identical to one obtained with authentically-derived thymine polyoxin C (vide infra). \textsuperscript{13}C NMR [(2:1) D\textsubscript{2}O-DMSO-d\textsubscript{6}, RT]: δ 11.8 (q, -5-CH\textsubscript{3}), 55.7 (d, - C-5'), 69.8 (d, - C-3'), 72.6 (d, - C-4'), 83.1 (d, - C-2'), 89.2 (d, - C-1'), 111.2 (s, +, C-5), 138.0 (d, - C-6), 151.7 (s, +, C-2), 165.4 (s, +, C-4), 169.3 (s, +, CO\textsubscript{2}H); HRMS (FAB/glycerol): m/e 302.0999, M + 1, 302.0988 calcd for C\textsubscript{11}H\textsubscript{16}N\textsubscript{3}O\textsubscript{7}.

\begin{center}
\textbf{5-Amino-1,5-dideoxy-1-(3,4-dihydro-5-methyl-2,4-dioxo-1(2H)-pyrimidinyl)-\textbeta-D-allofuranuronic Acid (Thymine Polyoxin C) (10).} To a solution of authentic polyoxin C (119) (14.5 mg, 0.046 mmol) in H\textsubscript{2}O (1.5 mL) was added PtO\textsubscript{2} (2.9 mg). The brown suspension was stirred under hydrogen for 1.5 h at which time the suspension turned black and the TLC in (2:1:1) \textsuperscript{8}BuOH-H\textsubscript{2}O-AcOH showed the formation of product, Rf 0.37, at the expense of staring material Rf 0.31 (char A). The catalyst was filtered off through a pad of Celite + activated carbon and the filtrate (15 mL) was concentrated in vacuo to give authentic thymine polyoxin C (10) as a
white solid (12.3 mg, 89% crude yield), mp 190-194 °C (shr 170 °C). $^1$H NMR (400 MHz, D$_2$O + DCl, pD = 0.70, 2 mg/0.4 mL, RT): δ 1.72 (s, 3 H, 5-CH$_3$), 4.20 (dd, $J = 6.8$ and 2.4 Hz, 1 H, H-4'), 4.27 (t, $J = 5.0$ Hz, 1 H, H-3'), 4.40 (d, $J = 2.5$ Hz, 1 H, H-5'), 4.53 (t, $J = 6.7$ Hz, 1 H, H-2'), 5.60 (d, $J = 3.7$ Hz, 1 H, H-1'), 7.17 (s, 1 H, H-6); HRMS (FAB/glycerol matrix): m/e 302.0999, M + 1, 302.0988 calcd for C$_{11}$H$_{16}$N$_3$O$_7$.

5-(Acetylamino)-1,5-dideoxy-1-(3,4-dihydro-5-methyl-2,4-dioxo-1(2H)-pyrimidinyl)-β-D-allofuranuronic Acid (N-Acetyl Thymine Polyoxin C) (120). To a solution of thymine polyoxin C (10) (5.8 mg, 0.016 mmol) in water (0.9 mL) was added a 0.15 M NaOAc solution (0.23 mL, 0.035 mmol) and Ac$_2$O (0.025 mL). The clear homogeneous solution (pH = 4) was stirred at room temperature for 4 h when the TLC in (2:1:1) n-BuOH-H$_2$O-AcOH showed the formation of product, $R_f$ 0.52, at the expense of starting material, $R_f$ 0.45 (char A). The mixture was extracted with EtOAc (6 x 3 mL), the aqueous layer containing the product was acidified to pH = 1 with 0.1 N HCl, and the water was removed in vacuo to give crude 120 as a white solid (7.8 mg) which contained NaCl. The NMR sample (5.2 mg) was treated with D$_2$O (1.0 mL) and the HDO + excess D$_2$O were evaporated prior to taking the $^1$H NMR spectrum. $^1$H NMR (400 MHz, DMSO-d$_6$, 5.2 mg/1 mL, RT): δ 1.76 (s, 3 H, 5-CH$_3$), 1.87 (s, 3 H, NCOCH$_3$), 4.04 (m, 3 H, H-2', H-3' and H-4'), 4.14 (d, $J = 2.7$ Hz, 1 H, H-5'), 5.76 (d, $J = 6.5$ Hz, 1 H, H-1'), 7.45 (br s, 1 H, H-6).
Methyl 5-(Acetylamino)-1,5-dideoxy-1-(3,4-dihydro-5-methyl-2,4-dioxo-1(2H)-pyrimidinyl)-β-D-allofuranuronate, 2,3-Diacetate (121). To a solution of N-acetyl polyoxin C (120) (0.9 mg) containing sodium chloride in MeOH (2 mL) was added Amberlyst-15 (5 mg). The yellow suspension was stirred at room temperature for 2 days at which time the TLC in (2:1:1) n-BuOH-H₂O-AcOH showed the formation of a product, Rf 0.75, at the expense of starting material, Rf 0.55 (char A). The catalyst was removed by filtration through Celite eluting with MeOH and the filtrate (10 mL) was concentrated in vacuo to give the product (1.5 mg). A solution of this ester (1.5 mg) in CH₂Cl₂ (0.5 mL) was treated with pyridine (0.05 mL) and Ac₂O (0.05 mL). The resulting clear solution was stirred at room temperature for 2 h at which time the TLC in (13:1) CHCl₃-MeOH showed the formation of product, Rf 0.24, and the disappearance of starting material at the origin. Therefore, all solvents were evaporated in vacuo to give a desired triacetate methyl ester 121 (1.3 mg). ¹H NMR (200 MHz, CDCl₃, RT): δ 1.92 (d, J = 1.1 Hz, 3 H, 5-CH₃), 2.04, 2.07, 2.09 (3 s, 3 x 3 H, 2 x OCOCH₃ and NCOCH₃), 3.80 (s, 3 H, CO₂CH₃), 4.36 (t, J = 4.6 Hz, 1 H, H-4'), 4.98 (dd, J = 7.5 and 3.8 Hz, 1 H, H-5'), 5.28 (t, J = 5.7 Hz, 1 H, H-3'), 5.53 (t, J = 5.8 Hz, 1 H, H-2'), 5.81 (d, J = 5.5 Hz, 1 H, H-1'), 6.20 (d, J = 7.6 Hz, 1 H, NH), 7.03 (d, J = 1.1 Hz, 1 H, H-6), 8.00 (br s, 1 H, N³H); HRMS (FAB/glycerol matrix): m/e 442.1455, M + 1, 442.1462 calcd for C₁₈H₂₄N₃O₁₀.
PEPTIDE COUPLING AND THE PROTECTED POLYOXIN J

Direct Coupling with γ-Lactone 49.

A mixture of lactone 49 (5.0 mg, 0.017 mmol) and HOBT (5.2 mg, 0.039 mmol) was treated with a stock solution of benzylamine in MeOH (0.32 M, 0.56 mL, 0.179 mmol). The white suspension was purged with Ar and heated in sealed tube at 80 °C for 1 h at which time the suspension had become a clear solution. The TLC in EtOAc showed the formation of two products, $R_f$ minor 0.52 and $R_f$ major 0.38, at the expense of 49, $R_f$ 0.65 (char A). The reaction mixture was partitioned between pH 4 buffer (1 mL) and EtOAc (3 x 5 mL). The combined organic layers were washed with saturated NaHCO$_3$ (1 mL) and brine (1 mL). The organic layer was dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo to give product (60 mg) contaminated with benzylamine. Flash chromatography on silica gel, eluting with EtOAc and then 10 % MeOH in EtOAc gave the pure minor benzylamide 123 ($R_f$ 0.52, 1.2 mg, 19% yield) and pure the major benzylamide 124 ($R_f$ 0.38, 2.6 mg, 37% yield). For 123: $^1$H NMR (200 MHz, DMSO-d$_6$, RT): 8 1.38 (s, 9 H, C(CH$_3$)$_3$), 3.61-3.72 (m, 2 H), 3.85-3.90 (m, 2 H), 4.12 (t, $J$ = 8.1 Hz, 1 H), 4.28 (d, $J$ = 6.1 Hz, 2 H, CH$_2$Ph), 4.83 (dd, $J$ = 7.55 and 6.1 Hz, 2 x OH, exchanged with D$_2$O), 6.45 (br s, 2 H, OCONH$_2$, slowly exchanged with D$_2$O), 6.83 (br d, $J$ = 7.7 Hz, NHBOC, slowly exchanged with D$_2$O), 7.26 (br s, 5 H, C$_6$H$_5$), 8.33 (t, $J$ = 6.1 Hz, NHCH$_2$Ph); HRMS (FAB/glycerol): m/e 398.1926, M + 1. 398.1927 calcd for C$_{18}$H$_{28}$N$_3$O$_7$. For 124: IR (CHCl$_3$): 3410, 1700, 1670, 1595 cm$^{-1}$; $^1$H
NMR (200 MHz, DMSO-d$_6$, RT): $\delta$ 1.38 (s, 9 H, C(CH$_3$)$_3$), 3.60 (br s, 1 H), 3.81 (t, $J$ = 8.9 Hz, 2 H), 3.94 (dd, $J$ = 11.1 and 4.4 Hz, 1 H), 4.10 (dd, $J$ = 7.9 and 4.1 Hz, 1 H), 4.30 (br s, 2 H, CH$_2$Ph), 4.85 (2 br s, 2 H, 2 x OH, exchanged with D$_2$O), 6.45 (br s, 3 H, OCONH$_2$ and NHCO$_2$, slowly exchanged with D$_2$O), 7.25 (br s, 5 H, C$_6$H$_5$), 8.26 (br s, 1 H, NHCH$_2$Ph, slowly exchanged with D$_2$O); HRMS (FAB/glycerol): m/e 398.1926, M + 1, 398.1930 calcd for C$_{18}$H$_{28}$N$_3$O$_7$.

**Synthesis of Bis-silylated N-BOC L-Serine (126).** Under an Ar atmosphere, a mixture of N-BOC L-serine 2a (0.203 g, 1.00 mmol) and solid imidazole (0.542 g, 8.01 mmol) was treated with a stock solution of TBSCI in DMF (1.56 M, 3 mL, 4.69 mmol). The resulting homogeneous solution was stirred for 2 h at room temperature at which time the TLC in (23.6:3.6:1.4:1.4) EtOAc-Pyridine-H$_2$O-HOAc showed the disappearance of starting material $R_f$ 0.16 and the formation of products, $R_f$ 0.52 (for the mono-silylated product) and $R_f$ 0.86 (for bissilylated product). In order to confirm the completion of the reaction, 1 mL of aliquot was taken and partitioned between brine (15 mL) and (1:1) hexanes-Et$_2$O (3 x 30 mL). The combined organic layer was cooled and washed with cold 1N HCl (5 mL) and brine (15 mL). The organic layer was dried over Na$_2$SO$_4$, filtered and concentrated *in vacuo* to give a product (118 mg) which was identified as the bis-silylated product by $^1$H NMR (vide infra). Therefore, the remaining reaction mixture was worked up as described above to afford the bissilylated product 126 (305 mg, combined product 424 mg, 97% yield) as a colorless oil. For 126: IR (neat):
3440, 1720 cm\(^{-1}\); \(^1\)H NMR (200 MHz, C\(_6\)D\(_6\), RT): \(\delta\) -0.02, -0.01 (2 s, 2 x 3H, OSi(CH\(_3\))\(_2\)Bu), 0.25, 0.29 (2 s, 2 x 3 H, CO\(_2\)Si(CH\(_3\))\(_2\)Bu), 0.89, 0.91 (2 s, 2 x 9H, 2 x Si(CH\(_3\))\(_2\)Bu), 1.44 (s, 9 H, NCO\(_2\)(CH\(_3\))\(_3\)), 3.82 (dd, \(J = 10.2\) and 2.7 Hz, H-3a), 3.95 (dd, \(J = 10.1\) and 2.3 Hz, H-3b), 4.46 (dt, \(J = 7.8\) and 2.4 Hz, H-2), 5.60 (d, \(J = 7.8\) Hz, NHCO\(_2\)).

### Synthesis of Mono-Silylated N-BOC L-Serine (127)

To a solution of bis-silylated N-BOC L-serine 126 (100 mg, 0.253 mmol) in MeOH (3 mL) and THF (1 mL) was added a stock solution of K\(_2\)CO\(_3\) in H\(_2\)O (0.72 M, 1 mL, 0.72 mmol). The resulting homogeneous solution was stirred for 1 h at room temperature. The TLC in EtOAc (2 mL) + HOAc (2 drops) showed the disappearance of starting material \(R_f\) 0.89 and the formation of product \(R_f\) 0.64. The solvent was removed to half volume and the reaction mixture was diluted with brine (3 mL) and cooled to 0 °C. The reaction mixture was acidified with 1 M KHSO\(_4\) till pH 4-5 and then extracted with Et\(_2\)O (3 x 30 mL) and the combined organic layers were washed with brine (10 mL), dried over Na\(_2\)SO\(_4\), filtered, and concentrated in vacuo to give a mono-silylated product 127 (89.0 mg, 100 % yield) as a colorless oil. For 127: IR (neat): 3500-2400, 1720, 1690 cm\(^{-1}\); \(^1\)H NMR (200 MHz, C\(_6\)D\(_6\), 60 °C): \(\delta\) -0.02 (s, 0.64 x 6 H, OSi(CH\(_3\))\(_2\)Bu), 0.01 (s, 0.36 x 6 H, OSi(CH\(_3\))\(_2\)Bu), 0.87 (s, 0.74 x 9 H, Si(CH\(_3\))\(_2\)Bu), 0.90 (s, 0.26 x 9 H, Si(CH\(_3\))\(_2\)Bu), 1.41 (s, 9 H, NCO\(_2\)(CH\(_3\))\(_3\)), 3.71 (dd, \(J = 10.2\) and 3.7 Hz, H-3a), 3.95 (dd, \(J = 10.1\) and 3.1 Hz, H-3b), 4.43 (br s, H-2), 5.46 (br s, NHCO\(_2\)), 6.27 (br s, CO\(_2\)H).
Peptide Coupling of mono-Silylated N-BOC L-Serine (127) by DCC Method.

Under an Ar atmosphere, the free amine 117 (7.3 mg, 0.0183 mmol) was treated with a stock solution of DCC in CH₂Cl₂ (0.28 M, 0.1 mL, 0.028 mmol) and a stock solution of DMAP in CH₂Cl₂ (0.08 M, 8.0 x 10⁻⁴ mmol). The homogeneous solution was stirred for 5 min at room temperature. To this homogeneous solution was then added a stock solution of mono-silylated N-BOC L-serine 127 in CH₂Cl₂ (0.069 M, 0.024 mmol). After stirring for 10 min, the homogeneous solution became a suspension indicating the formation of dicyclohexyl urea. This suspension was stirred for 4 h at which time the TLC in EtOAc showed the formation of product, Rf 0.72 at the expense of the starting amine, Rf 0.32 (char A). The reaction mixture was filtered through a cotton plug eluting with EtOAc (30 mL). The filtrate was washed with saturated NaHCO₃ (5 mL), cold 1N HCl (5 mL), and brine (5 mL). Each aqueous layer was re-extracted with EtOAc (2 x 30 mL) respectively and the combined organic layer was dried over Na₂SO₄, filtered and concentrated in vacuo to give crude product (20 mg) as a white solid. Flash chromatography on silica gel, eluting with (2:1) hexanes-EtOAc gave the pure dipeptide 128 (8.3 mg, 65% yield based on the starting amine). For 128: IR (CHCl₃): 3390, 1750, 1695 cm⁻¹; ¹H NMR (200 MHz, CDCl₃, 55 °C): δ 0.06 (s, 6 H, OSi(CH₃)₂Bu), 0.85 (s, 9 H, OSi(CH₃)₂Bu), 1.44 (s, 9 H, NCO₂(CH₃)₃), 1.91 (d, J = 1.2 Hz, 3 H, -CH₃), 2.05, 2.08 (2 s, 2 x 3 H, OCOCH₃), 3.69 (dd, J = 9.8 and 6.5 Hz, 1 H, H-3″a), 3.78 (s, 3 H, CO₂CH₃), 4.00
(dd, J = 9.9 and 4.2 Hz, H-3''b), 4.16 (m, H-2''), 4.30 (dd, J = 5.1 and 3.7 Hz, H-4''), 5.00 (dd, J = 7.9 and 3.7 Hz, H-5''), 5.25 (br d, J = 5.9 Hz, NHCO₂Bu), 5.30 (t, J = 6.0 Hz, H-2''), 5.58 (dd, J = 6.3 and 5.2 Hz, H-3''), 5.85 (d, J = 5.5 Hz, H-1''), 7.02 (d, J = 1.2 Hz, H-6), 7.45 (d, J = 8.1 Hz, NHCO₂), 8.28 (br s, 3N-H); LRMS (FAB/glycerol): 701, M + 1, 701.3065 calcd for C₃₀H₄₉N₄O₁₃Si.

Peptide Coupling of Bis-Silylated N-BOC L-Serine (127) via the WSC Method. Under an Ar atmosphere, a (4:1) mixture of silyl ester 126 and acid 127 (5.8 mg, 0.014 mmol) plus HOBT (4.5 mg, 0.033 mmol) and water soluble carbodiimide (WSC) (3.5 mg, 0.018 mmol) was dissolved in dry CH₂Cl₂ (0.25 mL) and stirred for 5 min at room temperature. To this colorless solution was added a stock solution of amine 117 in CH₂Cl₂ (0.05 M, 0.25 mL, 0.013 mmol). The homogeneous solution was stirred for 16 h at room temperature at which time the TLC in EtOAc (2 mL) and HOAc (2 drops) showed the formation of product Rf 0.80 at the expense of the starting amine Rf 0.20 (char A). Therefore, the reaction was diluted with CH₂Cl₂ (100 mL) and washed with 0.2 N HCl (10 mL) and brine (10 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated in vacuo to give a crude product (8.6 mg). Flash chromatography on silica gel, eluting with (2:1) EtOAc-hexanes gave a pure product 128 (7.8 mg, 87% yield based on the starting amine) which had an identical ¹H NMR spectrum as the previously prepared material (vide supra).
Coupling with Hydroxy acid 129 via Lactone 50. To a solution of lactone 50 (24.3 mg, 0.084 mmol) in dioxane (2.5 mL) was added a stock solution of LiOH·H₂O in H₂O (0.29 M, 0.176 mmol, 7.4 mg). The slightly yellow solution was stirred for 15 min at which time the TLC in EtOAc showed the disappearance of the starting lactone 50, Rf 0.63 and the formation of a product at the origin. The reaction mixture was partitioned between brine (5 mL) and EtOAc (30 mL). After the organic layer was discarded, the aqueous layer (pH 7-8) was cooled in ice bath and acidified with cold 1 N HCl till pH 2-3. The reaction mixture was extracted with EtOAc (3 x 30 mL) and the combined organic layer was dried over Na₂SO₄, filtered and concentrated in vacuo to give 129 (20.5 mg, 79% crude yield) as a colorless oil. The crude hydroxy acid 129 was immediately submitted to the next reaction.

Under an Ar atmosphere, 129 (19 mg, 0.062 mmol) and imidazole (62 mg, 0.911 mmol) were dissolved along with a stock solution of TBSCl in DMF (3.7 M, 0.2 mL, 0.74 mmol). The homogeneous solution was stirred further for 1.5 h at room temperature whereupon TLC in (23.5:3.5:1.5:1.5) EtOAc-pyridine-HOAc-H₂O showed the disappearance of 129, Rf 0.17 and several intermediates. The homogeneous solution was stirred at 40 °C for 21 h to complete the multiple protection. The reaction was cooled to room temperature and partitioned between brine (5 mL) and (1:1) hexanes-Et₂O (3 x 30 mL). The combined organic layer was cooled to 0 °C and washed
with 0.1N HCl (10 mL) and brine (10 mL), dried over Na₂SO₄, filtered and concentrated in vacuo to give 130 (24.5 mg, 61% crude yield) as a colorless oil.

Without further purification, the crude product 130 (20.4 mg, 0.031 mmol) was treated with solid HOBT (11.7 mg, 0.087 mmol) and solidWSC (9.4 mg, 0.049 mmol) under an Ar atmosphere. The mixture was dissolved in dry CH₂Cl₂ (1.5 mL) and stirred for 5 min at room temperature. To this colorless solution was added a solution of amine 117 (12.2 mg, 0.032 mmol) in distilled CH₂Cl₂ (0.5 mL). The solution was stirred for 15 h at room temperature after which the TLC in EtOAc (2 mL) and HOAc (2 drops) showed the formation of a product, Rf 0.74, at the expense of 117, Rf 0.20 (char A). The reaction mixture was diluted with CH₂Cl₂ (300 mL) and washed with 0.2N HCl (30 mL) and brine (30 mL), dried over Na₂SO₄, filtered and concentrated in vacuo to give crude product (30.5 mg). Flash chromatography on silica gel, eluting with (2:1) EtOAc-hexanes gave the recovered starting material 130 (11.4 mg, 56% recovery) and a product 131 (11.5 mg, 43% yield based on the starting amine 117). The recovered starting material 130 was resubmitted to the same conditions as the above, to afford more peptide 131 (2.3 mg, 39% yield) and 130 (2.9 mg, 57% yield). For 130; IR (CHCl₃): 3380, 1750, 1690, 1590 cm⁻¹; ¹H NMR (200 MHz, CDCl₃, 55 °C): δ 0.05, 0.09, 0.10 (3 s, 2 x 6 H, 2 x Si(CH₃)₂Bu), 0.86, 0.90 (2 s, 2 x 9 H, 2 x Si(CH₃)₂C(CH₃)₃), 1.38 (s, 9 H, NCO₂C(CH₃)₃), 1.92 (d, J = 1.1 Hz, 3 H, 5-CH₃), 2.04, 2.08 (2 s, 2 x 3 H, 2 x COOCH₃), 3.79 (s, 3 H, CO₂CH₃), 3.98-4.13 (m, 4 H), 4.25 (d, J = 5.3 Hz, 1 H), 4.37 (dd, J = 5.0 and 3.3 Hz, H-4'), 4.70 (br s,
2 H, OCONH₂), 4.94 (dd, J = 7.5 and 3.2 Hz, H-5'), 5.29 (t, J = 6.2 Hz, H-2), 5.61 (t, J = 5.8 Hz, H-3), 5.88 (d, J = 4.1 Hz, H-1), 6.12 (br s, NHCO₂Bu), 7.05 (d, J = 1.1 Hz, H-6), 7.37 (d, J = 4.2 Hz, NHCO₂), 8.14 (br s, 1 H, N3-H); H NMR (400 MHz, DMSO-d₆, 70 °C): δ 0.03, 0.08, 0.09, 0.12 (4 s, 2 x 6 H, 2 x Si(CH₃)₂Bu), 0.85, 0.89 (2 s, 2 x 9 H, 2 x Si(CH₃)₂C(CH₃)₃), 1.35 (s, 9 H, NCO₂C(CH₃)₃), 1.79 (s, 3 H, 5-CH₃), 2.02, 2.08 (2 s, 2 x 3 H, 2 x OCOCH₃), 3.67 (s, 3 H, CO₂CH₃), 3.92 - 3.98 (m, 3 H), 4.05 (d, J = 7.3 Hz, 1 H), 4.22 (m, 2 H overlapping with H-4'), 4.84 (dd, J = 8.1 and 4.4 Hz, H-5'), 5.46 (t, J = 5.5 Hz, H-2'), 5.53 (t, J = 6.1 Hz, H-3'), 5.81 (d, J = 5.2 Hz, H-1'), 6.17 (s, 3 H, NHCO₂ and OCONH₂), 7.37 (s, H-6), 8.18 (d, J = 7.5 Hz, NHCO₂), 11.20 (s, N3-H); LRMS (FAB/glycerol): 918, M + 1, 918.4200 calcd for C₃₉H₆₈N₅O₁₆Si₂.

Coupling with Hydroxyacid 122 via Lactone 49. To a solution of lactone 49 (9 mg, 0.031 mmol) in dioxane (1 mL) was added a stock solution of LiOH·H₂O in H₂O (0.29 M, 0.2 mL, 0.59 mmol). The white suspension was stirred for 15 min during which time the suspension had dissolved and the TLC in EtOAc showed the disappearance of the starting lactone 49, Rf 0.56 and the formation of a hydroxy acid 122 at the origin. The reaction mixture was partitioned between brine (5 mL) and EtOAc (30 mL). After the organic layer was discarded, the aqueous layer (pH 7-8) was cooled in ice bath and acidified with cold iN HCl till pH 2-3. The reaction mixture was extracted with EtOAc (3 x 30 mL) and the combined
organic layer was dried over Na$_2$SO$_4$, filtered and concentrated in vacuo to give 122 (9.4 mg, 99% crude yield) as a colorless oil. The crude hydroxy acid 122 was immediately submitted to the next reaction.

Under an Ar atmosphere, 122 (9.4 mg, 0.032 mmol) and imidazole (30 mg, 0.44 mmol) were dissolved with a stock solution of TBSCI in DMF (3.68 M, 0.15 mL, 0.552 mmol). The homogeneous solution was stirred for 16 h at 40 °C. The reaction mixture was then cooled to room temperature and partitioned between brine (5 mL) and (1:1) hexanes-Et$_2$O (3 x 30 mL). The combined organic layer was cooled to 0 °C and washed with 0.1 N HCl (10 mL) and brine (10 mL), dried over Na$_2$SO$_4$, filtered and concentrated in vacuo to give an 132 (19.3 mg, 93% crude yield) as a colorless oil.

Without further purification, the crude product 132 (7.7 mg, 0.012 mmol) was treated with solid HOBT (4.5 mg, 0.033 mmol) and solid WSC (3.6 mg, 0.019 mmol) under an Ar atmosphere. The mixture was dissolved in dry CH$_2$Cl$_2$ (1.5 mL) and stirred for 5 min at room temperature. The resulting colorless solution was added a stock solution of amine 117 (0.044 M, 0.25 mL, 0.011 mmol). The solution was stirred for 15 h at room temperature at which time the TLC in EtOAc (2 mL) and HOAc (2 drops) showed the formation of two products, $R_f$ 0.78 (for 133 and 134) and $R_f$ 0.63 (for 135), at the expense of 117, $R_f$ 0.22 (char A). The reaction mixture was diluted with CH$_2$Cl$_2$ (100 mL) and washed with 0.2 N HCl (10 mL) and brine (10 mL), dried over Na$_2$SO$_4$, filtered and concentrated in vacuo to give crude product (10.7 mg). Flash chromatography on silica gel, eluting with (2:1) EtOAc-hexanes gave the recovered starting
material 132 (4.4 mg, 44% yield), and a three product mixture 133, 134, and 135 (5.0 mg). Further purification by preparative TLC eluting with (13:1) CHCl₃-MeOH provided bis-silylated product 133 (1.0 mg) and two mono-silylated products each 134 (1.0 mg) and 135 (1.6 mg).

For 133; IR (CHCl₃): 3380, 1750, 1690, 1590 cm⁻¹; ¹H NMR (200 MHz, CDCl₃, 55 °C): δ 0.10, 0.11, 0.15 (3 s, 2 x 6 H, 2 x OSi(CH₃)₂Bu), 0.89, 0.94 (2 s, 2 x 9 H, 2 x OSi(CH₃)₂C(CH₃)₃), 1.44 (s, 9 H, NCO₂C(CH₃)₃), 1.94 (s, 3 H, 5-CH₃), 2.07, 2.08 (2 s, 2 x 3 H, 2 x OCOCH₃), 3.78 (s, 3 H, CO₂CH₃), 4.02-4.17 (m, 3H), 4.32-4.34 (m, 2 H), 4.38 (dd, J = 6.0 and 3.3 Hz, H-4'), 4.66 (br s, 2 H, OCONH₂), 5.11 (dd, J = 7.9 and 3.8 Hz, H-5'), 5.32 (t, J = 6.1 Hz, H-2'), 5.48 (t, J = 7.1 Hz, H-3'), 5.92 (br s, H-1'), 6.22 (br s, NHCO₂Bu), 7.21 (s, H-6), 7.54 (d, J = 7.5 Hz, NHCO₂), 8.14 (br s, N₃-H); ¹H NMR (400 MHz, DMSO-d₆, 70°C): δ 0.03, 0.07, 0.09, 0.12 (4 s, 2 x 6 H, 2 x OSi(CH₃)₂Bu), 0.84, 0.89 (2 s, 2 x 9 H, 2 x OSi(CH₃)₂C(CH₃)₃), 1.36 (s, 9 H, NCO₂C(CH₃)₃), 1.80 (s, 3 H, 5-CH₃), 2.03, 2.07 (2 s, 2 x 3 H, 2 x OCOCH₃), 3.66 (s, 3 H, CO₂CH₃), 3.94 (s, 3 H), 4.07 (d, J = 6.7 Hz, 1 H), 4.23 (m + t, J = 5.5 Hz, 2 H, H-4' for t), 4.78 (dd, J = 7.9 and 4.4 Hz, H-5'), 5.42 (t, J = 6.3 Hz, H-2'), 5.50 (t, J = 5.8 Hz, H-3'), 5.85 (d, J = 5.2 Hz, H-1'), 5.18-6.27 (br 2 s, 3 H, OCONH₂ and NHBoc), 7.43 (s, H-6), 8.10 (d, J = 7.3 Hz, NHCO₂), 11.2 (s, 1 H, N₃-H) ; LRMS (FAB/glycerol): 918, M + 1. 918.4200 calcd for C₃₉H₆₈N₅O₁₆Si₂.

For 134; IR (CHCl₃): 3380, 1745, 1690, 1595 cm⁻¹; ¹H NMR (200 MHz, CDCl₃, 55 °C): δ 0.05 (s, 6 H, Si(CH₃)₂Bu), 0.89 (s, 9 H, Si(CH₃)₂C(CH₃)₂), 1.25 (s, 9 H, NCO₂Bu), 1.92 (d, J = 1.1 Hz, 3 H, 5-CH₃), 2.06, 2.09 (2 s, 2 x 3 H, 2 x OCOCH₃), 3.59-3.64 (m, 3 H), 3.80 (s + m, 3 H + 2 H, CO₂CH₃ for s), 4.06 (s, 3 H,
OCONH$_2$ + NHCO$_2$Bu, 4.33 (t, $J = 4.5$ Hz, H-4'), 5.08 (dd, $J = 8.7$ and 4.2 Hz, H-5'), 5.31 (t, $J = 6.2$ Hz, H-2'), 5.47 (dd, $J = 6.3$ and 3.9 Hz, H-3'), 5.95 (d, $J = 5.9$ Hz, H-1'), 7.07 (d, $J = 1.2$ Hz, H-6), 7.36 (d, $J = 8.3$ Hz, NHCO$_2$), 7.87 (br s, N3-H); $^1$H NMR (400 MHz, DMSO-d$_6$, 70 °C): $\delta$ 0.04 (s, 6 H, Si(CH$_3$)$_2$Bu), 0.87 (s, 9 H, Si(CH$_3$)$_2$C(CH$_3$)$_3$), 1.25 (s, 9 H, NCO$_2$Bu), 1.79 (s, 3 H, 5-CH$_3$), 2.03, 2.06 (2 s, 2 x 3 H, 2 x OCOCH$_3$), 3.55 (m + t, $J = 5.0$ Hz, 3 H), 3.67 (s, 3 H, CO$_2$CH$_3$), 3.74 (t, $J = 5.0$ Hz, 2 H), 3.96-3.97 (br s, 3 H, NHBoc and OCONH$_2$), 4.31 (t, $J = 5.6$ Hz, H-4'), 4.89 (dd, $J = 8.4$ and 5.8 Hz, H-5'), 5.49 (t, $J = 6.1$ Hz, H-2'), 5.50 (dd, $J = 5.9$ and 4.1 Hz, H-3'), 5.83 (d, $J = 5.2$ Hz, H-1'), 7.42 (s, H-6), 7.87 (d, $J = 8.3$ Hz, NHCO$_2$), 11.21 (br s, N3-H).

For 135: IR (CHCl$_3$): 3300, 1745, 1690, 1590 cm$^{-1}$; $^1$H NMR (200 MHz, CDCl$_3$, 55 °C): $\delta$ 0.12, 0.13 (2 s, 6 H, Si(CH$_3$)$_2$Bu), 0.91 (s, 9 H, Si(CH$_3$)$_2$C(CH$_3$)$_3$), 1.43 (s, 9 H, NCO$_2$C(CH$_3$)$_3$), 1.91 (d, $J = 1.1$ Hz, 3 H, 5-CH$_3$), 2.05, 2.07 (2 s, 2 x 3 H, 2 x OCOCH$_3$), 3.13 (d, $J = 4.1$ Hz, OH), 3.75 (s, 3 H, CO$_2$CH$_3$), 3.84 (m, 1 H), 4.01 (ddd, $J = 6.1$, 4.2, and 2.0 Hz, H-4''), 4.14 (m, 1H), 4.20 (dd, $J = 8.0$ and 5.7 Hz, 1 H), 4.31 (dd, $J = 10.0$ and 6.8 Hz, 1 H), 4.43 (dd, $J = 5.92$ and 3.7 Hz, H-4''), 4.97 (br s + dd, 4 H, NHCO$_2$Bu, OCONH$_2$, and H-5' for dd), 5.43 (dd, $J = 6.5$ and 4.6 Hz, H-2''), 5.53 (t, $J = 6.1$ Hz, H-3''), 5.60 (d, $J = 4.5$ Hz, H-1''), 7.05 (d, $J = 1.2$ Hz, H-6), 7.43 (d, $J = 7.0$ Hz, NHCO$_2$), 8.73 (br s, N3-H); $^1$H NMR (400 MHz, DMSO-d$_6$, 70 °C): $\delta$ 0.08 (s, 6 H, Si(CH$_3$)$_2$Bu), 0.88 (s, 9 H, Si(CH$_3$)$_2$C(CH$_3$)$_3$), 1.39 (s, 9 H, NCO$_2$C(CH$_3$)$_3$), 1.79 (s, 3 H, 5-CH$_3$), 2.03, 2.07 (2 s, 2 x 3 H, 2 x OCOCH$_3$), 3.67 (s, 3 H, CO$_2$CH$_3$), 3.86 (s, 3 H), 4.05 (m, 1 H), 4.20 (dd, $J = 8.85$ and 1.92, 1 H), 4.28 (t, $J = 5.1$ Hz, H-4''), 4.66 (br s, NHBoc), 4.85 (dd, $J = 7.7$ and 5.7 Hz, H-5''), 5.45 (dd, $J = 6.3$ and 5.3 Hz, H-2).
5.50 (dd, \( J = 6.7 \) and 5.7 Hz, H-3), 5.81 (d, \( J = 5.1 \) Hz, H-1'), 6.10 - 6.21 (br s, 2 H, OCONH\(_2\)), 7.40 (s, H-6), 7.85 (d, \( J = 7.9 \) Hz, NHCO\(_2\)). 11.18 (br s, 1 H, N3-H)\(_2\)LRMS (FAB/glycerol): 804, M + 1, 804.3335 calc for C\(_{33}\)H\(_{54}\)N\(_5\)O\(_{16}\)Si.
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2. For a review and bibliography of penaldic acid, see: Chain, E. In Antibiotics; Florey, H. W. et al., Eds; Oxford University; New York, 1949, Vol. 2, pp 829-839.


6. (a) Arndt, F. Organic Syntheses; Wiley: New York, 1943, Collect. Vol. 2, p 165. (b) We thank Dr. N. S. Chandrakumar, G. D. Searle and Company for alerting us to the fact that N-BOC serine methyl ester could be prepared without significant racemization via esterification with methyl iodide, thereby avoiding the generation and the use of diazomethane on a large scale.


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13. The numbering system used in this thesis corresponds to the current CA index names for substructures i-iii. For details, see: Chemical Abstracts Service Index Guide; American Chemical Society: Washington, DC, 1989.


even though it might be further removed from the prochiral π-system. Dyong, L.; Wieman. R. *ibid.* 1980, 113, 1592.

22. Trippett, S.; Walker, D. M. J. Chem. Soc. 1961, 1266. (E)-α,β-unsaturated aldehyde 36 was also obtained in 89% purified yield by a treatment of 5b with a commercially available ylide, Ph3P=CHCHO in benzene/reflux conditions.


25. The erythro designation is used to relate the two adjacent asymmetric centers created after the nucleophilic addition to 5b, which, in an absolute sense, correspond to the relationship found for the asymmetric centers of erythrose, i.e., 2R,3S or 2S,3R. Likewise, the threo designation correspond to the relationship between the asymmetric centers of threose, i.e., 2R,3R or 2S,3S.


35. For the preparation of propiolaldehyde dimethyl acetal 57, prepared in 2 steps (37% overall distilled yield on a 5 mol scale) from acrolein by a route analogous to that reported for propiolaldehyde diethyl acetal: Le Coq, A.; Gorgues, A. in *Organic Syntheses;* Coates, R. M., Ed.; Wiley: New York, 1979; Vol. 59, pp 10-15. However, we found it more convenient and economical to use KOH as the base for the double dehydrohalogenation step rather than the 300 mol% of Bu₄N⁺HSO₄⁻ reported in the Organic Syntheses procedure: Sheehan, J. C.; Robinson, C. A. *J. Am. Chem. Soc.* 1949, 71, 1436.


39. For the chelation controlled addition to oxazolidine aldehyde 5, see: (a) ref. 36 (b) Garner, P.; Ramakanth, S. *J. Org. Chem.* 1986, 51, 2609.


44. Cha, J. K.; Christ, W. J.; Kishi, Y. Tetrahedron 1984, 2247; and references cited therein.


48. We did not experience any difficulty with this oxidation, which is performed in aqueous acetone (see Experimental Section), due to the formation of (inactive) lower valent ruthenium carboxylates. Cf. Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. J. Org. Chem. 1981, 46, 3936.


53. Acyclic Nucleosides such as this are not unknown. See for example: Wolfrom, M. L.; Foster, A. B.; Mewain, P.; Bebenburg, W. V.; Thompson, A. J. Org. Chem. 1961, 26, 3095.


55. A similar problem was encountered by Rosenthal and Cliff during their work on the synthesis of polyoxin analogues having the N-trifluoroacetamido glycin methyl ester moiety appended to C-3. see: Rosenthal, A.; Cliff, B. Carbohydrate Res. 1980, 79, 63.


68. It was found that commercially available N-BOC L-serine (United States Biochemical Corporation) was an entirely satisfactory starting material. However, for the unnatural D-series, it is more economical to prepare N-BOC D-serine as described.