BARNES, KEITH DOUGLAS

UTILIZATION OF UNSTABILIZED CARBOHYDRATE PHOSPHORANES: A TOTAL SYNTHESIS OF METHYL PERACETYL- ALPHA-HIKOSAMINIDE, THE UNDECOSE PORTION OF HIKIZIMYCIN (ANTHELMYCIN) AND STUDIES DIRECTED TOWARD A SYNTHESIS OF TUNICAMYCIN

The Ohio State University

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UTILIZATION OF UNSTABILIZED CARBOHYDRATE PHOSPHORANES: A TOTAL SYNTHESIS OF METHYL PERACETYL-α-HIKOSAMINIDE, THE UNDECOSE PORTION OF HIKIZIMYCIN (ANTHELMYCIN) AND STUDIES DIRECTED TOWARD A SYNTHESIS OF TUNICAMYCIN

DISSERTATION

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

By
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The Ohio State University
1980

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STATEMENT OF PROBLEM

In the past several years the structures of several complex nucleoside antibiotics with an undecose as the basic carbohydrate unit have been elucidated, namely, hikizimycin (or anthelmymcin 1) and the tunicamycin complex 6. The ten
consecutive chiral centers in the undecose portion of hikizimycin, hikosamine 4 has made it largely unapproachable by methods in the carbohydrate literature. Similarly the undecose portion of tunicamycin, tunicamine 11, has made it also largely unapproachable.

The recently developed chemistry of unstabilized carbohydrate phosphoranes 45,46 appeared to have great potential for the synthesis of a wide variety of complex carbohydrates. The goal of this research has been to utilize this recently developed chemistry of unstabilized carbohydrate phosphoranes to construct the undecoses hikosamine and tunicamine.
HISTORICAL

A. Hikizimycin (Anthelmycin)

1. Isolation

Anthelmycin \(1\) was first isolated in 1964 by Hamill and Hoehn,\(^1\) who described its fermentation, isolation, physical-chemical properties and biological activity. Anthelmycin was readily obtained from a strain of *Streptomyces longissimus*, found in a soil sample collected in Indiana, U.S.A., in a variety of fermentation media and extracted from the fermentation broth with cation-exchange resins.

\[
\begin{align*}
\text{CH}_2\text{OH} \\
\text{HOCH} \\
\text{HOCH} \\
\text{HCOH} \\
\text{HCOH} \\
\text{OCH} \\
\text{NH}_2
\end{align*}
\]

In 1970 the fermentation, isolation, physical-chemical properties and biological activity of a "new" antibiotic, hikizimycin, were described.\(^2\) Hikizimycin was extracted with cation-exchange resins or activated carbon from the fermentation broth of *Streptomyces A-5*, which was obtained from
a sample of soil collected at the Hikizi riverside, Kanagawa Prefecture, Japan.

It was demonstrated in 1977 that Hikizimycin and Anthelmymcin are identical by comparision of their X-ray powder patterns, bioautograms and $^{13}$C NMR spectra.

2. Biological Activity

Hamill and Hoehn demonstrated that anthelmymcin possessed broad but weak antimicrobial activity and Uchida and co-workers also observed antimicrobial activity with hikizimycin and found it to be especially active against phytopathogenic fungi. More importantly however was the anthelmintic activity which was observed with anthelmymcin. Oral administration of anthelmymcin to a host animal infected with parasites such as pinworms, roundworms, whipworms and strongyles resulted in the effective removal of these parasites. Illustrated in Table 1 is the activity which was observed with anthelmymcin at various dosage levels against the mouse pinworm, Syphacia obvelata.
Table 1
Activity observed with anthelmymcin at various dosage levels against the mouse pinworm, *Syphacia obvelata*.

<table>
<thead>
<tr>
<th>Wt. % Drug in diet</th>
<th>mg/kg</th>
<th>Number of animals</th>
<th>Clearance*</th>
<th>Worm reduction**</th>
</tr>
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<tbody>
<tr>
<td>Control</td>
<td>Control</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>.08</td>
<td>288</td>
<td>4</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>.04</td>
<td>203</td>
<td>5</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>.02</td>
<td>160</td>
<td>6</td>
<td>67</td>
<td>99</td>
</tr>
<tr>
<td>.01</td>
<td>76</td>
<td>6</td>
<td>83</td>
<td>99</td>
</tr>
<tr>
<td>.005</td>
<td>44</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* % Clearance = \( \frac{\text{Number of animals free of worms}}{\text{Total number of animals}} \) \times 100%

** % Worm reduction = \( \frac{\text{Average number of worms per control animals less average number of worms per treated animal}}{\text{Average number of worms per control animal}} \) \times 100%
Anthelmycin effected the elimination of 80% of the total population of *Ascaris suis* (large roundworms), 100% of *Oesophagostumum* sp. (nodular worms), and 100% of *Trichuris suis* (whipworms) when administered to swine at a level of 12 g per ton of normal swine ration.

A study of the acute toxicity of anthelmycin in mice showed the intravenous LD$_{50}$ to be about 5 mg/kg and the oral LD$_{50}$ about 150 mg/kg.$^1$

Hikizimycin was found to inhibit protein biosynthesis in intact cells of *Pseudomonas syringae*.$^4$ As illustrated in Figure 1, isoleucine incorporation was reduced within 15 minutes after addition of hikizimycin.

![Figure 1](image)

**Figure 1.** Effect of hikizimycin on the incorporation of $[^{14}C]$-isoleucine by intact cells of *Pseudomonas syringae* (time of addition of the antibiotic is indicated by the arrow. 1: control 2: hikizimycin 0.8 mg/ml. (reference 4)**
Hikizimycin has also been shown to inhibit both poly-(U)-directed polyphenylalanine biosynthesis and the puromycin reaction in cell-free systems of *Escherichia coli*. Figures 2 and 3 illustrate respectively the effect of concentrations of hikizimycin on polyphenylalanine biosynthesis and the formation of N-acetyl-[\(^{14}C\)]-phenylalanyl-puromycin in the cell-free system of *E. coli*. The well known aminohexosyl-cytosine antibiotic, gougerotin, is shown in Figures 2 and 3 to be a less potent inhibitor than hikizimycin.

Figure 2. Effect of concentrations of hikizimycin (1) and gougerotin (2) on the polyphenylalanine biosynthesis in the cell-free system of *E. coli* (reference 4)
Figure 3. Effect of concentration of hikizimycin (1) and gougerotin (2) on the formation of N-acetyl-[\(^{14}\)C]-phenylalanyl-puromycin in the cell-free system of *E. coli*. (reference 4)
Gonzales, Valquett, and Jimenez in studies to determine the mode of action of hikizimycin on the inhibition of protein synthesis in prokaryotic and eukaryotic ribosomes found that hikizimycin inhibited the ribosomal peptidyl transferase center thus preventing the peptide bond forming reaction.\textsuperscript{5}

3. Structure Elucidation

Initial structural studies\textsuperscript{2} based on UV data and degradation experiments suggested the presence of a \(N_1\)-substituted cytosine component\textsuperscript{2} and 3-amino-3-deoxy-D-glucose (kanosamine)\textsuperscript{3} as structural units of hikizimycin. The presence of cytosine, kanosamine and an unknown amino sugar component was confirmed by Das, Defaye and Uchida,\textsuperscript{6} and the molecular formula for hikizimycin established as \(C_{21}H_{37}N_{5}O_{14}\).

The final fragment, to be identified, obtained from the mild degradation\textsuperscript{7} of hikizimycin (Reaction 1) was shown to be an undecosamine, \(C_{11}H_{23}NO_{10}\), designated as hikosamine\textsuperscript{4}. Based upon spectral data and chemical degradation studies, Uchida and Das\textsuperscript{7} initially showed hikosamine to be a 4-amino-4-deoxy-aldoundecopyranose in which carbon atoms 1-5 have the D-gluco configuration. Subsequent isolation of D-glycer-D-galactoheptose after oxidative cleavage of the C\textsubscript{5}-C\textsubscript{6} bond of hikosamine...
Reaction 1. The mild degradation of hikizimycin 1.

1. \( H_2/Pd/C \)
2. \( CH_3OH/HCl \)

as \( N,N' \)-acetyl derivative

Hikosamine

Hikosaminyl cytosine

Kanosamine
demonstrated its structure to be 4-amino-4-deoxy-\(\text{D}-\text{glycero-}\text{D-galacto-}\text{D-glucoundecaplyranose}\).\(^8\) Partial degradation, yielding hikosaminyln cytosine \(2\), demonstrated the cytosine unit to be attached to \(C_1\) of hikosamine.

\[
1\text{-N-[2-O-(3-amino-3-deoxy-\(\text{\beta-D}\text{-glucopyranosyl})\text{-4-amino-4-deoxy-\(\text{\beta-D}\text{-glycero-}\text{D-galacto-}\text{D-glucoundecaplyranosyl}]}\text{cytosine}\]
\]

\(5\) was initially proposed as the structure of hikizimycin.\(^8\),\(^9\) Evidence for structure \(5\) in which the

kanosamine component \(3\) is glycosidically bound to the \(C_2\) hydroxyl of hikosaminyln cytosine was claimed to be supported by the behavior of hikizimycin and its fragments to periodiate oxidation. The \(\beta\)-configuration for the glycosidic linkages of the two amino sugars was suggested by
NMR and molecular rotation studies. Further confirmation of structure 5 was claimed to be supported by comparison of the $^{13}\text{C}$ NMR chemical shifts of selected model compounds with hikizimycin and its fragments.

Das, Nagarajan, Wenkert et al., through careful analysis of the $^{13}\text{C}$ NMR spectra of hikizimycin and its peracetyl derivative, demonstrated that structure 5 was incorrect, and, based on $^1\text{H}$ NMR, $^{13}\text{C}$ NMR and field desorption mass spectral data, established unequivocally structure 1 for hikizimycin, in which the kanosamine fragment is linked to the 6-hydroxyl of the hikosamine moiety. A systematic name for hikizimycin (anthelmymcin 1) is:

1-(6-O-(3-amino-3-deoxy-$\alpha$-D-glucopyranosyl)-4-amino-4-deoxy-$\alpha$-D-glycero-$\beta$-galacto-$\beta$-gluco-undecopyranosyl] cytosine.
B. Tunicamycin

1. Isolation

Tunicamycin which will be referred to as TM) was isolated by Takatsuki, Arima and Tamura, who described its fermentation, isolation, physical-chemical properties and biological activity. TM, produced by a new species of the genus Streptomyces named Streptomyces lysosuperifus, was isolated and purified from the fermentation media by way of solvent extraction followed by chromatography on silica gel.

![Chemical Structure of Tunicamycin](attachment:image.png)

2. Biological Activity

The antiviral activity of TM initially studied by Takatsuki, Arima, and Tamura lead to its isolation and demonstrated that it inhibited the multiplication of Newcastle disease virus and herpes simplex virus in cultured cells, and suppressed the occurrence of local lesions on
tobacco mosaic virus-infected leaf discs. Since this initial research, TM has been shown to have an effect (in vitro) on Semliki forest, influenza, avian sarcoma, vesicular stomatitis, Rous sarcoma, Sindbis, and Rauscher murine leukemia viruses.

Studies have demonstrated that TM affects viral membrane assembly by way of inhibition of glycosylation of glycoproteins that form part of a properly constructed viral envelope. Numerous in vitro studies have shown that glycosylation appears necessary for the assembly of properly functioning enveloped virus particles. For example, TM inhibited the incorporation of glucosamine into viral glycoproteins and was found to specifically inhibit the glycosylation and multiplication of Sindbis virus and vesicular stomatitis virus in BHK cells. That TM was not a general protein synthesis inhibitor was shown in that it did not affect the growth of non-enveloped encephalomyocarditis in BHK cells.

TM has been shown to be a rather specific antiviral agent and this important selective influence of TM has been studied in vitro under various circumstances. For example, SV-40 transformed cells have been shown to be more sensitive to TM than normal cells. Changes in cell surface morphology and cell growth with various transformed cell lines versus non-transformed cells have been
seen in the presence of TM. With SV-40 and polyme-
transformed mouse (3T3) cells and human WI-38 cells, in-
cubation with TM (1 ug/ml) caused detachment of the cells
from the surface and death within 24 hours, while similar
effects were not seen with normal cells, though cell growth
with 3T3 cells was inhibited. A more general investiga-
tion with nine cell lines demonstrated that transformed
cells were three to six times more sensitive than non-
transformed cells. A hypothesis put forward to explain
such results was that normal and transformed cell lines
have different sensitivities to inhibition of nutrient up-
take.

One route by which glycoproteins are formed involves
transfer of an oligosaccharide chain to a polyisoprenoid
carrier (dolichyl phosphate) and from the carrier to the
polypeptide through an N-linkage to asparagine. TM has
been demonstrated to inhibit the transfer of N-acetyl-
glucosamine from UDP-N-acetylglucosamine to dolichyl
phosphate, but it does not inhibit the further lengthen-
ing of the oligosaccharide once it is on the lipid back-
bone. Based on this result and other data the
proposal was made that TM mimicks both dolichyl phosphate
(the long hydrocarbon chain of TM) and UDP-N-acetylglucos-
amine (the remainder of the molecule), thus acting as a
bisubstrate analog.
3. Structure Elucidation

The structure of TM was established from spectral data and chemical degradation studies. TM was shown to contain as its structural units, uracil, fatty acids, N-acetyl glucosamine and a novel 11 carbon aminodeoxy-dialdose.

Acid hydrolysis (3N HCl, reflux, 3 hours) of TM (Reaction 2) and extraction of the hydrolyzate with ether afforded a mixture of fatty acids which demonstrated that TM was not a single compound, but rather a mixture of homologous antibiotics, each of which contains a mole of a different fatty acid. Appropriate processing of this hydrolyzate afforded glucosamine which was identified by TLC, IR and NMR spectral data and tunicaminy luracil.

Milder hydrolytic conditions (3N HCl, reflux, 1 hour) afforded a compound which on further hydrolysis afforded fatty acids and tunicaminy luracil, demonstrating that the amino group of tunicaminy luracil is substituted by the fatty acid.

That tunicaminy luracil showed reducing activity whereas tunicamycin was non-reducing, lead to the conclusion that C-11' of the tunicamine unit was glycosidically linked to the anomeric carbon of the glucosamine residue.
Reaction 2. The hydrolysis of Tunicamycin 6.
The structure of tunicaminy1 uracil \( LQ \) was shown to be \( 1-\beta-(10'-\text{amino}-6',10'-\text{dideoxy-\( L \)-glycero-\( D \)-gluco-\( D \)-allo-}
undecanodialdo-7',11'-pyranose-1',4'-furanosyl)\)-uracil based on careful analysis of the \(^1\text{H} \) NMR, \(^{13}\text{C} \) NMR and mass spectral data of tunicaminy1 uracil and a number of derivatives and comparison to the spectral data of selected model compounds.
C. Preparations of Complex Carbohydrates

1. Utilization of Methods Other Than the Wittig Condensation

In the past several years, the structures of a number of complex nucleoside antibiotics containing long chain carbohydrates have been elucidated. As mentioned previously, anthelmymcin (hikizimycin)\(^{1,10}\) and tunicamycin\(^{31,32}\) contain as their basic carbohydrate unit the undecoses hikosamine\(^{4}\) and tunicamine\(^{11}\), respectively. Sinefungin\(^{33}\)\(^{12}\) and the related factor C\(^{33}\)\(^{13}\) contain 10 carbon sugar units.

\[
\text{SINEFUNGIN} \quad 12
\]

\[
\text{FACTOR C} \quad 13
\]

A wide variety of naturally occurring carbohydrates and nucleosides have branched or chain-elongated structures. The syntheses of a number of these have been accomplished by a variety of useful methods involving simple one or two carbon additions to six or five carbon sugars.
However, approaches toward the construction of complex carbohydrates such as hikosamine 4 and tunicamine 11, involving successive simple one or two carbon additions to six or five carbon sugars, are unsuitable because of the problem associated with the stereochemical control of each successive asymmetric center added. Hence, the construction of these types of molecules requires a synthetic strategy in which the basic carbon skeleton can be formed in a minimum number of steps and with control of as much stereochemistry as possible.

One recent example34 employing this concept involved the condensation of the dianion of a mono-unprotected erythrose derived dithiane with 1,2:3,4-di-O-isopropylidene-α-D-galacto-hexodialdo-1,5-pyranose to form a new carbon-carbon bond in unspecified yield.
A number of other isolated cases of complex carbohydrate formation include: a) electrolytic reduction of glucose to produce D-mannitol plus a dodecitol of unknown configuration,\textsuperscript{35} b) the linkage of two carbohydrates through a triple bond by a double addition sequence with an acetylenic Grignard reagent,\textsuperscript{36} and c) the dimerization of α-diazoketoses derived from certain sugars, followed by base cleavage to afford the branched-chain sugars.\textsuperscript{37}
These sequences, however, lack generality and have not developed into useful synthetic methodology in the carbohydrate field.
2. Utilization of the Wittig Condensation

Since the Wittig reaction was first employed in the carbohydrate field, when glyceraldehyde was condensed with carboethoxymethylenetriphenylphosphorane in 1962,\textsuperscript{38} it has been a valuable synthetic tool in carbohydrate chemistry.

\[
\begin{align*}
\text{CHO} & \quad \text{Ph}_3\text{P} = \text{C}-\text{OCH}_2\text{CH}_3 \\
\text{CH}_2\text{CH} & \quad \text{CH} = \text{CH}\text{C}-\text{OCH}_2\text{CH}_3
\end{align*}
\]

Wittig condensations of a variety of phosphoranes with both aldehydo and keto sugars have yielded previously inaccessible unsaturated sugars which are capable of undergoing a wide range of useful transformations. For example, additions to a double bond (mainly hydration and hydrogenation) lead to branched chain or chain-elongated sugars.

The mild reaction conditions and high yields of the Wittig condensation have made it an extensively used method for chain extension of such highly functionalized molecules as carbohydrates. Most of the Wittig condensations described in the carbohydrate field involve
condensations of stabilized as well as unstabilized phosphoranes with protected sugar aldehydes and ketones and to a lesser extent, partially protected or free sugars. A number of excellent reviews exist on the subject, and their contents will not be repeated here.

As demonstrated in the preceding section, a definite need existed for the development of a useful, general synthetic methodology for the construction of complex carbohydrates containing 9 or more carbons. This problem was successfully addressed by Secrist and Wu, who recently developed a method for the generation of a number of unstabilized carbohydrate phosphoranes and their condensation with various carbohydrate aldehydes, (as well as other aldehydes) to give excellent yields of complex carbohydrates.

Prior to this work, very little attention had been directed toward the formation of carbohydrate phosphoranes. Zhdanov had generated the stabilized carbohydrate-containing phosphoranes but both as expected demonstrated very low reactivity and only condensed with a few activitated aromatic aldehydes.

The obvious alternative to the unreactive stabilized carbohydrate phosphoranes of Zhdanov would of course be the use of unstabilized carbohydrate phosphoranes which would show much higher reactivity. A major obstacle
Other aldehydes
no reaction
however in the use of an unstabilized carbohydrate phosphorane is the presence of a leaving group $\beta$ to the phosphorus which would occur in the vast majority of carbohydrates. Generation of the phosphoranes might lead to cleavage of the carbon-oxygen bond $\beta$ to the phosphorus to form a vinyl phosphonium salt. A number of instances have been reported in which this $\beta$-elimination had occurred and led to the decomposition of ylides. For example, the ylides derived from 16 and 17 have been shown to decompose very readily, as evidenced by the rapid disappearance of the ylide color. 49
Vinyltriphenyl phosphonium bromide 18 has been prepared employing a β-elimination and similar intramolecular eliminations have been observed in the preparation of cyclopropylidene 52 and cyclobutylidene 51 phosphoranes 19 and 20.

Secrist and Wu found it possible to avoid or decrease the problem associated with β-elimination leading to decomposition of ylides by careful manipulation.
of experimental conditions (mainly solvent and temperature.)

A re-examination\textsuperscript{53} of the phosphoranes derived from 16 and 17 with $\alpha$-substituents, which have been reported not viable for condensations, demonstrated that by careful control of experimental conditions successful condensations occurred in good yield. For example, treatment of 16 with n-BuLi in 2.5:1 THF-HMPA at -60$^\circ$C under nitrogen generated the ylide, which condensed with a number of aromatic aldehydes, affording the olefinic products in excellent yields.

\[
\begin{align*}
\text{Ph}_3\text{PCH}_2^+ & \quad \text{I}^\ominus \\
\text{CH} & \quad \text{CH}_2 \\
\text{O} & \quad \text{O} \\
\text{CH}_3 & \quad \text{CH}_3 \\
\text{16} & \quad \text{16}
\end{align*}
\]

\[
\begin{align*}
1) \text{nBuLi, -60}^\circ & \quad \text{THF} \quad \text{HMPA} \\
\text{X} & \quad \text{CHO}
\end{align*}
\]

\[
\begin{align*}
X = \text{H} & \quad \text{cis} \quad 77\% \\
& \quad \text{trans} \quad 1\%
\end{align*}
\]

\[
\begin{align*}
X = \text{Cl} & \quad \text{cis} \quad 76\% \\
& \quad \text{trans} \quad 2\%
\end{align*}
\]

Condensation of the ylide derived from 17 under similar conditions with benzaldehyde provided 30% yield of a single \textit{cis} product and 30% recovery of starting material. The low yield was attributed to the poor solubility of 17, even when an increased amount of HMPA was used.
Initially the generation and reactivity of the ylide derived from methyl-5-deoxy-2,3-O-isopropylidene-5-(triphenylphosphonio)-β-D-ribofuranoside iodide 21 was examined in order to explore the potential of unstabilized carbohydrate ylides.\textsuperscript{45,53} In 21, having the oxygen β to the phosphorus maintained in the molecule through another set of bonds provides a particularly favorable case, because if β-elimination occurred, intramolecular reclosure would regenerate the ylide. This reversible β-elimination was observed with the ylide generated from
tetrahydrofurfuryltriphenylphosphonium bromide 22.

\[
\begin{align*}
\text{O} & \quad \text{PPh}_3 \\
\text{CH} & \quad \text{Br} \\
\text{H} & \quad \text{Ph} \\
\end{align*}
\]

\[
\begin{align*}
\text{PhCHO} & \quad \text{DMF, NaH} \\
110^\circ, 2d \\
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{CH} = \text{CHPh} \\
\text{CH} & \quad \text{Ph} \\
\text{H} & \quad \text{Ph} \\
\end{align*}
\]

Treatment of 21 with 1 equivalent of n-BuLi at -50°C under nitrogen in 2:1 THF-HMPA generated the red-brown ylide which condensed with benzaldehyde to afford a 79% yield of two olefinic products 23 and 24. Catalytic reduction (H₂, Pd/C) of these two products both afforded the same compound 25, indicating that they were simply olefinic cis and trans isomers.
It was conclusively demonstrated that 23 and 24 did not have the expected \( \alpha\)-D-ribo configuration but rather the \( \alpha\)-L-lyxo configuration. Condensation of the ylide derived from 21 with several other aromatic and aliphatic aldehydes gave products in all cases possessing the \( \alpha\)-L-lyxo configuration.
The isolation of the $\alpha$-L-lyxo products from the condensation with aldehydes indicated that equilibration of the $\beta$-D-ribo ylide to the $\alpha$-L-lyxo ylide through an open-chain structure (26, 27, 28) must have occurred. Isolation of the epimerized phosphonium salt 29 was accomplished by generation of the ylide in pure THF and quenching with Dowex 50(H+) ion exchange resin. One possible explanation for the epimerization is that perhaps a chelation effect between the phosphorus$^-$ and O-3 assists in driving the equilibrium toward the $\alpha$-L-lyxo configuration.

\[
\text{[Ylide]} + \text{ArCHO} \rightarrow \begin{array}{c}
\text{Ar}
\end{array}
\]

<table>
<thead>
<tr>
<th>Ar</th>
<th>OVERALL % YIELD</th>
<th>RELATIVE RATIOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>79</td>
<td>61</td>
</tr>
<tr>
<td>p-ClPh</td>
<td>79</td>
<td>37</td>
</tr>
<tr>
<td>p-CH$_3$OPh</td>
<td>79</td>
<td>not completely separable</td>
</tr>
</tbody>
</table>
Condensation of 21 with ketones afforded complex mixtures of products with the major product in all cases being the self-condensation product 30. One possible mechanism for the formation of 30 is given on the following page.
With the ultimate goal of constructing undecoses relating to hikizimycin and tunicamycin, Secrist and Wu examined the reactions of the galactose phosphorane $\text{31}$, derived from phosphonium salt $\text{32}$, including its reaction with several carbohydrates aldehydes.$^{46,53}$

![Chemical Structure](image)

Treatment of $\text{32}$ with 1 equivalent of n-BuLi at $-60^\circ\text{C}$ in 2:1 THF-HMPA generated the red-colored ylide $\text{31}$, which condensed with a variety of simple aldehydes in good yield. In all cases examined the $\alpha$-$\text{a-D-galacto}$ configuration was retained during the condensation, hence there is no evidence as to whether or not the sugar ring is opening and reclosing once the ylide is generated.

Condensation of $\text{31}$ under the usual conditions with methyl 2,3-$\text{a-D-isopropylidene a-D-ribo}$-pentodialdo-1,4-furanoside $\text{33}$ afforded a single product $\text{34}$ in 64% yield.
75% CH₂CHO

77% (1/1, l/cis/trans)

68% CH₂CHO

86% (1/1, l/cis/trans)

77% (1/1, cis/trans)

31

22

nBuLi

THF·HMPA

-60°
Ozonomysis-reduction produced only two carbohydrate alcohols 35 and 36 indicating no configurational changes in either partner of the condensation.
Similarly, condensation of 31 with 2,3,4,5-di-O-isopropylidene aldehydo-\(D\)-arabinose 37 also produced a single isomer 38 in 84% yield. Again ozonolysis-reduction confirmed the configurational integrity of both halves.

Examination of the \(^1\)H NMR spectra of 34 and 38 established the geometries about their double bonds to be in both cases \(\text{cis}\). Isomerization studies conclusively confirmed the \(\text{cis}\) geometries.
The research described here demonstrated that carbohydrate phosphoranes are indeed viable intermediates for the construction of complex carbohydrates. 34 and 38 are structurally very similar to the undecoses hikosamine 4 and tunicamime 11. By proper protection and functionalization of the appropriate precursors for both partners in the condensation, the syntheses of the undecoses 4 and 11 should be realized in a relatively short sequence.
RESULTS AND DISCUSSION

A. Synthesis of Methyl Peracetyl-α-Hikosaminide. The Undecose Portion of the Nucleoside Antibiotic Hikizimycin

The strategy employed toward the synthesis of methyl-peracetyl-α-hikosaminide \(39\) (methyl 4-acetamido-2,3,6,7,8,9,10,11-octa-O-acetyl-4-deoxy-α-D-glycero-D-galacto-D-gluco-undecopyranoside), a fully protected derivative of hikosamine 4, revolved around construction of the basic carbon framework utilizing the recently developed chemistry of carbohydrate phosphoranes \(45,46\) described in the previous section.

A logical retrosynthetic analysis of hikosamine (Reaction 3) suggested the condensation of a five- or six-carbon unstabilized carbohydrate phosphorane with a six- or five-carbon carbohydrate aldehyde to form the \(\text{C}_6-\text{C}_7\) carbon-carbon double bond. In this manner by appropriate selection
Reaction 3. A Retrosynthetic Analysis of Hikizimycin (or Anthelmymcin)
of the precursors all the asymmetric centers have been
fixed exactly as desired, except those, of course, of the
newly formed double bond. Appropriate oxidation of the
double bond at a later stage would then introduce the hydrox-
yls at C$_6$ and C$_7$. Assuming that the nitrogen at C$_4$ can be
introduced by the nucleophilic displacement of some oxygen
leaving group, the precursors to carbons 1-6 and 7-11
respectively would be D-galactose and D-arabinose. The
possibility existed of condensing a galactose derived alde-
hyde with an arabinose phosphorane or condensing an arabi-
nose aldehyde with a galactose derived phosphorane.

An initial attempt toward the synthesis of hikosamine was based on the idea of the selective removal of the 3,4-
Q-isopropylidene group of 40. The synthesis of 40 was
carried out by the condensation of the unstabilized D-
galacto phosphorane 31 with the D-arabino aldehyde 41.

If the selective deprotection of 40 at carbons 3 and
4 could be achieved it would be possible to selectively in-
troduce a nitrogen at C$_4$ by the nucleophilic displacement
of an oxygen leaving group. The hydroxyls at C$_3$ and C$_4$
could be differentiated because the hydroxyl at C$_4$ is axial
whereas the C$_3$ hydroxyl is equatorial.

A variety of reaction conditions were utilized in an
attempt to carry out the selective deprotection, but none
met with any success. In all cases removal of both
isopropylidene groups was observed.

The major obstacle in the aforementioned attempted synthesis was the introduction of an amino group at C₄. This suggested that a suitable approach toward hikosamine would necessitate proper selectivity at some stage of the synthesis for the introduction of the amino group at C₄. This selectivity could be realized by the construction of an olefin similar to 40 but with different protecting groups built into the molecule in order to show different reactivities in later deblocking or introduction of an amino or latent amino functionality at C₄ of the C₁-C₆ precursor in the Wittig condensation such as to yield an olefin with an amino or latent amino functionality at C₄.

Taking the former approach, the D-galacto-6-aldehyde 42 was prepared (see next page). This aldehyde was successfully condensed with the ylide 31 affording 43 in 60% yield.
\[ \text{(CH}_3\text{)}_2\text{SO}_4 \xrightarrow{\text{KOH, THF}} \text{NBS} \xrightarrow{\text{CCl}_4, \Delta} \text{NaN}_3 \xrightarrow{\text{DMF, 120\degree C, 3 hrs.}} \]

40-45%
Condensation of 42 with a suitably protected \textit{D-arabino} phosphorane would give a product in which the C\textsubscript{4} hydroxyl could readily be deprotected selectively by hydrogenolysis at some stage of the synthesis followed by introduction of a nitrogen by appropriate manipulation. However the use of methyl ether protecting groups on the C\textsubscript{2} and C\textsubscript{3} hydroxyls made this compound unattractive due to the known difficulties in deprotection of methyl ethers. Other protecting groups
could possibly have been used on such an aldehyde as but the other approach in which a nitrogen functionality at would be introduced before the condensation appeared to be more desirable. This approach was particularly attractive because it avoided a number of manipulations to introduce a nitrogen at on an already complex molecule. Attention was hence directed toward the preparation of a suitable precursor to carbons 1-6 of hikosamine with an amino or latent amino functionality at .

As mentioned previously the possibility exists of condensing a or derived phosphorane with a or derived aldehyde. The latter alternative was considered to be a more desirable route, because if an amino or latent amino functionality was present in the phosphorane as would be the case in the
former alternative, this would most likely necessitate careful protection of the amino functionality. Therefore considering the possible complications of having an amine functionality within the same molecule in which a phosphorane would be generated, a synthesis was designed in which the D-galacto derived portion of hikosamine (C₁-C₆) containing the amino functionality would be introduced as the aldehyde in the condensation and the D-arabino derived portion (C₇-C₁₁) as the phosphorane.

Aldehyde 50 was selected as an appropriately protected and functionalized precursor to carbons 1-6. Reduction of the azide at a later stage would generate an amine at C₄.

The synthesis of 50 was accomplished in ten steps from methyl α-D-galactopyranoside. Tritylation at C₆ of methyl 2,3-di-O-benzyl-α-D-galactopyranoside ⁵⁵ followed by mesylation at C₄ and detritylation afforded the previously unknown 4-O-methanesulfonyl derivative ⁴⁷ in 57% yield. Nucleophilic displacement of the mesyl group with sodium azide in DMF yielded the azido-alcohol ⁴⁸ possessing the α-D-gluco configuration in 92%. 
Dicyclohexylcarbodiimide-dimethylsulfoxide oxidation of 48 gave the slightly unstable aldehyde which was conveniently isolated as the stable crystalline imidazolidine derivative 49 in 76% yield. Liberation of the aldehyde was accomplished by hydrolysis with THF-aqueous HCl followed by chromatography. Azeotropic removal of water from the initially formed aldehyde-aldehyde hydrate mixture produced the aldehyde 50 in 87% yield, which was typically utilized immediately.
An initial study of the stability and behavior of 50 toward the Wittig condensation with a carbohydrate phosphorane was examined by condensation at -65°C in 2:1 THF-HMPA with 31. Appropriate isolation afforded 51 as the only product in 65% yield.

Having 50 as an appropriately protected and functionalized precursor to C₁-C₆ of hikosamine, attention was directed toward the preparation of an appropriately protected arabinose phosphonium salt as a precursor to C₇-C₁₁.

Condensation of ylide 52 with 50 afforded only 15% yield of the desired product 53. Since 52 showed poor
reactivity and/or stability, efforts were directed toward the preparation of the di-O-cyclohexyldiene protected D-arabino phosphonium salt 58. The synthesis of 58 was carried out in standard fashion from 2,3,4,5-di-O-cyclohexyldiene-D-arabinitol 55. Conversion of 55 to the 1-iodo compound 57 was carried out in good yield via the p-toluene-sulfonate 56. Quaternization of 57 with triphenylphospbine in sulfolane at 110°C afforded 58 in 62% yield as a pale yellow foam. As in previous work, sulfolane was found to be a far superior solvent for this transformation.

An initial study of the reactivity of 58 demonstrated that the phosphorane 59 could be generated by the usual procedure with n-BuLi at -65°C in 2:1 THF-HMPA under nitrogen and condensed with benzaldehyde to afford a mixture of cis and trans olefinic products 60 and 61 in greater than 55% yield.
D-arabinose $\xrightarrow{1) \text{EtSH, H}^+} \xrightarrow{2) \text{O}_2, \text{H}^+}$

$\xrightarrow{1) \text{HgCl}_2, \text{HgO}, \text{H}_2\text{O},(\text{CH}_3)_2\text{CO}} \xrightarrow{2) \text{NaBH}_4}$

$\xrightarrow{1) \text{TsCl, C}_3\text{H}_5\text{N},}$

$2) \text{NaI, DMF, Na}_2\text{CO}_3$

$\xrightarrow{\text{PPh}_3 \text{ sulfolane}, 110^\circ\text{C}}$

$\xrightarrow{\text{THF-HMPA}, -78^\circ\text{C}} \xrightarrow{2) \text{PhCHO}} >55\%$

$\text{60 and 61}$
As previously mentioned, the position 8 to the phosphorous in the ylide derived from the D-ribo phosphonium salt 21 was epimerized by opening and reclosure of the sugar ring. Since a similar epimerization could have occurred at C2 of 59 by way of vinyl phosphonium salt formation and expulsion of alkoxide followed by reclosure, it was necessary to prove that the configuration at C2 remained unchanged. Confirmation that the D-arabino configuration was retained during the condensation was proven by ozonolysis of the cis-trans mixture of olefins 60 and 61 followed by LiAlH4 reduction. Only one carbohydrate alcohol was obtained which was identical to the known compound 55 by TLC, 1H NMR and 13C NMR.

\[ \text{CH-CHPh} \quad \rightarrow \quad \text{CH2OH} \]

60 and 61
When ylide 59 was condensed with 50 at -65°C under nitrogen in 2:1 THF-HMPA a single product 62 is obtained in 50% yield. Reduction of the azide to an amine and appropriate oxidation of the double bond followed by de-protection would convert 62 to hikosamine. A *cis* double bond would require a *trans*-hydroxylation procedure and a *trans* double bond a *cis*-hydroxylation procedure in order to attain the configuration of hikosamine at both C6 and C7. Hence it was absolutely essential to know the geometry about the double bond of 62.

In all cases46,59 of complex carbohydrate formation by way of unstabilized carbohydrate phosphoranes, the geometry about the double bond has been shown to be exclusively *cis*. For example, as mentioned previously the newly formed double bonds of 34 and 38 have been shown to be *cis*. The formation of only the *cis* compounds was not unexpected since
it was known that unstabilized ylides generally give predominately cis products, though exclusive formation of a cis product is unusual.

The geometry about the newly formed double bond in 62 was established as follows. Examination of the 60 and 90 MHz $^1$H NMR spectra of 62 in both CDCl$_3$ and benzene-d$_6$ proved fruitless since the chemical shifts of the two vinyl hydrogens were virtually identical and the coupling constants could not be determined. Treatment of 62 with LiAlH$_4$ afforded the amine 63 in 80% yield. Examination of the 60 MHz $^1$H NMR spectra of 63 in CDCl$_3$ and benzene-d$_6$ and the acetamido and trifluoroacetamido derivatives of 63 provided no information on the olefinic coupling constants.
However at 400 MHz the $^1$H NMR resonances for the olefinic protons were cleanly separated and a coupling constant $J_{6,7} = 10.8$ Hz was measured, clearly indicating a cis double bond for 63 and hence a cis double bond for 62.

The two olefinic resonances of 63 are the AB portion of an XABY system. However, the patterns have almost collapsed to an eight line system so that the chemical shifts could be calculated as an ABX system. With that approximation, the chemical shifts of the olefinic protons were found to be 5.72 and 5.50 ppm.
Figure 4. Partial 400 MHz $^1$H NMR spectrum of **63** in CDC$_3$.

Since it was absolutely essential to know the correct geometry of **62** for the purpose of hydroxylation of the double bond, confirmation of the olefinic geometry chemically by isomerization studies$^{57}$ was also sought. Irradiation of a cyclohexane solution of **63** in the presence of two equivalents of diphenyl disulfide for 35 minutes with a medium pressure mercury lamp afforded a 3:2 mixture of the starting cis isomer **63** and a newly formed isomer **64** in 96% total yield. Further irradiation resulted in a loss of yield. The isomers were readily separable by column chromatography.
Examination of the 400 MHz $^1$H NMR spectrum of the newly formed isomer gave a coupling constant $J_{6,7} = 15.8$ Hz, indicative of a trans double bond. Again the olefinic resonances of 64 are the AB portion of an XABY system and the chemical shifts calculated as 5.94 and 5.76 ppm.

Figure 5. Partial 400 MHz $^1$H NMR spectrum of 64 in CDC$_3$. 
The cis double bond of 62 requires a trans-hydroxylation procedure to attain the configuration of hikosamine at C$_6$ and C$_7$. Any trans-hydroxylation procedure should result in the production of two diastereoisomers, one having the configuration of hikosamine and the other having the opposite configuration at C$_6$ and C$_7$.

The initial approach to accomplish the trans-hydroxylation of 62 involved the Prevost reaction of the olefin with I$_2$ and silver acetate or silver benzoate to form the diacetate or dibenzoate respectively with overall anti addition to the double bond. However even under very forcing Prevost conditions (refluxing toluene for several days) no reaction was detected with silver benzoate and only a trace amount of a compound believed to be the intermediate iodoacetate with silver acetate.
As an alternate approach, trans hydroxylation was envisioned as possible by way of epoxidation followed by $S_{N}^{2}$ opening of the epoxide ring with an oxygen nucleophile, resulting in an overall anti addition to the double bond.

Epoxidation of 62 was an unexpectedly difficult transformation but, after 20 hours at 80°C with m-CPBA, the reaction afforded a 2:1 ratio of diastereoisomers 65 and 66 in 70% yield. At lower reaction temperatures and longer times a higher $65/66$ ratio was formed. The isomers were readily separable by chromatography.
Numerous ring opening reactions were attempted on the azido epoxides 65 and 66 and also on the amino epoxides 67 and 68. The azides were reduced to the amines by conversion to the phosphoimines followed by hydrolysis in 60% yield. This was done to avoid possible complications arising from reaction of some of the epoxide opening reagents with the azido group. In all cases there was observed either no epoxide ring opening or decomposition under more forcing conditions.
Some of the nucleophilic ring opening conditions which were attempted included reaction of the epoxides with KOH in DMSO with 18-crown-6 at temperatures ranging from 25°C to 140°C. No reaction was observed at temperatures up to 100°C and decomposition occurred at higher temperatures. Reaction of the epoxy compounds with KO₂ in DMSO with 18-crown-6 at room temperature gave no reaction. Higher temperatures with KO₂ lead to decomposition of this reagent. Reaction with sodium methoxide likewise gave no reaction.

Since it is well known that epoxide ring openings are greatly accelerated in acidic media, a number of electrophilic reagents were employed to attempt the epoxide ring opening. These included a number of different acids (acetic acid, formic acid, trifluoroacetic, and perchloric acid) under a variety of reaction conditions, such as different temperatures, solvents and concentrations. Deprotection of the cyclohexylidene ketals were observed as expected, but the epoxide ring remained intact in all cases.

For example, treatment of the azido epoxides 65 and/or 66 with 9:1 trifluoroacetic acid-water at room temperature for 1 day followed by acetylation afforded 15% yield of a diacetate and 45% of a tetraacetate 69, both having an intact epoxide ring.
Since the trans hydroxylation procedures which were attempted on the cis double bond all met with no success, this strategy was abandoned and attention was directed toward the cis hydroxylation of a compound having a trans double bond.

As previously mentioned the cis amino olefin 63 was readily isomerized to the trans olefin 64 in 38% yield (90% based on recovered cis isomer 63). The cis olefin could readily be recycled. Acetylation of 64 gave the acetamido compound 70 in 73% yield.
Of the number of cis hydroxylation procedures available, such as oxidations with OsO₄, KMnO₄, or the Woodward hydroxylation procedure, hydroxylation with OsO₄ is generally the superior method. A major disadvantage however is that OsO₄ is expensive and highly toxic. In many instances the same cis hydroxylation can be accomplished more economically by the use of OsO₄ in catalytic amounts with a less expensive oxidant such as chlorate, oxygen in an alkaline medium, hydrogen peroxide (Milas reagent), or N-methylmorpholine-N-oxide to regenerate the OsO₄.
A preliminary study showed that the cis azido olefin 62 could readily be hydroxylated with OsO₄- KClO₃.

Therefore attention was directed toward the hydroxylation of 70 with a catalytic amount of OsO₄. Treatment of 70 with a catalytic amount of OsO₄ and using KClO₃ as the oxidant required a reaction time of 12 hours at 55°C to afford 47% of a single diol 71. It was not surprising that only one isomer was obtained since it is well known that OsO₄ normally attacks a double bond from the least hindered side to give predominately if not exclusively one product.
A number of other products were formed, which have not been completely characterized, but were believed to be α-ketol byproducts which are frequently encountered with chlorates as oxidants.

To circumvent this problem the hydroxylation was carried out using N-methyl-morpholine-N-oxide rather than KClO₃ as the oxidant. Osmylations using N-methyl-morpholine-N-oxide as the oxidant have been shown to yield no detectable quantities of α-ketols.

After 5 hours at room temperature followed by appropriate workup, 71 was obtained in 78% yield. There were no appreciable amounts of other products.
If the integrity of the synthesis has thus far been sound, diol 71 should possess either the correct configuration of hikosamine at all asymmetric centers or the opposite configuration at C_6 and C_7. At this point the best method for determination of the absolute configuration at C_6 and C_7 was to convert 71 to a hikosamine derivative from the hikizimycin research. Methyl peracetyl-α-hikosaminide 39 was characterized as part of the research^2,6,7,8 which was directed toward the structural elucidations of hikosamine and hikizimycin (Reaction 4). Conversion of 71 to a peracetylated methyl glycoside was envisioned as readily possible by deprotection followed by acetylation.

Simultaneous hydrogenolysis of the benzyl groups and hydrolysis of the cyclohexylidene groups of 71 gave a water soluble compound which was directly acetylated to afford 47% of the peracetylated methyl glycoside 39 (58% based on recovered material resulting from incomplete deprotection of the cyclohexylidene ketals).

Synthetic 39 was indistinguishable from 39 prepared from hikizimycin in terms of melting point (synthetic 39 177-178°C, lit. mp 180.5-181.5°C, mixture melting point undepressed); specific rotation [synthetic 39 [α]_D^{22} + 90° (c 0.58, CHCl_3); lit. [α]_D^{29} + 85° (c 1.0, CHCl_3)]^7; thin layer chromatographic data; and 400 MHz _1^H NMR data, where spectra of 39 from synthesis and natural sources were superimposable.
Reaction 4. The degradation of hikizimycin yielding methyl peracetyl-hikosaminide.
Thus cis hydroxylation of the trans double bond of 70 produced only one of the two possible diastereoisomeric diols whose configuration was demonstrated by conversion exclusively to methyl peracetyl-α-hikosaminide.

Attempted hydrolysis of the glycosidic linkage of 39 to yield free hikosamine demonstrated that this linkage was very resistant to such hydrolysis. The hydrolysis was attempted using a variety of reaction condition. In all cases no reaction or decomposition at higher temperatures occurred.
Figure 6. 400 MHz $^1$H NMR spectrum of Methyl Peracetyl-$\alpha$-Hikosaminide in CDCl$_3$
B. Studies Directed Toward a Synthesis of Tunicamycin

As with the synthesis of methyl peracetyl-α-hikosaminide, described in the preceding section, the strategy toward the synthesis of tunicamycin again revolves around the construction of the basic carbon framework by use of carbohydrate phosphoranes. Tunicamycin contains as its basic carbohydrate unit, the undecose, tunicamine. As
Reaction 5. Retrosynthetic analysis of tunicamycin.
illustrated in Reaction 5 the skeleton of tunicamine can be approached via formation of the C₅-C₆ bond from D-galactose and D-ribose precursors. Further examination of the structure of tunicamycin reveals it to contain the additional structural units, uracil, N-acetyl glucosamine and fatty acids all linked to the central carbohydrate, tunicamine II. The amino group of tunicamine is substituted by the fatty acid with the uracil moiety linked to C₁ and N-acetylglucosamine glycosidically linked α-α to C₁. The research described herein has been directed toward the construction of the undecose tunicamine II and the construction of the undecose substituted at C₁ with the uracil moiety, namely tunicaminyl uracil ⁹.
As previously mentioned, the precursors to carbons 1-5 and 6-11 of tunicamine respectively would be D-ribose and D-galactose. The choice as to which of these precursors would be the aldehyde partner and which one the phosphorane partner in the Wittig condensation has in this situation been clearly defined. The D-ribo phosphonium salt 21 as described earlier rapidly epimerized at C_4 yielding L-lyxo products after condensation. Hence, considering this probable complication, the syntheses to be described have been designed such that the D-ribo derived portion (C_1-C_5) has been introduced as the aldehyde in the condensation and the D-galacto derived portion (C_6-C_{11}) as the phosphorane.

As illustrated in Reaction 5 the possibility exists of introducing the nitrogen at C_{10} before the condensation, having an amino or latent amino functionality present in the phosphorane, or introducing the nitrogen after the condensation by selective deprotection and appropriate manipulation of the C_{10} hydroxyl. Both of these alternatives have
been explored. The former alternative appears particularly attractive because it would avoid a number of manipulations to introduce the nitrogen at C\textsubscript{10} on an already complex molecule. Attention was therefore initially directed toward the preparation of a galactosamine derived phosphorane.

An amino functionality present in the same molecule in which a phosphorane will be generated of course requires appropriate protection. Of the amine protecting groups in the literature, the phthalimidio group presented itself as one of the more likely to survive the conditions of the Wittig condensation. Hence, the synthesis of a galactosamine derived phosphonium salt with an N-phthaly1 blocking group, specifically 82, was explored.

![Image of molecular structure]

Methyl 2-benzamido-2-deoxy-\alpha-D-galactopyranoside\textsuperscript{65, 75}, prepared in six steps from glucosamine hydrochloride, was silylated at C\textsubscript{6} with t-butylchlorodiphenylsilane, affording the silyl ether. Immediate isopropylidenation of the silyl ether yielded the previously unknown 76 in 72%.
Treatment with (n-Bu)$_4$NF or NaOH gave 77. Conversion of 77 to 82 can be envisioned as possible by N-debenzoylation, followed by N-phthalyl protection and conversion of the 6-hydroxyl to a phosphonium salt in standard fashion (tosylation, conversion to the iodo compound and the quaternization with triphenylphosphine). Attempts to effect the N-debenzoylation failed (i.e. NaOH, H$_2$O, ethylene glycol at 160°C) and this route toward 82 was abandoned.

The 4,6-O-benzylidene compound 78 prepared from 75 could be readily N-debenzoylated in good yield. Treatment with phthalic anhydride in refluxing DMF afforded the phthalyl derivative 79 in 50% yield. Treatment of 79 with NBS gave
the bromo-benzoate in good yield (70%) which was debenzoylated affording the diol \( \sim \) in 65% yield. Isopropylidenation yielded \( \sim \) in 65% yield and quaternization of \( \sim \) with triphenylphosphine in sulfolane at 110°C afforded \( \sim \) in 64% yield as a pale yellow solid.

Phosphonium salt \( \sim \) displayed very poor solubility in numerous solvents, including acetonitrile, benzene, DMF, methanol, and ethanol. More importantly, \( \sim \) was insoluble or only slightly soluble in both THF and HMPA, the solvents of choice for the Wittig condensation. Phthalimido groups
have been well known for conferring poor solubility characteristics to various amino sugars and undoubtedly such was the case with 82. Attempted condensation of 82 with benzaldehyde in 4:1 THF-DMSO, a solvent mixture in which 82 was soluble, at -20°C gave no reaction, other than decom-position of the phosphonium salt.

As mentioned earlier, the phthalimido group was select-ed to protect the nitrogen functionality of a galactosamine derived phosphonium salt because it appeared well suited to survive the conditions of the Wittig condensation. Of the other amine protecting groups in the literature, none of them appeared suitable. Therefore, a new strategy was undertaken, involving the construction of a D-galacto phosphonium salt which when condensed with a D-ribo aldehyde would yield an olefin which could selectively be deprotected at C\textsubscript{10} and the C\textsubscript{10} hydroxyl in some manner elaborated into an amine.

Phosphonium salt 86 was selected as an appropriately
protected precursor to carbons 6-11. Selective removal of t-butyldiphenylsilyl group after condensation with a \(\text{D-ribo}\) aldehyde could be accomplished with either \((n-Bu)_4\text{NF}\) or \(\text{NaOH}\). The starting material for the synthesis of \(86\) was methyl 6-bromo-6-deoxy-\(\text{\textalpha-\text{D-}\text{galactopyranoside}}\) \(83\), prepared in three steps from methyl-\(\text{\textalpha-\text{D-}\text{galactopyranoside}}\) \(44\).

\[
\begin{align*}
44 & \xrightarrow{\text{\(\text{PhCHO, \text{ZnCl}_2}\)}} 45 \\
& \xrightarrow{\text{1. \text{NBS, \text{BaCO}_3}}} 46 \\
83 & \xrightarrow{\text{\(\text{CH}_3\text{CCH}_3, \text{CH}_3\)} (\text{H}_2\text{SO}_4) \text{MeOH-\text{CH}_2\text{Cl}_2}}} 84
\end{align*}
\]

Isopropylidenation afforded the previously unknown compound \(84\) in 92% yield and treatment of \(84\) with t-butyldichlorodi-phenylsilane gave \(85\) in quantitative yield. Quaternization with triphenylphosphine in refluxing acetonitrile for six days afforded \(86\) in 87% yield. The reaction also proceeded
well in sulfolane at 90°C, however difficulty was encountered in removing the sulfolane after the reaction was complete.

The red colored ylide 87 derived from 86 was generated by addition of 1 equivalent of n-BuLi to the salt 86 dissolved in 2:1 THF-HMPA at -65°C under nitrogen. The ylide was well behaved at low temperatures and when condensed with methyl 2,3-O-isopropylidene-α-D-ribo-pentodialdo-1,4-furanoside 33 afforded a single product 88 in 55% yield.
Since epimerization at C₄ of 33 could have occurred under the basic conditions of the Wittig condensation and since it was also possible for ylide 87 to open and reclose the sugar ring as was observed with the ylide derived from the ribose phosphonium salt 21, the configurations of both halves of 88 needed confirmation. Ozonolysis-reduction of 88 produced only two carbohydrate alcohols, one of which was readily identifiable as 36 by TLC and ¹H NMR. Desilylation of the other alcohol 89 with (n-Bu)₄NF afforded 90 which was identical to methyl 3,4-0-isopropylidene-α-D-galactopyranoside 67 by TLC and ¹H NMR. Hence no configurational changes occurred in either half.
Examination of the 60 MHz $^1$H NMR spectrum of 88 in CHCl$_3$ proved fruitless in determining the geometry about the double bond since the chemical shifts of the two vinyl hydrogens were virtually identical and the coupling constants could not be determined. Even at 400 MHz in CDCl$_3$ the chemical shifts of the olefinic protons were indistinguishable and the coupling constants could not be determined. However, generation of a computer simulated spectrum of 88 gave a coupling constant of $J \approx 11$ Hz, clearly indicating a cis double bond.

**Figure 7.** Partial 400 MHz $^1$H NMR spectrum of 88 in CDCl$_3$ (olefinic protons).
Treatment of 88 with (n-Bu)$_4$NF afforded the C$_{10}$ free hydroxyl compound 91 in 73% yield. Conversion of the C$_{10}$ hydroxyl to an amine and appropriate hydration of the double bond followed by deprotection would convert 91 to tunicanine.

Oxidation of 91 with chromium trioxide-pyridine afforded the 10-keto compound 92 in 95% yield. Immediate treatment of 92 with hydroxylamine hydrochloride in ethanol-pyridine gave a 1:1 mixture of the syn and anti oximes 93 and 94 in 93% yield.

Reduction of the oximes would yield the equatorial and/or axial C$_{10}$ amines, with the isomer composition most likely dependent on the reducing agent employed. Treatment of the
mixture of 93 and 94 with LiAlH₄ afforded one major amino isomer 95 and a very minor amount of the other amino isomer in 29.1% yield. Treatment of 95 with benzoyl chloride-

pyridine yielded the 10-benzamido compound 96 in 71%.
To determine the configuration of the amino group of 96 an ozonolysis-reduction was carried out to yield two carbohydrate alcohols, 36 (identifiable as methyl 2,3-O-isopropylidene-\(\beta\)-D-ribo-furanoside by TLC and \(^1\)H NMR) and 97. Comparison of 97 with methyl 2-benzamido-2-deoxy-3,4-O-isopropylidene-\(\alpha\)-D-galactopyranoside 77 (the synthesis of which was described earlier) by \(^1\)H NMR clearly showed it to be a different compound. Therefore 97 must possess the
D-talo configuration and hence reduction of the oximes \(^{93}\) and \(^{94}\) with LiAlH\(_4\) afforded the amino isomer \(^{95}\) which does not possess the desired configuration at C\(_{10}\).

\[ \text{D-talo configuration and hence reduction of the oximes} \]

\[ \text{with LiAlH}_4 \text{ afforded the amino isomer} \]

\[ \text{which does not possess the desired configuration at C}_{10}. \]

An extensive study of other reducing agents to effect the reduction of the oximes which would lead to the correct isomer or a tolerable ratio of isomers is required.

As mentioned earlier, work has been directed toward the construction of tunicaminy1 uracil \(^9\) (the undecose, tunicamine, substituted at C\(_1\) with the uracil moiety). Although this work has thus far been cursory, it deserves brief mention.
Condensation of 86 with the protected uridine derivative 98 under the usual conditions afforded a complex nucleoside 99 in 25% yield. N-debenzoylation of 99 was readily accomplished by treatment with methanolic ammonia to afford 100 in 87% yield. Conversion of the C10 protected hydroxyl to an amine and appropriate hydration of the double bond followed by deprotection would convert 100 to tunicaminy1 uracil.
The uracil moiety of 100 presented itself as a possibly useful functionality for the regio specific introduction of the hydroxyl at C$_5^-$ of the C$_5^-$-C$_6^-$ double bond. Treatment of the olefin 100 with reagents such as N-iodosuccinimide or N-bromosuccinimide could lead to formation of an anhydro nucleoside such as 101 which when followed by attack at C$_5^-$ or C$_2$ with an oxygen nucleophile would introduce an oxygen at C$_5^-$ and regenerate the uracil moiety.
Treatment of 100 with N-bromosuccinimide in acetonitrile at room temperature formed a C₅ bromo substituted compound as judged by TLC and UV data. Further reaction at elevated temperatures lead to decomposition and formation of unidentified products which did not possess UV data to fit an anhydro nucleoside such as 101. Similar reaction with N-iodosuccinimide gave no reaction at room temperature and decomposition at elevated temperatures.

Epoxidation of 100 with m-CPBA at room temperature proceeded well to afford 82% of a 3:2 ratio of diastereoisomeric epoxides 102 and 103 which were readily separable by preparative TLC. An initial attempt to effect anhydro nucleoside formation with concomitant epoxide opening was attempted with a trace of p-toluenesulfonic acid. Two unidentified products were isolated which did not possess UV data to fit anhydronucleosides.
As obvious, this work has been cursory and an extensive study of the reaction conditions (temperatures, solvent, and electrophilic reagent) to effect the anhydronucleoside formation is required.
SUMMARY

Utilizing the recently developed chemistry of unstabilized carbohydrate phosphoranes, the fully protected derivative methyl peracetyl-α-hikosaminide 39 of hikosamine 4, the undecose unit of the nucleoside antibiotic hikizimycin 1, was synthesized. Construction of 39 with the proper chirality at all ten consecutive asymmetric centers involved two key steps. First, a Wittig condensation between the appropriately protected and functionalized five-carbon unstabilized carbohydrate phosphorane 59 and six-carbon carbohydrate aldehyde 50 produced exclusively the Z olefin 62. The final two chiral centers were incorporated by cis hydroxylation with osmium tetroxide and N-methylmorpholine N-oxide after photochemical isomerization of 63 to the E olefin 70. Deprotection of 71 followed by acetylation gave 39. Comparison of synthetic 39 with 39 prepared from natural sources demonstrated them to be identical in all respects.

The research directed toward the synthesis of the complex nucleoside antibiotic tunicamycin 6, again as with the synthesis of methyl peracetyl-α-hikosaminide, revolved around the construction of the basic carbon framework by the use of unstabilized carbohydrate phosphoranes. Condensation of the six-carbon carbohydrate phosphorane 87 with the five-carbon aldehyde 33 produced the olefin 88. Conversion of 88 to
tunicamine \textsuperscript{11}, the undecose unit of tunicamycin, would involve regio specific hydration of the double bond and conversion of the C\textsubscript{10} protected hydroxyl to an amine of correct configuration. A reductive amination of \textsuperscript{92} (prepared by selective deprotection of \textsuperscript{88} at C\textsubscript{10} followed by oxidation to the ketone) would introduce the amine at C\textsubscript{10}. Treatment of \textsuperscript{92} with hydroxyl-amine produced a mixture of \textsuperscript{syn} and \textsuperscript{anti} oximes \textsuperscript{93} and \textsuperscript{94} which when reduced with LiAlH\textsubscript{4} yielded \textsuperscript{95}, one of the two possible amine isomers, determined by degradation to possess the incorrect configuration at C\textsubscript{10}, hence an extensive study of other reducing agents to effect the reduction of the oximes to yield the correct amine isomer is required.

A cursory study directed toward the construction of tunicaminy1 uracil \textsuperscript{9}, was also carried out. Condensation of \textsuperscript{87} with the protected uridine 5'-aldehyde \textsuperscript{98} produced \textsuperscript{99} which was readily N-debenzyloated. The uracil moiety of \textsuperscript{100} appeared to be a useful functionality for the regio specific introduction of the hydroxyl at C\textsubscript{5'} of the C\textsubscript{5''}-C\textsubscript{6'} double bond by way of formation of an anhydronucleoside as \textsuperscript{101}, followed by attack at C\textsubscript{5''} or C\textsubscript{2} with an oxygen nucleophile to introduce an oxygen at C\textsubscript{5'} and regenerate the uracil moiety. Initial attempts at anhydronucleoside formation proved unsuccessful and additional work is required. Isomerization of \textsuperscript{100} to the E olefin may facilitate anhydrornucleoside formation.
EXPERIMENTAL

Melting Points  Melting points were determined on a Thomas-Hoover capillary melting-point apparatus and are corrected.

Infrared Spectra  Infrared spectra were recorded on a Perkin-Elmer 467 grating infrared spectrophotometer, and only selected absorptions are given.

$^1$H NMR Spectra  $^1$H NMR spectra were measured with Varian EM-360 or Bruker WH-400 instruments. The superconducting Bruker operated at a field strength of 94 kilo gauss with a proton observed frequency of 400.134 MHz. The Bruker was equipped with an Aspect 2000 computer with 48 K 24-bit words of data memory and a Diablo disk drive with a 1.2 million K capacity. The Bruker was operated in the Fourier-Transform mode. Chemical shifts were expressed in parts per million downfield from internal tetramethylsilane.

$^{13}$C NMR Spectra  $^{13}$C NMR spectra were measured with a Bruker WP-80. Chemical shifts were expressed in parts per million downfield from internal tetramethylsilane. All $^{13}$C assignments were supported by the splittings in off-resonance decoupling experiments.
Mass Spectra  Mass spectra were recorded with an AEI-MS9 spectrometer at 70eV.

Optical Rotations  Optical rotations were measured on a Perkin-Elmer model 141 polarimeter in a 1-dm tube.

Irradiations  Irradiations were carried out employing a 450-W Hanovia #679A36 medium-pressure mercury arc lamp.

Microanalyses  Microanalyses were done by Galbraith Laboratories, Inc.

Ozone  Ozone was generated with a Welsbach Ozonator T-408.

Dimethylformamide (DMF)  Dimethylformamide was dried by vacuum distillation from calcium hydride.

Dimethyl Sulfoxide (DMSO)  Dimethyl sulfoxide was dried by vacuum distillation from calcium hydride.

Hexamethylphosphoric Triamide (HMPA)  Hexamethylphosphoric triamide was dried by distillation from calcium hydride.

Petroleum Ether  In all cases petroleum ether (38-56°C) was employed.
Tetrahydrofuran (THF)  Tetrahydrofuran was dried by distillation from sodium and benzophenone.

Tetramethylene Sulfone (sulfolane)  Tetramethylene sulfone was dried by distillation from calcium hydride.

Methanol (MeOH)  Methanol was dried by distillation from magnesium turnings.

Dicyclohexylcarbodiimide (DCC)
(Z)-1-(Methyl 2,3-di-O-methyl-4-O-benzyl-α-D-galacto-pentopyranosid-5-yl)-2-(1,2,3,4-di-O-isopropylidene-α-D-galacto-pentopyranos-5-yl) ethylene (43).

A stirred solution of 32 (0.40 g, 0.000633 mol) in 3.3 mL of 2:1 THF-HMPA was cooled to -65°C under nitrogen and n-BuLi (0.0006963 mol) was added via syringe. After stirring for 30-45 sec methyl 2,3-di-O-methyl-4-O-benzyl-6-aldehydo-α-D-galactopyranoside (0.19 g, 0.0006122 mol) in 0.5 mL of THF was added and the solution allowed to warm up slowly to -10°C over a period of 1 h. A 1:1 petroleum ether-ether mixture was added and precipitated triphenylphosphine oxide was filtered off, washing the solids with 1:1 petroleum ether-ether. Volatile solvents were removed from the filtrate under reduced pressure and the residue taken up in 50 mL of 4:1 ether-petroleum ether, washed with 30 mL of H₂O, 30 mL of saturated aqueous NaHSO₃, 15 mL of saturated aqueous NaCl and dried over MgSO₄. The solvents were removed under reduced pressure and the residue purified by preparative TLC (elution with ether) to afford 0.193 g (60%) of 43 as a white foam. ¹H NMR (60 MHz, benzene-d₆) δ 1.10, 1.18, 1.49, 1.54 [4s, 12, 2C(CH₃)₂], 3.28, 3.30, 3.38 (3s, 9, 3OCH₃), 3.8-4.6 (m, 9, H₁-H₅, H₅-H₁₁), 4.61-4.92 (m,
Methyl-4,6-O-benzylidene-α-D-galactopyranoside (45).

To a stirred suspension of methyl α-D-galactopyranoside 44 (35.0 g, 0.165 mol) dried at 100°C under vacuum for several hours and 115 mL of benzaldehyde was added ZnCl₂ (24.7 g, 0.18 mol). After 4 days at RT, 130 mL of H₂O and 28 mL of MeOH was added. The solution was then washed with 2x300 mL portions of petroleum ether to remove the excess benzaldehyde. The petroleum ether extracts were back extracted with a mixture of 130 mL of H₂O and 14 mL of MeOH. To the combined aqueous layers was added Na₂CO₃ (21.0 g, 0.198 mol) in H₂O and the precipitated ZnCO₃ removed by suction filtration. The precipitate was washed thoroughly with MeOH and then extracted twice with boiling MeOH. The filtrate and extracts were combined and concentrated at reduced pressure to yield an off white solid which was dissolved in 400 mL of CHCl₃. The CHCl₃ solution was washed with 100 mL of H₂O, 50 mL of aqueous saturated NaCl, treated with charcoal and dried over Na₂SO₄. Removal of solvent yielded 41.5 g (89%) of product as a white solid, mp 170-174°C (lit. mp 177-178°C).
Methyl 2,3-di-O-benzyl-4,6-O-benzylidene-α-D-galactopyranoside

To a mechanically stirred suspension of sodium hydride (23.4 g, 0.487 mol of a 50% mixture with oil, which was then washed with petroleum ether to remove the oil) and 115 mL of DMF was added dropwise a solution of 45 (45.8 g, 0.162 mol) in 175 mL of DMF over a period of 1 h. After an additional 45 min of stirring at RT, the solution was cooled to 0°C, benzyl chloride (65 mL, 0.568 mol) was added dropwise over a period of 1 h, and stirring continued for 20 h at RT. The solution was evaporated via vacuum distillation to yield a light brown solid which was dissolved in 1300 mL of CH₂Cl₂, washed with 300 mL of H₂O, 250 mL of saturated aqueous NaCl, treated with charcoal and dried over MgSO₄. Removal of solvent yielded an off white solid which was recrystallized once from ethanol to yield 67.7 g (90%) of product as a white solid, mp 169-171°C (lit 173-174°C).

Methyl 2,3-di-O-benzyl-α-D-galactopyranoside (46)

A stirred solution of methyl 2,3-di-O-benzyl-4,6-O-benzylidene-α-D-galactopyranoside (35.0 g, 0.0757 mol) in 420 mL of MeOH and 35 mL of 1N HCl was heated under reflux for 20 h.
After addition of 5 g of NaHCO₃ in 60 mL of H₂O the solution was concentrated under reduced pressure to remove MeOH. Water (250 mL) was added and the mixture was again evaporated; this procedure was repeated 3 times. The syrupy product was dissolved in 700 mL of CHCl₃, washed with 175 mL of saturated aqueous NaHSO₃, 90 mL of H₂O, 175 mL of saturated aqueous NaCl, treated with charcoal, and dried over MgSO₄. The solvent was evaporated under reduced pressure and the resultant syrup washed with 400 mL of hot petroleum ether. On standing the clear syrup crystallized giving 46 as a white solid (28 g, 100%), mp 83-85°C (lit 5587-88°C).

**Methyl 2,3-di-O-benzyl-4-O-methylsulfonyl-α-D-galactopyranoside (47).**

A stirred solution of 46 (28 g, 0.0748 mol) and triphenylmethyl chloride (22.9 g, 0.0823 mol) in 125 mL of pyridine was heated at 75°C for 18 h under nitrogen. The solution was cooled to 0°C and methane-sulfonyl chloride (11.6 mL, 0.15 mol) added. The solution was stirred 2 h at 0°C and then 2 days at RT. After removal of pyridine via vacuum distillation the dark residue was dissolved in 550 mL of CH₂Cl₂ and the solution was washed with 170 mL of H₂O, 170 mL of saturated aqueous NaCl, treated with 10 g of charcoal, and dried over MgSO₄. The solvent was removed under reduced pressure yielding the crude 6-Ω-
trityl-4-O-mesyl compound. A stirred solution of the crude 6-O-trityl-4-O-mesyl compound in 4:1 HOAc-H₂O (300 mL) was heated at 100°C for 4 h. The solution was cooled and the precipitate removed by suction filtration. The filtrate was evaporated under reduced pressure, the residue obtained was dissolved in 600 mL of CH₂Cl₂, washed with 85 mL of H₂O, 170 mL of saturated aqueous NaHCO₃, 85 mL of saturated aqueous NaCl, treated with charcoal and dried over MgSO₄. Removal of solvent under reduced pressure yielded a yellow syrup composed of two major compounds by TLC (2:1 ether-petroleum ether, Rf 0.2 and 0.4). These compounds were identified as 47 and methyl 2,3-di-O-benzyl-4-O-methylsulfonyl-6-O-acetyl-α-D-galactopyranoside, respectively. Treatment of the mixture with 500 mL of MeOH and 30 mL of concentrated aqueous NH₄OH at RT revealed one major spot by TLC (2:1 ether-petroleum ether, Rf 0.2) after 4 h. The solution was concentrated under reduced pressure and the residue dissolved in 300 mL of ether, washed with 50 mL of H₂O, 50 mL of saturated aqueous NaCl, treated with charcoal and dried over MgSO₄. The ethereal solution was concentrated and the residue obtained purified by column chromatography (silica gel, 5x50 cm column, elution with 2:1 ether-petroleum ether) to afford 19.2 g (57%) of 47 as a colorless foam. Preparative TLC (elution with 2:1 ether-petroleum ether) provided analytically pure material: IR (neat) 2.86, 3.29, 3.42, 6.69, 6.89, 7.35, 8.54 μ.
Methyl 2,3-di-O-benzyl-4-deoxy-4-azido-α-D-glucopyranoside (48).

A mixture of 47 (28.5 g, 0.0631 mol) and sodium azide (16.4 g, 0.252 mol) in 260 mL of DMF was stirred at 120°C for 5 h. The DMF was removed via vacuum distillation and the residue dissolved in 700 mL of ether. The ethereal solution was washed with 200 mL of saturated aqueous NaHCO₃, 100 mL of saturated aqueous NaCl, treated with charcoal, and dried over MgSO₄. The solvent was removed under reduced pressure yielding 23.1 g (92%) of 48 as a pale yellow syrup. This material was suitable for use in the subsequent reaction without further purification.

Preparative TLC (elution with ether) provided analytically pure material: IR (neat) 2.91, 3.44, 4.76, 6.68, 6.86, 7.35, 7.87 μ; ¹H NMR (60 MHz, CDCl₃) δ 3.32 (s, 3, OCH₃), 3.4-3.9
(m, 6, H₂-H₆,H₆), 4.56 (d, 1, H₁), 4.67 (d, 2, CH₂C₆H₅), 4.86 (d, 2, CH₂C₆H₅), 7.26-7.30 (m, 10, Ar-H); $^{13}$C NMR (CDCl₃) δ 55.44 (OCH₃), 61.66, 62.09 (C₄, C₆), 70.01, 73.36, 75.69, 79.96 (C₂, C₃, C₅, 2 CH₂C₆H₅, 1 overlapping), 98.36 (C₁), 127.83, 128.07, 128.27, 128.41, 128.56 (o, m, and p aromatics, 3 overlapping), 137.98, 138.12 (ipso aromatic); $[^a]_{D}^{29}$ +102.5° (c 1.08, CHCl₃).

Anal. Calcd for C₂₁H₂₅O₅N₃: C, 63.14; H, 6.31; N, 10.52.

Found: C, 63.06; H, 6.52; N, 10.24.

Methyl 2,3-di-O-benzyl-4-deoxy-4-azido-6-deoxy-6,6'-(N,N'-diphenylethlenediamino)-α-D-glucopyranoside (49).

To a stirred solution of 48 (14.1 g, 0.0353 mol), and DCC (18.2 g, 0.0883 mol) in 340 mL of 1:1 DMSO-benzene was added dichloroacetic acid (1.46 mL, 0.0176 mol). After 4 h at RT the mixture was cooled to 0°C and a solution of oxalic acid dihydrate (6.7 g, 0.053 mol) in H₂O was added slowly (foaming). The mixture was stirred 20 min at RT, diluted with 1700 mL of ethyl acetate and the dicyclohexylurea was filtered from the solution and washed with a small amount of ethyl acetate. The filtrate was then washed with 4x600 mL portions of H₂O, 300 mL of saturated aqueous NaCl, and dried over MgSO₄. The solution was evaporated under reduced pressure, the residue taken up in a small amount of
ether-petroleum ether, and a small amount of dicyclohexylurea filtered off. The solution was again evaporated to a syrup and followed by azeotropic removal of water with benzene to yield a pale yellow syrup. The syrup was dissolved in 225 mL of MeOH and stirred with dianilinoethane (11.2 g, 0.0529 mol) and acetic acid (2.6 mL) at RT for 24 h. The crystalline product was filtered off, washed well with MeOH and dried in vacuum with P$_2$O$_5$ to yield 15.8 g (76%) of off white suitable for subsequent deprotection to the aldehyde. Recrystallization from ethanol-CHCl$_3$ provided analytically pure material.

mp 166-167°C (needles); IR (KBr) 3.41, 3.51, 4.72, 6.25, 6.65, 6.80, 7.18, 7.49 μ; $^1$H NMR (60 MHz, CDC$_3$) δ 3.00 (s, 3, OCH$_3$), 3.3-4.1 (m, 8, H$_2$-H$_5$, -CH$_2$CH$_2$), 4.55 (m, 3, H$_1$, CH$_2$C$_6$H$_5$), 4.78 (d, 2, CH$_2$C$_6$H$_5$), 5.71 (s, 1, H$_6$), 6.5-7.4 (m, 20, Ar-H); $^{13}$C NMR (CDC$_3$) δ 46.41, 47.63 (-CH$_2$CH$_2$-), 55.34 (OCH$_3$), 62.04 (C$_4$), 70.40, 72.92, 73.16, 75.74, 79.96, 80.35 (C$_2$,C$_3$,C$_5$,C$_6$, 2 CH$_2$C$_6$H$_5$), 98.17 (C$_1$), 112.88, 113.12, 117.39, 117.78, 127.88, 128.36, 129.38, 129.48 (o, m, and p aromatics, 12 overlapping), 137.88, 138.02 (ipso to C aromatic), 145.50, 146.67 (ipso to N aromatic); [α]$_D^{31}$ -6.51° (c 1.48, CHCl$_3$).

Anal. Calcd for C$_{35}$H$_{37}$O$_4$N$_5$: C, 71.04; H, 6.30; N, 11.84.

Found: C, 70.85; H, 6.42; N, 11.76.
Methyl 2,3-di-O-benzyl-4-deoxy-4-azido-6-aldehydo-α-D-glucopyranoside (50).

To an ice-cooled stirred solution of 49 (6.0 g, 0.0101 mol) in 180 mL of THF was added 45 mL of 6N HCl. The solution was stirred 30 min at 0°C and an additional 3.5 h at RT, after which the solvent was removed under reduced pressure yielding a light brown residue. To the residue was added 200 mL of ether and the insoluble salts were removed by filtration and washed with 100 mL of ether. The filtrate was washed with 25 mL of H₂O, 50 mL of saturated aqueous NaCl, and dried over MgSO₄. The solution was concentrated and the residue purified by preparative TLC (elution with 1:1 ether-petroleum ether) to yield the monohydrate. Azeotropic removal of water with benzene afforded 3.52 g (87%) of 50 as a pale yellow syrup. IR (neat) 3.32, 3.43, 3.51, 3.54, 3.68, 4.72, 5.75, 6.70, 6.91, 7.39 μ; ¹H NMR (60 MHz, CDCl₃) δ 3.36 (s, 3, OCH₃), 3.4-4.1 (m, 4, H₂-H₅), 4.66 (m, 3, H₁, CH₂C₆H₅), 4.88 (d, 2, CH₂C₆H₅), 7.2-7.4 (m, 10, Ar-H), 9.62 (s, 1, H₆); Product instability precluded satisfactory elemental analysis.
(Z)-1-(Methyl 2,3-di-O-benzyl-4-deoxy-4-azido-α-D-glucopyranosid-5-yl)-2-(1,2,3,4-di-O-isopropylidene-α-D-galacto-pentopyranos-5-yl) ethylene (51).

A stirred solution of 3Z (0.366 g, 0.0005791 mol) in 3 mL of 2:1 THF-HMPA was cooled to -65°C under nitrogen and n-BuLi (0.000637 mol) was added via syringe. After stirring for 60 sec 50 (0.230 g, 0.0005944 mol) in 0.5 mL of THF was added and the solution allowed to warm up slowly to -10°C over a period of 1 h. A 1:1 petroleum ether-ether mixture was added and precipitated triphenylphosphine oxide was filtered off, washing with 1:1 petroleum ether-ether. Volatile solvents were removed from the filtrate under reduced pressure and the residue taken up into 4:1 ether-petroleum ether, washed with H2O, saturated aqueous NaHSO3, saturated aqueous NaCl, and dried over MgSO4. The solvent was evaporated at reduced pressure and the residue purified by preparative TLC (elution with ether) to afford 0.235 g (65%) of 51 as a clear syrup:

IR (neat) 3.39, 3.43, 4.76, 6.68, 6.89, 7.24, 7.93 μ;

1H NMR (60 MHz, CDCl3) δ 1.20-1.35, 1.47, 1.54 [4s, 12, 2C(CH3)2], 3.36 (s, 3, OCH3), 3.4-4.9 (m, 12, H2-H5, H8-H11, 2CH2C6H5), 5.55 (d, 1, H1), 5.65-5.9 (H6, H7), 7.1-7.4 (m, 10, Ar-H).
2,3,4,5-di-0-Cyclohexylidene-D-arabinose diethylthioacetal (54).

To an ice-cooled stirred mixture of D-arabinose diethylthioacetal (15.0 g, 0.0585 mol), anhydrous cupric sulfate (15.0 g), and cyclohexanone (150 mL) was added concentrated H₂SO₄ (1.5 mL). After 1 h at 0°C and an additional 3 h at RT, the cooper salts were removed by filtration and the solution neutralized by bubbling NH₃ through the solution. The ammonium sulfate formed was removed by filtration. Water (250 mL) was added and the mixture evaporated under reduced pressure to remove excess cyclohexanone; this procedure was repeated three times. The reddish-brown residue obtained was taken up in 375 mL of ether, washed with 75 mL of saturated aqueous NaCl, treated with charcoal, and dried over MgSO₄. The solvent was evaporated at reduced pressure and the residue purified by column chromatography (silica gel, 5x75 cm column, elution with 1:4 ether-petroleum ether) to afford 23.0 g (94%) of 54 as a colorless syrup.
**D-Arabinose-diethylthioacetal**

To a stirred solution of D-arabinose (50 g, 0.333 mol) in 50 mL of concentrated aqueous HCl was added ethanethiol (59 mL, 0.806 mol). After 10 min at RT, excess ethanethiol was distilled off with gentle heating, and the mixture cooled to 0°C. Cold H₂O was added to break up the yellow solid, the solid collected by suction filtration and washed with cold H₂O. A total of 400 mL of H₂O was used. The crude product was then recrystallized from 350 mL of H₂O to yield 16.1 g (66%) of the product as off white flakes: mp 125-126°C (lit mp 126°C).

**2,3,4,5-di-O-cyclohexylidene-D-arabinitol (55)**

A stirred mixture of 54 (15.0 g, 0.0361 mol), yellow mercuric oxide (21.9 g, 0.101 mol), and mercuric chloride (21.5 g, 0.0794 mol) in 250 mL of 10:1 acetone-H₂O was heated at gentle reflux for 2 h. The mixture was cooled to RT, filtered and the collected solids washed with 120 mL of acetone. The filtrate and washings were combined and concentrated under reduced pressure in the presence of mercuric oxide (4.0 g) and the residue obtained extracted with 4x120 mL portions of hot CHCl₃. The combined extracts were washed with 190 mL of 1N KI and 50 mL of H₂O. The aqueous washes were back extracted
with 2x50 mL portions of CHCl₃. The CHCl₃ solution was then washed with 120 mL of saturated NaCl, treated with charcoal, and dried over MgSO₄. The solvent was evaporated at reduced pressure to yield a yellow syrup. The yellow syrup was dissolved in 115 mL of MeOH and NaBH₄ (1.77 g, 0.0469 mol) was added. After stirring for 1.5 h at RT 40 mL of H₂O was added and the solution stirred for 30 min. The solution was concentrated at reduced pressure to remove the MeOH, the watery residue diluted with 300 mL of CH₂Cl₂, washed with 100 mL of saturated aqueous NaCl, treated with charcoal, and dried over MgSO₄. Removal of solvent at reduced pressure afforded 10.1 g (90%) of 55 as clear syrup.

1-O-p-Toluenesulfonyl-2,3,4,5-di-O-cyclohexylidene-D-arabinitol (56).

To an ice-cooled stirred solution of 55 (10.1 g, 0.0324 mol) in pyridine (14.1 mL) was added p-toluenesulfonyl chloride (7.42 g, 0.0389 mol). After 2 h at 0°C and an additional 16 h at RT, water (10 mL) was added and the mixture was stirred 1 h at RT to destroy excess p-toluenesulfonyl chloride. The solution was then diluted with 600 mL of ether, washed with 90 mL of H₂O, 90 mL of saturated aqueous NaHCO₃, 90 mL of saturated NaCl, treated with charcoal, and dried over MgSO₄. Removal of solvent at reduced pressure followed by
co-evaporation with toluene, to remove pyridine, afforded
15.1 g (100%) of 56 as a pale yellow syrup. On standing for
several weeks the syrup crystallized (mp 67-69.5°C). Pre-
parative TLC (elution with 1:4 ether-petroleum ether) pro-
vided analytically pure material: IR (neat) 3.39, 3.48, 6.27,
6.89, 7.30, 7.79 μ; 1H NMR (60 MHz, CDCl3) δ 1.3-1.6 (m, 20,
cyclohexylidenes), 2.40 (s, 3, CH3), 3.7-4.4 (m, 7, H1, H1-
H5, H5, H1-), 7.51 (dd, 4, Ar-H); 13C NMR (CDCl3) δ 21.56 (CH3),
23.74, 23.98, 25.00, 25.10, 34.66, 36.31, 36.41, 36.60 (8
-CH2- of cyclohexylidene, 2 overlapping), 67.43 (C5), 69.76
(C1), 76.85, 77.73 (C2-C4, C2, C1, C1 overlapping), 110.35,
110.86 (2 cyclohexylidene quaternary carbons), 128.02,
129.72 (o and m aromatics, 2 overlapping), 133.22, 144.68
(ipso aromatics); [α]D25+15.51° (c 1.27, CHCl3); exact mass
m/e 466.2037 (calcd, 466.2025).

Anal. Calcd for C24H34O7S: C, 61.78; H, 7.34.

Found: C, 61.47; H, 7.35.
A stirred mixture of 56 (15.0 g, 0.0321 mol), sodium carbonate (6.8 g, 0.0643 mol), and sodium iodide (14.5 g, 0.0964 mol) in 25 mL of DMF was heated at 125°C under nitrogen. After 1 h the mixture was cooled to RT and diluted with 1 L of 2:1 ether-petroleum ether. The solution was washed with 300 mL of H₂O, 200 mL of saturated aqueous NaHCO₃, 250 mL of saturated aqueous NaCl, treated with charcoal, and dried over MgSO₄. The solvent was evaporated at reduced pressure and the residue purified by column chromatography (silica gel, 3.5x45 cm column, elution with 1:4 ether-petroleum ether) to afford 12.9 g (95%) of 57 as a pale yellow syrup. Preparative TLC (elution with 1:4 ether-petroleum ether) provided analytically pure material: IR (neat) 3.38, 3.47, 6.86, 7.27, 7.74 μ; ¹H NMR (60 MHz, CDCl₃) δ 1.25-1.8 (m, 20, cyclohexylidenes), 3.3-4.25 (m, 7, H₁, H₂-H₅, H₅,); ¹³C NMR (CDCl₃) δ 8.11(C₁), 23.21, 23.89, 24.15, 34.86, 36.65, 37.04 (-CH₂- cyclohexylidenes, 3 overlapping), 67.48 (C₅), 76.76, 80.98 (C₂, C₃, C₄, 1 overlapping), 110.45 (cyclohexylidenes quaternary carbons, 1 overlapping); [α]₂⁰D +23.86° (c 1.19, CHCl₃); exact mass m/e 422.0960 (calcd m/e 422.0956).

Anal. Calcd for C₁⁷H₂⁷O₄I: C, 48.35; H, 6.44.

Found: C, 48.53; H, 6.63.
1-Deoxy-1-triphenylphosphonio-2,3,4,5-di-O-cyclohexylidene-D-arabinitol Iodide (58).

A stirred solution of 57 (12.9 g, 0.03048 mol) and triphenylphosphine (12.0 g, 0.0457 mol) in 15 mL of tetramethylenesulfone was heated at 110°C under nitrogen for 24 h. The pale yellow solution was diluted with 50 mL of CHCl₃ and then added dropwise to 1800 mL of vigorously stirred ether. The product oiled out as a yellow syrup contaminated with small amounts of tetramethylenesulfone. The trituration procedure was again repeated to yield a syrup free of tetramethylenesulfone. Drying at high vacuum afforded 12.95 g (62%) of 58 as a pale yellow foam. Preparative TLC (elution with 9:1 CH₂Cl₂-MeOH) provided analytically pure material: IR (neat) 3.40, 3.49, 6.31, 6.96, 7.33, 8.87 μ; ¹H NMR (60 MHz, CDC₃) δ 1.1-1.7 (m, 20, cyclohexylidenes), 3.47-4.39 (m, 7, H₁₁, H₁-H₅, H₅'), 7.45-8.05 (m, 15, Ar-H); ¹³C NMR (CDCl₃) δ 23.55, 23.84, 24.22, 24.22, 24.71, 25.05, 26.75, 29.42, 34.62, 35.97, 36.27, 36.41 (-CH₂- cyclohexylidenes, -CH₂-P), 67.24 (C₅), 73.31, 76.08, 80.78 (C₂, C₃, C₄), 110.64, 111.71 (cyclohexylidenes quaternary carbon), 116.13, 120.50 (ipso to P, 1 overlapping), 130.11, 130.79, 133.70, 134.19, 135.21, 135.35 (o,m, and p aromatics, 9 overlapping); [α]D³¹ +30.37° (c 0.41, CHCl₃).
Anal. Calcd for C\textsubscript{35}H\textsubscript{42}O\textsubscript{4}Pi: C, 61.41; H, 6.18.

Found: C, 61.62; H, 6.35.

1-C-Phenyl-3,4:5,6-di-O-cyclohexyldene-1,2-dideoxy-D-arabino-hex-1-enitol (60 and 61).

A stirred solution of 58 (0.30 g, 0.000438 mol) in 2.7 mL of 2:1 THF-HMPA was cooled to -65°C under nitrogen and \( \pi \)-BuLi (0.0004818 mol) was added via syringe. After stirring for 30-45 sec benzaldehyde (0.000657 mol) was added and the solution allowed to warm up slowly to -10°C over a period of 1 h. A 1:1 ether-petroleum ether mixture was added and precipitated triphenylphosphine oxide was filtered off, washing with 1:1 ether-petroleum ether. Volatile solvents were removed from the filtrate under reduced pressure and the residue taken up in 50 mL of 4:1 ether-petroleum ether, washed with 30 mL of \( \mathrm{H}_2\mathrm{O} \), 30 mL of saturated aqueous \( \mathrm{NaHSO}_3 \), 15 mL of saturated aqueous \( \mathrm{NaCl} \), and dried over \( \mathrm{MgSO}_4 \). The solvent was evaporated under reduced pressure and the residue purified by preparative TLC (elution with 1:6 ether-petroleum) to afford 0.087 g (52%) of a mixture of \textit{cis} (60) and \textit{trans} (61) isomers as a clear syrup. (predominately \textit{cis})

\textsuperscript{1}H NMR (60 MHz, \( \mathrm{CDCl}_3 \)) \& 1.2-1.8 (m, 20, cyclohexyldienes), 3.6-4.2 (m, 4, \( \mathrm{H}_4,\mathrm{H}_5,\mathrm{H}_6,\mathrm{H}_6' \)), 4.51-4.87 (m, 1, \( \mathrm{H}_3 \)), 5.47-5.83 (m, 1, \( \mathrm{H}_2 \)), 6.71 (d, J 11 Hz, \( \mathrm{H}_1 \) of \textit{cis}), 7.15-7.6 (m, 5, Ar-H).
Ozonolysis-Reduction of the 60 and 61 Mixture. Formation of 2,3,4,5-di-O-Cyclohexylidene-D-arabinitol (55).

Ozone was passed through a hexane solution (5 mL) of the cis (60) and trans (61) mixture (0.055 g, 0.000143 mol) for 3 min at 0°C; nitrogen was then passed through, and an excess of an ethereal solution of LiAlH₄ was added at -30°C. The solution was warmed to RT, heated at reflux for 1 h and worked up by addition of H₂O to quench the excess LiAlH₄ followed by dilution with ether and extraction. The ethereal solution was dried over MgSO₄ and the solvent evaporated under reduced pressure. The residue was purified by preparative TLC (elution with 2:1 ether-petroleum ether) to afford 0.021 g (47%) of a single carbohydrate alcohol: ¹³C NMR (CDCl₃) δ 23.84, 24.04, 25.10, 34.81, 36.46, 36.56 (-CH₂- cyclohexylidenes, 2 overlapping), 63.02 (C₁), 67.72 (C₅), 76.85, 78.75, 80.59 (C₂, C₃, C₄), 109.96, 110.50 (cyclohexylidenes quaternary carbon).

For comparison purposes: ¹³C NMR (CDCl₃) of 55 δ 23.87, 24.06, 23.91, 25.12, 34.78, 36.46, 36.58 (-CH₂- cyclohexylidenes, 1 overlapping), 63.04 (C₁), 67.72 (C₅), 76.83, 78.79, 80.57 (C₂, C₃, C₄), 109.96, 110.55 (cyclohexylidenes quaternary carbon).
Methyl-(Z)-4.6.7-trideoxy-2.3-di-O-benzyl-4-azido-8.9:10.11-di-O-cyclohexylidene-D-arabino-α-D-gluco-undec-6-enopyranoside (62).

A stirred solution of 58 (2.92 g, 0.00427 mol) in 18 mL of 2:1 THF-HMPA was cooled to -65°C under nitrogen and n-BuLi (0.00427 mol) was added via syringe. After stirring for 30-45 sec, 50 (1.3 g, 0.00329 mol) in 3 mL of THF was added and the solution allowed to warm up slowly to -10°C over a period of 1 h. A 1:1 ether-petroleum ether mixture was added and precipitated triphenylphosphine oxide was filtered off, washing with 1:1 ether-petroleum ether. Volatile solvents were removed from the filtrate under reduced pressure and the residue taken up in 300 mL of 4:1 ether-petroleum ether, washed with 2x120 mL portions of H₂O, 80 mL of saturated aqueous NaHSO₃, 80 mL H₂O, 80 mL of saturated aqueous NaCl and dried over MgSO₄. The solvent was evaporated at reduced pressure and the residue purified by column chromatography (silica gel, 2.5x50 cm column, elution with 1:2 ether-petroleum ether) to afford 1.10 g (50%) of 62 as a clear syrup. The product was accompanied by a small amount of impurity (~5%) having similar mobility in a number of TLC systems, which made analysis difficult. In the subsequent reduction of the azide to the amine, this impurity can readily be removed. IR (neat) 3.42, 3.52, 4.73, 6.66, 6.87, 7.29, 7.80 μ; ¹H NMR (60 MHz, CDCl₃)
\( \delta 1.3-1.7 \) (m, 20, cyclohexyldienes), 3.39 (s, 3, OCH\(_3\)), 3.4-4.2 (m, 7, H\(_2\),H\(_3\),H\(_4\),H\(_9\),H\(_{10}\),H\(_{11}\),H\(_{11}\)), 4.4-4.9 (m, 7, H\(_1\),H\(_5\),H\(_8\),2 CH\(_2\)C\(_6\)C\(_5\)), 5.3-5.9 (m, 2, H\(_6\),H\(_7\)), 7.1-7.4 (m, 10, Ar-H);

\(^{13}\text{C NMR (CDCl}_3\) \( \delta 23.93, 25.15, 35.00, 36.60, 36.90 (-\text{CH}_2\text{-cyclohexyldienes, 4 overlapping}), 55.59 (\text{OCH}_3), 66.22 (\text{C}_4), 66.85 (\text{C}_{11}), 67.00, 73.36, 75.78, 76.61, 79.62, 79.76, 81.46 (\text{C}_2,\text{C}_3,\text{C}_5,\text{C}_8,\text{C}_9,\text{C}_{10},2 \text{CH}_2\text{C}_6\text{H}_5, 1 overlapping), 98.36 (\text{C}_1), 110.30 (\text{cyclohexyldienes quaternary carbon, 1 overlapping}), 127.78, 128.12, 128.22, 128.41, 128.51 (o,m, and p aromatics, 5 overlapping), 129.67, 132.68 (\text{C}_6,\text{C}_7), 138.02, 138.27 (ipso aromatic); [\alpha]_D^{22} -18.09^\circ (\text{c 1.78, CHCl}_3).

**Methyl-(Z)-4.6.7-trideoxy-2,3-di-O-benzyl-4-amino-8,9;10,11-di-O-cyclohexyldiene-D-arabino-2-D-gluco-undec-6-enopyranoside (63).**

To a stirred suspension of LiAlH\(_4\) (0.37 g, 0.0097 mol) in 17 mL of THF was added dropwise a solution of 62 (2.19 g, 0.00324 mol) in 25 mL of THF. After 2 h under nitrogen at RT, 14 mL of ethyl acetate was slowly added, followed by careful addition of 11 mL of H\(_2\)O. The mixture was filtered and the residue washed well with ether. The filtrate was evaporated under reduced pressure and the residue taken up in 200 mL of ether, washed with 40 mL of H\(_2\)O, 40 mL of saturated aqueous NaCl, and dried over MgSO\(_4\). The solvent was removed under reduced
pressure and the residue purified by column chromatography (silica gel, 2.5x40 cm column, elution with 1:1 ether-petroleum ether) to afford 1.68 g (80%) of \( \text{63} \) as a clear syrup. Preparative TLC (elution with 1:1 ether-petroleum ether) provided analytically pure material: IR (neat) 2.96, 3.41, 3.49, 6.66, 6.87, 7.28, 7.99 \( \mu \); \(^1\)H NMR (60 MHz, CDCl\(_3\)) \( \delta \) 1.2-1.9 (m, 20, cyclohexylenedienes), 3.35 (s, 3, OCH\(_3\)), 3.45-4.1 (m, 7, H\(_2\),H\(_3\),H\(_4\),H\(_9\),H\(_{10}\),H\(_{11}\)), 4.4-4.9 (m, 7, H\(_1\),H\(_5\), H\(_8\),2 CH\(_2\)C\(_6\)H\(_5\) ), 5.2-5.8 (m, 2, H\(_6\),H\(_7\) ), 7.2-7.35 (m, 10, Ar- H); \(^1^3\)C NMR (CDCl\(_3\)) \( \delta \) 23.98, 25.20, 35.05, 36.61, 37.04 (-CH\(_2\)-cyclohexylenedienes, 5 overlapping), 55.34 (OCH\(_3\)), 57.00 (C\(_4\)), 66.85 (C\(_{11}\)), 68.89, 73.07, 75.89, 76.42, 80.49, 81.37, 81.66 (C\(_2\),C\(_3\),C\(_5\),C\(_8\),C\(_9\),C\(_{10}\), 2CH\(_2\)C\(_6\)H\(_5\), 1 overlapping), 98.65 (C\(_1\)), 110.21 (cyclohexylenedienes quaternary carbon, 1 overlapping), 127.68, 127.98, 128.12, 128.46 (o,m, and p aromatics, 6 overlapping), 131.96, 132.05 (C\(_6\),C\(_7\)), 138.32, 139.04 (ipso aromatic); [\( \alpha \)]\(_D\)\(^{24}\) -8.72° (c 2.04, CHCl\(_3\)).

Anal. Calcd for C\(_{38}\)H\(_{51}\)O\(_8\)N: C, 70.24; H, 7.91; N, 2.16.

Found: C, 70.30; H, 8.12; N, 2.16.
Methyl-4,6,7-trideoxy-2,3-di-O-benzyl-4-azido-6,7-epoxy-8,9:10,11-di-O-cyclohexyldiene-D-arabino-α-D-gluco-undecopyranoside (65 and 66).

A stirred solution of 62 (0.515 g, 0.000762 mol), m-CPBA (0.387 g, 0.001905 mol), and several crystals of 2,6-di-t-butyl-4-methyl phenol (radical inhibitor) in 5.2 mL of 1,2 dichloroethane was heated at 80°C for 19 h. The solution was cooled to RT, 12 mL of 10% aqueous NaHSO₄ added, and this solution stirred for 30 min. The reaction mixture was diluted with 185 mL of ether and the aqueous layer separated. The ethereal solution was washed with 60 mL of saturated aqueous NaHCO₃, 60 mL of saturated aqueous NaCl, and dried over MgSO₄. The solvent was evaporated under reduced pressure to yield a crude mixture of diastereoisomeric epoxides which were purified and separated by preparative TLC (elution with 9:1 benzene-ether) to afford 0.122 g (23.2 %) of 65 (Rₓ=0.85, elution with 9:1 benzene-ether) and 0.244 g (46.3%) of 66 (Rₓ=0.80, elution with 9:1 benzene-ether) as white foams:

65: IR (KBr) 3.24, 3.27, 3.31, 3.44, 4.77, 6.90, 7.32, 7.87 μ;
1H NMR (60 MHz, CDCl₃) δ 1.2-1.8 (m, 20, cyclohexyldienes), 3.0-3.2 (m, 2, H₆,H₇), 3.39 (s, 3, OCH₃), 3.55-4.45 (m, 9, H₂-H₅,H₈-H₁₁,H₁₁'), 4.55 (d, 1, H₁), 4.80 (d, 2, CH₂C₆H₅),
4.90 (d, 2, CH₂₃H₅), 7.2-7.5 (m, 10, Ar-H); exact mass m/e 691.3482 (calcd m/e 691.3468).

65: IR (neat) 3.24, 3.27, 3.30, 3.40, 4.75, 6.85, 7.30 μ;

¹H NMR (60 MHz, CDCl₃) J 1.1-1.8 (m, 20, cyclohexylidenes), 3.03-3.25 (m, 2, H₆, H₇), 3.35 (s, 3, OCH₃), 3.4-4.4 (m, 9, H₂-H₅, H₈-H₁₁, H₁₁'), 4.59 (d, 1, H₁), 4.66 (d, 2, CH₂C₆H₅), 4.87 (d, 2, CH₂C₆C₅), 7.1-7.5 (m, 10, Ar-H); ¹³C NMR (CDCl₃) J 22.38, 23.98, 25.15, 25.24, 25.97, 34.91, 36.31, 36.94, 37.19, 37.57 (-CH₂- cyclohexylidenes), 55.44 (OCH₃), 57.48 (C₆, C₇, 1 overlapping), 64.42 (C₄), 66.12 (C₁₁), 67.97, 73.41, 75.54, 75.84, 79.67, 79.76, 80.69 (C₂, C₃, C₅, C₈, C₉, C₁₀, 2CH₂C₆H₅, 1 overlapping), 98.21 (C₁), 110.35, 111.18 (cyclohexylidenes quaternary carbon), 127.88, 128.17, 128.27, 128.46, 128.61 (o, m, and p aromatics, 3 overlapping), 137.93, 138.12 (ipso aromatic); exact mass m/e 691.3482 (calcd m/e 691.3468).

**Methyl-4,6,7-trideoxy-2,3-di-O-benzyl-4-amino-6,7-epoxy-8,9,10,11-di-O-cyclohexylidene-D-arabino-α-D-gluco-undecopyranoside** (67 and 68).

A solution of 65 (0.110 g, 0.000159 mol) and triphenylphosphine (0.063 g, 0.0002385 mol) in 1.0 mL of THF was stirred at RT. After 3 h 1 mL of 12N KOH and a catalytic amount of 18-crown-6
was added and the solution heated at 65°C for 40 h. The solution was then cooled to RT, diluted with ether, washed with saturated aqueous NaCl and dried over MgSO₄. The solvent was removed under reduced pressure and the residue purified by preparative TLC (elution with 3:1 ether-petroleum ether) to afford 0.056 g (53%) of product. IR (neat) 2.7-3.2, 3.41, 3.48, 6.92, 7.32, 7.85, 8.95 μm; ¹H NMR (60 MHz, CDCl₃) δ 1.2-1.7 (m, 20, cyclohexyldienes), 1.8-2.0 (d, 2, NH₂), 2.82-3.14 (m, 2, H₆,H₇), 3.40 (s, 3, OCH₃), 3.48-4.4 (m, 7, H₂,H₄,H₅,H₉,H₁₀,H₁₁,H₁₂), 4.5-5.0 (m, 7, H₁,H₅,H₈,2CH₂C₆H₅). Similar reaction with 66 afforded product in 68% yield.

Methyl-4,6,7-trideoxy-2,3-di-O-benzyl-4-azido-6,7-epoxy-8,9,10,11-tetra-O-acetyl-D-arabino-α-D-gluco-undecopyranoside (69).

A solution of 66 (0.042 g, 0.000065 mol) in 4.5 mL of 9:1 trifluoroacetic acid-water was stirred at RT. After 20 min the solution was evaporated via vacuum distillation at RT and the residue treated with 1 mL of 1:1 pyridine-acetic anhydride. After stirring for 24 h at RT the solution was concentrated under reduced pressure by co-evaporation with toluene and the residue purified by preparative TLC to afford 0.020 g (42%) of 69.
$^1$H NMR (60 MHz, CDCl$_3$) δ 2.0-2.2 (4s, 12, 4CH$_3$-C-O), 3.31-
3.4 (m, 2, H$_6$,H$_7$), 3.40 (s, 3, OCH$_3$), 3.45-5.6 (m, 14, H$_1$-
H$_5$,H$_8$-H$_{11}$,H$_{11}$,2CH$_2$C$_6$H$_5$), 7.27-7.43 (m, 10, Ar-H).

Methyl-(E)-4,6,7-trideoxy-2,3-di-O-benzyl-4-acetamido-8,9:10,
11-di-O-cyclohexylidene-D-arabino-4-D-gluco-undec-6-eno-
pyranoside (70).

A solution of 63 (1.6 g, 0.00246 mol) and diphenyl disulfide (1.08 g, 0.00492 mol) in 10 mL of cyclohexane was irradiated for 35 min. The solution was concentrated and separation of the E and Z isomers was accomplished by column chromatography (silica gel, 2.5x45 cm column, elution with 1:1 ether-petroleum ether). Intermediate fractions containing mixtures of E and Z isomers were rechromatographed by preparative TLC (elution 3 times with 1:1 ether-petroleum ether), to yield 0.924 g (58%) of starting Z isomer, which could be recycled, and 0.606 g (38%) of the E isomer (90% based on recovered Z isomer). The E isomer (0.606 g, 0.000932 mol) was treated with 1:2 acetic anhydride-pyridine (15 mL) at RT. After 24 h the solution was concentrated under reduced pressure by co-evaporation with toluene and the residue purified by preparative TLC (elution 3 times with 2:1 ether-petroleum ether) to afford 0.474 g (73%)
of 70 as a white foam: IR (neat) 3.06, 3.41, 3.50, 6.06,
6.42, 6.88, 7.30 μ; $^1$H NMR (60 MHz, CDC13) δ 1.3-1.7 (m,
20, cyclohexyldienes), 1.77 (s, 3, NAc), 3.33 (s, 3, OCH₃)
3.5-4.3 (m, 9, H₂-H₅,H₈-H₁₁,H₁₁'), 4.5-4.9 (m, 5, H₁,
2CH₂C₆H₅), 5.11 (d, 1, NH), 5.72-5.86 (m, 10, Ar-H); $^{13}$C NMR
(CDC1₃) δ 23.50, 23.89, 24.08, 25.20, 34.96, 36.36, 36.56,
36.65 (-CH₂- cyclohexyldienes, CH₃O-, 3 overlapping), 54.81
(C₄), 55.34 (OCH₃), 66.51 (C₁₁), 70.69, 73.41, 74.62, 76.27,
77.87, 79.04, 80.35, 81.12 (C₂,C₃,C₅,C₈,C₉,C₁₀, 2CH₂C₆H₅),
98.36 (C₁), 110.21 (cyclohexyldienes quaternary carbon, 1
overlapping), 127.73, 128.02, 128.17, 128.27, 128.51. 128.70
(o,m, and p aromatics, 4 overlapping), 132.05 (C₆,C₇, 1
overlapping), 138.17, 138.85 (ipso aromatic), 169.53 (CH₃O);
[α]$_D^{24}$ -10.69° (c 1.68, CHCl₃).
Anal. Calcd for C₄₀H₄₅O₉N: C, 69.44; H, 7.72; N, 2.02.
Found: C, 69.28; H, 7.89; N, 1.91.

Methyl 2,3-di-O-benzyl-4-deoxy-4-acetamido-8,9:10,11-di-
O-cyclohexyldiene-a-hikosamine (71).

Method A:
To a stirred solution of 70 (0.388 g
0.000561 mol) in 9 mL of 5:1 THF-H₂O
was added a crystal of OsO₄. The solution immediately darkened and after
5 min at RT N-methyl morpholine-N-oxide
(0.084 g, 0.000617 mol) was added. After 5 h at RT, saturated aqueous NaHSO₃ was added and the solution stirred for 10 min. The solution was diluted with 150 mL of ether, washed with 25 mL of 3N HCl, 25 mL of saturated aqueous NaHCO₃, 25 mL of saturated aqueous NaCl, treated with charcoal, and dried over MgSO₄. The solvent was removed under reduced pressure and the residue purified by preparative TLC (elution 3 times with 3:1 ether-petroleum ether) to afford 0.318 g (78%) of 7₂ as a white foam: IR (neat) 2.88-3.07, 3.40, 3.49, 6.05, 6.44, 6.87, 7.30 μ; ¹H NMR (60 MHz, CDCl₃) δ 1.3-1.7 (m, 20, cyclohexyldene), 1.77 (s, 3, NAc), 3.40 (s, 3, OCH₃), 3.6-4.3 (m, 11, H₂-H₁₁, H₃₁₁*), 4.5-4.9 (m, 5, H₁, 2CH₂C₆H₅), 5.5 (d, 1, NH), 7.3-7.4 (m, 10, Ar-H); ¹³C NMR (CDCl₃) δ 23.50, 23.74, 23.84, 23.93, 25.05, 34.71, 36.00, 36.48, 36.58 (-CH₂- cyclohexyldenes, CH₃C, 2 overlapping), 52.14 (C₄), 55.44 (OCH₃), 67.46 (C₁₁), 70.66, 70.90, 71.10, 73.38, 74.55, 76.42, 79.74, 80.42 (C₂, C₃, C₅-C₁₀, 2CH₂C₆H₅, 2 overlapping), 97.73 (C₁), 110.04, 110.86 (cyclohexyldenes quaternary carbon), 127.78, 127.98, 128.10, 128.34, 128.51 (o,m, and p aromatics, 5 overlapping), 138.15, 138.63 (ipso aromatic), 170.58 (CH₃C); exact mass m/e 725.3791 (calcd 725.3774). Difficultly removable minor impurities made a proper elemental analysis unobtainable.
Method B:

To a stirred solution of 70 (0.264 g, 0.000382 mol) in 4.4 mL of 1:1 THF-H₂O was added a crystal of OsO₄. The solution immediately darkened and after 5 min at RT KClO₃ (0.056 g, 0.000458 mol) was added. After 2 days at 55°C the reaction mixture was processed as described in Method A to afford 0.131 g (47%) of 71.

Methyl Peracetylg-α-hikosaminide (39).

A vigorously stirred suspension of 10% Pd/C (13 mg) and 71 (0.131 g, 0.0001804 mol) in 4:1 MeOH-H₂O (2.5 mL) to which 5 drops of concentrated aqueous HCl was added was hydrogenated at RT and pressure. After 24 h the suspension was filtered through a pad of Celite and evaporated at reduced pressure. The residue was dissolved in H₂O, the solution neutralized with Amberlite IR 45(OH⁻), and evaporated under reduced pressure. The residue was treated with 1:1 acetic anhydride-pyridine (5 mL). After stirring for 24 h at RT the solution was concentrated under reduced pressure by co-evaporation with toluene and the residue purified by preparative TLC (elution with 9:1 CH₂Cl₂-MeOH) to afford 0.062 g (47%) of 39. Recrystallization from ethanol gave white needles.
mp 177-178°C (lit. mp 180.5-181.5°C, 7 mixture melting point undepressed), $[\alpha]_D^{23} +90.78^\circ (c 0.575, CHCl_3) [\text{lit. } [\alpha]_D^{29} +85^\circ (c 1.0, CHCl_3) ]^7$. $^1H$ NMR (400 MHz, CDCl$_3$) 1.97-2.19 (9s, 27, 90Ac), 3.2 (s, 3, OCH$_3$), 3.83 (dd, 1, H$_5$), 4.00-4.22 (2dd, 2, H$_{11}, H_{11'}$), 4.58 (dd, 1, H$_4$), 4.72 (m, 1, H$_6$), 4.75 (d, 1, H$_2$), 4.84 (d, 1, H$_1$), 5.02-5.06 (m, 1, H$_{10}$), 5.20 (t, 1, H$_3$), 5.40 (dd, 1, H$_9$), 5.45 (dd, 1, H$_8$), 5.69 (d, 1, NH), 5.86 (dd, 1, H$_7$), $J_{1,2}=3.4$ Hz, $J_{2,3}=10.3$ Hz, $J_{3,4}=10.3$ Hz, $J_{4,5}=11.1$ Hz, $J_{4,NH}=9.3$ Hz, $J_{5,6}=2.7$ Hz, $J_{6,7}=1.2$ Hz, $J_{7,8}=10.0$ Hz, $J_{8,9}=2.0$ Hz, $J_{9,10}=9.3$ Hz, $J_{10,11}=2.8$ Hz, $J_{10,12}=5.4$ Hz, $J_{11,12}=12.4$ Hz. The 400 MHz $^1H$ NMR spectrum of 39 prepared from natural sources is identical to that prepared synthetically.
Methyl 2-benzamido-2-deoxy-3,4-0-isopropylidene-6-O-t-butyldiphenylsilyl-α-D-galactopyranoside (76).

To a stirred solution of 75 (1.43 g, 0.00481 mol) in 4.0 mL of DMF was added imidazole (0.72 g, 0.0106 mol) and t-butyldiphenylsilyl chloride (1.37 mL, 0.00529 mol). After 4 h at RT the solution was diluted with 100 mL of ether, washed with 2x25 mL portions of H₂O, 25 mL of saturated aqueous NaCl and dried under reduced pressure yielding the crude 6-O-t-butyldiphenylsilyl ether. The crude 6-O-t-butyldiphenylsilyl ether was dissolved in 70 mL of acetone and treated with CuSO₄ (4.61 g, 0.0289 mol) and 3 drops of concentrated H₂SO₄. After stirring 17 h at RT the solution was neutralized by addition of solid Na₂CO₃ and the inorganic salts removed by filtration. The filtrate was concentrated and the residue obtained purified by column chromatography (silica gel, 2.5x50 cm column, elution with 1:1 ether-petroleum ether) to afford 2.00 g (72%) of 76 as a white foam: ¹H NMR (60 MHz, CDCI₃) δ 1.09 (s, 9, C(CH₃)₃), 1.32, 1.60 (2s, 6, C(CH₃)₂), 3.30 (s, 3, OCH₃), 3.9-4.55 (m, 6, H₂⁻H₆, H₆), 4.81 (d, 1, H¹), 6.31 (d, 1, NH), 7.2-7.9 (m, 15, Ar-H).
Methyl 2-benzamido-2-deoxy-3,4-O-isopropylidene-α-D-galactopyranoside (77).

A stirred solution of 76 (1.5 g, 0.00260 mol) and powdered NaOH (0.52 g, 0.0130 mol) in 30 mL of 9:1 ethanol-H$_2$O was heated at 60°C. After 20 h the solution was cooled and the ethanol removed under reduced pressure. The watery residue obtained was dissolved in 20 mL of CHCl$_3$, washed with 20 mL of H$_2$O, 30 mL of saturated aqueous NaCl and dried over MgSO$_4$. The solvent was removed under reduced pressure and the residue obtained purified by column chromatography (silica gel, 2.5x15 cm column, elution with ether) to afford 0.68 g (77%) of 77 as a white foam: $^1$H NMR (60 MHz, CDCl$_3$) δ 1.33, 1.58 [2s, 6, C(CH$_3$)$_2$], 3.35 (s, 3, OCH$_3$), 3.8-4.45 (m, 6, H$_2$-H$_6$,H$_6$), 4.75 (d, 1, H$_1$), 6.43 (d, 1, NH), 7.2-7.9 (m, 5, Ar-H).

Methyl 4,6-O-benzylidene-2-deoxy-2-phthalimido-α-D-galactopyranoside (79).

A stirred solution of 78 (1.34 g, 0.00451 mol) and phthalic anhydride (0.734 g, 0.00499 mol) in 6.7 mL of DMF was heated at reflux under nitrogen for 1.5 h. The solution was cooled, diluted with 100 mL of CHCl$_3$, washed with 2x25 mL portions of H$_2$O, 25 mL of saturated NaCl,
treated with charcoal and dried over MgSO$_4$. The solvent was removed under reduced pressure and the residue obtained purified by column chromatography (silica gel, 2.5x45 cm column, elution with 95:5 CH$_2$Cl$_2$-MeOH) to afford 1.28 g (69%) of 79 as a yellow foam. $^1$H NMR (60 MHz, CDCl$_3$) $\delta$ 3.30 (s, 3, OCH$_3$), 3.72-4.70, 5.25-5.60 (m, 6, H$_2$-H$_6$,H$_6^0$), 4.92 (d, 1, H$_1$), 5.58 (s, 1, CHC$_6$H$_5$), 7.2-7.9 (m, 9, Ar-H).

Methyl 4-O-benzoyl-6-bromo-2,6-dideoxy-2-phthalimido-α-D-galactopyranoside.

A stirred solution of 79 (1.28 g, 0.00311 mol), barium carbonate (3.07 g, 0.0155 mol) and N-bromosuccinimide (0.609 g, 0.00342 mol) in 85 mL of 3:1 carbon tetrachloride-tetrachloroethane was heated at reflux under nitrogen. After 1.5 h the solution was cooled, solids removed by filtration and washed with CH$_2$Cl$_2$. The filtrate and washings were combined and evaporated under reduced pressure. The syrupy residue obtained was dissolved in 250 mL of CH$_2$Cl$_2$, washed with 25 mL of H$_2$O, 25 mL of saturated aqueous NaCl, treated with charcoal and dried over MgSO$_4$. The solvent was removed under reduced pressure and the residue obtained purified by preparative TLC (elution with ether) to afford 1.12 g, (74%) of methyl 4-O-benzoyl-6-bromo-2,6-dideoxy-2-phthalimido-α-D-galactopyranoside. $^1$H NMR (60 MHz,
pyridine-d$_5$) at 3.35 (s, 3, OCH$_3$), 3.6-6.3 (m, 7, H$_1$-H$_6$,H$_6^*$), 7.1-8.4 (m, 9, Ar-H).

Methyl 6-bromo-2,6-dideoxy-3.4-Q-isopropylidene-2-phthalimidomorphogalactopyranoside (81).

To a stirred solution of methyl 4-Q-benzoyl-6-bromo-2,6-dideoxy-2-phthalimidomorphogalactopyranoside (2.44 g, 0.00498 mol) in 240 mL of CH$_2$Cl$_2$ was added a solution of methanolic sodium methoxide (0.114 g, 0.00498 mol of sodium added to 60 mL of methanol). After 10 min at RT the solution was neutralized by addition of excess amberlite IR-120(H$^+$) ion exchange resin, the resin removed by filtration and the solvent removed under reduced pressure. The residue obtained was purified by column chromatography (silica gel, 2.5x30 cm column, elution with 9:1 CH$_2$Cl$_2$-MeOH) to afford 1.25 g (65%) of methyl 6-bromo-2,6-dideoxy-2-phthalimidomorphogalactopyranoside 80. The 80 obtained was dissolved in 40 mL of CH$_2$Cl$_2$ and treated with 10 mL of acetone, 10 mL of 2,2-dimethoxypropane and 2 drops of concentrated H$_2$SO$_4$. After stirring for 1 h at RT the solution was neutralized by addition of solid NaCO$_3$ and the inorganic salts removed by filtration. The filtrate was concentrated under reduced pressure and the residue obtained purified by column chromatography (silica gel, 2.5x20 cm column, elution with
97:3 CH₂Cl₂-MeOH) to afford 0.84 g (61%) of 81 as a semi-solid: ¹H NMR (60 MHz, CDCl₃)  δ 1.32, 1.52 [2s, 6, C(CH₃)₂], 3.36 (s, 3, OCH₃), 3.52-5.83 (m, 7, H₁-H₆,H₆⁻), 7.6-8.0 (m, 4, Ar-H).

**Methyl 2,6-dideoxy-3,4-O-isopropylidene-2-phthalimido-6-(triphenylphosphonic)-α-D-galactopyranose Bromide (82).**

A stirred solution of 81 (0.1 g, 0.000234 mol) and triphenylphosphine (0.092 g, 0.000352 mol) in 0.2 mL of sulfolane was heated at 110°C under nitrogen for 3 days. The solution was diluted with 1 mL of CHCl₃ and added dropwise to 50 mL of vigorously stirred ether and the precipitated solid filtered and washed with ether. The white solid was dried under vacuum to yield 0.103 g (64%) of 82; mp 240°C (decomp); ¹H NMR (60 MHz, CDCl₃)  δ 1.38, 1.49 [2s, 6, C(CH₃)₂], 2.34 (s, 3, OCH₃), 4.2-5.85 (m, 7, H₁-H₆,H₆⁻), 7.3-8.2 (m, 19, Ar-H).

**Methyl 6-bromo-6-deoxy-α-D-galactopyranoside (83).**

To a stirred solution of MeOH (250 mL) under nitrogen was carefully added sodium metal (0.318 g, 0.0138 mol). After the sodium had completely reacted, methyl 4-O-benzoyl-6-bromo-6-deoxy-α-
\(\alpha\)-galactopyranoside \(66\) (5.0 g, 0.0138 mol) in MeOH was added. After 15 min at RT, acetic acid (1.58 mL, 0.0276 mol) was added, the solution stirred at RT for 15 min and then concentrated at reduced pressure. The residue obtained was purified by column chromatography (silica gel, 2.5x60 cm column, elution with 9:1 \(\text{CH}_2\text{Cl}_2\)-MeOH) to afford 2.95 g (83%) of \(83\) as a yellow syrup.

**Methyl 6-bromo-6-deoxy-3,4-O-isopropylidene-\(\alpha\)-D-galactopyranoside (84).**

To a stirred solution of \(83\) (8.6 g, 0.0334 mol) in 250 mL of acetone and 50 mL of 2,2-dimethoxypropane was added 15 drops of concentrated \(\text{H}_2\text{SO}_4\). After 1 h at RT the solution was neutralized by addition of solid \(\text{Na}_2\text{CO}_3\), the inorganic salts removed by filtration and washed well with acetone. The combined filtrate and washings were concentrated under reduced pressure and the residue obtained purified by column chromatography (silica gel, 3.0x60 cm column, elution with ether) to afford 9.16 g (92%) of \(84\) as a clear syrup. On standing for several weeks the syrup crystallized (mp 62-65°C). Preparative TLC (elution with 3:1 ether-petroleum
ether) provided analytically pure material: IR (KBr) 2.75, 3.30, 6.79, 7.18, 10.23, 10.92, 11.40, 12.50 $\mu$; $^1$H NMR (60 MHz, CDCl$_3$) $\delta$ 1.34, 1.49 [2s, 6, C(CH$_3$)$_2$], 3.48 (s, 3, OCH$_3$), 3.49-4.35 (m, 6, H$_2$-H$_6$, H$_6^*$), 4.75 (d, 1, H$_1$); $^{13}$C NMR (CDCl$_3$) $\delta$ 25.68, 27.33 [C(CH$_3$)$_2$], 30.54 (C$_6$), 55.49 (OCH$_3$), 68.50, 69.18, 73.16, 75.69 (C$_2$-C$_5$), 98.12 (C$_1$), 109.91 [C(CH$_3$)$_2$]; exact mass m/e $M^+$-CH$_3$ 281.0032 (calcd 281.0025).

Anal. Calcd for C$_{10}$H$_{17}$O$_5$Br: C, 40.42; H, 5.77.
Found: C, 40.25; H, 5.69.

Methyl 2-O-t-butyldiphenylsilyl-6-bromo-6-deoxy-3,4-O-isopropylidene-$\alpha$-$\delta$-galactopyranoside (85).

To a stirred solution of 84 (8.45 g, 0.0284 mol) in 18 mL of DMF was added imidazole (4.26 g, 0.0626 mol) and t-butyldiphenylsilyl chloride (8.13 mL, 0.0313 mol). After 1 day at RT the DMF was removed via vacuum distillation and the residue dissolved in 500 mL of 1:1 ether-petroleum ether. The solution was washed with 200 mL of H$_2$O, 50 mL of 5% KOH, 200 mL of H$_2$O, 200 mL of saturated aqueous NaCl, treated with charcoal and dried over MgSO$_4$. The solvent was removed under reduced pressure to afford 15.1 g (99%) of 85 as a pale yellow syrup. This material was suitable for use in the subsequent reaction without further purification. Preparative TLC (elution with 1:4 ether-petroleum ether) provided
pure material: IR (neat) 3.23, 6.16, 6.69, 7.14, 8.13, 10.81, 11.49, 12.10 \mu; \textsuperscript{1}H NMR (60 MHz, CDCl\textsubscript{3}) \delta 1.19 [s, 9, C(CH\textsubscript{3})\textsubscript{3}], 1.21, 1.30 [2s, 6, C(CH\textsubscript{3})\textsubscript{2}], 3.28 (s, 3, OCH\textsubscript{3}), 3.34-4.40 (m, 7, H\textsubscript{1}-H\textsubscript{6},H\textsubscript{6}'), 7.21-7.9 (m, 10, Ar-H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}) \delta 19.37 [C(CH\textsubscript{3})\textsubscript{3}], 26.41, 27.82 [2, C(CH\textsubscript{3})\textsubscript{2}], 26.99 [C(CH\textsubscript{3})\textsubscript{3}], 30.63 (C\textsubscript{o}), 55.25 (OCH\textsubscript{3}), 67.97, 72.05, 73.74, 77.14 (C\textsubscript{2}-C\textsubscript{5}), 99.67 (C\textsubscript{1}), 109.28 [C(CH\textsubscript{3})\textsubscript{2}], 127.68, 129.82, 135.89, 136.23, (o, m, and p aromatics, 4 overlapping), 133.12, 134.48 (ipso aromatic); exact mass m/e M*-CH\textsubscript{3} 519.1215 (calcd 519.1203).

Methyl 2-O-t-butyldiphenylsilyl-6-deoxy-3,4-O-isopropylidene-6-(triphenylphosphonio)-\alpha-D-galactopyranose Bromide (86).

A stirred solution of 85 (1.39 g, 0.00260 mol) and triphenylphosphine (1.02 g, 0.00389 mol) in 3.5 mL of acetonitrile was heated at reflux under nitrogen for 5 days. The pale yellow solution was concentrated under reduced pressure and the residue obtained purified by filtration through a column of silica gel (2.5x30 cm column, elution with 9:1 CH\textsubscript{2}Cl\textsubscript{2}-MeOH) to afford 1.81 g (87%) of 86 as a pale yellow foam: IR (KBr) 3.26, 6.88, 7.14, 8.96, 9.56, 9.87, 11.48 \mu; \textsuperscript{1}H NMR (60 MHz, CDCl\textsubscript{3}) \delta 1.05 [s, 9, C(CH\textsubscript{3})\textsubscript{3}], 1.26, 1.32 [2s, 6, C(CH\textsubscript{3})\textsubscript{2}], 2.36 (s, 3, OCH\textsubscript{3}), 3.47-4.95 (m, 7, H\textsubscript{1}-H\textsubscript{6},H\textsubscript{6}'), 7.2-7.98 (m, 25, Ar-H); \textsuperscript{13}C NMR
(CDC\textsubscript{3}) N 19.32 [\text{C(CH\textsubscript{3})\textsubscript{3}}], 24.56 (CH\textsubscript{2}-P), 26.31, 27.82 [\text{C(CH\textsubscript{3})\textsubscript{2}}], 26.90 [\text{C(CH\textsubscript{3})\textsubscript{3}}], 55.25 (OCH\textsubscript{3}), 63.84, 64.18, 71.46, 74.13 (C\textsubscript{2}-C\textsubscript{5}), 99.82 (C\textsubscript{1}), 108.99 [\text{C(CH\textsubscript{3})\textsubscript{2}}], 117.58, 121.91 (ipso aromatic to P, one overlapping), 127.59, 127.68, 129.72, 129.87, 130.35, 133.02, 133.80, 134.29, 134.58, 135.84, 136.23 (o,m,p, and ipso aromatic, 16 overlapping).

(Z)-1-(Methyl 2,3-O-isopropylidene-\text{\textalpha}D-ribo-tetrofuranosid-4-yl)-2-(methyl 2-O-t-butyldiphenylsilyl-3,4-O-isopropylidene-\text{\textalpha}D-galacto-pentopyranosid-5-yl) ethylene (88).

A stirred solution of 86 (2.4 g, 0.00301 mol) in 16.4 mL of 2:1 THF-HMPA was cooled to -65°C under nitrogen and n-BuLi (0.00331 mol) was added via syringe. After stirring for 30-45 sec, 33 (0.73 g, 0.000361 mol) in 2.7 mL of THF was added and the solution allowed to warm up slowly to -10°C over a period of 1 h. A 1:1 ether-petroleum ether mixture was added and the resultant precipitated triphenylphosphine oxide was filtered off and washed with 1:1 ether-petroleum ether. Volatile solvents were removed from the filtrate under reduced pressure and the residue taken up in 250 mL of 1:1 ether-petroleum ether, washed with 2x85 mL portions of H\textsubscript{2}O, 50 mL of saturated aqueous NaHSO\textsubscript{3}, 50 mL of H\textsubscript{2}O, 85 mL of saturated aqueous saturated NaCl, treated
with charcoal and dried over MgSO₄. The solvent was evaporated at reduced pressure and the residue purified by column chromatography (silica gel, 2.5x45 cm column, elution with 1:2 ether-petroleum ether) to afford 1.06 g (55%) of 88 as a clear syrup: IR(neat) 3.2, 6.8, 7.1, 8.0, 8.9, 11.3, 14.3; ¹H NMR (60 MHz, CDCl₃) δ 1.10 [s, 9, C(CH₃)₃], 1.27, 1.44 [12, 2C(CH₃)₂], 3.2, 3.30 (2s, 6, 2OCH₃), 3.6-4.97 (m, 9, H₁-H₅, H₈-H₁₁), 5.60-5.78 (m, 2, H₆,H₇), 7.2-7.85 (m, 10, Ar-H); ¹³C NMR (CDCl₃) δ 19.37 [C(CH₃)₃], 25.0, 26.41, 26.51, 27.96 [2C(CH₃)₂], 26.99 [C(CH₃)₃], 54.42 (OCH₃), 55.68 (COH₃), 63.21, 72.0, 75.83, 82.82, 85.4, 85.69 (C₂-C₄,C₇-C₁₀, one overlapping), 99.62 (C₁₁), 109.28 (C₁), 108.9, 112.34 [2C(CH₃)₂], 127.64, 128.75, 129.77, 130.83, 133.22, 134.63, 135.89, 136.27 (o, m, p, and ipso aromatics, H₅,H₆, 4 overlapping); exact mass m/e M⁺-CH₃ 625.2850 (calcd 625.2833).

(Z)-1-(Methyl 2,3-O-isopropylidene-α-D-ribo-tetrofuranosid-4-yl)-2-(methyl 3,4-O-isopropylidene-α-D-galacto-pentopyranosid-5-yl)ethylene (91).

To a stirred solution of 88 (0.91 g, 0.00142 mol) in 9.1 mL of THF was added tetra n-butylammonium fluoride trihydrate (0.896 g, 0.00284 mol).
After 15 h at RT the solution was concentrated under reduced pressure and the residue obtained purified by column chromatography (silica gel, 2.5x15 cm column, elution with 3:1 ether-petroleum ether) to afford 0.413 g (73%) of 91 as a colorless syrup: IR (neat) 2.80, 3.35, 6.92, 7.28, 11.60, 12.65, 12.96 μ; 1H NMR (60 MHz, CDCl₃) δ 1.30, 1.48, 1.50 [4, 2C(CH₃)₂], 3.27 (s, 3, OCH₃), 3.48 (s, 3, OCH₃), 3.6-5.05 (m, 9, H₁-H₄, H₇-H₁₁), 5.67-5.87 (m, 2, H₅,H₆).

(Z)-1-(Methyl 2,3-O-isopropylidene-β-D-ribo-retrofuranosid-4-yl)-2-(methyl 2-deoxy-3,4-O-isopropylidene-2-oximino-α-D-galacto-pentopyranosid-5-yl) ethylene (93 and 94).

To a stirred solution of CH₂Cl₂ (35 mL) and pyridine (1.00 mL, 0.0123 mol) under nitrogen was carefully added chromium trioxide (0.616 g, 0.00615 mol). After 15 min at RT 91 (0.413 g, 0.00103 mol) in 5 mL of CH₂Cl₂ was added followed by the immediate addition of acetic anhydride (0.58 mL, 0.00615 mol). After 1 h at RT the solution was poured into 100 mL of ethyl acetate, the precipitated salts removed by filtration and the filtrate concentrated under reduced pressure. The residue obtained was washed through a short plug of silica gel (elution with ethyl acetate) to afford 0.391 g (95%) of
the 10-keto compound 92 as a clear syrup: IR (neat) 3.32, 5.67, 6.89, 7.26, 11.55 μ. The 10-keto compound 92 was dissolved in 1:1 ethanol-pyridine (5mL) and treated with hydroxylamine hydrochloride (0.203 g, 0.00292 mol). After 1 day at RT the solution was evaporated at reduced pressure followed by co-evaporation with toluene to remove pyridine. The residue obtained was dissolved in 100 mL of CH₂Cl₂, washed with 20 mL of H₂O, 20 mL of saturated aqueous NaCl and dried over MgSO₄. Removal of solvent at reduced pressure afforded 0.377 g (93%) of a ~1:1 mixture of syn and anti oxime isomers 93 and 94 as a colorless syrup: IR (neat) 2.80, 3.34, 6.90, 7.23 μ; ¹H NMR (60 MHz, CDCl₃) δ 1.2-1.6 [m, 12, 2C(CH₃)₂], 3.29 (s, 3, OCH₃), 3.39, 4.43 (2s, 3, OCH₃ syn and anti), 4.2-5.5 (m, 8, H₁-H₄, H₇-H₁₁), 5.62-5.90 (m, 2, H₅,H₆).

(Z)-1-(Methyl 2,3-O-isopropylidene-α-D-ribo-tetrafuranosid-4-yl)-2-(methyl 2-benzamido-2-deoxy-3,4-O-isopropylidene-α-D-talo-pentopyranosid-5-yl) ethylene (96).

To a stirred suspension of LiAlH₄ (0.024 g, 0.000643 mol) in 0.75 mL of THF was added dropwise a solution of 93 and 94 (0.089 g, 0.000214 mol) in 1 mL of THF. After 7 h under nitrogen at 55°C the solution was
cooled to RT and 2 mL of H₂O carefully added dropwise. The solution was diluted with 75 mL of ether, washed with 15 mL of saturated NaCl and dried over MgSO₄. The solvent was removed under reduced pressure and the residue purified by preparative TLC (elution with ether) to afford 0.025 g (29.1%) of an amino compound 95. The amino compound 95 (0.025 g, 0.0000622 mol) was treated with benzoyl chloride (0.008 mL, 0.0000684 mol) in 0.5 mL of pyridine. After 1 day at RT the solution was concentrated under reduced pressure by co-evaporation with toluene and the residue purified by preparative TLC (elution with ether) to afford 0.022 g (71%) of 96 which appears to be one major compound as judged by TLC and ¹H NMR: ¹H NMR (60 MHz, CDCl₃) δ 1.28, 1.5 [12, 2C(CH₃)₂], 3.27 (s, 3, OCH₃), 3.29 (s, 3, OCH₃), 4.3-5.1 (H₁-H₄, H₇-H₁₁), 5.63-5.8 (m, 2, H₅, H₆), 6.47 (d, 1, NH), 7.3-8.1 (m, 5, Ar-H).

\[ (Z)-1\text{-(2,3-O-cyclohexylidene-\(\beta\)-D-ribo-tetrofuranosid-4-yl)}-\text{N\textsuperscript{3}-benzoylurac-1-yl]-2-(methyl 2-O-t-butylphenylsilyl-3,4-O-isopropylidene-\(\alpha\)-D-galacto-pentopyranosid-5-yl)ethylene} \] (99).

A stirred solution of 86 (0.179 g, 0.000212 mol) in 1.2 mL of 2:1 THF-HMPA was cooled to -65°C under nitrogen and n-BuLi (0.000233 mol)
was added via syringe. After stirring for 30-45 sec the uridine $5'$-aldehyde $98$ (0.114 g, 0.000276 mol) in 0.2 mL of THF was added and the solution allowed to warm up slowly to $-10^\circ$C over a period of 1 h. A 1:1 ether-petroleum ether mixture was added and the resultant precipitated triphenyl-phosphine oxide was filtered off, washing with 1:1 ether-petroleum ether. Volatile solvents were removed from the filtrate under reduced pressure and the residue taken up in 2:1 ether-petroleum ether, washed with H$_2$O, saturated aqueous NaHSO$_3$, H$_2$O, saturated aqueous NaCl and dried over MgSO$_4$. The solvent was evaporated at reduced pressure and the residue purified by preparative TLC (elution with ether) to afford 0.046 g (25.4%) of $99$ as a white foam. $^1$H NMR (60 MHz, CDCl$_3$) $\delta$ 0.9-1.9 [m, 25, C(CH$_3$)$_2$, C(CH$_3$)$_3$, cyclohexylidene], 3.27 (s, 3, OCH$_3$), 3.56-5.23 (m, 9, H$_1$-H$_4$,H$_7$-H$_{11}$), 5.48-5.87 (m, 4, H$_5$,H$_6$,H$_5$,H$_6$), 7.1-8.0 (m, 15, Ar-H).

(Z)-1-[1-(2,3-O-cyclohexylidene-$\alpha$-D-ribo-terrofuranosid-4-yl urac-1-yl]-2-(methyl 2-O-t-butyldiphenylsilyl-3,4-O-isopropylidene-$\alpha$-D-galacto-pentopyranosid-5-yl) ethylene

A solution of $99$ (0.044 g, 0.0000515 mol) in 3 mL of methanol saturated with ammonia was stirred at RT. After 1 h the solution was concentrated
under reduced pressure and the residue purified by preparative TLC (elution with ether) to afford 0.034 g (87%) of 100 as a white foam; UV $\lambda_{\text{max}}$ (abs ethanol) 257 nm; $^1$H NMR (60 MHz, CDCl$_3$) $\delta$ 0.95-1.9 [m, 25, C(CH$_3$)$_2$, C(CH$_3$)$_3$, cyclohexylidene], 3.30 (s, 3, OCH$_3$), 3.55-5.2 (m, 9, H$_1$-H$_4$,H$_7$-H$_{11}$), 5.5-6.95 (m, 4, H$_5$,H$_6$,H$_5$,H$_6$), 7.1-7.9 (m, 11, NH, Ar-H).

$^{1}$-$\text{L}$-$(2,3,0$-cyclohexylidene-$\beta$-D-ribo-retrofuranosid-4-yl)$
urac-1-yl-2-(methyl 2-0-$\text{t}$-butylidiphenylsilyl-3,4-0-isopropylidene-$\alpha$-D-galacto-pentopyranosid-5-yl) oxirane (102 and 103).

A solution of 100 (0.109 g 0.000145 mol) and m-CPBA (0.063 g, 0.0003632 mol) in 2 mL of 1,2-dichloroethane was stirred at RT. After 22 h the solution was concentrated under reduced pressure to yield a crude mixture of diastereomeric epoxides which were purified and separated by preparative TLC (2 elutions with 3:1 ether-petroleum ether) to afford 0.037 g (33.3%) of one isomer 102 (R$_f$=0.65, elution 2 times with 3:1 ether-petroleum ether) and 0.054 g (48.6%) of the other isomer 103 (R$_f$=0.60, elution 2 times with 3:1 ether-petroleum ether) as white foams.
102: UV $\lambda_{\text{max}}$ (abs ethanol) 257 nm; $^1\text{H NMR} \ (60 \text{ MHz, CDCl}_3) \delta$
0.9-1.9 [m, 25, C(CH$_3$)$_2$, C(CH$_3$)$_3$, cyclohexylidene], 3.25
(s, 3, OCH$_3$), 3.15-3.35 (m, 2, H$_5^\text{a}$,H$_6^\text{a}$), 3.52-5.25 (m, 9, H$_4^\text{a}$, H$_7^\text{a}$, H$_{11}^\text{a}$)
5.43-5.88 (m, H$_5$,H$_6$), 7.1-7.9 (m, 11, NH, Ar-H).

103: UV $\lambda_{\text{max}}$ (abs ethanol) 253 nm; $^1\text{H NMR} \ (60 \text{ MHz, CDCl}_3) \delta$
0.9-1.9 [m, 25, C(CH$_3$)$_2$, C(CH$_3$)$_3$, cyclohexylidene], 3.29
(s, 3, OCH$_3$), 3.2-3.47 (m, 2, H$_5^\text{a}$,H$_6^\text{a}$), 3.35-5.3 (m, 9, H$_1^\text{a}$-
H$_4^\text{a}$,H$_7^\text{a}$-H$_{11}^\text{a}$), 5.43-5.83 (m, 2, H$_5$,H$_6$), 7.1-7.9 (m, 11, NH,
Ar-H).

Ozonolysis-Reduction of 88.

The procedure employed was exactly as previously described for the ozonolysis-reduction of 60 and 61, producing two carbohydrate alcohols, one which was identifiable as 36 by TLC and $^1\text{H NMR}$. Desilylation of the other alcohol 89 afforded 90 which was identical to methyl 3,4-O-isopropylidene-$\alpha$-$\text{D}$-galactopyranoside 67 by TLC and $^1\text{H NMR}$. 

Ozonolysis-Reduction of 96.

The procedure employed was exactly as previously described for the ozonolysis-reduction of 60 and 61, producing two carbohydrate alcohols. One of the alcohols was identical by TLC and $^1\text{H NMR}$ data to 36. The other alcohol was not identical to methyl 2-benzamido-2-deoxy-3,4-O-isopropylidene-$\alpha$-$\text{D}$-galactopyranoside 77 , therefore demonstrating that 96 probably possess the ralo configuration at C$_{10}$.
BIBLIOGRAPHY


