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Synthesis of aminodeoxy, branched-chain, and thio sugars in relation to anthracycline glycosides

Shah, Pankaj Shashikant, Ph.D.

The Ohio State University, 1988

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UMI
SYNTHESIS OF AMINODEOXY, BRANCHED-CHAIN, AND THIO SUGARS
IN RELATION TO ANTHRACYCLINE GLYCOSIDES

DISSERTATION

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

By
Pankaj Shashikant Shah, M.Sc.

* * * * *

The Ohio State University
1988

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To My Grandparents and Parents,
especially
To My Beloved Father
The Late Shri Shashikant Vandavandas Shah
ACKNOWLEDGMENTS

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CHAPTER I
INTRODUCTION

The anthracycline drugs daunorubicin (daunomycin) (1) and doxorubicin (adriamycin) (2) are useful anticancer agents with activities against a variety of solid tumors and hematological malignancies.\textsuperscript{1,2} Daunorubicin was discovered by two different groups, independently in 1963. Di Marco and coworkers\textsuperscript{3a} isolated it from cultures of \textit{Streptomyces peucetius} and named it as daunomycin. Dubost and coworkers\textsuperscript{3b} isolated it from cultures of \textit{Streptomyces coeruleorubius} and named it as rubidomycine after which its structure and stereochemistry were established by Arcamone and co-workers in 1968 and 1970, respectively.\textsuperscript{5,6} It consists of a naphthaquinone chromophore connected by a glycosidic linkage to an amino sugar called daunosamine, as shown in the following formula.

Doxorubicin, which is produced by mutant strains of the daunomycin producing microorganism, Streptomyces peucetius, was also discovered by Arcamone and co-workers, in 1969. 7,8

Since that time, several different related compounds have been isolated from microbial cultures, viz., the 4-0-demethyl analog carminomycin (3), the 13-dihydro analog of daunomycin called duborimycin (4), the disaccharide derivative daunosaminyl daunomycin (5), rhodinosyl daunomycin (6), the baumycins (7), nogalamycin (8), and aclacinomycin (9), and many others.

4 Duborimycin

5 Daunosaminyl daunomycin
6 Rhodinosyl daunomycin

7 Baumycin
Nogalamycin

Aclacinomycin A

Aclacinomycin B


15. T. Oki, J. Antibiotics, 30 (1977) 570.

The parent drugs, 1 and 2, especially doxorubicin (2) are widely used in cancer chemotherapy. However, they have been found to have generalized toxicity, manifested by myelosuppression, and especially a dangerous and dose-limiting cardiomyopathy.\footnote{1}\footnote{2} Hence the development of new analogs, by chemical manipulation of the biosynthetic product, or by total synthesis, is still under active investigation in many research groups.\footnote{16}
An important structural feature of the daunorubicin-doxorubicin group of antibiotics is the presence of the amino sugar daunosamine, 3-amino-2,3,6-trideoxy-L-lyxo-hexose (10). Daunosamine is one of the eight 3-amino-2,3,6-trideoxyhexoses known thus far as being present in antibiotic molecules. The others are acosamine (11) and actinosamine (12) from actinoidin,\(^{17}\) ristosamine (13) from ristomycin,\(^{18}\) rhodosamine (14) from rhodomycin,\(^{19}\) vancosamine (15) from vancomycin,\(^{20}\) D-rhodosamine (16) from megalomycins,\(^{21}\) and angolosamine (17) from angolomycin.\(^{22}\)
Analogs of the antitumor anthracyclines manifesting modifications in the sugar stereochemistry and substitution are expected to modify those parameters of anthracycline efficacy which are attributable to active transport or facilitated diffusion. Furthermore, enzyme reactions, influencing tissue distribution and metabolism of the drug, may also be modified on the basis of the known dependence of such processes on structure and stereochemistry of carbohydrate derivatives.

The initial X-ray diffraction studies of a daunomycin--DNA complex by Pigram and co-workers indicated potential significance of the amino group of the sugar for electrostatic binding, as the chromophore was observed to intercalate between base pairs and the sugar was situated in
the major DNA groove, forming stabilizing electrostatic bonds between
the amino group and the second phosphate residue from the intercalation
site. However, subsequent NMR$^{24}$ and X-ray diffraction$^{25}$ studies of
daunorubicin--polynucleotide complexes have not confirmed these
findings. Instead, the amino group of the sugar appears to lie in the
minor groove, and not to interact with DNA. An alternative explanation
was proposed to account for the importance of the amino group of the
sugar for antitumor activity, and this was attributed to its ability to
bind with cardiolipin in cell membranes. A number of investigators$^{27-33}$
have stressed the importance of this interaction to explain the
antitumor activity as well as cardiotoxic behavior.

(1972) 17.
7204.
27. R. Goldman, T. Facchnetti, D. Bach, A. Raz, and M. Shinitzky,
28. S.A. Murphree, T.R. Tritton, P.L. Smith, and A.C. Sartorelli,
As the amino group of the sugar was thought to be essential for such binding, any modification at that site could have altered the activities of anthracycline glycoside analogs. As a result, a number of N-substituted anthracyclines were synthesized by different researchers in efforts to obtain drugs having increased antitumor activity. These substitutions ranged from alkylation with methyl or ethyl substituents to N-piperdino and N-morpholino derivatives. Table 1 shows the comparative biological activities of these compounds, which were evaluated for antitumor activity against the intraperitoneally (i.p.) implanted murine P-388 lymphocytic leukemia. Mice received


an i.p. injection of $10^6$ cells on day 0 and i.p. treatment with the anthracycline analog was initiated at least 24 h later. In the early stages of such studies, the anthracyclines were administered daily, but later on, a more stringent schedule with delayed, intermittent treatment was employed, with the drug administered on days 5, 9, and 13. Median survival times of treated and non-treated controls were determined and the results were expressed as a percent T/C where:

$$\% \ T/C = \frac{\text{median survival time of test animals}}{\text{median survival time of control animals}} \times 100.$$  

A T/C value $\geq 120\%$ is considered indicative of activity, whereas a T/C $\leq 85\%$ indicates acute toxicity. Doxorubicin (adriamycin) was selected as the parent drug for comparisons of activities. The $\% \ T/C$ of an analog was divided by $\% \ T/C$ of adriamycin to provide a ratio called A/P, i.e., analog to parent ratio. Consequently an A/P ratio of $> 1$ would indicate that the analog is superior to adriamycin in the murine P-388 assay.
<table>
<thead>
<tr>
<th>$R^a$</th>
<th>$R^{1a}$</th>
<th>% T/C</th>
<th>$A/P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>NH$_2$</td>
<td>143</td>
<td>0.82</td>
</tr>
<tr>
<td>OH</td>
<td>NH$_2$</td>
<td>174</td>
<td>1.00</td>
</tr>
<tr>
<td>H</td>
<td>NHCH(CH$_3$)$_2$</td>
<td>148</td>
<td>0.85</td>
</tr>
<tr>
<td>H</td>
<td>N(CH$_3$)$_2$</td>
<td>145</td>
<td>0.83</td>
</tr>
<tr>
<td>OH</td>
<td>N(CH$_3$)$_2$</td>
<td>125</td>
<td>0.72</td>
</tr>
<tr>
<td>H</td>
<td>N(CH$_2$CH$_3$)$_2$</td>
<td>141</td>
<td>0.81</td>
</tr>
<tr>
<td>H</td>
<td>NHCH$_2$Ph</td>
<td>226</td>
<td>1.29</td>
</tr>
<tr>
<td>OH</td>
<td>NHCH$_2$Ph</td>
<td>200</td>
<td>1.14</td>
</tr>
<tr>
<td>H</td>
<td>PhCH$_2$NCH$_2$CH$_2$OH</td>
<td>240</td>
<td>1.38</td>
</tr>
</tbody>
</table>
| H     | $\text{\begin{diagram}
\text{H}
\text{NH}
\end{diagram}}$ | 108 | 0.62 |
| H     | $\text{\begin{diagram}
\text{CH$_3$O}
\text{N}
\end{diagram}}$ | 217 | 1.25 |
| H     | $\text{\begin{diagram}
\text{O}
\text{N}
\end{diagram}}$ | 178 | 1.02 |
| H     | $\text{\begin{diagram}
\text{O}
\text{CN}
\end{diagram}}$ | 207 | 1.19 |

$^a$Substituents on structure given on preceding page.
As may be seen from Table 1, N-alkylation decreased the activity whereas methoxypiperidino and morpholino substituents at C-3' increased the potency of the drug. With N-benzyl substitution, the activity increased substantially in both types of analogs, the best example found being the N-benzyl-N-(2-hydroxyethyl) derivative, which has an oxygen atom two atoms away from nitrogen which also has a benzyl substituent.

The other approach towards making analogs differing in the sugar moiety was by preparing configurational variation of the daunosamine component at one or more of the four chiral centers, viz., 1', 3', 4' and 5'. The 1' analogs, i.e., α-daunorubicin and α-doxorubicin were synthesized by Koenigs-Knorr condensation of the aglycon and an appropriately protected daunosaminyl chloride. Biological testing showed these anomic variants to have much lower activity than the parent drugs.


The 4'-epi analog, i.e., the acosamine or L-arabino derivative, was prepared from daunosamine as shown in Scheme 1. When attached to the aglycons, the resultant drugs were found to possess similar biological activity to the parent drug in the doxorubicin analog, concomitant with a decreased toxicity. Again both β-isomers (epimers) showed much lower activity.
The \( \text{\textit{L}} \)-ribo and \( \text{\textit{D}} \)-ribo as well as \( \text{\textit{L}} \)-xylo derivatives were prepared by several different researchers including Horton and co-workers, who also established the first effective large-scale synthesis of daunomycin from the readily available methyl \( \text{\textit{D}} \)-mannopyranoside.\(^{41-50}\)

Schemes 2-5 show some of the reaction sequences used to synthesize these compounds.


Scheme 3a

\[ \begin{align*}
1 & \xrightarrow{\text{CH}_2\text{Br}} 2 \quad R = \text{H} \\
2 & \xrightarrow{\text{HCl}} 3 \quad R = \text{SO}_2\text{Me}
\end{align*} \]

Scheme 3b

\[ \begin{align*}
1 & \xrightarrow{\text{CH}_2\text{OH}} 2 \quad R = \text{H} \\
2 & \xrightarrow{\text{H}_2, \text{Ni}} 3 \quad R = \text{H} \\
3 & \xrightarrow{\text{H}_2, \text{Ni}} 4 \quad R = \text{Me}
\end{align*} \]
In order to establish structure--activity relationships, the biological activities of these compounds were determined \textit{in vivo} in the murine assay, and the results shown in in Table 2.

![Chemical Structure](image)

Table 2

<table>
<thead>
<tr>
<th>R</th>
<th>R'</th>
<th>% T/C</th>
<th>A/P</th>
<th>Screen</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>α-β-ribo</td>
<td>231</td>
<td>1.02</td>
<td>P-388</td>
</tr>
<tr>
<td>OH</td>
<td>α-β-arabino</td>
<td>194</td>
<td>1.11</td>
<td>&quot;</td>
</tr>
<tr>
<td>H</td>
<td>β-β-arabino</td>
<td>115</td>
<td>0.66</td>
<td>&quot;</td>
</tr>
<tr>
<td>H</td>
<td>α-β-arabino</td>
<td>125</td>
<td>0.71</td>
<td>&quot;</td>
</tr>
<tr>
<td>H</td>
<td>α-β-lyxo</td>
<td>150</td>
<td>0.90</td>
<td>L-1210</td>
</tr>
<tr>
<td>H</td>
<td>α-β-arabino</td>
<td>143</td>
<td>0.86</td>
<td>&quot;</td>
</tr>
<tr>
<td>H</td>
<td>α-β-ribo</td>
<td>137</td>
<td>0.83</td>
<td>&quot;</td>
</tr>
<tr>
<td>H</td>
<td>α-β-xylo</td>
<td>120</td>
<td>0.72</td>
<td>&quot;</td>
</tr>
<tr>
<td>OH</td>
<td>α-β-lyxo</td>
<td>166</td>
<td>1.00</td>
<td>&quot;</td>
</tr>
<tr>
<td>OH</td>
<td>α-β-arabino</td>
<td>150</td>
<td>0.90</td>
<td>&quot;</td>
</tr>
<tr>
<td>OH</td>
<td>α-β-ribo</td>
<td>161</td>
<td>0.97</td>
<td>&quot;</td>
</tr>
</tbody>
</table>
As may be seen from Table 2, none of the analogs were better than
the parent drug except the L-arabino analog in the doxorubicin series in
the murine P-388 leukemia screen. Also, the activity increases when the
R group at C-14 is -OH, i.e., the doxorubicin type of compounds. As the
4'-epi analog was found to be active, several modifications were made at
that position, viz., 4'-deoxy, 4'-O-methyl, 4'-epi-0-methyl and
all of them showed good activity in the P-388 screen. The 4'-epi analog
of doxorubicin has recently been introduced into the market under the
trade name "Epirubicin".

52. G. Cassinelli, F. Arcamone, and A. DiMarco, Ger. Pat. 2,757,107
(1979) 121-123.

Horton and co-workers set out to provide a factual basis to
substantiate or reject the rather generally held dogma that an amino
group at the 3'-position was essential for biological activity, and that
substitution at the 2'-position led to loss of activity. A range of
structural variants in the glycon portion was designed to furnish a
comprehensive series of stereochemical and substitutional variants in
the daunosamine moiety. The Horton--Weckerle route to synthesize
daunosamine proved to be the most versatile route to synthesize all of
these different sugar analogs, as may be seen from Schemes 6 and 7.
Schemes 6 & 7

\[\text{Scheme 6:} \quad \text{1} \xrightarrow{\text{5 steps}} \text{2} \xrightarrow{\text{H}_2\text{, Ni}} \text{3} \xrightarrow{\text{NaOMe}} \text{4}
\]

\[\text{Scheme 7:} \quad \text{1} \xrightarrow{\text{Bo(OH)}_2, \text{HCl}} \text{2} \xrightarrow{\text{11LiAlH}_4, \text{27 Ac}_2\text{O}} \text{4} \xrightarrow{\text{NBS}} \text{5} \xrightarrow{\text{H}_2\text{, Pd}} \text{6}
\]
The 6-bromide intermediate was transformed into the 3,6-diamino sugar having the D-ribo stereochemistry, and the corresponding carboxylic acid derivative, which is an amino sugar derivative that is simultaneously an amino acid. It should be noted that the bromide precursor was not satisfactory for access to the L-xylo amino sugar because of the formation of an epimine when silver fluoride-mediated 5,6-elimination was attempted. Hence, the L-xylo derivative was synthesized from the 3-ketone as shown in Scheme 8.

Scheme 8.

The reduction of 3-ketone which gave almost exclusively the alcohol having the D-ribo stereochemistry which provided 3-hydroxylated analogs of daunosamine, known as digitoxose and 2,6-dideoxy L-lyxo-hexose, as shown.57
When the 2-deoxy-D-arabino-hexose was coupled with the daunomycinone using Koenigs-Knorr procedure, the α-D-anomer preponderated, whereas repetition of that procedure with the 6-deoxy sugar of the same configuration gave a mixture of anomers in approximately equal proportions. In the same manner, when the D-ribo 3-oxygenated analog was coupled by way of its p-nitrobenzoylated glycosyl chloride, again it gave a 5:3 mixture of anomers which could not be resolved readily by chromatography. The 2,6-dideoxy-L-lyxo-hexose ("2-deoxy-L-fucose") was converted into its triacetate and then transformed into its glycosyl chloride which coupled very well with daunomycinone giving exclusively the α-anomer, as shown in Scheme 9. This compound was identical with daunorubicin in all respects except for the replacement of the amino group by hydroxyl.
As the rationale for the biological activity of daunorubicin had frequently invoked a key role for the amino group, the 3-hydroxylated compound might have been expected to have little or no activity. However, as may be seen from Table 3, the 3'-hydroxylated analog, and also its 3',4'-diacetate displayed very good activity in the P-388 assay, albeit at dose levels considerably higher than those used with parent drugs, which also suggested that these compounds had a much lower acute toxicity. The other 3'-hydroxylated analog prepared was 3'-deamino-4'-epi-3'-hydroxy-daunorubicin and -doxorubicin as the 4'-epi analog in the parent series was found active.
Table 3

Biological Activity of Daunomycinone Glycosides on P-388 Lymphocytic Leukemia in Mice

<table>
<thead>
<tr>
<th>R</th>
<th>R'</th>
<th>% T/C</th>
<th>A/P</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>&quot;2-deoxy $\alpha$-fucose&quot;</td>
<td>192</td>
<td>1.1</td>
</tr>
<tr>
<td>H</td>
<td>2-deoxy-$\alpha$-fucose 3',4'-diacete</td>
<td>186</td>
<td>1.06</td>
</tr>
<tr>
<td>OH</td>
<td>2-deoxy-$\alpha$-fucose 3',4'-diacete</td>
<td>269</td>
<td>1.54</td>
</tr>
<tr>
<td>H</td>
<td>2,6-dideoxy-$\alpha$-$\delta$-ribo</td>
<td>101</td>
<td>0.58</td>
</tr>
<tr>
<td>H</td>
<td>2,6-dideoxy-$\beta$-$\delta$-ribo</td>
<td>102</td>
<td>0.58</td>
</tr>
<tr>
<td>H</td>
<td>2,6-dideoxy-$\delta$-arabino ($\alpha + \beta$ mixture)</td>
<td>100</td>
<td>0.58</td>
</tr>
<tr>
<td>H</td>
<td>3,6-diamino-2,3,6-trideoxy-$\alpha$-$\delta$-ribo</td>
<td>103</td>
<td>0.59</td>
</tr>
</tbody>
</table>
Thus, the 3'-deamino L-family analogs of daunorubicin have very low activity, and the 3'-amino L-family analogs are also not much better. On the other hand, the 3'-deamino-\(\alpha\)-sugars made the compounds more active than doxorubicin. These results provided the factual basis to reject the generally held dogma that an amino group at 3'-position was essential for biological activity. Also new variants with hydroxyl group instead of amino at the 3'-position were prepared.\(^\text{75}\)

The other major area of interest was the question of a substituent at position 2 of the glycon,\(^\text{62,63}\) which had been hypothesized to cause inactivation. Halogen was introduced at C-2 by using the alkoxyiodination reaction of Thiem\(^\text{62}\) applied to the acetylated glycals of \(\alpha\)-fucose and \(\alpha\)-rhamnose. This procedure gave a 2'-iodo substituent in the stereochemical configuration trans to the aglycon, which again results in the desired \(\alpha\)-linkage, as shown in Scheme 10. Both of the resultant compounds showed very good activity in the P-388 assay. In fact the compound derived from \(\alpha\)-rhamnal showed even higher activity, with T/C 247. This result prompted synthesis of different 2'-halo analogs of daunomycin and doxorubicin analogs, \textit{viz.}, 2'-chloro, 2'-bromo in the dauno- as well as the doxo- series.\(^\text{65,66}\)

Table 4 gives the relative biological activity profile of these analogs. It should be mentioned at this point that by this time, having analogs with different anthracyclinone moiety had been prepared, and as the 4-demethoxy analog had shown activity, these halo sugars were also attached to 4-demethoxyadriamycinone.

As the fluorine atom is much smaller than iodine, and with far greater electronegativity, it may show interesting biological activity. Hence, it was attached at 2'-position of the glycon by a Japanese group, as shown in Schemes 11 and 12, yielding different analogs of 3-amino-2-fluoro-2,3,6-trIDEOXY sugars.\textsuperscript{70,75}

---

### Table 4

**Biological Activity Profile of Some 2'-Halo Doxorubicin and Daunorubicin Analogs Against P-388 Lymphocytic Leukemia in Mice**

![Chemical Structure](Image)

<table>
<thead>
<tr>
<th>R</th>
<th>R'</th>
<th>% T/C</th>
<th>A/P</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>2'-ido-α-L-talo-3,4-diacetate</td>
<td>172</td>
<td>0.98</td>
</tr>
<tr>
<td>H</td>
<td>2'-ido-α-L-manno-3,4-diacetate</td>
<td>247</td>
<td>1.42</td>
</tr>
<tr>
<td>H</td>
<td>2'-bromo-α-L-talo-3,4-diacetate</td>
<td>145</td>
<td>0.83</td>
</tr>
<tr>
<td>H</td>
<td>2'-bromo-α-L-manno-3,4-diacetate</td>
<td>278</td>
<td>1.60</td>
</tr>
<tr>
<td>H</td>
<td>2'-chloro-α-L-manno-3,4-diacetate</td>
<td>248</td>
<td>1.63</td>
</tr>
<tr>
<td>H</td>
<td>2'-fluoro-α-L-talo-</td>
<td>184*</td>
<td>1.11*</td>
</tr>
<tr>
<td>OH</td>
<td>2'-fluoro-α-L-talo-</td>
<td>740*</td>
<td>4.46*</td>
</tr>
</tbody>
</table>

*Tested in the L-1210 screen
The allylic rearrangement reaction with glycals as described by Priebe and Zamojski \(^{76}\) was utilized to obtain daunorubicin analogs having alkylthio-group replacement at the 3'-position. Thus, starting from di-O-acetyl-L-fucal, there was obtained the 3'-(methylthio)-3'-epi analog of daunorubicin \(^{77,78}\) and a similar sequence from di-O-acetyl-L-rhamnal afforded the 3'-(methylthio)-4'-epi analog of daunorubicin \(^{77,78}\) as shown in Schemes 13 and 14.
These two compounds did show some activity, but not to a level as high as that displayed by the 3'-hydroxy or 3'-acetoxy analogs.

As mentioned earlier, vancomamine is a branched-chain amino sugar that is the sugar component of vancomycin, an antibiotic which occurs naturally, has its configuration exactly the same as that of daunosamine, but it has a C-methyl branch at C-3. Its C-3 epimer, i.e.,
3-amino-2,3,6-trideoxy-3-C-methyl L-xylo-hexose also has been found to occur in antibiotic A35512B. Hence, various approaches have been devised to synthesize vancosamine as shown in Schemes 15 and 16.


Schemes 15 & 16

(1) $R_1 = \text{Ph}, R_2 = \text{OMe}$

(2) $R_1 = \text{CN}, R_2 = \text{MeSO}_3$

(3) $R_1 = \text{MeSO}_2, R_2 = \text{CN}$

(4) $R_1 = \text{CH}_2, R_2 = \text{NH}$

(5) $R_1 = \text{NH}, R_2 = \text{CH}_2$

(6) $R_1 = \text{NH}, R_2 = \text{Me}$

(7) $R_1 = \text{Me}, R_2 = \text{NH}_2$

(8) $R_1 = \text{OH}, R_2 = \text{Me}$

(9) $R_1 = \text{Me}, R_2 = \text{OH}$

(10) $R_1 = \text{Me}, R_2 = \text{NHAc}$

(11) $R_1 = \text{Br}, R_2 = \text{PhCO}$

(12) $R_1 = \text{H}, R_2 = \text{PhCO}$

(13) $R_1 = \text{H}, R_2 = \text{H}$

(14) $R_1 = \text{PhCO}, R_2 = \text{Ac}, R_3 = \beta-\text{OMe}$

(15) $R_1 = \text{H}, R_2 = \text{Ac}, R_3 = \beta-\text{OMe}$

(16) $R_1 = \text{H}, R_2 = \text{H}, R_3 = \text{OH}$

(17) $R_1 = \text{Me}, R_2 = \text{Me}$

(18) $R_1 = \text{Me}, R_2 = \text{NHAc}$

(19) $R_1 = \text{Me}, R_2 = \text{Ac}$

(20) $R_1 = \text{Me}, R_2 = \text{OAc}$

(21) $R_1 = \text{Me}, R_2 = \text{MeOH}$

(22) $R_1 = \text{Ph}, R_2 = \text{OMe}$

(23) $R_1 = \text{Ph}, R_2 = \text{OMe}$

(24) $R_1 = \text{OH}, R_2 = \text{CN}$

(25) $R_1 = \text{CN}, R_2 = \text{OH}$

(26) $R_1 = \text{OMe}, R_2 = \text{CN}$

(27) $R_1 = \text{H}, R_2 = \text{Ac}$

(28) $R_1 = \text{H}, R_2 = \text{Ac}$

(29) $R_1 = \text{H}$

(30) $R_1 = \text{Ac}$

(31) $R_1 = \text{Ac}$

MOM = CH$_2$OMe
Other branched-chain analogs of daunosamine were also prepared\textsuperscript{88} where a methyl branch was attached at position 4'. As the 4'-epi as well as 4'-methoxy analogs were found to be active, 4'-C-methyl-4'-epi and its methoxy analogs were also prepared and attached to the aglycon.\textsuperscript{88}

\begin{align*}
  &\text{R} = \text{H, OH} \\
  &\text{R'} = \text{H, Me}
\end{align*}

The cytostatic activity\textsuperscript{83} of the analog having vancosamine attached
daunomycinone had an activity inferior to that of doxorubicin, or even
daunorubicin, but had a very low toxicity and hence at optimal
therapeutic doses, the % T/C values were comparable to those of
daunorubicin against P-388 as well as L1210 leukemia.

All of the 4'-C-methyl analogs, both in the $\text{L}-\text{lyxo}$ and $\text{L}-\text{arabino}$
series, were found to retain substantially the efficacy of the parent
compounds, as may be seen from the following table.

\begin{table}
\centering
\caption{Biological Activity of Some Branched Chain Sugar Analogs
of Daunorubicin and Doxorubicin}
\begin{tabular}{llll}
\hline
R & R' & % T/C & A/P \\
\hline
H & daunosamine & 175 & 0.87 \\
H & 4'-C-methyl & 155 & 0.77 \\
H & 4'-epi-4'-C-methyl & 163 & 0.81 \\
H & 4'-C-methyl-4'-O-methyl & 160 & 0.80 \\
H & 4'-epi-4'-C-methyl-4'-O-methyl & 150 & 0.75 \\
OH & daunosamine & 201 & 1.00 \\
OH & 4'-C-methyl-4'-O-methyl & 172 & 0.85 \\
OH & 4'-epi-4'-C-methyl-4'-O-methyl & 205 & 1.02 \\
\hline
\end{tabular}
\end{table}
Recently, a few new daunosamine analogs have been synthesized where an oxygen atom in the parent compound is replaced by a carbon atom. Lukacs and co-workers have reported a synthesis of a carbocyclic analog of daunosamine and D-ristosamine from a common intermediate established in the Horton--Weckerle synthesis of daunosamine. The 5,6-enoside was hydrolyzed using Ferrier's procedure to a cyclohexanone ring, which on treatment with methylenetriphenylphosphorane gave the unsaturated intermediate as shown. This intermediate on catalytic hydrogenation furnished the two compounds.

Scheme 17
A similar analog was prepared by Acton$^{91}$ and co-workers, where the glycosidic oxygen was replaced by a carbon atom making a C-glycosyl derivative of daunosamine.$^{92}$ This was then converted into the anthracycline analog via a Diels–Alder cycloaddition with quinizarin quinone, giving 4-demethoxy-9-deacetyl-daunorubicin analogs which showed cytotoxic effects in a preliminary test vs. L1210 cells in culture.

Scheme 18
Other analogs that have been prepared are the furanoside derivatives of daunosamine attached to the aglycon. Yamaguchi and Kojima were the first to prepare such derivatives of daunosamine. Several other investigators have prepared such furanose derivatives of daunosamine and ristosamine to date.

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An interesting result with consequences on the general views of molecular requirements for bioactivity was the finding that the furanose analog of 3',4'-diepidaunorubicin had the \( \% \ T/C = 175 \), which was similar to that of its pyranose analog \( \% \ T/C = 181 \). Similarly, the carminomycine analogs containing aminodeoxy-L-lyxo-hexofuranosyl...
derivatives at 0-7 had similar activity against P-388 lymphocytic leukemia, as the parent compound itself.95

Branched-Chain Sugars

The naturally occurring, branched-chain sugars were classified as rare sugars101,102 until the 1960's, but the discovery of numerous new sugars as the glycosidic component of various antibiotics during the past two decades has stimulated extensive research on their chemistry and biochemistry.103,104 Most of the branched-chain sugars occurring naturally arise in antibiotic compounds derived from microorganisms, mainly various strains of Streptomyces105 whereas two sugars, viz., 3-C-(hydroxymethyl)-D-glycero-tetrose (apiose) and 2-C-(hydroxymethyl)-D-ribose (hamemelose) occur widely in a variety of plants.106,107
So far, methyl, formyl, hydroxymethyl, 1-hydroxyethyl, acetyl, and 2-hydroxyacetyl side-chains have been found in these sugars, and almost all of them are terminal deoxy sugars as well. Generally, these branched chain sugars found in nature have a polar substituent at the branching carbon atom; tertiary alcohols are commonest, but arcanose, cladinose, and nogalose have a methyl ether group, L-chromose B has an acetate group, aldgarose has a cyclic carbonate group, and vancosamine and everninose have an amino and a nitro group, respectively, at the branch point.

The most commonly occurring branched-chain sugar in antibiotics is mycarose (28), i.e., 2,6-dideoxy-3-C-methyl-L-ribo-hexose which has been found in over fifteen kinds of antibiotics like magnamycin, carbomycin,
erythromycin C, erythromycin D, leucomycin, spiramycin, angolamycin, formacidin, chromocyclomycin, etc. Its 3-methyl ether, called cladinose, occurs in erythromycin. The other 6-deoxy-3-C-methyl sugars that occur naturally are as follows: 6-deoxy-3-C-methyl-D-mannose or D-evalose (29), which occurs in everninomycins B, C, D, and -2. Its L-enantiomer occurs in flambamycin, while the 2,3,4 trimethyl ether called nogalose (30) occurs in nogalamycin. 6-Deoxy-3-C-methyl-L-talose occurs as its 2-methyl ether (31), called vinelose, in Acetobacter vinelandii.


The other epimers of mycarose, viz., 2,6-dideoxy-3-C-methyl-L-arabino-hexose, called olivomycose or epimycarose (32), occurs in olivomycin \(^{125,116}\) whereas its D-enantiomer, called D-evermicose, occurs in everninomycins. \(^{118-121}\) The corresponding L-xylo sugar called axenose (33) is found in axenomycins A, B, and D \(^{127}\) and its 3-methyl ether called arcanose (34) occurs in lankamycin. \(^{128}\) It should be noted at this point that 2,6-dideoxy-3-C-methyl- L-lyxo-hexose (35), the only other epimer remaining in the 2,6-dideoxy-3-C-methyl hexoses series has not been reported as yet to occur naturally.

Synthesis of Branched Chain Sugars:

Two principal approaches have been used in the synthesis of branched-chain sugars. The first route utilizes a suitable carbonyl derivative of a sugar, which is treated with an organometallic, or a Wittig reagent, or with diazomethane, to introduce the branching substituent. Alternatively, the sugar has been built up from simple noncarbohydrate intermediates giving products as racemates.
1. **Addition Reactions of Carbohydrate Carbonyl Derivatives:**

This is the most exploited path to synthesize branched-chain sugars as numerous different strategies can be used in order to convert the branching into the desired product, as may be seen in Scheme 20.104

Scheme 19

- **Glycosiduloses**
- **Cyanomethyl deriv.**
- **Spiro-aziridine**
- **Branched amino sugar**

- **Branched sugar (A)**
- **Spiro-epoxide**
- **Alkylidene deriv.**
- **Branched nitro sugar**

- **Nitromethyl deriv.**
- **Formyl deriv.**
- **Hydroxymethyl deriv.**

- **Ethynyl deriv.**
- **Vinyl deriv.**
- **Acetyl deriv.**
- **1-Hydroxyethyi deriv.**

- **2-Hydroxyacetetyl deriv.**
- **1,2-Dihydroxyethyl deriv.**
- **Oxiranyl deriv.**

**Synthesis of Branched Sugars by the Addition Reaction to Glycosiduloses and the Conversion of Branchings.**
Streptose was synthesized from 5-deoxy-1,2-O-isopropylidene-\(\alpha\)-\(\beta\)-arabinofuranose by oxidation to the \(\beta\)-threo-pentos-3-ulos derivative followed by treatment with vinylmagnesium bromide to give the corresponding 3-\(\xi\)-vinyl furanose, which an ozonolysis and mild acid hydrolysis furnished streptose, as may be seen in Scheme 20.

Scheme 20


D-Mycarose and D-cladinose were prepared by Overend and co-workers using methylmagnesium iodide on methyl 4,6-O-benzylidene-2-deoxy-\(\alpha\)-\(\beta\)-erythro-hexopyranosid-3-ulos, which gave exclusively equatorial attack giving a product having the \(\beta\)-ribo configuration. This compound was easily converted into the 6-deoxy sugars D-cladinose and D-mycarose as shown in Scheme 21.
Jüng and Klemer\textsuperscript{130} prepared the glycals (cyclic enol ethers) mycaral and olivomycal from \textsubscript{L}-rhamnose as shown in Scheme 22. The 2,3-benzylidene acetal was treated with sec-BuLi to get the 2-glycos-deoxy-3-uloside which with methylmagnesium iodide gave the \textsubscript{L}-ribo-hexopyranoside. On the other hand, when the benzylidene acetal was treated with methylolithium, it gave a mixture of \textsubscript{L}-ribo and \textsubscript{L}-arabino glycals. As already mentioned earlier,\textsuperscript{83,84} vancosamine, the 3-\textsubscript{C}-methyl-branched amino sugar was prepared by different routes employing a spiro aziridine ring and spiro oxirane ring. In another example,
condensation of methyl 3,4-O-isopropylidene-α-L-erythro-hexopyranosid-2-ulose with 2-(1,3-dithianyl)lithium, followed by demercaptalation, reduction of the 2-C-formyl group, and mild acid hydrolysis afforded methyl α-hamameloside. Hamemelose and ephihamemelose were also prepared by addition of diazomethane to the corresponding glycos-2-uloside, as shown in Scheme 23.
Another approach developed was through cyclization of dialdehydes with nitroalkanes. They provide a simple means for simultaneous introduction of a nitro group and an alkyl branch into a carbocyclic or pyranoid ring, as shown in Scheme 24.
2. **Total Synthesis from non-carbohydrate precursors:**

Raphael and Roxburgh reported the first synthesis of a naturally occurring branched-chain sugar, preparing DL-apiose in seven steps from an intermediate obtained from reaction of diethyl malonate and 2-bromoacetaldehyde diethyl acetal.\(^\text{138}\)
Racemic evermicose was synthesized by the stereospecific epoxidation of ethyl trans-3-hydroxy-3-C-methyl-DL-glycero-hex-4-enoate obtained by the Reformatsky reaction of trans-3-penten-2-one with ethyl bromoacetate. The 4,5-epoxide having the xylo configuration, on hydrolytic cleavage rendered regioselectively the 1,4-lactone having the D-L-arabino configuration. Reduction of the lactone with lithium aluminum hydride gave the desired compound, as shown in Scheme 25.139

Scheme 25


Racemic vancosamine was prepared140 by Claisen rearrangement of the vinyl ether, as shown in Scheme 26. Amination of the allylic position was accomplished by addition of bis(tosylimino)selenide with the abstraction of an allylic proton,141 followed by [3,3]-sigmatropic rearrangement. cis-Hydroxylation and hydrolysis gave the D-L-vancosamine triacetate in low yield.
Biological Activity of Branched-Sugar Nucleosides:

As mentioned earlier, most of the naturally occurring branched-chain sugars have been isolated from such natural antibiotics as erythromycin and chromomycin. Also, branched-chain sugar analogs of daunomycin and adriamycin have been shown to possess some biological activity. Findings on the antiviral activity of 2'-C-methyl and 3'-C-methylcytidines, and also the presence of poly(apiose) in plant cell-walls have further stimulated the synthesis of branched-sugar nucleosides by conventional methods. The adenine nucleoside (36) has been shown to inhibit multiplication of the herpes-1 (HF) virus, and displays enhanced growth-inhibitory activity against human lymphoblastic
leukemia cells in vitro. At 50% concentration, inhibition of RNA synthesis by cordycepin, the parent compounds was half that of the compounds (37) and (38), which was almost complete; and this also applied to the synthesis of DNA and protein.143

\[ \text{N} \]
\[ \text{R} \quad \text{OH} \]
\[ 1. \text{R} = \text{H} \]
\[ 2. \text{R} = \text{NH}_2 \]
\[ n = 3 \quad 37 \]
\[ n = 5 \quad 38 \]


Another interesting observation was that the thioguanine α- and β-nucleoside analogs containing 2,3-dideoxy-3-C-(hydroxymethyl)-D-erythro-pentofuranose (39) were found to possess similar inhibitory activity against the growth of WI-L2 human lymphoblastoid cells. They are phosphorylated and incorporated into the DNA of Mecca lymphosarcoma in mice to the same degree, and also are more effective than the parent analog, 2'-deoxythio-α-guanosine (40).144 These results indicated that the oxygen atom of the furanose ring and the 2'-methylene group are correspondingly interchangeable, and the acceptance is improved if primary hydroxyl groups are provided at both C-3' and C-5'.
Thio Sugars:

Those sugar derivatives in which bivalent sulfur replaces one of the oxygen atoms are termed thio sugars, and the position of the sulfur atom in the thio sugar molecule is denoted by means of a numerical prefix. The first example of naturally occurring thioglycosides was reported as early as in 1831 when Robiquet and Boutron\textsuperscript{145,146} isolated sinalbin from mustard seeds and showed that it liberated a reducing sugar on acid hydrolysis. The currently accepted structure of this thioglycoside (41) was proposed by Ettlinger\textsuperscript{147} in 1956. The extensive investigations of Kjaer and co-workers\textsuperscript{148} have revealed many new mustard-oil glucosides which support the general structure (42).\textsuperscript{149}

\[\begin{align*}
\text{HOCH}_2\text{TG} & \quad \text{HOCH}_2\text{TG} \\
\text{HOCH}_2\text{TG} & \quad \text{HOCH}_2\text{TG}
\end{align*}\]
A yeast nucleoside containing a thio sugar has been shown to be 6-amino-9-(5-S-methyl-5-thio-D-ribofuranosyl)-9H-purine; i.e., 5-deoxy-5-(methylthio)adenosine (43). Methionine reacts as its S-(5-deoxyadenosyl-5) derivative (44), a compound having the sulfonium ion structure, and the demethylated product is S-(5-deoxyadenosyl-5) homocysteine (45), which was isolated in 1954, and was synthesized chemically in 1955.

<table>
<thead>
<tr>
<th>R</th>
<th>CH₃O-OC(CH₃)₃⁻</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃SO(CH₃)₃⁻</td>
<td>CH₃SO(CH₃)₃⁻</td>
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<tr>
<td>CH₃SO(CH₃)₃⁻</td>
<td>CH₃SO(CH₃)₃⁻</td>
</tr>
<tr>
<td>p-CH₃OC₆H₄CH₃⁻</td>
<td>C₆H₄⁻</td>
</tr>
<tr>
<td>C₆H₄(CHOH)CH₃⁻</td>
<td>m-CH₃OC₆H₄CH₃⁻</td>
</tr>
<tr>
<td>C₆H₄CO-CH₂CH(CH₃)₂-</td>
<td>C₆H₄CO-O(C₆H₄)⁻</td>
</tr>
<tr>
<td>CH₃S(CH₃)₃⁻</td>
<td>CH₃S(CH₃)₃⁻</td>
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<td>CH₃-CH(CH₃)₃⁻</td>
<td>CH₃CO(CH₃)⁻</td>
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<td>CH₃(CH₃)CO(CH₃)₃⁻</td>
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<td>CH₃(CH₃)CO(CH₃)₃⁻</td>
<td>CH₃(CH₃)CO(CH₃)₃⁻</td>
</tr>
</tbody>
</table>

Fischer and Delbrück\textsuperscript{154} had synthesized a phenyl 1-thio-D-glucoside by the reaction of 2,3,4,6-tetra-O-acetyl-\(\alpha\)-D-glucosyl bromide with sodium thiophenoxide in 1909. The first thio sugar having sulfur atom in a position other than C-1 was synthesized by Freudenberg and Wolf\textsuperscript{155} in 1927 when they prepared a 3-thio glucose derivative by thermal rearrangement of 3-O-[(methylthio)thiocarbonyl] derivative of 1,2:5,6-di-O-isopropylidene-\(\alpha\)-D-glucofuranose, as shown in Scheme 27. Several different methods of preparing such thio sugars have been devised since then,\textsuperscript{126} viz., nucleophilic displacements of halides and sulfonates, nucleophilic displacements of epoxides and episulfides, addition of thiol reagents to unsaturated carbon atoms, and reactions involving bridged sulfonium intermediates.\textsuperscript{156}
Sugars Having Sulfur in the Ring:

This class of sugars has not been found occurring naturally as yet. The first example of this series, 5-thio-D-xylopyranose (46), was synthesized independently, and reported simultaneously from three different laboratories in 1961, as shown in Scheme 28.


With sodium thiocyanate, 1,2-O-isopropylidene-5-O-p-tolylsulfonyl-\(\alpha\)-D-xylofuranose (47) gave a thiocyanate that reacted with sodium sulfide to give (48).\(^{157}\) A better synthesis was the treatment of (49) with sodium thiosulfate, followed by reduction of the resulting Bunte salt with sodium borohydride.\(^{158}\) The same compound was obtained by nucleophilic displacement of the tosyl group with potassium thioacetate followed by deacetylation,\(^{136}\) or by the nucleophilic displacement using sodium \(\alpha\)-toluenethioxide, followed by scission of the resultant \(S\)-benzyl
compound with sodium in liquid ammonia. Acid hydrolysis of the furanose (50) resulted in the formation of 5-thio-D-xylopyranose. In a similar manner 5-thio-D-ribopyranose was synthesized by Hughes and Clayton. 160

5-Thiohexoses are prepared not only by nucleophilic substitution, but also by nucleophilic opening of a 5,6-epithio, or 3,5-anhydro ring. 161 5,6-Dideoxy-5,6-epithio-1,2-O-isopropylidene-α-D-glucofuranose (51) was converted into its 5-thioacetate as shown in Scheme 29. 162, 163 This compound on acid hydrolysis underwent a ring-opening expansion, and subsequent acetylation gave 1,2,3,4,6-penta-O-acetyl-5-thio-α-D-glucopyranose (52).

Scheme 29

Another route to 5-thio-α-D-glucopyranose was devised through the nucleophilic ring-opening of 3,5-anhydro-1,2-α-isopropylidene-β-L-idofuranose with benzylthio anion. The resulting 5-S-benzyl-1,2-α-isopropylidene-5-thio-α-D-glucofuranose, on reductive debenzylation and hydrolysis, furnished 5-thio-α-D-glucopyranose in crystalline form.

Treatment of methyl 2,3-α-isopropylidene-4-α-p-tolylsulfonyl-α-L-rhamnopyranoside (53) with potassium thiobenzoate in N,N-dimethylformamide gave, by rearrangement and ring contraction, methyl S-benzoyl-6-deoxy-2,3-α-isopropylidene-5-thio-α-L-talofuranoside (54) and not the expected corresponding 4-thio ester. Removal of the S-benzoyl group from (55) with sodium methoxide, followed by acid hydrolysis gave 6-deoxy-5-thio-α-L-talopyranose as shown in Scheme 30.
$\delta$-Ethyl-6-deoxy-6-thio-$\delta$-galactose was obtained in two different ways by Samuel Baker. In the first method, 1,2:3,4-di-$\delta$-isopropylidene-6-$\delta$-p-tolylsulfonyl-$\delta$-galactose (57) was treated with concentrated hydrochloric acid and ethanethiol to yield the diethyl dithioacetal (58), which on treatment with 2 equivalents of sodium ethanethiolate gave 6-$\delta$-ethyl-6-thio-$\delta$-galactose diethyl dithioacetal. In the second method, the diisopropylidene derivative (59) was directly treated with sodium ethanethiolate, and the product after hydrolysis to remove isopropylidene groups gave (60) as shown in Scheme 31.

Scheme 31

2-Acetamido-2-deoxy-5-thio-D-glucose was prepared by three different routes. Guthrie and co-workers synthesized it by methanolysis of the thioacetate (61) followed by deblocking procedures, while Bognar, Whistler and coworkers synthesized it via episulfide ring opening which in turn was prepared by treating the corresponding epoxide with thiourea, as shown in Scheme 32. In a similar manner, Hasegawa and co-workers

Scheme 32

and co-workers prepared 2-acetamido-2-deoxy-5-thio-\(\alpha\)-D-gluco,\textsuperscript{171} \(\beta\)-galacto,\textsuperscript{172} and \(\beta\)-mannopyranose.\textsuperscript{173}


In anticipation of interesting biological properties, Mack and Brossmer\textsuperscript{174} recently reported synthesis of 6-thiosialic acids and 6-thio-\(\beta\)-N-acetyl-\(\alpha\)-neuraminic acid, starting from the triacetylmannothiazoline as shown in Scheme 33.

This method of converting amino sugars into thioacetamido sugars via a thiazoline intermediate was devised by Bognar and co-workers\textsuperscript{175} when they prepared a 2-amino-2-deoxy-3-thio-mannopyranose derivative, as shown in Scheme 34.
Scheme 33

1b → I → II → III → 7a → IV → 7b

V → 7c

R = R₁ = H

V → 7d

R = Ac, R₁ = CH₃

11X

1 = 2 = VIII

10a

R = Ac, R₁ = Me

10b

R = R₁ = H

: Acetone, H₂SO₄ conc., 0°C. II: MeOH/H₂O/ACOH (50/50/0.5), 24 h, rt. III: Oxaloacetate/ i₂, pH 7.5-8, 15 h, rt. IV: H⁺(Amberlite). V: H₂O, pH 6, 90°C. VI: HCl, Ac₂O/ACOH (1/2), °C. VII: NaN₃, Acetone. VIII: 1 N NaOH/MeOH (4/1). IX: TMSN₃, SnCl₄, CH₂Cl₂, 15 h, rt.

Scheme 34


Although penicillins, cephalosporins, and many other antibacterials having a sulfur atom in the ring have been discovered or synthesized, the biochemical activity of sugars having sulfur in the hemiacetal ring
has not yet been investigated extensively. Free 5-thio-α-D-xylopyranose (46) shows a strong, very specific, inhibitory action on α-D-xylosidases and xylobiase. 5-Thio-D-glucopyranose has been found to have bacteriostatic activity and is not as sweet as D-glucose.


There has been considerable work on the biological activity of 5-thio-D-glucopyranose. Metabolism of 5-thio-D-glucopyranose and 6-thio-D-fructofuranose was studied by Whistler and coworkers, who found them to be essentially non-toxic. 6-Thio-α-D-fructofuranose was found to be unusually sweet in taste. 5-Thio-D-glucose was also found to be a competitive inhibitor of D-glucose, interfering with formation of D-glucose-6-phosphate. In order to investigate the mechanisms by which heat affected cancer cells, Kim and coworkers used 5-thio-D-glucose under aerobic and hypoxic conditions at temperatures ranging from 37 to 43°C. It was found that drug or heat alone killed a minimum number of cells, whereas both together increased the number of cells killed under hypoxic conditions. Skov and coworkers found that 5-thio-D-glucose was absorbed into the eye with no observable toxicity and
when it was administered concurrently with implantation of ocular melanoma, the tumor was half the size of the controls. A series of 62 gold (I) coordination complexes were prepared by Mirabell and coworkers and were tested for their cytotoxic activity against B16 melanoma and P-388 leukemia cells in vitro and in vivo against P-388 leukemia cells in mice. They found that 2,3,4,6-tetra-O-acetyl-1-thio-glucosyl-gold complexes were the most active. The in vivo activity of these compounds appeared to be optimal with a substituted phosphine and a thio sugar as the ligands. Thus, there is much current research in this area. Furthermore, 5-thio-D-glucal, (63), a cyclic enol thioether,


synthesized by Korytnyk and co-workers, was found to be a competitive inhibitor of glycosidases.
Recently, Capon and Macleod have isolated 5-thio-D-mannose, from
the marine sponge *Clatharia pyramida* which in addition to being the
first reported modified free sugar from a sponge, represents the only
naturally occurring example of a thio sugar with the sulfur atom in the
ring.

1200-1201.
The anthracycline antibiotics daunorubicin and doxorubicin are potent anticancer agents. The major disadvantage associated with their use is their cumulative acute cardiotoxicity. Rational approaches to analogs of lower cardiotoxicity and/or increased potency, are thus of high interest, and suitable glycon-modified anthracyclines offer high promise.

As described earlier, branched-chain sugars and thio sugars are frequent constituents of antibiotics. Hence, it was of interest to prepare, and investigate the biological activity of daunorubicin analogs containing a branched-chain sugar and a thio sugar isosteric with daunosamine.

Although these were synthetically difficult final targets, the routes of access to these sugars presents intrinsic general interest and value. As already mentioned earlier, the branched-chain sugar 2,6-dideoxy-3-C-methyl-L-lyxo-hexopyranose has not been found naturally, whereas the three other possible configurational isomers have been isolated from natural antibiotics. Hence this as-yet unreported sugar could be utilized to prepare analogs of other antibiotics, as well as the target anthracycline glycoside.
Similarly, 5-thio daunosamine itself may possess interesting biological activities in the manner shown by 5-thio-D-glucopyranose and 5-thio-D-xylopyranose.

The proposed route to these molecules involves, as will be seen, various intermediates established in the Horton--Weckerle synthesis of daunosamine. A parallel objective was to re-evaluate the steps in this synthesis to determine the possibility for further optimization of the steps to daunosamine, which again would help in obtaining large quantities of the intermediates required for set targets. Also, as the analytical instruments available at the time of this synthesis of daunosamine were not as sophisticated as those now available, the recording of good and unambiguous $^1$H and $^{13}$C NMR spectral data for intermediates in the Horton--Weckerle synthesis was of value.

Lastly, the various daunosamine derivatives thus prepared may be utilized for comparative study of their tautomeric behavior in different solvents, following the protocols used earlier in this laboratory with other amino sugars. These studies may provide insight into the effect of the 3-acylamino-2,3,6-trideoxy framework in its effect on the anomeric compositions of these sugars at equilibrium. The specific objectives of this investigation may be summarized as follows:

1. Retrace the Horton-Weckerle route to the large-scale synthesis of daunosamine, incorporating recent modifications and provide definitive spectral data on the intermediates.

2. Study the anomeric compositions of different acylamino derivatives of daunosamine at equilibrium.
3. Synthesize the 3-\(\text{C}\)-methyl-3-hydroxy analog of daunosamine, \textit{viz.}, 2,6-dideoxy-3-\(\text{C}\)-methyl-\(\text{L}\)-\text{lyxo}-hexopyranose, couple it to daunomycinone, and investigate the antitumor activity of the resultant glycoside.

4. Synthesize 5-thiodaunosamine, \textit{viz.}, 3-amino-2,3,6-trIDEOXY-5-thio-\(\text{L}\)-\text{lyxo}-hexopyranose, attach it to daunomycinone, and investigate the biological activity.
Synthesis of Daunosamine:

Daunosamine, the sugar component of the anthracycline antibiotics daunorubicin and doxorubicin, has been synthesized by various different approaches starting from carbohydrate as well as non-carbohydrate precursors. Amongst them, the first large-scale preparation, devised by Horton and Weckerle still remains the most elegant and viable approach due to the ready availability of the relatively cheap starting material, methyl α-D-mannopyranoside, and the ease of work-up and separation processes as shown in Scheme 35.

\[ \text{Scheme 35} \]
Virtually all of the subsequent syntheses from carbohydrate precursors have certain common features, which can be summarized as follows:

a) Introduction of an amino functionality at C-3 has been effected either by $S_N2$ displacement with azide ion or by stereoselective reduction of an oxime intermediate.

b) Introduction of a methyl group at C-5 and establishment of the L-configuration has been done by either catalytic reduction of 5,6-ene when the intermediate is in the pyranose form, or via lithium aluminum hydride reduction of a 5,6-anhydro ring when the intermediate is in furanoside form.

c) Deoxygenation at C-2 has been carried out by various different methods, including methoxymercuration-demercuration of a glycal derivative, desulfurization of an $S$-benzyl group, or by the Klemer and Rodemeyer reaction.
Since quite a few different synthesis have been based upon the Horton-Weckerle approach, it was decided to retrace the same path for preparing daunosamine, incorporating modifications suggested in similar approaches and thus, prepare different N-substituted derivatives of daunosamine and study their anomeric composition at equilibrium.

Preparation of 2,3:4,6-di-O-benzylidene-α-D-mannopyranoside (2). The procedure used in the Horton-Weckerle synthesis, worked remarkably well when conducted on a 200 g scale. α,α-Dimethoxytoluene was prepared as described by Evans, and was added to methyl α-D-mannopyranoside and dry N,N-dimethylformamide containing a catalytic quantity of anhydrous p-toluenesulfonic acid. The flask, fitted with an air condenser and attached to a water aspirator, was heated on an oil bath at 65-75°C for 4 h. The mixture was poured with vigorous stirring using a mechanical stirrer, into ice-water containing sodium hydrogencarbonate, when a white precipitate of the product, a mixture of diastereomeric acetals, appeared. This was washed with water, filtered and dried. The yields were always in the range of 95-98%.

Preparation of methyl 4,6-O-benzylidene-2-deoxy-α-D-erythro-hexopyranosid-3-ulose (3). Commercially available tetrahydrofuran (Gold Label from Aldrich Chemical Co.) was found to be suitable for this reaction. For large-scale preparations, the reaction was kept between -30° and -40° for about 1 h, and on work-up with ammonium chloride and water, crystalline ketone 3 was obtained in very good yield, on a 100 g scale.
Preparation of methyl 4,6-0-benzylidene-2-deoxy-α-D-erythro-hexopyranosid-3-ule oxime (4). The procedure as originally described by Overend and colleagues worked well on the 100 g scale. During the neutralization of hydroxylamine hydrochloride, the mixture was kept under nitrogen, as carbon dioxide from air can potentially decompose the hydroxylamine. This was found particularly suitable for large-scale reactions as the mixing of reagents for neutralization required longer times. The procedure described by Arcamone and coworkers using free hydroxylamine base was also found quite convenient, as the solutions of hydroxylamine hydrochloride and sodium hydroxide were mixed together and the salt filtered off. The alcoholic solution of hydroxylamine had to be evaporated to half its volume before adding the ketone in order to obtain a satisfactory yield of the first crop of the crystalline oxime, which was generally around 60-65% from the crude glycosulose 3.

Preparation of methyl 3-amino-4,6-0-benzylidene-2,3-dideoxy-α-D-ribo-hexopyranoside (5) and its acylation products (6), (7) and (8). The reduction of oxime 4 with lithium aluminum hydride afforded a mixture of epimers at C-3 with the ratio of 86:14 of *ribo:arabino* configurations as established in the Horton--Weckerle route. The yield was ~95%. Following acetylation of the amines, the two resultant acetamido derivatives had remarkably different solubilities in toluene. The *ribo* derivative 6 was completely soluble in toluene, whereas the *arabino* derivative 7 was completely insoluble and separated as white crystals when the mixture was mixed with toluene. This was one of the most crucial steps in this route, as no columns were necessary to separate
the two epimers. The only drawback here is that the acetamido group
requires slightly harsh conditions for later hydrolysis. In a modified
step, Arcamone and coworkers\textsuperscript{188} reduced the oxime with aluminum amalgam
to give exclusively the product having the D-ribo configuration, and
hence a readily hydrolyzable trifluoroacetate group could be put on the
amine. When this reaction was tried in our laboratory, it was found
that the quality of aluminum played an important role. Three different
types of aluminum foils were tried. The most inexpensive, "Reynolds
Wrap" when tried, gave a mixture of products and the reaction mixture
turned dark grey to black. On trying the 99.9\% pure aluminum from
"Alfa", the reaction worked very well, with only one product seen on the
t.l.c. after acetylation. Also, it was observed that the reaction
mixture gave a white precipitate and not a dark-grey or black one as
seen in the previous case. As this aluminum foil was very expensive, it
would not be suitable for large-scale adaptation of the procedure.
Hence, a thicker quality of the same grade 99.9\% pure aluminum was
tried, which was relatively less expensive. The reaction this time took
a much longer time for completion and again, it gave a mixture of
products. Hence, it seems that not only the purity of the aluminum
used, but also the thickness of the foil made a difference, which in
turn suggests that this reduction is surely a surface phenomenon. A
subsequent improvement in this reaction came in 1986 when Terashima and
coworkers\textsuperscript{190} reported the use of Vitride or Red-Al in toluene. These
also worked quite well in our hands. These reactions are summarized in
Scheme 36.
SCHEME 36

4 \[ \xrightarrow{\text{LiAlH}_4, \text{Et}_2\text{O}} \] 5a + 5e

- 5a: 86% yield
- 5e: 14% yield

Yields:
- 90%
- 75%
- 59%

\[ \xrightarrow{\text{Al/Hg, EtOH, 45-50}} \]

Red - Al or Vitride

100% yield

SCHEME 36
Preparation of methyl 3-acetamido-4-O-benzoyl-6-bromo-2,3,6-trIDEOxy-a-D-ribo-hexopyranoside (9). Treatment of the ribo acetamido derivative 6 with N-bromosuccinimide in carbon tetrachloride, by the general procedure of Hanessian,202 led to the opening of the 1,3-dioxane ring giving the 4-O-benzoyl-6-bromo-6-deoxy derivative of 9, as white crystals, in 50-60% yield. The mother liquor, which was quite dark when put on a column of silica gel and washed with dichloromethane, afforded 10-15% more the of product.


Preparation of methyl 3-acetamido-4-O-benzoyl-2,3,6-trideoxy-a-D-erythro-hex-5-enopyranoside (12). The dehydrobromination of the bromide 9 was effected with silver fluoride as reported without any difficulty, to afford the 5,6-unsaturated derivative 10 as a syrup in quantitative yield. Anhydrous silver fluoride97 was conveniently prepared by treating silver carbonate with aqueous hydrofluoric acid in a platinum crucible. The water was boiled off by heating the crucible with a flame while constantly stirring the solution with a wooden rod. When the last traces of water were being removed, the crucible was heated from the top with an infrared lamp so that no traces of water remained. The anhydrous silver fluoride thus prepared was immediately transferred into a dark bottle and kept tightly closed in a dessicator which was stored in the dark. Commerically available anhydrous silver
R = CH₃  9
CF₃  10

R = CH₃  11
CF₃  12

DBU
Toluene
reflux
85 %

DBU
HMPT, rt
90 %

DBU
Benzene
reflux
75 %

SCHEME 37
fluoride with a 99.9% purity was also found to be satisfactory for this reaction but other technical-grade silver fluoride samples gave poor yields, with some other by-products. As silver fluoride is rather expensive, the newer procedures proposed to effect the same elimination utilize DBU as the base. Arcamone and coworkers had suggested the use of DBU in hexamethylphosphoric triamide (HMPT) as the solvent, whereas Terashima and coworkers used DBU in benzene to effect this conversion. K. Agyei-Aye and Horton had effected similar conversion on another compound using DBU in toluene. Hence this reaction was tried with DBU and toluene, which too worked very well, affording the 5,6-enopyranoside in >90% yield.

Preparation of methyl 3-acetamido-2,3,6-trideoxy-a-D-erythro-hex-5-enopyranoside (13). The O-deacylation of 10 was quantitatively effected by catalytic transesterification, using sodium methoxide in methanol at room temperature. The reaction mixture could be neutralized with ion-exchange resins instead of filtering through a column of silica gel.
The resulting syrup was utilized immediately for the next step without any delay.

Preparation of methyl 3-acetamido-2,3,6-trideoxy-\(\alpha-L\)-lyxo-hexopyranoside (14). The syrupy compound 11 underwent catalytic hydrogenation over palladium-on-barium sulfate with complete stereospecificity, affording methyl \(N\)-acetyl-\(\alpha\)-daunosaminide in essentially quantitative yield as reported.

Preparation of 3-amino-2,3,6-trideoxy-\(\alpha-L\)-lyxo-hexose hydrochloride (15). \(N\)-Deacetylation was effected using aqueous barium hydroxide and the resultant aminoglycoside was hydrolyzed with aqueous hydrochloric acid, affording daunosamine hydrochloride in good yield as a crystalline \(\alpha\)-L anomer.

Preparation of \(N\)-acetyldaunosamine (16). The glycoside 12, when subjected to hydrolysis with aqueous acetic acid, gave \(N\)-acetyldaunosamine as the crystalline \(\alpha\)-L-anomer, and this was recrystallized from ethyl acetate.

Preparation of \(N\)-benzoyldaunosamine (17). When a cold aqueous solution of daunosamine hydrochloride was treated with benzoyl chloride in acetone in the presence of potassium hydrogen carbonate, the \(N\)-benzoylation was effected in 40% yield. The compound had to be purified by preparative t.l.c. and recrystallized from acetone in order to obtain the white crystalline \(\alpha\)-L-anomer of \(N\)-benzoyldaunosamine.
SCHEME 38
Preparation of N-trifluoroacetyldaunosamine (18). The free amino-glycoside obtained after hydrolysis of methyl N-acetyl-\(\beta\)-daunosaminide with barium hydroxide, when treated with trifluoroacetic anhydride in cold methanolic solution, afforded the N-trifluoroacetamido derivative. This was then subjected to hydrolysis with 50% acetic acid and converted into the desired free sugar in ~45% yield.

As all of the foregoing compounds were known, their analytical data like melting points, rotations and NMR spectra were recorded and compared with those of their original counterparts. As \(^{13}\)C NMR spectra were not recorded in the original work, these data along with the revised \(^1\)H NMR spectral data are recorded in Tables 6 and 7.

\(^{13}\)C NMR Spectral Analysis of Compounds 3-14

The \(^{13}\)C NMR spectrum of the mixture of isomeric dibenzylidene acetals 2 (isomeric at the benzylic position of the five-membered ring) was fully interpreted by Lipták and coworkers, and as may be seen from Table 7, the results obtained during this investigation are in close agreement with theirs. The glycosulose 3 showed the characteristic carbonyl resonance for C-3 at 169.64 ppm. At the same time, C-2 suffered an upfield shift because of the deoxygenation, showing its resonance at 46.43 ppm. The C-4 resonance had moved downfield by ~5 ppm as it was attached to the carbonyl group of C-3. The oxime 4 had the characteristic resonance of a \(-\text{C}=\text{N}-\) group at 149.36 ppm. The C-2 and C-4 resonances had moved upfield from their former positions in the glycosulose 3 and were observed at 30.20 and 78.08 ppm, respectively.
As expected, reduction of the oxime 4 to the free amino compound 5 shifted the C-3 resonance upfield, to 46.2 ppm. Also, the C-5 resonance had shifted upfield at 57.59 ppm, paralleling a change in the shape of the ring as now the exocyclic double-bonds of carbonyl or oximino groups were no longer present. The $^{13}$C NMR spectra of the acylamino derivatives 6 and 8 having the D-ribo configuration, had a close resemblance as may be seen from Table 7. The trifluoroacetyl group showed two quartets for the carbonyl carbon and the carbon belonging to the CF$_3$ group because of the coupling with three fluorine atoms. The arabino derivative 7, obtained as the minor product by reducing the oxime 4 with lithium aluminum hydride and subsequent acetylation, had all of its resonances more downfield than its 3-epimer 6. This may be due to the equatorial disposition of the acylamino group which can deshield the ring carbons more effectively by its diamagnetic anisotropic effect. This downfield shift was more prominent for the C-2, C-3, C-4 and C-5 carbons.

The 4-O-benzoyl-6-bromo derivatives 9 and 11 showed the expected upfield shifts for C-6 and C-4 resonances as now they were not attached to alkoxy groups. The C-4 resonances for both were observed at -70 ppm because benzoate groups were present on them. The C-6 resonances were observed at -32 ppm because of the presence of the halogen. The dehydrohalogenated derivative 10 had its resonances for C-5 and C-6 at
150.89 and 98.19 ppm, respectively, confirming the presence of the exocyclic double bond. The deesterified product 13, which still had the exocyclic double bond, did not show an upfield shift for C-4 but the signals for adjacent carbons C-5 and C-3 had moved downfield. The shielding effect on β-carbons due to esterification has been well documented. Hence on deesterification, this shielding effect ceased to exist, moving C-3 and C-5 downfield. The methyl glycoside of the N-acetyldaunosamine 14 had its anomeric resonance at 101.4 ppm, whereas most of the intermediates encountered during this synthesis had their anomeric resonances at 99 ppm, except for the compounds having an exocyclic double bound, viz., 3, 10 and 13. This may be attributed to the conformational change from $4C_1$ to $1C_4$ that took place on reduction. The C-6 resonance was now observed at 16.62 ppm, and C-5 had moved to 69.31 ppm.

The free sugars 15, 16, 17 and 18, which provide a representative range of derivatives, were of interest to permit a comparative study of their tautomeric behavior, as conducted earlier in this laboratory with other amino sugar derivatives. Their compositions at equilibrium were determined from $^1$H NMR spectra in two different solvents, viz, Me$_2$SO(d$_6$) and D$_2$O. The four compounds were monitored as they approached equilibrium in solution.
Table 6

$^1$H NMR Spectral Data for Compounds 3-8

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<th>H-6</th>
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<td>($J_{4,5}$)</td>
<td>($J_{5,6}$)</td>
<td>($J_{6',6}$)</td>
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<td>3.38 s</td>
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*a* In chloroform-δ, with tetramethylsilane as the internal standard.

*b* Signal multiplicities; b, broadened; d, doublet; m, multiplet; q, quartet; s, singlet.
### Table 6 (continued)

**1H NMR Spectral Data for Compounds 9-14**

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<td>(J₁₂ₑ)</td>
<td>(J₂₈₂ₑ)</td>
<td>(J₂₃)</td>
<td>(J₃₄)</td>
<td>(J₄₅)</td>
<td>(J₅₆)</td>
<td>(J₆₆')</td>
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<td>5.00 dd (4.1)</td>
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<td>3.52 s</td>
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**Chemical Shifts (δ)**: ppm (first-order couplings, Hz, in parentheses).

*a* In chloroform-d, with tetramethylsilane as the internal standard.

*b* Signal multiplicities: b, broadened; d, doublet; m, multiplet, q, quartet; s, singlet.
Table 7

$^{13}$C NMR Spectral Data for Compounds 2-6

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$^a$In chloroform-d.

$^b$Endo and exo isomers, respectively.
Table 7 (continued)

$^{13}$C NMR Spectral Data for Compounds 7-14

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</table>

$^a$In chloroform-$d$. 
Compositions of 15, 16, 17 and 18 at their Mutarotational Equilibrium

Mutarotational Equilibrium:

When a reducing sugar, above an aldotetrose or a 2-pentulose, is dissolved in water, a solution is obtained that always contains, in principle, at least six compounds: the two pyranoses, the two furanoses, and the acyclic (open-chain) carbonyl form and its hydrate. These various forms are often referred to as the "tautomeric forms" of the sugar. Each of these forms is a distinct compound, differing from other forms in its chemical, physical, and biological properties. Knowledge of the composition of sugars in solutions is fundamental to carbohydrate chemistry. The physical and chemical properties of the sugars in solution depend on the proportions of their various forms and their biological properties may also show such dependence.

![Diagram of tautomeric forms of a hexose](image)

**Figure 1.** Various tautomeric forms of a hexose.

- Favored when anomeric effect predominates
- Favored when steric effect predominates
Pyranoses are the most stable forms of most sugars in aqueous solution. The difference between the free energies of pyranoses and furanoses is quite substantial; when neither of them has serious destabilizing interactions, it is about 8 kJ/mol. This is because the substituents of a six-membered ring can be all fully staggered whereas, that is not possible in other ring systems. Perlín has suggested a possible additional explanation based on the work of Kabayama and Patterson who suggested that the pyranoses have a special ability to interact with the "structural" component of liquid water. The spacing of hydroxyl groups on a pyranose ring corresponds to tetrahedrally coordinated oxygen atoms hydrogen-bonded into the dynamic, tridyrmite arrays suggested for water, and mutual stabilization of this water structure and of pyranoses will result, particularly if their hydroxyl groups are predominantly equatorial. Such stabilization would not occur with furanose forms.

Because the conformations of the pyranose ring are well defined, the steric interactions within each isomer were considered, and the relative stability of different isomers and conformers were estimated first by Reeves who had assigned arbitrary "instability factors" to certain features of pyranose forms. Subsequently, Angyal introduced a simple, semi-quantitative method whereby he estimated the approximate free-energy terms for conformational interaction-energies, and also for the anomeric effect. Interactions between axial groups and between vicinal gauche groups were determined, in aqueous solution and at ambient temperature, from the equilibria of cyclitols with their borate complexes and from the anomeric equilibria of aldopyranoses. Thus,
Angyal gave two types of free-energy values, viz., interaction energies based upon steric effects and interaction energies based upon polar effects, i.e., the anomeric effect. These values can be added up to estimate the conformational free energies of α and β pyranoses and the difference between the two may be used to predict the ratio of α:β-pyranose forms at equilibrium.


As the furanose forms are very flexible, with low energy barriers amongst different conformations, a simple calculation of free energies by the use of a set of interaction energies is not possible, although some general conclusions about interactions within them, and about their relative stabilities have been drawn. In furanoses, the vicinal carbon atoms cannot be fully staggered; therefore, interactions between
vicinal cis substituents become important. Hence, if the substituent groups at either C-2 or C-3 is removed, it causes the furanose content to increase in the mutarotationally equilibrated solution.\textsuperscript{218}


Anomeric Effect:

The term "anomeric effect" was introduced by Lemieux in 1958 as a result of a detailed study of the anomerization of acetylated pento- and hexo-pyranoses.\textsuperscript{219} It had been found that the $\alpha$-D anomer was more stable than $\beta$-D-anomer in anomerically equilibrated mixtures of methyl D-glucopyranosides,\textsuperscript{220} penta-$\alpha$-acetyl-D-glucopyranosides,\textsuperscript{221} and peracetylated D-glucopyranosyl halides\textsuperscript{222,223} even though the substituent on C-1 was undoubtedly attached in the axial position in the $\alpha$-D anomer. Similar results had been obtained with pentopyranose tetraacetates when taken in conjunction with their conformational equilibria,\textsuperscript{225} indicating that the anomer having the substituent on C-1 axially attached was more stable.

This predisposition of a polar substituent at C-1 of a pyranoid ring to assume the axial orientation, contrary to expectations based solely on steric considerations, was termed the "anomeric effect". Thus, the anomeric effect refers to the tendency of an electronegative substituent at C-1 of a pyranoid ring to assume the axial rather than equatorial orientation as expected merely on steric grounds. This phenomenon is not restricted to carbohydrate systems and it is in fact displayed in many types of heterocyclic compounds.  


Edward\textsuperscript{230} attributed this phenomenon to an unfavorable dipole--dipole interaction between the carbon--oxygen bonds on the ring and the bond from the anomeric carbon atom to the equatorial polar substituent. Lemieux and Chu\textsuperscript{224,226} explained this effect as electrostatic interaction between the C-1 to substituent and C-5--O-5 bonds. This interaction was later termed the "rabbit-ear effect," and was considered to arise from a repulsion of the electric dipoles engendered by the parallel disposition of electron-pairs occupying non-bonding orbitals of the ring hetero-atom and the electronegative atom bonded directly to the anomeric carbon atom.\textsuperscript{212,231,232} This "rabbit-ear effect" interpretation has largely been discarded by subsequent investigators.\textsuperscript{233}

\begin{center}
\includegraphics[width=0.5\textwidth]{rabbit-ear-effect-diagram.png}
\end{center}

\textsuperscript{230} J. T. Edward, Chem. Ind., London (1955), 1102.
For the past two decades, Horton and coworkers\textsuperscript{234a,b,235} have investigated extensively in this area including the compositions of different amino sugars and their derivatives at anomeric equilibrium.


As already discussed earlier, daunosamine and its derivatives have been extensively investigated in the past few years. Although a systematic study of the anomeric composition of daunosamine derivatives has not been undertaken yet,\textsuperscript{208} Fronza and coworkers\textsuperscript{236} studied the anomeric equilibria of different amino sugars generally encountered in the anthracycline antibiotics including the N-benzoyl derivatives of daunosamine, acosamine and ristosamine.

In this work it was of interest to study the compositions at anomer equilibria of the four different N-acyldaunosamine derivatives, viz., daunosamine hydrochloride 15, N-acetyl-daunosamine 16, N-benzoyldaunosamine 17, and N-trifluoroacetyl-daunosamine 18, and thus observe the effect of different substituents on nitrogen on the final composition at equilibrium in solvents like dimethyl sulfoxide (Me₂SO) and water, and calculate the free-energy differences between the α and β-pyranose forms of each of these sugars, which may be employed in comparative estimation of the interaction energies of 6-deoxy and 3-amino-3-deoxy groups.

Results and Discussion:

For each sugar studied, the interconversion of tautomeric forms in solution was observed by nmr spectroscopy. As established earlier, this methodology, when employed, does not give anomeric compositions to the degree of accuracy that careful polarimetric studies might furnish, but the latter requires both of the anomeric pyranoses be available in pure form and no appreciable amount of furanoses or open-chain froms be present at the equilibrium. Advantages of the nmr method are that it can give approximate tautomeric compositions even when no crystalline form of the sugar is available, and it can indicate whether a crystalline sugar is a single tautomeric form or a co-crystallized mixture of forms. Also, with the help of current high field FT-NMR instruments, it is possible to observe the peaks for small proportions of furanoses and other forms that may be present in addition to two pyranoses at equilibrium. Figure 2 (a-d) shows partial ¹H NMR
Figure 2a. Partial $^1\text{H}-\text{NMR}$ spectrum of 15 in D$_2$O.

Figure 2b. Partial $^1\text{H}-\text{NMR}$ spectrum of 16 in D$_2$O.
Figure 2c. Partial $^1$H-NMR spectrum of 17 in D$_2$O.

Figure 2d. Partial $^1$H-NMR spectrum of 18 in D$_2$O.
spectra of compounds 15, 16, 17, and 18, and demonstrates these equilibrium mixtures.

The procedures involved the observation of the nmr signals for H-1, OH-1, H-3, H-5 and other proton resonances of the compounds under study. As there was the possibility of overlapping of signals, due to the concurrent presence of different forms, the integral values for some signals were prone to error. Hence, the signal showing the cleanest separation was chosen for integration. Details of the nmr measurements made in the present work are recorded in Table 8. The initial anomeric compositions of compounds 15, 16, 17 and 18 were observed in Me₂SO and these solutions were then allowed to reach mutarotational equilibrium. After 9 days no significant further change in their compositions was observed. A few drops of D₂O were added to these solutions and the resultant changes in their anomeric compositions were recorded. These compounds were then dissolved in D₂O and their anomeric compositions were recorded after the solutions had reached mutarotational equilibrium. Table 9 records all the data collected in the foregoing experiments.

As may be seen from Table 9, the α-pyranose form, exclusive at the outset, predominated in all four sugars at equilibrium when Me₂SO was the solvent and the ratio of α:β pyranoses decreased in the order NH₃Cl > NHCOCF₃ > NHCOPh > NHCOCH₃ for the 3-substituent. Addition of a few drops of D₂O to these solutions changed the ratio of α:β pyranose to augment the amount of β-pyranose, but still the α-pyranose form predominated. With D₂O as the solvent, the β-pyranose form was found to be the predominant component present at equilibrium in all four compounds.
Table 8

$^1$H NMR Spectral Data for Compounds 15, a 16, 17 and 18

<table>
<thead>
<tr>
<th>Compound</th>
<th>H-1</th>
<th>H-2a</th>
<th>H-2e</th>
<th>H-3</th>
<th>H-4</th>
<th>H-5</th>
<th>H-6</th>
<th>OH-1</th>
<th>OH-4</th>
<th>NH</th>
<th>COCH$_3$</th>
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<tbody>
<tr>
<td>15a</td>
<td>5.13</td>
<td>1.60</td>
<td>1.80</td>
<td>3.52</td>
<td>3.43</td>
<td>3.96</td>
<td>1.08</td>
<td>6.25</td>
<td>5.29</td>
<td>7.87</td>
<td></td>
</tr>
<tr>
<td>15b</td>
<td>4.60</td>
<td>1.72</td>
<td>------</td>
<td>3.26</td>
<td>------</td>
<td>1.13</td>
<td>6.62</td>
<td>5.30</td>
<td>7.95</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16a</td>
<td>5.09</td>
<td>1.33</td>
<td>1.75</td>
<td>4.10</td>
<td>3.32</td>
<td>3.95</td>
<td>1.03</td>
<td>5.97</td>
<td>4.58</td>
<td>7.51</td>
<td>1.79</td>
</tr>
<tr>
<td>16b</td>
<td>4.58</td>
<td>1.49</td>
<td>1.79</td>
<td>3.76</td>
<td>3.27</td>
<td>3.44</td>
<td>1.09</td>
<td>6.40</td>
<td>4.58</td>
<td>7.50</td>
<td>1.79</td>
</tr>
<tr>
<td>17a</td>
<td>5.17</td>
<td>1.48</td>
<td>2.02</td>
<td>4.41</td>
<td>3.53</td>
<td>4.06</td>
<td>1.11</td>
<td>6.10</td>
<td>4.76</td>
<td>7.95</td>
<td></td>
</tr>
<tr>
<td>17b</td>
<td>4.69</td>
<td>1.63</td>
<td>1.79</td>
<td>4.06</td>
<td>3.46</td>
<td>3.56</td>
<td>1.17</td>
<td>6.51</td>
<td>4.75</td>
<td>8.02</td>
<td></td>
</tr>
<tr>
<td>18a</td>
<td>5.12</td>
<td>1.39</td>
<td>1.98</td>
<td>4.17</td>
<td>3.45</td>
<td>4.00</td>
<td>1.05</td>
<td>6.11</td>
<td>4.82</td>
<td>9.01</td>
<td></td>
</tr>
<tr>
<td>18b</td>
<td>4.62</td>
<td>1.52</td>
<td>1.75</td>
<td>3.87</td>
<td>3.38</td>
<td>3.50</td>
<td>1.11</td>
<td>6.49</td>
<td>4.82</td>
<td>9.10</td>
<td></td>
</tr>
</tbody>
</table>

$^a$a = $\alpha$-pyranose form; b = $\beta$-pyranose form
Table 9
Percent Composition of Some N-Acyl Daunosamine Derivatives
at Equilibrium in Different Solvents

<table>
<thead>
<tr>
<th>R</th>
<th>Me₂SO</th>
<th>Me₂SO + D₂O</th>
<th>D₂O</th>
</tr>
</thead>
<tbody>
<tr>
<td>NH₃Cl</td>
<td>α</td>
<td>73.5</td>
<td>68.0</td>
</tr>
<tr>
<td></td>
<td>β</td>
<td>26.5</td>
<td>28.0</td>
</tr>
<tr>
<td></td>
<td>f</td>
<td>---</td>
<td>4.0</td>
</tr>
<tr>
<td>NHTFA</td>
<td>α</td>
<td>59.0</td>
<td>44.5</td>
</tr>
<tr>
<td></td>
<td>β</td>
<td>28.5</td>
<td>41.5</td>
</tr>
<tr>
<td></td>
<td>f</td>
<td>12.5</td>
<td>14.0</td>
</tr>
<tr>
<td>NHCOPh</td>
<td>α</td>
<td>48.0</td>
<td>44.0</td>
</tr>
<tr>
<td></td>
<td>β</td>
<td>35.0</td>
<td>37.0</td>
</tr>
<tr>
<td></td>
<td>f</td>
<td>17.0</td>
<td>19.0</td>
</tr>
<tr>
<td>NHAc</td>
<td>α</td>
<td>45.5</td>
<td>46.0</td>
</tr>
<tr>
<td></td>
<td>β</td>
<td>41.5</td>
<td>43.0</td>
</tr>
<tr>
<td></td>
<td>f</td>
<td>13.0</td>
<td>11.0</td>
</tr>
</tbody>
</table>

α = α-pyranose, β = β-pyranose, f = furanoses and other forms.
In D$_2$O the ratio of $\alpha$:$\beta$ pyranoses was nearly the same for compounds 15, 16, and 17 whereas it was slightly higher for 18. These results may be rationalized as follows:

Strictly from steric considerations, the $\alpha$-pyranoses should be more stable than $\alpha$-pyranoses. As these compounds 15, 16, 17 and 18 were found to be $\alpha$-pyranoses in their crystalline state, it seems that the polar effects, i.e., the anomeric effect, was predominant.

As may be seen from Figure 1, the process of anomeric equilibration, i.e., mutarotation, takes place under acid-base catalysis. Me$_2$SO is a good H-bond acceptor but not an H-bond donor. Hence, only the -OH or -NHR groups present in the molecule could potentially act as H-bond donors, either inter- or intra-molecularly. As suggested by Horton and coworkers, the amino group should participate effectively in intra-molecular hydrogen bonding with a cis hydroxyl group, in this case being the -OH group on C-4, which may diminish the availability of these H-bond donors resulting in a very slow equilibration process in Me$_2$SO as observed.

As Me$_2$SO cannot solvate the -OH group at C-1 effectively, the equatorial hydroxyl effect observed with water because of the increase in steric bulk is not predominant in Me$_2$SO. Hence, the equilibrium composition is dictated by the anomeric effect which is predominant in Me$_2$SO resulting in the greater $\alpha$-pyranose content at equilibrium as observed. These results are in accordance with the results obtained by Perlin and coworkers who have proposed that the anomeric effect varies inversely with the dielectric constant of the solvent and is greatest when the substituent atom or group on that carbon forms a
highly polar bond with the carbon atom. Accordingly, the dielectric constant of water being 75 as compared to 49 of Me₂SO, the anomeric effect should be less significant in water compared to that in Me₂SO which may result in the higher α-pyranose form present in the equilibrium mixture.

The decrease in the ratio of α:β pyranoses in the order NH₃Cl > NHCOF₃ > NHCOPh > NHCOCH₃ may be attributed to the electronegativity of the substituent group present on nitrogen. Although this substituent is not adjacent to the anomeric center, it may play a significant role in altering the anomeric compositions of such sugars. Qualitatively, this may be rationalized as follows:

Figure 3 shows that the two dipoles due to -NH₂R and the lone pairs of electrons on the ring oxygen atom are oriented in the downward direction; i.e., the "y" components of the dipoles will add to each other while the "x" components will be against each other. The net result can be expected to be a greater pull in the y-direction with an increasingly better electron-withdrawing group on nitrogen, favoring formation of more α-pyranose form in order to offset the downward pull.

As already discussed earlier, mutarotation takes place under acid-base catalysis. Addition of D₂O to these solutions prepared with Me₂SO, not only furnished the required H-bond donor to cause the mutarotation to go faster, but also changed the equilibrium compositions to augment the amount of the β-pyranose and furanoses. This change in favor of β-pyranose may be attributed to the solvation of 1-OH group caused by the addition of water which may increase the equatorial hydroxyl effect.
The α-form still predominated probably due to the presence of large amounts of Me₂SO compared to the solute and D₂O.

When the $^1H$ NMR spectra of these compounds were recorded with only $D_2O$ as the solvent, the equilibrium compositions changed dramatically. The $\beta$-pyranose form was now the predominant component present at equilibrium in all four compounds, as may be seen from Table 9. The ratio of $\alpha:\beta$ pyranoses was nearly the same for compounds 15, 16 and 17, while it was slightly higher for 18.

As already stated earlier, the water molecules can effectively stabilize the equatorial hydroxyl groups because of their own orientation into a more stable tridymite structure as well as the solvation of the substituent group that would increase the steric bulk and hence the interactions if remained in axial position. Thus, the equilibrium was favorable towards the $\beta$-pyranose anomers in all four compounds. Besides stabilizing the equatorial hydroxyl group on the anomeric position, the water molecules could break the internal hydrogen bond between the amino group and the cis hydroxyl group, i.e., the 4-OH group. If the water molecules could effectively solvate the substituent group on nitrogen and thereby mitigate its electron-withdrawing effect, then that substituent group would not exert much of its polar effects on the anomeric composition, but will exert the steric effect because of the increase in its steric bulk, caused by solvation. Thus the amount of $\alpha$-pyranose form would decrease in favor of the $\beta$-pyranose form because of greater steric effects and less predominant polar effects.

As the $-$NHCOCF$_3$ group is highly electron-withdrawing, it is probable that its internal H-bond with the 4-OH group would be stronger compared to other nitrogen substituents and hence it may not be solvated to the same extent as the other groups by water molecules. Hence, the
α-pyranose content in the equilibrated solutions of 18 was observed to be slightly higher than the other three sugars 15, 16 and 17 for which the ratios of amount of β:α pyranoses were very similar.

Conformational Free Energy Calculations:

From the observed equilibrium compositions, it was possible to calculate the difference in the conformational free energies ΔG of α and β pyranose forms of the compounds 15, 16, 17 and 18 according to the equation,

$$\Delta G = -RT \ln K$$

where R is the universal gas constant, T the absolute temperature and K is the equilibrium constant for the reaction, i.e.,

$$\xrightarrow{\text{α-pyranose}} \xleftarrow{\text{β-pyranose}}$$

Thus, the ΔG values for the observed ratios of β/α pyranoses in different solvents were calculated and are recorded in Table 10. These observed ΔG values were then compared with the estimated values obtained by calculating the sum total of all the possible interactions energies in the two conformations as described by Angyal. These estimated values for interaction energies were obtained for aqueous solutions and hence could be compared with the observed ΔG values in D2O only.

To estimate the conformational free energy of a pyranoid sugar in one of its chair conformations, all of the interaction energies and the
anomeric effect (if present) are totalled as described by Angyal. For the compounds 15, 16, 17 and 18 all the other interactions would remain the same as they have the same configuration, viz.,

\[ \Delta G = 2(Oa:Ha) - \text{(anomeric effect)} \]
\[ = 2(0.45) - 0.85 = 0.05 \text{ kcal/mol} \]
Accordingly, all four compounds 15, 16, 17 and 18 should give the \( \beta/\alpha \) ratio of 53:47. Obviously, the observed ratios for \( \beta/\alpha \) pyranoses are different, and more in favor of \( \beta \)-pyranoses at equilibrium since the 3-acylamino-3-deoxy and 6-deoxy groups are not accounted for in these calculations.

### Table 10

<table>
<thead>
<tr>
<th>Compound</th>
<th>([\alpha]_D)</th>
<th>DMSO</th>
<th>DMSO + D(_2)O</th>
<th>D(_2)O</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 (-\text{NH}_3\text{Cl})</td>
<td>-55°</td>
<td>0.35</td>
<td>0.43</td>
<td>0.49</td>
</tr>
<tr>
<td>16 (-\text{NHCOCH}_3)</td>
<td>-102°</td>
<td>0.93</td>
<td>1.00</td>
<td>1.55</td>
</tr>
<tr>
<td>17 (-\text{NHCOPh})</td>
<td>-78°</td>
<td>0.73</td>
<td>0.81</td>
<td>1.5</td>
</tr>
<tr>
<td>18 (-\text{NHCOCF}_3)</td>
<td>-96°</td>
<td>0.49</td>
<td>0.68</td>
<td>1.3</td>
</tr>
</tbody>
</table>
Conclusion:

The foregoing results establish that all of the four sugars 15, 16, 17, and 18 exist exclusively in the \( \alpha \)-pyranose form when they are in crystalline state. They undergo mutarotational equilibration very slowly in \( \mathrm{Me}_2\mathrm{SO} \) with \( \alpha \)-pyranose form still predominating in the equilibrium solution. The electron-withdrawing capabilities of the substituent groups on nitrogen correlated with the ratios of \( \alpha:\beta \) pyranoses. In \( \mathrm{D}_2\mathrm{O} \), the apparent influence of the substituent group on nitrogen decreased substantially, whereas the steric effects became more prominent. Hence, the ratios of \( \alpha:\beta \) pyranoses were very similar as all four compounds had the same configuration and closely related structures, with the exception of \( N \)-trifluoroacetyl daunosamine (18), which showed some influence of the highly polar trifluoroacetyl group. The difference in free energies (\( \Delta G \)) calculated from the observed equilibrium compositions did not match with those estimated from calculations involving free-energy interactions as the values for anomeric effect in such a ring structure have not been derived or calculated as yet. Hence, the observed values of \( \Delta G \) can be employed in comparative estimation of the interaction energies of 6-deoxy and 3-amino-3-deoxy groups.

3'-Hydroxy-3'-C-methyl analog of daunorubicin. As discussed earlier, branched-chain sugars occur in many naturally occurring antibiotics. The synthetic 3-C-methyl analog of daunorubicin, having the daunomycinone coupled with the branched-chain sugar, vancosamine, was found to be moderately active. This result is complementary to our interest
to make the 3-hydroxy analog of vancosamine, viz., 2,6-dideoxy-3-\(\text{C}\)-methyl-\(\text{E}\)-lyxo-hexopyranose and attach it to the aglycon. This sugar does not occur naturally, although the other three \(\text{E}\) isomers of this sugar, viz., mycarose, axenose, and olivomycose do occur naturally. Hence, it could in principle, be utilized to prepare the analogs of those naturally occurring sugar antibiotics which contain any of these three sugars.

Again, the basic steps of the Horton--Weckerle route to synthesize daunosamine were exploited for this synthesis. Instead of converting the ketone 3 to its oxime and finally an amino group, the ketone was treated with methylmagnesium iodide in order to introduce the 3-\(\text{C}\)-methyl branch, as well as the tertiary hydroxyl group, in the \(\text{D}\)-ribo configuration. The rest of the steps would essentially remain the same leading to the desired sugar.

Grignard addition to the ketone 3. According to the procedure described by Flaherty, Overend and Williams,\(^{129}\) this Grignard addition does not work if carried out in ether alone. The reagent had to be displaced from ether by using 1,2-dimethoxyethane, and the precipitated Grignard reagent is then active enough to add to the ketone 3. The procedure worked well as described, giving the tertiary alcohol in \(-75\%\) yield. The attack of the methyl group was exclusively from the equatorial side. Axial attack would have been sterically hindered because of the presence of an axially oriented methoxyl group at C-1. Thus, the stereospecific attack of the Grignard reagent afforded the alcohol 19 with the desired \(\text{D}\)-ribo stereochemistry, as shown in Scheme 39.
Scheme 39

Reagents and conditions: MeMgl, Et₂O, glyme, --10°C

Yield:
- M 19: 75%
- 20: 10%
- 21: 65--70%
The $^1$H NMR spectrum as well as other relevant data were found to be in good agreement with the data recorded by other researchers. After work-up, and recrystallization of the product from hexane, addition of acetone to the mother liquor afforded white crystals of the glycal 20, already a known compound, but not observed for this Grignard addition reaction. The glycal 20 has the $\alpha$-arabino configuration, indicating an axial attack of the Grignard reagent. This may take place if the elimination of methanol had preceded the nucleophilic attack, as otherwise the Grignard reagent would encounter steric hindrance from the axially oriented methoxyl group at C-1. Thus, the Grignard reagent may have acted as a base first and then as a nucleophile, giving the glycal 20 with $\alpha$-arabino configuration. The melting point, $^1$H NMR spectrum and other relevant data were in close agreement with those recorded in the literature for this compound prepared by a different route. No glycal having the $\alpha$-ribo configuration was isolated. The $^{13}$C NMR spectrum of glycal 20 showed no OCH$_3$ signal at 55 ppm. The C-1 and C-2 resonances were observed at 142.36 ppm and 108.79 ppm, respectively, known to be typical for glycals.
Preparation of methyl 4-0-benzoyl-6-bromo-2,6-dideoxy-3-C-methyl-a-D-ribo-hexopyranoside (21). This compound was prepared by the procedure described by Dyong and Schulte\textsuperscript{204} in 80% yield. The physical constants and spectral data were in close agreement with the corresponding literature values.

Methyl 4-0-benzoyl-2,6-dideoxy-3-C-methyl-a-D-ribo-hex-5-enopyranoside (22). As the bromides 9 and 11 had afforded the desired dehydrobrominated products 10 and 12 in good yields on treatment with DBU in refluxing toluene, the same method was attempted to convert the bromide 21 into the 5,6-enopyranoside 22. Even after refluxing for more than 24 h, no change was observed, and all of the starting material 21 was recovered. The same observation was recorded when the solvent was changed either to benzene or HMPA. The reaction did not take place even when an eight times excess of DBU was used.

When anhydrous silver fluoride was employed to carry out the dehydrohalogenation of 21 in dry pyridine, the reaction was relatively slow but went to completion after stirring for 2-3 days at room temperature. After work-up and purification by column chromatography, white prisms of 22 were isolated in 65% yield.

These results may be rationalized on the basis of electronic effects and steric effects.
SCHEME 40

21

DBU
Toluene
reflux
No Reaction

DBU
HMPT, rt
No Reaction

DBU
Benzene
reflux
No Reaction

AgF
Pyridine

22
The elimination of HBr worked successfully for compounds 60, 9, and 11 in the presence of DBU with such solvents as toluene, benzene, or HMPA. This elimination could have taken place either by the $E_2$ or the $E_1CB$ process. DBU, being a good hindered base, was successful in abstracting the H-5 proton from 60, and even the sterically hindered H-5 proton of 9 and 11. Although compounds 9 and 11 have the same stereochemistry as compound 21, viz., the $\text{D-ribo}$ configuration, DBU was not successful in abstracting off the H-5 proton in bromide 21. This may be due to the fact that DBU would first abstract the more acidic $-\text{NHCOOR}$ and $-\text{OH}$ protons from these compounds. The negative charge thus generated could be delocalized in the acylamino group, but could not do the same when generated on the oxygen atom of the hydroxyl group. Thus, electronic repulsion, as well as steric crowding, could have kept DBU from abstracting the H-5 proton in 21 by not letting the base come into the vicinity of the diaxially hindered H-5, which in turn would prevent the reaction from taking place. When silver fluoride was used, the electrophilic pull generated by the affinity of silver for halides could have created a partial positive charge on C-6, which would bring the
transition-state energy lower and stabilize the intermediate. Also, small size of F\(^{-}\) would permit it to readily enter the cavity formed by the two diaxially oriented groups, and abstract the H-5 proton, and driving the reaction forward. Thus, the electrophilic pull by silver and the nucleophilic pull by fluoride could have assisted each other permitting the reaction to go to completion, rendering the desired hex-5-enopyranoside 22. Hence, it may be concluded that for dehydrohalogenations, DBU or other hindered bases may be used for the convenience of having a homogeneous reaction mixture, easy work-up procedures and less time requirements, at least when the molecule is not very demanding. However, the procedurally less convenient anhydrous silver fluoride procedure may come out superior when steric and electronic demands are greater, because of the dual role played by the reagent.

The \(^1\)H NMR as well as \(^{13}\)C NMR spectra of 22 were in accordance with the structure of a hex-5-enopyranoside. First of all, the absence of an H-5 proton in the \(^1\)H NMR spectrum revealed that the bromide 21 was no longer present. Also, the pseudo triplets observed for H-4 at 5.4 ppm and H-6 and H-6' at 4.75 and 4.63 ppm, respectively, had coupling constants of a typical allylic system, i.e., -1.5 Hz and -1.8 Hz. The signals for both the H-2 protons appeared together as a multiplet at 2 ppm, indicating that the \(^4\)C\(_1\) conformation of the compound 22 was not in a perfect chair form because of the presence of the exocyclic double bond. The carbon spectra showed the resonance for C-5 at 151.3 and C-6 at 100.42 ppm, i.e., in the C=C region. As expected, the intensity of C-5 was low because of its quaternary nature.
Figure 4. Partial $^1$H-NMR spectrum of methyl 4-$\text{O}$-benzoyl-2,6-dideoxy-3-$\text{O}$-methyl-$\alpha$-$\text{D}$-erythro-\-hex-5-enopyranoside (22).
Figure 5. 75 MHz, $^{13}$C-NMR spectrum of methyl 4-$\alpha$-benzoyl-2,6-dideoxy-3-$\alpha$-methyl-$\alpha$-$\beta$-erythro-hex-5-enopyranoside (22).
Methyl 2,6-dideoxy-3-\textsubscript{C}-methyl-\textsubscript{D}-ribo-hex-5-enopyranoside (23). The 4-\textsubscript{O}-benzoyl derivative 22 was saponified under the Zemplén's catalytic deacylation conditions involving a trace of sodium methoxide in dry methanol. The reaction was complete within 0.5 h at -25°. After neutralizing the mixture with H\textsuperscript{+} ion-exchange resins, solution was evaporated to a syrup that contained the desired enopyranoside 23, along with some polar impurities. The mixture was passed through a small bed of silica gel to afford 23 free from methyl benzoate and polar impurities, but the yield was very poor (-10%). As enol ethers of this type are known to be unstable, it is probable that compound 23 had polymerized or undergone self-addition to form different compounds. The reaction was also attempted at low temperatures, but similar results were obtained. The \textsuperscript{1}H NMR spectra recorded immediately after obtaining the compound from the column clearly showed the absence of aryl protons from a benzoyl group, and the H-4 signal had moved upfield to 3.8 ppm.

Reduction of the hex-5-enopyranoside 22. As the yields of saponification reaction could not be improved, the 4-\textsubscript{O}-benzoyl derivative 22 was subjected to hydrogenation directly, without de-esterifying the 4-\textsubscript{O}-benzoyl group. As may be seen from Scheme 41, when palladium-on-barium sulfate (10%) was used as the catalyst, no apparent conversion took place, even after 2 days, with an excess of catalyst, although the same catalyst had worked very well in the Horton-Weckerle's synthesis of daunosamine, affording stereospecifically the \textsubscript{L}-lyxo isomer as the only product. Palladium supported on a polymer did not work either, and hence palladium-on-charcoal (5%) was tried. The reaction
SCHEME 41
worked well, affording both of the possible 5-epimers, viz., the D-ribo derivative 24 (methyl 4-O-benzoyl-α-D-mycaroside) and the L-lyxo derivative 25 (methyl 4-O-benzoyl-3-C-methyl-β-L-lyxo-hexopyranoside) in the ratio of 1:2.4, respectively. When Raney nickel was used as the catalyst, the ratio of α-D-ribo derivative 24 to β-L-lyxo derivative 25 was found to be 1:3.5. Thus, instead of having 100% stereospecificity as obtained in the synthesis of daunosamine, a certain proportion of D-ribo derivative was also obtained, probably because of the orientation of the 3-C-methyl group which might have made the binding of the double bond to the catalyst surface from that side slightly hindered. According to the Brown-Brewster-Schecter Rule, the exocyclic double bond on the six-membered ring should flatten the ring in order to get the substituents on the sp² carbons coplanar. As a result, the 5,6-enoside 22 would not remain in a perfect chair conformation and the ring-flattening would cause the 3-C-methyl group to be in a pseudo-axial position in one of the possible conformers as shown in Figure 6.

![Possible preferred conformations of compound 22 leading to the formation of 24 and 25.](image-url)
This may result in some binding of the catalyst surface from the opposite face, giving the product with the \(\beta\)-ribo configuration after reduction. The two epimers thus obtained were readily separated by column chromatography affording 24 and 25, in pure form.

The \(^1\text{H}\) and \(^{13}\text{C}\) NMR spectra of the reduced products 24 and 25 were distinctly different. The fast-moving component 24 had all of its physical constants comparable to those recorded for methyl 4-0-benzoyl-\(\alpha\)-\(\beta\)-mycaroside. The resonance for H-4 at 4.8 ppm had \(J_{4,5} = 9.0\) Hz showing a diaxial relationship, in the \(\text{C}_1\) chair conformation. The signals for H-2's were well separated at 1.91 and 2.1 ppm, with small coupling constants of 4 and 1.5 Hz, respectively, indicating the H-1 proton to be in equatorial disposition. On the other hand, compound 25 showed its H-4 signal as a broad singlet at 4.9 ppm, while H-5 was a doubled quartet at 3.85 ppm with \(J_{4,5} = 1.1\) Hz. The very small coupling between H-4 and H-5 was indicative of them being \(\text{cis}\) oriented, with the dihedral angle approaching 90°. This is a typical observation made for many sugars having protons H-4 and H-5 oriented \(\text{cis}\) to each other.\(^\text{206}\)

The signal for H-1 was observed as a doublet of doublets which, being a part of a complex ABX system, would only give a value of \(J_{1,2a} + J_{1,2e} = 12.1\) Hz, which in turn is too large for the H-1 proton to be in an equatorial disposition. Thus, the \(^1\text{H}\) NMR spectra indicated that 25 was indeed the desired isomer having the \(\beta\)-\(\text{lyxo}\) configuration.
Figure 7. Partial $^1$H-NMR spectrum of methyl 4-Q-benzoyl-2,6-dideoxy-3-Q-methyl-$\beta$-L-lyxo-hexopyranoside (25).
Figure 8. Partial $^{13}$C-NMR spectrum of methyl 4-O-benzoyl-2,6-dideoxy-3-O-methyl-\(\alpha\)-D-ribo-\-hexopyranoside (24).
Figure 9. Partial 75-MHz, $^{13}$C-NMR spectrum of methyl 4-Ω-benzoyl-2,6-dideoxy-3-Ω-methyl-\(\beta\)-L-lyxo-hexopyranoside (25).
Table 11

\(^1\)H NMR Spectral Data for Compounds 3, 19, 20 and 21

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<th>Compound(^a)</th>
<th>H-1 (J_{1,2})</th>
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<th>H-2' (J_{1,2'})</th>
<th>H-4 (J_{4,5})</th>
<th>H-5 (J_{5,6})</th>
<th>H-6 (J_{6,6'})</th>
<th>H-6' (J_{5,6'})</th>
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<th>3-CH(_3)</th>
<th>PHCH</th>
<th>Aryl</th>
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<td>3.92 t (9.9)</td>
<td>4.38 dd</td>
<td>3.38 s</td>
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<td>4.33 dd (10.0)</td>
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\(^a\)In chloroform-d, with tetramethylsilane as the internal standard

\(^b\)Signal multiplicities; b, broadened; d, doublet; m, multiplet; q, quartet; s, singlet.
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<th>C-4</th>
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<th>C-6</th>
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<th>Ph-CH</th>
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<sup>a</sup>In chloroform-d.
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<th>H-2a (J₂ₑ-₂a)</th>
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<th>H-5 (J₅₆)</th>
<th>H-6 (J₆₆')</th>
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<td>2.16</td>
<td>5.5 t</td>
<td>---</td>
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<td>4.70 t</td>
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*In chloroform-d with tetramethyl silane as the internal standard.

*Signal multiplicities; b, broadened; d, doublet; m, multiplet; q, quartet; s, singlet; t, triplet.
Table 14

$^{13}$C NMR Spectral Data for Compounds 22, 24 and 25

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<th>C-3 (ppm)</th>
<th>C-4 (ppm)</th>
<th>C-5 (ppm)</th>
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<th>O-CH$_3$ (ppm)</th>
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<td>56.57</td>
<td>25.20</td>
<td>166.77</td>
<td>133.26</td>
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</table>

$^a$ in chloroform-d.
The $^{13}$C NMR spectrum of 25 showed the anomeric carbon resonance at 100.8 ppm, whereas the corresponding resonance for the D-ribo derivative 24 appeared at 98.5 ppm. The assignments for other carbon resonances were made using selective proton decoupling in a continuous wave mode. The $^{13}$C shift for C-4 was observed to be downfield of the C-5 resonance. The presence of an ester group, in this case benzoate, may have deshielded C-4 and at the same time, the $\beta$-carbons, viz., C-3 and C-5 would suffer an upfield shift as described by Bock and Pedersen.$^{99}$

Hydrolysis and acylation of the L-lyxo isomer 25. The methyl glycoside 25 was readily hydrolyzed to the free sugar by heating it with 40% acetic acid solution under reflux for 1 h. The aqueous solution was evaporated to dryness and treated with pyridine and acetic anhydride to give the corresponding acetate, which from $^1$H NMR spectrum was found to be predominantly the $\alpha$ anomer. The tertiary hydroxyl group at C-3 still remained free and did not undergo acetylation under these conditions. On using ten-fold excess of acetic anhydride, partial diacetylation was observed, which indicated that the tertiary hydroxyl group was accessible for protection if the right conditions were used. When the

---


CH
OMe
OH
OBz
25

40 % AcOH
reflux

DMAP, py.
Ac₂O

Ac₂O
pyridine

SCHEME 42
free sugar 26 or its monoacetate 27 was treated with pyridine and acetic anhydride in the presence of 4-dimethylaminopyridine, the diacetate was formed readily and was isolated as a syrup. As \( \text{L-\(p\)-nitrobenzoates} \) are known to be good intermediates for coupling reactions, this derivative was likewise prepared from 26 in excellent yields, using the same procedure as that used for the monoacetate 27. Again, the \( \beta \) anomer 29 was isolated as the major product in excellent yield (90%) as a white crystalline solid.

The \( ^1H \) NMR spectra of the free sugar 26 in CDCl\(_3\) had many overlapping signals, indicating the presence of more than one anomer in the syrup, but on acetylation or \( p\)-nitrobenzoylation under the conditions described above, the \( \beta \)-acyl derivative was obtained exclusively. The resonance for the anomeric proton of 27 was observed at 5.78 ppm as a doublet of doublets with the coupling constants of 10.5 Hz and 2.4 Hz, indicative of a diaxial relationship between H-1 and H-2a. Similarly, the anomeric proton of 29 gave a signal at 5.99 ppm as a doublet of doublets with the coupling constants of 10.5 and 2.5 Hz. Also, the signals for H-2a (axial) and H-2e (equatorial) were well separated and thus the first-order coupling constants could be easily calculated, which was not the case with the methyl \( \beta \)-glycoside 25. The diacetate 28 showed the resonance for H-2 protons shifted downfield by 0.4 ppm and for H-4 the downfield shift was 0.5 ppm. Also, the \( ^{13}C \) shift for C-3 in 28 was observed at 79 ppm, instead of 70 ppm when the tertiary hydroxy group was free in compound 27.

As the methyl glycoside 25 was hydrolyzed in the presence of refluxing acetic acid, the tertiary hydroxyl group could have potentially
Figure 10. Partial $^1$H-NMR spectrum of 1-O-acetyl-4-O-benzoyl-2,6-dideoxy-3-O-methyl-$\beta$-L-lyxo-hexopyranose (27).
Figure 10 (continued). Partial $^1$H-NMR spectrum of 1-O-acetyl-4-O-benzoyl-2,6-dideoxy-\textit{-3-O-methyl-$\beta$-L-hexopyranose} (27).
Figure 11. Partial $^1$H-NMR spectrum of 1-$\mathcal{O}$-(p-nitrobenzoyl)-4-$\mathcal{O}$-benzoyl-2,6-dideoxy-3-$\mathcal{O}$-methyl-$\beta$-$\mathcal{L}$-lyxo-hexopyranose (29).
Figure 12. Partial 75-MHz, $^{13}$C-NMR spectrum of 1-$\alpha$-acetyl-4-$\beta$-benzoyl-2,6-dideoxy-3-$\alpha$-methyl-$\beta$-L-hexopyranose (27).
Figure 13. Partial 75-MHz $^{13}$C-NMR spectrum of 1-O-(p-nitrobenzoyl)-4-O-benzoyl-2,6-dideoxy-3-O-methyl-$\beta$-L-lyxo-hexopyranose (29).
generated a carbonium ion at that center which could result in the inversion of that steric center. In order to verify the configuration of the 3-OH group, nuclear Overhauser effect (NOE) experiments were conducted with compound 27.

In the past, several different methods have been used to determine the configuration at the branch point of branched-chain sugars, ranging from making cuprammonium complexes\textsuperscript{207} to intramolecular ring-formation giving hemiacetal, aminal, isopropylidene acetate and others.\textsuperscript{239-242} Horton and coworkers\textsuperscript{243} showed the application of lanthanide shift reagents in the \textsuperscript{1}H NMR spectra, where the shift gradients of ring protons of a tertiary alcohol and the corresponding secondary alcohol were compared and thereby determine the configuration of the tertiary center in branched-chain sugars.

\begin{itemize}
\end{itemize}
As the NOE studies do not involve any chemical modifications or complexing agents, it was decided to utilize that method for determining the configuration at C-3.

Each of the proton signals were irradiated one after the other and the resulting change in the intensities of other signals were recorded. When the anomeric proton H-1 was irradiated, a strong positive NOE effect was observed for H-5 (8.31%), whereas H-2e gave a positive signal of 3.9% and the 3-ζ-methyl signal showed a positive effect of 4.59%. These results indicate that the 3-ζ-methyl, H-5 and H-2e are on the same side or in the vicinity of H-1. Irradiation of the H-4 proton gave positive signals for all the vicinal groups attached, viz., 3-ζ-methyl, 3-hydroxy, H-6-CH₃, and H-5. On irradiating H-5, the strong positive signal obtained for H-1 reinforced the β-configuration at the anomeric position. Also the positive signal for 3-ζ-methyl suggested that H-5, H-1 and 3-ζ-methyl groups are located in the neighborhood of each other, suggesting L-lyxo configuration. Positive effects were observed again for H-1, H-4, H-5, H-2e, and -OH group when the 3-ζ-methyl group was irradiated reinforcing the results obtained by irradiating H-1 and H-5. When the H-6 methyl group was irradiated, apart from H-4 and H-5, a
Figure 14. Partial $^1$H-NMR noe-difference spectrum of 1-O-acetyl-4-O-benzoyl-2,6-dideoxy-3-C-methyl-$\beta$-L-hexopyranose (27).
Table 15

$^1$H NMR Spectral Data for Compounds 27, 28 and 29

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*a* In chloroform-d with tetramethyl silane as the internal standard.

*b* Signal multiplicities; b, broadened; d, doublet; m, multiplet; q, quartet; s, singlet.
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$^a$In chloroform-d.
positive enhancement was observed for the -OH proton at 2.3 ppm, confirming the \( \text{L-lyxo} \) configuration of the molecule.

These results unambiguously indicate that no isomerization at the steric center C-3 took place during the acid hydrolysis of compound 25, and also confirm the stereospecific equatorial attack of the nucleophile when the ketone 3 was treated with methylmagnesium iodide.

The \(^{13}\)C NMR data for 1-O-acyl derivatives of 25 showed the anomeric C-1 resonance near 91 ppm, and not at 100-101 ppm as observed for their methyl \( \beta \)-glycosides. It has been noted\(^{226}\) earlier that methylation of a free hydroxy group causes a large downfield shift, whereas acylation causes a downfield shift of about only 1-4 ppm. However, for the diacetate 28, the shift observed for C-3 was 79.37 ppm, downfield by \(-9\) ppm from the C-3 resonance in the monoacetate 27.

**Coupling of daunomycinone with 1-O-acyl derivatives of 26.** The classical, Koenigs-Knorr\(^{244,245}\) method was first applied using the 1-O-acetyl derivative 27. This did not give the desired coupled product, and a mixture of polar components was formed. A milder method of converting the 1-O-acyl into the 1-bromo derivative with bromo trimethylsilane\(^{246}\) was applied to the 1-O-acetyl derivative 27. After work-up, t.l.c. indicated that all of the starting material had been consumed and four new spots were observed. On treating this intermediate with methanol in the presence of mercuric chloride and mercuric oxide, no methyl glycoside was detected. The same two methods as stated above were used to convert the 1,3-di-O-acetate 28 into its 1-halide derivatives, but similar results were observed. It seemed that
SCHEME 43
the 1-halide formed as the intermediate could have either eliminated, giving rise to a glycal that could have further polymerized. Also, the tertiary alcoholic group at C-3 might have reacted under acidic conditions, giving rise to a carbonium ion at that center which could have further reacted forming different products. Hence, a direct coupling procedure was tried where no 1-halide intermediate was required to be isolated, by employing trimethylsilyl trifluoromethanesulfonate which form a triflate at C-1, which in turn being a good leaving group could generate an oxocarbonium ion at C-1 with ease.


When the 1-O-acetyl derivative 27 was treated with trimethylsilyl triflate at -40°, and stirred while allowing it to reach -5°, the solution turned dark and all of the starting material was consumed. On addition of daunomycinone, no reaction took place, even after stirring for 24 h at room temperature, indicating that again the starting sugar had either reacted with itself or decomposed. No identifiable products could be isolated from the mixture.
When trimethylsilyl triflate was added to a mixture containing the 1-O-acetyl derivative and daunomycinone, two distinct spots were seen on t.l.c. at -5--0°C, indicating that coupling had taken place. Heating the reaction up to room temperature led to the conversion of the slow-moving component into the fast-moving component, which was obtained as the sole product after work-up. After isolation and purification, the product obtained was examined by $^1$H NMR spectroscopy. The spectrum did not show the signals for 4'-O-benzoyl, nor for 4'-H. Also, H-5' had moved downfield by more than 1 ppm. Hence, it was definitely not the desired coupled product. In the next attempt, the mixture was kept at -5--0°C for a period of 3 h, when the daunomycinone was converted only into the product having the lower $R_f$ value. On work-up and purification by preparative t.l.c., the product isolated showed all of the expected signals of a daunomycine glycoside in its $^1$H NMR spectrum. When the 1-O-p-nitrobenzoate 29 was used as the sugar for coupling reaction, similar results were obtained as above, with no apparent improvements on the yield of the coupled product. Much daunomycinone remained unreacted during this period of time, and this was recovered by preparative t.l.c. No improvement in the extent of the reaction was seen even if the mixture was kept at -5--0°C for 24 h to 48 h.

The $^1$H NMR spectrum of 52 showed the characteristic signals of phenolic hydroxyl groups at 14.05 and 13.32 ppm. The three aryl protons' resonances corresponding to the H-1, H-2 and H-3 of the aglycon were observed at 8.12, 7.40 and 8.05 ppm, respectively. The signal for anomeric proton H-1' was observed at 5.69 ppm as a doublet, with a coupling constant $J_{1',2} = 4.4$ Hz, indicative of the $\alpha$-linkage. Signals
for H-4' and H-5' were observed at 5.01 ppm as a singlet and 4.35 ppm as a quartet, respectively. Thus, there was no coupling observed between H-4' and H-5 which indicated that their dihedral angle must be 90°.
The signal for H-7 of the aglycon was observed as a doublet of doublets at 5.31 ppm, and that of HO-9 was observed as a singlet at 4.42 ppm. The doublet corresponding to H-6' methyl group was observed at 1.3 ppm and the 3-C-methyl signal was observed at 1.45 ppm. Thus, all the characteristic signals of both components of the coupled product were observed within the expected range for their corresponding chemical shifts. Formation of ~8% of β-anomer was observed from the $^1$H NMR spectral analysis.

The UV spectrum of 52 showed the typical $\lambda_{max}$ values for the chromophore at 220, 230, 238, 254, 286, 500, and 538 nm. Attempts to observe the $M^+ + 1$ signal by FAB and CI mass-spectral analysis were unsuccessful. The FAB mass-spectrum showed the signals for $MH^+ -$ glycon, $MH^+ -$ aglycon, and other characteristic signals generated from the fragmentation of these components.

Thus, all these data supported the proposed structure of 52 as the desired coupled product. Efforts are underway to prepare larger quantities of 52 in order to complete its characterization and hydrolyze it to get the final drug for biological testing.
Figure 15. $^1$H-NMR spectrum of 7-$\Omega$-(4-$\Omega$-benzoyl-2,6-dideoxy-3-$\Omega$-methyl-$\alpha$-$\beta$-lyxo-hexopyranosyl) daunomycinone (52).
Figure 16. Partial $^1$H-NMR spectrum of 7-Ω-(4-Ω-benzoyl-2,6-dideoxy-3-Ω-methyl-α-Ω-lyxo-hexopyranosyl) daunomycinone (52).
Conclusion:

Thus, the benzoyl derivative of the 3-hydroxy-3-\(\alpha\)-methyl analog of daunosamine, viz., 4-\(\Omega\)-benzoyl-2,6-dideoxy-3-\(\zeta\)-methyl-\(\alpha\)-lyxo-hexopyranose was prepared from methyl \(\alpha\)-\(\zeta\)-mannopyranoside in 15\% overall yield. The Horton-Weckerle route to synthesize daunosamine with minor modifications proved to be versatile enough to accommodate the synthesis of such unusual molecules. Although the sugar analog of daunosamine was prepared in a good overall yield, its coupling reaction with daunomycinone did not work as well as expected. Hence, if the biological tests performed with the unprotected coupled product of 52 shows some promise, then routes to synthesize the final coupled product in better yield may need to be investigated.
Synthesis of 5-thiodaunosamine. As already described earlier in the introduction, a sulfur atom in the sugar ring instead of oxygen in a sugar may change the properties of the parent sugar-containing drug drastically. The bond lengths along C-1--S--C-5 are then larger and also the rate of hydrolysis\textsuperscript{156} of the acetal linkage (the anomeric bond), would be higher. Hence it was decided to attempt the preparation of 5-thiodaunosamine and attach it to daunomycinone and comparing the biological activity of this conjugate with that of the parent drug.

Several possible routes may be envisaged to synthesize 5-thiodaunosamine. The route chosen for the present investigation was based upon two guidelines. First, a route having a minimum number of steps and starting with a readily available starting material; second, the application of established procedures giving promise of high yields of products with easy work-up and separation procedures.

As may be seen from Scheme 44, on following the retrosynthetic pathway, an $S_N^2$ substitution with inversion at C-5 with thioacetate on a $\text{D}$-ristosamine derivative could lead to the desired product. $\text{D}$-Ristosamine, as may be recalled, was prepared in excellent yields by Horton and coworkers\textsuperscript{42} starting from methyl $\alpha$-$\text{D}$-mannopyranoside. Hence $\text{D}$-ristosamine with suitable protective groups was first prepared, using the same route with slight modifications.
5 -- Thiodaunosamine

SCHEME 44

D -- Ristosamine
Synthesis of 4-O-Benzoyl-2,3,6-trideoxy-3-trifluoroacetamido-D-ribo-
hexose (4-O-benzoyl-3-trifluoroacetamido-D-ristosamine, 32). Methyl 3-
amino-4,6-O-benzylidene-2,3-dideoxy-a-D-ribo-hexopyranoside (5) was
prepared in good yield, as already described earlier. The free amino
sugar was protected by N-trifluoroacetylation, using the procedure of
Arcamone and coworkers. A solution of the 3-trifluoroacetamido
derivative 8 in carbon tetrachloride was treated with N-bromosuccinimide
in the presence of barium carbonate to afford the 4-O-benzoyl-6-bromo
derivative 11 in 65-70% yield as white crystals. This was then
subjected to hydrogenolysis, using Raney nickel catalyst in the presence
of triethylamine acting as an acid scavenger. The D-ristosamine
glycoside 31 obtained as a syrup in 92% yield was hydrolyzed to the
corresponding free sugar 32 by refluxing it with 40% acetic acid for 8-
12 h. As these compounds (31 and 32) were new derivatives
of D-ristosamine, a small amount of each was purified by column
chromatography and the relevant physical constants were recorded. In an
attempt to purify the free sugar 32 by vacuum distillation, it was found
that the distillate thus obtained had undergone pyrolytic elimination,
leading to the corresponding glycal 33.

The $^1$H and $^{13}$C NMR spectra of compounds 31, 32, and 33 matched
closely to those of similar compounds. The multiplet seen for H-5 of
the 6-bromo derivative 11 had changed into a doublet of quartets for the
reduction product 31. The H-6 doublet of doublets of 11 had moved
upfield to 1.27 ppm and was observed as a sharp doublet. The H-1 proton
of 32 (the free sugar obtained after hydrolysis) showed a doublet at 5.3
ppm with a coupling constant of 2 Hz, which indicated that only the $\alpha$
SCHEME 45

4 \xrightarrow{\text{Al / Hg, EtOH}} 5 \xrightarrow{(\text{CF}_3\text{CO})_2\text{O, Et}_3\text{N}} 8

TFA = \text{COCF}_3

\text{NBS, CCl}_4 \rightarrow 9 \xrightarrow{\text{Ra - Ni, H}_2} 31

155
Figure 17. Partial $^1$H-NMR spectrum of methyl 4-O-benzoyl-6-bromo-2,3,6-trideoxy-3-trifluoroacetamido-$\alpha$-D-ribo-hexopyranoside (11).
Figure 18. Partial $^1$H-NMR spectrum of methyl 4-$\text{O}$-benzoyl-2,3,6-trideoxy-3-trifluoroacetamido-$\text{O}$-$\text{O}$-$\text{nbo}$-hexopyranoside (31).
Figure 19. 75-MHz, $^{13}$C-NMR spectrum of methyl 4-\(\beta\)-benzoyl-6-bromo-2,3,6-trideoxy-3-trifluoroacetamido-\(\alpha\)-\(\beta\)-hexopyranoside (11).
Figure 20. 50-MHz, $^{13}$C-NMR spectrum of 4-$\alpha$-benzoyl-2,3,6-trideoxy-3-trifluoroacetamido-$\alpha$-D-ribo-hexopyranose (32).
Table 17

\textsuperscript{1}H NMR Spectral Data for Compounds 31-33

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\textsuperscript{a}In chloroform-d\textsubscript{6}, with tetramethylsilane as the internal standard.

\textsuperscript{b}Signal multiplicities: b, broadened; d, doublet; m, multiplet; q, quartet; s, singlet.
Table 18

$^{13}$C NMR Spectral Data for Compounds 31-33

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$^a$In chloroform-d.
anomer was present in the deuterated chloroform solution of 32. The glycal 33 showed two characteristic doublets (at 6.54 and 4.78 ppm). The $^{13}$C NMR spectrum of 31 showed the C-6 resonance at 17.7 ppm, i.e., upfield by ~15 ppm from the 32.3 ppm observed for the bromide 11. Also, the $\text{-NHCOCF}_3$ group showed two quartets at 115.8 and 157 ppm, corresponding to $\text{-CF}_3$ and C=O carbons respectively, the multiplicity being due to the C-F coupling. The coupling constants for C-F were found to be 286 Hz for the $\alpha$-carbon, i.e., the CF$_3$ group and 36 Hz for the $\beta$-carbon, i.e., the CO group.

Ethanethiolysis of the D-ristosamine derivative 32. The classic procedure for preparing dithioacetals of free sugars devised by Emil Fischer$^{248}$ was used in modified form to obtain the diethyl dithioacetal of 32 by dissolving 32 in ethanethiol and adding a catalytic amount of hydrochloric acid at 0°. Although the reaction was carried out at this low temperature, formation of 1-thioglycosides of 32, i.e., 36 and 37, as by-products could not be entirely suppressed. The reaction did not progress at all at temperatures below -10°, whereas between -10° and -5° it was extremely slow. Similar results were obtained when H$^+$ ion-exchange resin was used as the catalyst. It has been suggested$^{249}$ that

248. E. Fischer, Ber. 27 (1894), 673-679.
Scheme 46
the formation of dithioacetals occurs under kinetic control. Allowing the reaction to proceed for longer periods of time essentially produces the thermodynamic equilibrium; thioglycosides are also formed along with the dithioacetal in a ratio dependent on the thermodynamic stabilities of these components. As may be observed from Figure 21, the dithioacetal may undergo nucleophilic attack by the oxygen atom at C-5, resulting in the formation of a 1-thioglycoside with expulsion of ethanethiol. It was thus of interest to examine what would happen if 1,3-propanedithiol was used instead of ethanethiol. In principle, this should suppress the formation of 1-thioglycoside, as the dithioacetal now forms a six-membered ring which should be thermodynamically more stable. When that reaction was attempted, again a mixture of thioglycosides and dithioacetal was obtained. As ethanethiol was easier to handle than 1,3-propanedithiol, it was decided to go along with the diethyl dithioacetal of 32.

After chromatographic separation of 1-thioglycosides from the mixture, it was observed that the spot on t.l.c. corresponding to the dithioacetal actually was a mixture of two dithioacetals, viz., the 4-O-benzoyl diethyl dithioacetal (34) and the 5-O-benzoyl diethyl dithioacetal 35, in the ratio 10:1 respectively. This migration of acyl groups under acidic conditions is quite well-known.250-253
The two diethyl dithioacetals 34 and 35 were not easy to separate by conventional column chromatography and hence, for analytical purposes, they were separated by HPLC. The $^1$H NMR spectra of these diethyl dithioacetals 34 and 35 showed the resonance for H-4 at 4.98 and 3.96 ppm, respectively, indicating that the benzoyl was present on HO-4.
Figure 22. Partial $^1$H-NMR spectrum of 4-$O$-benzoyl-2,3,6-trideoxy-3-trifluoroacetamido-$\beta$-ribo-hexose diethyl dithioacetal (34).
Figure 23. Partial $^1$H-NMR spectrum of 5-$\beta$-benzoyl-2,3,6-trideoxy-3-trifluoroacetamido-$\beta$-ribo-hexose diethyl dithioacetal (34).
Figure 24. Partial $^1$H-NMR spectrum ethyl 4-$\beta$-benzoyl-2,3,6-trideoxy-3-trifluoroacetamido-1-thio-$\alpha$-$\beta$-hexopyanoside (36).
Figure 25. Partial $^1$H-NMR spectrum ethyl 4-$\text{O}$-benzoyl-2,3,6-trideoxy-3-trifluoroacetamido-1-thio-$\beta\text{-D-ribo}$-hexopyranoside (37).
Figure 26. Partial 50-MHz, $^{13}$C-NMR spectrum of 4-$\alpha$-benzoyl-2,3,6-trideoxy-3-trifluoroacetamido-$\alpha$-ribo-hexose diethyl dithioacetal (34).
Figure 27. Partial 75-MHz, $^{13}$C-NMR spectrum of 5-$\Omega$-benzoyl-2,3,6-trideoxy-3-trifluoroacetamido-$\beta$-D-ribo-hexose diethyl dithioacetal (34).
Figure 28. Partial 50-MHz, $^{13}$C-NMR spectrum ethyl 4-$\beta$-benzoyl-2,3,6-trideoxy-3-trifluoroacetamido-1-thio-$\beta$-D-ribo-hexopyranoside (37).
Table 19

$^1$H NMR Spectra Data for Compounds 34-37

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<td>2.06 ddd (14.9)</td>
<td>4.9 m (3.1, 9.4)</td>
<td>4.98 dd (3.4)</td>
<td>4.08 m (6.4)</td>
<td>1.36 d (8.3)</td>
<td>7.31 d (6.4)</td>
<td>2.58 q (6.4)</td>
<td>1.26 t (8.3)</td>
<td>8.06-7.44</td>
</tr>
<tr>
<td>35</td>
<td>3.78 dd (5.5)</td>
<td>--- 2.18 m (8.5)</td>
<td>4.54 m (4.3)</td>
<td>3.96 bs (6.4)</td>
<td>5.16 m (6.4)</td>
<td>1.48 d (8.7)</td>
<td>7.12 d (6.4)</td>
<td>2.60 q (6.4)</td>
<td>1.19 t (8.5)</td>
<td>8.05-7.43</td>
<td></td>
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<tr>
<td>36</td>
<td>5.41 dd (1.5)</td>
<td>2.55 m (6.1)</td>
<td>2.04 m (16.1)</td>
<td>4.78 m (4.4)</td>
<td>4.97 dd (4.2)</td>
<td>4.35 dq (9.6)</td>
<td>1.29 d (6.2)</td>
<td>7.81 bd (1.9)</td>
<td>2.65 dq (6.4)</td>
<td>1.33 t (4.2)</td>
<td>7.97-7.38</td>
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<td>2.28 dt (14.5)</td>
<td>4.69 m (3.3)</td>
<td>4.98 dd (4.3)</td>
<td>3.88 dq (9.6)</td>
<td>1.34 d (6.2)</td>
<td>6.59 bs (6.2)</td>
<td>2.76 dq (6.2)</td>
<td>1.32 t (4.2)</td>
<td>7.97-7.40</td>
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</tbody>
</table>

*aIn chloroform-d$_2$ with tetramethylsilane as the internal standard.

*bSignal multiplicities; b, broadened; d, doublet; m, multiplet; q, quartet; s, singlet.
Table 20

13C NMR Spectral Data for Compounds 34-37

<table>
<thead>
<tr>
<th>Compound</th>
<th>C-1</th>
<th>C-2</th>
<th>C-3</th>
<th>C-4</th>
<th>C-5</th>
<th>C-6</th>
<th>SCH₂CH₃</th>
<th>SCH₂CH₃</th>
<th>Aryl</th>
<th>CF₃</th>
<th>COCF₃</th>
<th>COPh</th>
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<td>49.59</td>
<td>79.10</td>
<td>67.27</td>
<td>19.30</td>
<td>24.52</td>
<td>14.07</td>
<td>128.2</td>
<td>115.82</td>
<td>157.21</td>
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<td>75.25</td>
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<td>24.69</td>
<td>14.22</td>
<td>128.19</td>
<td>115.91</td>
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<td>166.75</td>
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<td>77.52</td>
<td>35.04</td>
<td>47.44</td>
<td>72.36</td>
<td>71.58</td>
<td>18.36</td>
<td>24.86</td>
<td>14.96</td>
<td>128.59</td>
<td>115.06</td>
<td>157.21</td>
<td>163.15</td>
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<tr>
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<td>77.05</td>
<td>33.58</td>
<td>45.21</td>
<td>72.30</td>
<td>62.86</td>
<td>17.41</td>
<td>25.15</td>
<td>14.49</td>
<td>128.4</td>
<td>115.09</td>
<td>157.28</td>
<td>163.21</td>
</tr>
</tbody>
</table>

*In chloroform-d.
in 34, whereas HO-4 was free in compound 35. Alternatively, the resonance for H-5 was observed at 4.08 ppm for 34 and at 5.16 ppm for compound 35, as a quintet confirming the presence of a benzoyl group on HO-5 in 35. Also, the methyl and methylene groups of the thioacetal gave rise to two groups of quartets and triplets at ~2.6 and 1.2 ppm, indicating that the two ethylthio groups were in different magnetic environments. The H-1 resonance was observed at ~3.8 ppm for both compounds; it was a doublet of doublets due to the presence of two ethylthio groups on C-1, which may have some shielding effect. The $^{13}$C NMR spectra for the dithioacetals showed the C-1 resonances at 48 ppm, whereas the thioglycosides had the C-1 resonances at -77 ppm. Thus, the shielding effect caused by sulfur atoms on C-1 could be observed very well in all these examples.

p-Toluenesulfonylation of the dithioacetals 34 and 35. The mixture of dithioacetals 34 and 35, when treated with 5 equivalents of p-tolylsulfonyl chloride in the presence of pyridine, only the 4-O-benzoyl derivative 34 was p-tolylsulfonylated at the 5-position; the 5-O-benzoyl derivative 35 remained unreacted, even after 48 h of stirring at room temperature. As the mobility of the 5-O-p-tolylsulfonyl derivative 38 was much more than that of the 5-O-benzoyl derivative 35 on silica gel, the two compounds could be easily separated by column chromatography. Furthermore compound 35, which remained unreacted, thus could be obtained in pure form in larger quantities.

The $^1$H and $^{13}$C NMR spectra of the 5-O-p-tolylsulfonyl derivative 38 were in accordance with the proposed structure. As expected, the H-5
proton resonance was observed at 4.9 ppm as a doublet of quartets. It was interesting to note that the signal for H-5, which otherwise showed a quintet with the coupling constant of 6.4 Hz because of the C-6 methyl group and H-4 as the vicinal protons for 34 and 35, now showed a distinct doublet of quartets, probably because of restricted rotation of the C-4--C-5 bond, as two bulky groups may be too sterically hindered to cross over for rotation. Thus the dihedral angles may no longer be able to be averaged out, leading to an observed quintet with the same coupling constant for H-4--H-5 and H-5--H-6.

Displacement of the 5-O-p-tolylsulfonyloxy group of the dithioacetal 38. When the 5-O-p-tolylsulfonyl derivative 38 was treated with potassium thioacetate in N,N-dimethylformamide and the mixture heated to 100°, a product having a very high mobility on silica gel plates was formed and was eluted with 6:1 toluene--acetone. After isolation and purification by column chromatography, this compound (39) on 1H NMR spectral analysis showed the absence of the 5-O-p-tolylsulfonyloxy group. At the same time, there were no signs of a signal for thioacetate group near 2.3 ppm as expected. Most of the other signals remained at the same place with the exception of the H-3 resonance, which had moved upfield by -0.7 ppm to 4.77 ppm, and the shape of the multiplet had changed. Also, the doublet of quartets for H-5 at 4.5 ppm had a different coupling constant with H-4 than that of the precursor. The most remarkable point was the absence of an -NH proton resonance in the 1H NMR. The 13C NMR spectrum showed carbonyl resonance for the COCF₃ group at 147 ppm which is in the range for C=O groups. From these
CH(SEt)_2 - CH(SEt)_2
   \[\begin{array}{c}
   \text{CH}_2 \\
   \text{HCNHCOCF}_3 \\
   \text{HCOBz} + \\
   \text{HCOH} \\
   \text{CH}_3
   \end{array} \]

34 + 35

\[\text{TsCl} \quad \text{Pyridine} \]

HCOBz + 35
HCOH
CH(Ts)

CH(SEt)_2
   \[\begin{array}{c}
   \text{CH}_2 \\
   \text{HCNHCOCF}_3 \\
   \text{HCOOCH}_3
   \end{array} \]

38

NaOMe
MeOH

KSAc
DMF

CH(SEt)_2
   \[\begin{array}{c}
   \text{CH}_2 \\
   \text{HCNHCOCF}_3 \\
   \text{HCOH} \\
   \text{CH}_3
   \end{array} \]

40

39

SCHEME 47
lines of evidence, it may be concluded that the compound 38 was an oxazine derivative formed by intramolecular displacement reaction rather than the $S_N2$ displacement with thioacetate anion, as shown in Figure 29.

This kind of internal oxazine or oxazoline ring formation by the acylamino groups has been observed in many different instances.\textsuperscript{255-257} Hence, in order to compete with this intramolecular displacement by oxygen of the trifluoroacetyl group, a better nucleophile (thiocyanate anion) was used, but again the same results were obtained. Even when a crown ether, or HMPA were used, no apparent change was observed; t.l.c. analysis still showed the same spot corresponding to the oxazine derivative 39.
Figure 30. $^1$H-NMR spectrum of 4-$Q$-benzoyl-5-$Q$-(p-tolylsulfonyl)-2,3,6-trideoxy-3-trifluoroacetamido-$D$-ribo-hexose diethyl dithioacetal (38).
Figure 31. $^1$H-NMR spectrum of the oxazine 39.
Figure 32. Partial $^{13}$C-NMR spectrum of 4-O-benzoyl-5-O-(p-tolylsulfonyl)-2,3,6-trideoxy-3-trifluoroacetamido-D-ribo-hexose diethyl dithioacetal (38).
Figure 33. Partial 50-MHz, $^{13}$C-NMR spectrum of the oxazine 39.
<table>
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<tr>
<th>Compound&lt;sup&gt;a&lt;/sup&gt;</th>
<th>H-1 (J&lt;sub&gt;1,2&lt;/sub&gt;)</th>
<th>H-2 (J&lt;sub&gt;1,2&lt;/sub&gt;)</th>
<th>H-2' (J&lt;sub&gt;2,3&lt;/sub&gt;)</th>
<th>H-3 (J&lt;sub&gt;2,3&lt;/sub&gt;)</th>
<th>H-4 (J&lt;sub&gt;3,4&lt;/sub&gt;)</th>
<th>H-5 (J&lt;sub&gt;4,5&lt;/sub&gt;)</th>
<th>H-6 (J&lt;sub&gt;5,6&lt;/sub&gt;)</th>
<th>NH</th>
<th>SCH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;</th>
<th>SCH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;</th>
<th>Aryl</th>
<th>pTs-CH&lt;sub&gt;3&lt;/sub&gt;</th>
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<tbody>
<tr>
<td>38</td>
<td>3.77 dd (4.5)</td>
<td>2.27 ddd (9.7)</td>
<td>2.04 ddd (15.1)</td>
<td>4.77 m</td>
<td>5.09 t (4.1)</td>
<td>4.90 dq (4.1)</td>
<td>1.42 d (6.5)</td>
<td>7.46</td>
<td>2.62 q</td>
<td>1.24 t</td>
<td>7.33</td>
<td>2.41 s</td>
</tr>
<tr>
<td>39</td>
<td>4.20 dd</td>
<td>---</td>
<td>2.03 m</td>
<td>4.14 m</td>
<td>5.18 t (2.4)</td>
<td>4.54 dq (2.2)</td>
<td>1.42 d (6.5)</td>
<td>---</td>
<td>2.72 q</td>
<td>1.29 t</td>
<td>8.02</td>
<td>---</td>
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<td>---</td>
<td>2.2 m</td>
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<td>1.31 d (6.2)</td>
<td>7.48 d</td>
<td>2.69 q</td>
<td>1.26 t</td>
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<sup>a</sup>In chloroform-<d>, with tetramethylsilane as the internal standard.

<sup>b</sup>Signal multiplicities; b, broadened; d, doublet; m, multiplet; q, quartet; s, singlet.
Table 22

$^{13}$C NMR Spectral Data for Compounds 38, 39 and 40

<table>
<thead>
<tr>
<th>Compound</th>
<th>C-1</th>
<th>C-2</th>
<th>C-3</th>
<th>C-4</th>
<th>C-5</th>
<th>C-6</th>
<th>SCH₂CH₃</th>
<th>SCH₂CH₃</th>
<th>Aryl</th>
<th>CF₃</th>
<th>COCF₃</th>
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<td>69.29</td>
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<td>24.17</td>
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<td>14.48</td>
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<tr>
<td>40</td>
<td>48.11</td>
<td>35.78</td>
<td>51.07</td>
<td>76.59</td>
<td>68.54</td>
<td>19.13</td>
<td>24.68</td>
<td>24.26</td>
<td>14.22</td>
<td>115.86</td>
<td>157.40</td>
<td></td>
</tr>
</tbody>
</table>

---

*a* In chloroform-<d>
As the dithioacetal derivative 38 could not be converted into the desired 5-thiodaunosamine by this route, a different strategy had to be used which would keep the acylamino group far from C-5. The easiest way to do that was to form a furanoside ring, which would keep the two groups in trans configuration as shown in Figure 34.

![Figure 34. Furanoside derivatives of D-Ristosamine.](image-url)
As discussed earlier, these kinds of $S_N^2$ displacements on furanoses have already been utilized for preparing 5-thio sugars.157-160 Another advantage of proceeding via the furanose route was the utilization of the 5-0-benzoyl derivative 35, together with the 4-0-benzoyl diethyl dithioacetal 34, as may be seen from Scheme 48.

Deesterification of diethyl dithioacetals 34 and 35 to give 2,3,6-trideoxy-3-trifluoroacetamido-\(\beta\)-ribo-hexose diethyl dithioacetal (40). The mixture of dithioacetals 34 and 35 was deprotonated by Zemplén's conditions for transesterification, i.e., with a trace of sodium methoxide in methanol. Removal of ester groups was complete within 0.5 h at room temperature. After neutralization with $H^+$ ion-exchange resins and filtration, the methanolic solution was evaporated to a syrup that crystallized from ethyl acetate--hexane to give white crystals of the diethyl dithioacetal 40. Recrystallization afforded pure 40 in ~80% yield.

The $^1H$ NMR spectra of 40 showed the absence of aryl protons. The signals for H-1, H-4, and H-5 were all observed in the region of 3-5 ppm as overlapping multiplets. The $^{13}C$ NMR spectra showed a small upfield shift for C-4 at 76.6 ppm as compared to 79.1 ppm observed for its precursor. The $^{13}C$ signal assignment was made by selective decoupling of the resonances in a coupled spectra. Also, it was very interesting to note the $\alpha$- and $\beta$-effects of esterification when the $^{13}C$ NMR spectrum of 40 was compared with those of its precursors 34 and 35. The $^{13}C$ resonances for C-3, C-4 and C-5 for 40 were observed at 51, 76.6, and 68.6 ppm, respectively. In the $^{13}C$ NMR spectrum of the 4-0-benzoyl
Figure 35. Partial $^1$H-NMR spectrum of 2,3,6-trideoxy-3-trifluoroacetamido-D-ribo-hexose diethyl dithioacetal (40).
Figure 36. Partial $^{13}$C-NMR spectrum of 2,3,6-trideoxy-3-trifluoroacetamido-D-ribo-hexose diethyl dithioacetal (40).
derivative 34, the resonance of C-3, C-4 and C-5 were observed at 49.6, 79.1 and 67.3 ppm, respectively. The upfield shifts of C-3 and C-5 by -1.5 ppm and downfield shift of C-4 by -2.5 ppm clearly indicated the α- and β-carbon effects of esterification. In comparable manner, the $^{13}$C NMR shifts for C-3, C-4, and C-5 for the 5-0-benzoyl derivative 34 were observed at 50.7, 75.3, and 71.3 ppm, respectively. Again C-5 had moved downfield by -3 ppm, whereas C-4 had moved upfield by -1.3 ppm. Also, the C-6 signal had moved upfield from 19.1 to 16.2 ppm, attributable to the β-effect.

Methyl 2,3,6-trideoxy-3-trifluoroacetamido-α- and β-0-ribo-hexofuranoside (41 and 42). When the diethyl dithioacetal 40 was treated with mercuric chloride and mercuric oxide in the presence of methanol, demercaptalation took place, affording the furanosides 41 and 42 in almost 80% yield. The work-up consisted of making a mercuric chloride—pyridine complex which would remain insoluble whereas the product would be soluble in water. This procedure separates out the mercuric chloride, which is highly soluble in organic solvents. An attempt was made to separate mercuric salts by dissolving them in 30% potassium iodide solution and extracting out the product with dichloromethane, but as the product was soluble in water, the yields were poor, even after proceeding through 5-10 extractions. Recently, Szarek and coworkers...
Scheme 48

\[
\begin{align*}
\text{CH (SEt)}_2 & \quad \text{HgO, HgCl}_2 \\
\text{CH}_2 & \\
\text{HCNHCOCOF}_3 & \quad \text{MeOH} \\
\text{HCOH} & \\
\text{HCOH} & \\
\text{CH}_3 & \\
\textbf{40} & \quad \text{H}_3\text{C}=\text{VSO}_2
\end{align*}
\]

Ts = H$_3$C—C=S—O$_2$

\[
\begin{align*}
\text{H}_3\text{COH} & \\
\text{H}_3\text{COH} & \\
\text{CH}_3 & \\
\text{NHTFA} & \\
\text{41} & +
\end{align*}
\]

\[
\begin{align*}
\text{H}_3\text{COH} & \\
\text{TsO—C—H} & \\
\text{NHTFA} & \\
\text{43} & +
\end{align*}
\]

TS = H$_3$C—C=S—O$_2$

\[
\begin{align*}
\text{H}_3\text{COH} & \\
\text{TsO—C—H} & \\
\text{NHTFA} & \\
\text{44} &
\end{align*}
\]
have suggested the use of 5% iodine in methanol to hydrolyze dithio-acetals instead of using mercuric salts. When an attempt was made to prepare the furanosides 41 and 42 by this method, a mixture of products was obtained which could not be readily identified. On acetylation of this mixture, definite signals were observed for a mixture of furanosides as well as pyranosides. Hence that method was not further pursued.

The mixture of furanosides 41 and 42 was put on a column of silica gel. Elution with chloroform gave first the α-furanoside 41, followed by the β-furanoside. Both furanosides were obtained as crystalline solids and were characterized by $^1$H NMR and $^{13}$C NMR and by microanalysis. Assignment of configuration at C-1 for the α-furanoside 41 and the β-furanoside 42 was made by using Hudson's rule of isorotation. (The H-1 signals were almost coincident at 5.1 ppm.) Hudson's rule states that, in D-sugars, the rotation of α-glycoside is always more positive than that of the β-glycoside whereas in L-sugars, it is more negative. The specific rotation of the first fraction, compound 40, was +45.5° in chloroform whereas that of the second fraction, i.e., 41 was observed to be -91° in chloroform. Hence compound 40 was indeed
the α-glycoside and 41 was the β-glycoside. The anomeric proton resonance for 40 showed a doublet ($J_{1',2} = 4.3$) at 5.14 ppm, whereas that of 41 showed a doublet of doublets at 5.12 ppm with coupling constants of 1.6 and 5.6 Hz. Correspondingly, the H-2 signals also showed a doublet of doublets for 41 and doublet of doublets of doublets for 42. The $^{13}$C NMR spectra of 41 and 42 were very similar, with C-1 resonances at 105 ppm and C-4 resonances at 90 and 89 ppm, respectively, which are characteristic of furanoside derivatives. Although these two compounds 41 and 42 were prepared by El Khadem and coworkers by a different method, their physical constants and other relevant data were not reported.

5-0-p-Toluenesulfonylation of furanosides 41 and 42. When the furanosides 41 and 42 were subjected to 5-0-p-toluenesulfonylation in pyridine, it took about 30 h for the reaction to go to completion. After the usual work up procedures, the tosylate 43 obtained from the α-furanoside 41 afforded a white crystalline product, whereas its β-anomer 44 obtained from the furanoside 42 was isolated as a syrup that was further purified by column chromatography. Both the p-toluenesufonates were obtained in excellent yields (~95%).

The $^1$H NMR spectra of 43 and 44 showed very similar resonances for H-1, H-2's, H-3, and H-6 to those of their precursors. The H-5 proton signal for 43 was observed downfield at 4.77 ppm as a doublet of a quartet, which collapsed to a doublet when the H-6 resonance was saturated by irradiation. Similarly, the H-5 proton resonance for 44 was observed downfield at 4.55 ppm as a quintet which too collapsed to a
Figure 37. Partial $^1$H-NMR spectrum of methyl 2,3,6-trideoxy-3-trifluoroacetamido-$\beta$-D-ribo-hexofuranoside (42).
Figure 38. Partial $^1H$-NMR spectrum of methyl 2,3,6-trideoxy-3-trifluoroacetamido-5-O-(p-tolylsulfonyl)-$\alpha$-$\beta$-D-ribo-hexofuranoside (43).
Figure 39. Partial $^1$H-NMR spectrum of methyl 2,3,6-trideoxy-3-trifluoracetamido-5-O-(p-tolylsulfonyl)-
-β-D-ribo-hexofuranoside (44), with irradiation at 1.3 ppm (H-6) in the inset.
Figure 40. Partial $^{13}$C-NMR spectra of 2,3,6-trideoxy-3-trifluoroacetamido-$\alpha$- and $\beta$-D-ribo-hexofuranosides (41) and (42).
Figure 41. Partial $^{13}$C-NMR spectra of 2,3,6-trideoxy-3-trifluoracetamido-5-O-(p-tolysulfonyl)-
-$\alpha$- and $\beta$-D-fuco-hexofuranosides (43) and (44).
Table 23

$^1$H NMR Spectral Data for Compounds 41-44

<table>
<thead>
<tr>
<th>Compound</th>
<th>H-1 (J$_{1,2}$)</th>
<th>H-2 (J$_{2,2'}$)</th>
<th>H-2' (J$_{1,2'}$)</th>
<th>H-3 (J$_{2,3}$)</th>
<th>H-4 (J$_{3,4}$)</th>
<th>H-5 (J$_{4,5}$)</th>
<th>H-6</th>
<th>OCH$_3$</th>
<th>NH</th>
<th>Aryl</th>
<th>O-CH$_3$</th>
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<td>3.76 dd (2.3)</td>
<td>3.9 m (3.9)</td>
<td>1.27 d (6.5)</td>
<td>3.39 s</td>
<td>7.1 bd</td>
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<td></td>
</tr>
<tr>
<td>42</td>
<td>5.12 dd (1.6)</td>
<td>2.49 ddd (13.8)</td>
<td>2.08 ddd (5.6)</td>
<td>4.67 m (6.6, 8.0)</td>
<td>3.81 t (4.4)</td>
<td>3.89 dq (4.5)</td>
<td>1.26 d (6.3)</td>
<td>3.40 s</td>
<td>6.42 bd</td>
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<tr>
<td>43</td>
<td>4.87 d (4.3)</td>
<td>2.25 ddd (13.7)</td>
<td>1.82 d (7.8)</td>
<td>4.55 t (7.8)</td>
<td>3.82 bs</td>
<td>4.77 dq (2.8)</td>
<td>1.29 d (6.7)</td>
<td>3.32 s</td>
<td>7.11 m</td>
<td>7.78 d</td>
<td>2.45 s</td>
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<td>44</td>
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<td>2.21 m (13.3)</td>
<td>2.05 m (5.1)</td>
<td>4.29 m (8.1, 7.4)</td>
<td>3.86 t (6.3)</td>
<td>4.55 m (6.3)</td>
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<td>3.26 s</td>
<td>6.67 d</td>
<td>7.78 d</td>
<td>2.38 s</td>
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</tbody>
</table>

$^a$In chloroform-d$_3$, with tetramethylsilane as the internal standard.

$^b$Signal multiplicities; b, broadened; d, doublet; m, multiplet; q, quartet; s, singlet.
Table 24

$^{13}$C NMR Spectral Data for Compounds 41-44

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<tr>
<th>Compound</th>
<th>C-1</th>
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<th>C-3</th>
<th>C-4</th>
<th>C-5</th>
<th>C-6</th>
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<th>CF₃</th>
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<td>156.10</td>
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*a* In chloroform-δ.
doublet on irradiating the H-6 doublet at 1.27 ppm. These results undoubtedly confirmed the structures of 41 and 42 to be furanosides as the 5-JH groups there were free, and these in turn underwent esterification to yield the p-toluenesulfonates 43 and 44. The $^{13}$C NMR spectrum also confirmed these results by showing a shift of the C-5 resonances in both of these compounds 43 and 44 to 78.63 ppm and 79.18 ppm, respectively, and downfield by -11 ppm from corresponding signals for their precursors 41 and 42. Compared to this $\alpha$-effect, the $\beta$-effect was marginal as the C-4 and C-6 resonances suffered an upfield shift of ~2 ppm.

Methyl 5-$\delta$-acetyl-2,3,6-trIDEOxy-3-trifluoroacetamido-5-thio-$\alpha$- and $\beta$-L-lyxo-hexofuranosides (45 and 46). (Methyl 5-$\delta$-acetyl-5-thio daunosaminide $\alpha$ and $\beta$-furanosides) The 5-O-p-tolylsulfonyl derivatives 43 and 44 were subjected to SN2 displacement with potassium thioacetate in N,N-dimethylformamide. No reaction took place at temperatures <90°. At 100°, the reaction was complete within 4 to 8 h. After evaporation of N,N-dimethylformamide and partitioning the residue between dichloromethane and water, the organic extracts were combined and evaporated to give a dark syrup, which was further purified by column chromatography.

The $\beta$-$\delta$-ribo derivative 44 afforded the crystalline $\alpha$-$\delta$-lyxo-5-acetylthio derivative 46 in 65% yield. The $\alpha$-$\delta$-ribo p-toluenesulfonate 43 afforded the $\beta$-$\delta$-lyxofuranoside 45 as a syrup in 60% yield. Apart from the desired product 45, a second component was isolated from the column which had similar mobility on t.l.c. when eluted with 14:1
chloroform–methanol or 6:1 toluene–acetone. This component, 47, was presumably the 5-epimer of 44, judging from its \(^1\)H NMR, \(^{13}\)C NMR, and mass-spectral data. The yield of 47 was -5-10%.

The \(^1\)H NMR spectrum of the thioacetate 46 showed the absence of the aryl peaks corresponding to the p-tolylsulfonyl group. The H-5 resonance had moved upfield to 3.65 ppm, indicative of the thioacetate group present at C-5. Also, the resonance for the thioacetate methyl group was observed at 2.32 ppm as a singlet, which confirmed the presence of the thioacetate group. The H-1 signal for 46 was observed as a doublet of doublets at 5.05 ppm, whereas the H-1 signal for 45 was observed at 5.1 ppm as a doublet. The H-5 resonance was again observed as a multiplet at 3.62 ppm with its couplings for H-4--H-5 equal to the H-5--H-6 coupling and thus showing a quintet. When the thioacetate 46 was subjected to NOE studies, positive enhancements for H-2, H-4, H-5 and -OCH\(_3\) signals were observed when H-3 was irradiated. This result confirmed the anomeric configuration in 46 to be α. This in turn, confirmed the anomeric assignments made earlier according to Hudson's rule for compounds 41--47.

In contrast, the second component obtained from the residue of that mixture, viz., 47, had its H-5 signal as a doublet of a quartet at 3.77 ppm and the H-4 signal as a doublet of doublets at 3.95 ppm. As may be seen from Figures 43 and 44, the coupling constants for H-4 in 45 and 47 were not the same, although their multiplicities and the chemical shifts were very similar. The C-4 resonances in the \(^{13}\)C NMR spectra of all the three compounds (45, 46, and 47) were observed at 88.82, 86.23 and 87.55 ppm, respectively. This established without any doubt that all three of
Figure 42. Partial 300-MHz, $^1$H-NMR spectrum of methyl 5-$\tilde{\text{S}}$-acetyl-2,3,6-trideoxy-3-trifluoroacetamido-5-thio-\(\alpha\)-L-lyxo-hexofuranoside (46).
Figure 43.
Partial $^1$H-NMR nOe difference spectrum of methyl 5-$\text{S}$-acetyl-2,3,6-trideoxy-3-trifluoroacetamido-5-thio-$\alpha$-$L$-hexopyranoside (46).
Figure 44. Partial $^1$H-NMR spectrum of methyl 5-$\beta$-acetyl-2,3,6-trIDEOXY-3-trifluoroacetamido-5-thio-$\beta$-$\alpha$-XO-hexofuranoside (45).
Figure 45. Partial $^1$H-NMR spectrum of methyl 5-$\beta$-acetyl-2,3,6-trideoxy-3-trifluoroacetamido-5-thio-$\alpha$-D-threo-hexofuranoside (47).
Figure 46. $^{13}$C-1H Correlation spectrum of methyl 5-$\beta$-acetyl-2,3,6-trideoxy-3-trifluoroacetamido-5-thio-$\beta$-$\alpha$-hexofuranoside (45).
Figure 47  $^{13}$C-$^1$H Correlation spectrum of methyl 5-$\text{S}$-acetyl-2,3,6-trideoxy-3-trifluoroacetamido-5-thio-$\alpha$-$\text{D}$-ribo-hexofuranoside (47).
Figure 48. $^{13}$C-$^1$H Correlation spectrum of methyl 5-5-acetyl-2,3,6-trideoxy-3-trifluoroacetamido-5-thio-$\alpha$-L-thio-hexoturanoside (46).
them were furanosides. The C-5 resonances were also observed to be in a very similar range, i.e., at 40.61, 41.28, and 41.6 ppm, respectively. These results suggest that the structures of all these three compounds may be very similar, with a minor configurational variation at some centers. As the thioacetates 45 and 47 were isolated from the same reaction, i.e., the reaction of the α-D-ribo-p-toluenesulfonate derivative 43 with potassium thioacetate, it was considered probable that 45 and 47 were the C-5 epimeric thioacetates. Apart from the standard ¹H NMR and ¹³C NMR spectra, the C–H correlation spectra were also recorded for these compounds in order to consolidate the structural attribution for these compounds.

The mass-spectral data for these compounds were also found to be extremely similar. The fast-atom-bombardment (FAB) technique as well as the electron-impact (EI) techniques, both showed very similar fragmentation patterns, all date supportive of the idea that the parent ring structures were identical.

In order to consolidate assignment of the correct configuration to these compounds, they were hydrolyzed to their respective free sugars by using 40% acetic acid. Compounds 45 and 46 produced the same free sugar, whereas 47 gave a different sugar. This evidence was the proof that 45 was indeed the desired L-lyxo isomer and hence 47 may have been the D-ribo isomer.

The formation of 47 is unusual. It may be explained in terms of participation by the ring-oxygen atom to form an oxonium ion intermediate as shown in Figure 49.
**Scheme 50**

- 45: NHTFA
- 46: NHTFA
- 48: NHTFA
- 49: NHTFA
- 50: NHTFA

- **45 → 46**: Treatment with 40% AcOH for 1 hour at reflux leads to the conversion of 45 to 46.
- **48**: Formation through reaction with Ac₂O in pyridine.
- **50**: Resultant product.
Oxonium ion intermediates in $S_N^2$ processes are known where they lead to retention in configuration because of two successive $S_N^2$ reactions.\textsuperscript{261} Thus the back-side attack by the ring oxygen may form an oxonium ion intermediate, which can suffer nucleophilic attack by thioacetate anion at two positions. If the thioacetate anion attacks at C-5, then a five-membered ring giving $\alpha$-$\beta$-\textit{ribo} hexofuranoside would be formed. If the anion attacks at C-4, then a $\beta$-$\alpha$-\textit{arabinohexopyranoside} would be formed. As 47 was found to be a furanoside from $^1H$ NMR and $^{13}C$ NMR spectral data, the attack should have taken place at C-5. The

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\textsuperscript{261} H. Weiner and R. A. Sneen, J. Am. Chem. Soc. 87 (1965), 287-291.

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Figure 49. Action of Potassium Thioacetate on Compound 43.
p-toluenesulfonate derivative 44 did not give any other product besides the desired $S_N2$ displacement product 46. This indicates that the compounds 43 and 44 may be existing in different conformers such that the oxonium ion formation may be possible in 43 but not in 44. As this is an unusual and hence a rare example of its kind in the synthesis with carbohydrate precursors involving $S_N2$ type nucleophilic substitution, more work needs to be done in order to get a better insight into the processes taking place during such substitution reactions.

Hydrolysis of the thioacetates 45 and 46. In efforts to convert the furanoside thioacetates 45 and 46 into a six-membered 5-thio sugar having the sulfur atom in the ring, several different procedures were attempted. Initially, a direct acetolysis was tried whereby the methyl furanoside would be converted directly into a thiopyranose 1,4-diacetate according to the method developed by Whistler and Anisuzzaman.\(^{254}\) A very polar substance was formed as observed by t.l.c. monitoring. On chromatographic purification and $^1H$ NMR analysis, this product showed no signs of the desired thiopyranose derivative. The product could not be identified. Next, another acid hydrolysis was tried, using 50% acetic acid and refluxing the mixture for two days.\(^{262}\) In the beginning, the methyl glycoside underwent hydrolysis within 1 h but after that again an
extremely polar substance was seen to be forming at the expense of the free furanose formed earlier. When all of the free furanose had been consumed, the mixture was evaporated and then acetylated in the presence of pyridine. Again no identifiable products could be isolated from the mixture. Hence, to check out this procedure again, the reaction was next stopped half-way through and the mixture acetylated. The product obtained was identified as the 1-acetate of the furanose derivative 46.

Hasegawa, Kiso and coworkers were successful in obtaining 2-acetamido-2-deoxy-5-thio-α-D-mannopyranose by hydrolyzing the corresponding furanoside-5-thioacetate with a mixture of 2 M hydrochloric acid and acetic acid. When this method was attempted, again very polar products were formed but upon acetylation with pyridine and acetic anhydride, an extremely faint spot was seen by t.l.c. at Rf = 0.5 with 14:1 chloroform–methanol as the eluent. After purifying the mixture chromatographically, the product obtained in very small quantity was subjected to 1H NMR spectral analysis. The spectrum showed the new compound 51 having signals corresponding to a glycal, along with an acetate on H-4 and an acetamido group instead of trifluoroacetamido at C-3. Hence, in all probabilities, compound 51 was the glycal of the...
Unidentifiable mixture of polar compounds.
Figure 50. Partial $^1$H-NMR spectrum of 5-$\beta$-acetyl-2,3,6-trideoxy-3-trifluoroacetamido-5-thio-$\alpha$-lyxo-hexofuranose (48).
Figure 51. $^{13}$C-NMR spectrum of 5-$\xi$-acetyl-2,3,6-trideoxy-3-trifluoroacetamido-5-thio-$\xi$-lyxo-hexofuranose (48).
Figure 52. $^{13}$C-NMR spectrum of a mixture of $\alpha$-N-acetyl-5-$\beta$-acetyl-2,3,6-trideoxy-3-trifluoroacetamido-5-thio-$\alpha$ and $\beta$-L-threo-hexofuranoses (49 and 50).
Table 25

$^1$H NMR Spectral Data for Compounds 45-49

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<th>H-3</th>
<th>H-4</th>
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<th>H-6</th>
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<th>NH</th>
<th>SAc</th>
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<th>OAc</th>
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<td>($J_{2,2''}$)</td>
<td>($J_{1,2''}$)</td>
<td>($J_{2,3}$)</td>
<td>($J_{3,4}$)</td>
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<td>3.89 t</td>
<td>3.65 m (7.02)</td>
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<td>2.36 s</td>
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<td>2.07 s</td>
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$^a$In chloroform-d, with tetramethylsilane as the internal standard.

$^b$Signal multiplicities: b, broadened; d, doublet; m, multiplet; q, quartet; s, singlet.
Table 26

$^{13}$C NMR Spectral Data for Compounds 45-48

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<th>C-1</th>
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<th>C-5</th>
<th>C-6</th>
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<td>156.01</td>
<td>194.98</td>
<td>169.00</td>
<td>21.12</td>
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*In chloroform-d.
desired thiopyranose, but the yield was extremely poor (-5%). Surprisingly, the trifluoroacetyl group had been cleaved under these acidic conditions, which had been used to keep the trifluoroacetamido group intact.

As the acid hydrolysis procedures did not work satisfactorily, alkaline hydrolysis was tried. Again, at first, a method used by Whistler and coworkers was tried. They had successfully converted a 5-S-acetyl-5-thioaldofuranose-1-O-acetate into the corresponding 5-thiohexopyranose. Accordingly, 0.2 M sodium methoxide was added to a methanolic solution of the 1-O-acetyl derivative 49 at 0° under an atmosphere of argon. Again, very polar compound was formed, probably through conversion of the N-trifluoroacetamido group into amino group. Hence, after neutralization and evaporation of the solvent, the product was acylated, first with trifluoroacetic anhydride in the presence of methanol and then, after evaporation, the dried syrup was treated with pyridine and acetic anhydride. The product was found to have many signals in the downfield region of the $^1$H NMR.

Obviously, some elimination had taken place, but the product could not be identified. The only fact that could be deduced from the NMR spectrum was that the desired product or a derivative thereof had not been found. When the deacylation of thioacetate 46 was tried first with sodium methoxide in methanol, it gave the free amino compound, probably because of the nucleophilic attack by the resultant RS⁻ produced during the reaction. After adding acetic acid to neutralize the mixture and evaporating the solvent, the residue was hydrolyzed in 50% acetic acid in order to produce the free sugar which, if formed, could undergo ring
expansion to give the thiopyranose. As the starting material was already very polar, the purification of the product would have been difficult if it were not acetylated. After acetylation, the product obtained was purified by a small column and was found to be a mixture of two or three components. Some of the signals matched those of the glycal 51 obtained earlier under acidic conditions.

As under alkaline conditions, disulfide formation\(^\text{263}\) as well as elimination reactions\(^\text{264}\) are well known, a milder method was attempted using potassium cyanide\(^\text{263,265}\) in methanol. Cyanide ion can even cleave the disulfide if it is formed during the reaction. Again, a polar compound, presumably containing a free amino group, was produced which was further hydrolyzed with acid and then acetylated. This time, a clean product was obtained which was found to be the glycal 51 but the yield was not high, -25-30%. The \(^1\text{H NMR}\) spectrum of 51 was well resolved and showed the characteristic doublet of doublets at 6.2 ppm for H-1 and at 5.6 ppm for H-2. The H-4 resonance was also a doublet of doublets, at 4.95 ppm. This downfield resonance of H-4 is clearly associated with the presence of an acetate group at C-4. The two

\begin{itemize}
\end{itemize}
SCHEME 52
Figure 53. Partial ¹H-NMR spectrum of 1,5-anhydro-3,4-Q-diacetyl-2,3,6-trideoxy-L-lyxo-hex-1-enitol (51).
singlets observed in the acetate region, at 2.1 and 2.0 ppm, may thus be assigned to the acetamido group at C-3 and acetate group at C-4, respectively. The doublet for 6-deoxy, i.e., the methyl group at C-5, was observed at 1.38 ppm with a coupling constant of 7 Hz. Also, the coupling between H-4 and H-5 was found to be 7 Hz, this magnitude being attributable to the quasi-axial and quasi-equatorial dispositions of these protons.

Only two examples of a thiopyranose glycal are noted in the literature, that of 5-thio-D-glucal and its diacetate.178


On comparing the \(^1\)H NMR spectral data, most of the coupling constants and chemical shifts were found to be in accordance with the \(\alpha\)-lyxo structure suggested for compound 51. Analysis by FAB mass spectrometry showed the \(M^+ + 1\) peak, confirming the proposed molecular formula.

Thus, it seems that the trifluoroacetamido group is not stable under conditions of hydrolysis of the thioacetate group. The free amino group thereby produced may induce polymerization or may give rise to different competing reactions producing a mixture of products. Hence, the attempts to obtain N-trifluoroacetyl-5-thiodaunosamine on a large scale were unsuccessful. This goal may be achieved by two ways; either by changing the protective group on nitrogen to a rather more stable acetyl group and carrying out similar reactions, or by making a
disulfide and protecting the free-amino group produced in the process with some other protective group. The disulfide may then be hydrolyzed to a free sugar and then cleaved in the presence of a mild reagent like dithiothreitol or 1,3-propanedithiol. These reactions are still under active investigation.
1. The Horton-Weckerle synthesis of daunosamine was still the most viable approach for a large scale synthesis of daunosamine.

2. The anomer composition of different acylamino derivatives of daunosamine were determined in Me₂SO and D₂O and the free energy differences [ΔG] between α and β-pyranoses were calculated from the observed ratios of the two anomers, which may be useful to estimate the interaction energies of such 3-acylamino-2,3,6-trideoxy configurations.

3. 3-Hydroxy-3-C-methyl analog of daunosamine was prepared in 20% overall yield starting from methyl α-D-mannopyranoside and was successfully coupled with daunomycinone which remains to be evaluated for its biological activity after deprotection.

4. The approach to prepare 5-thio daunosamine involving an S_N2 displacement in the open chain α-ristsosamine derivative did not work and instead gave an oxazine derivative.
5. The furanose derivatives of 5-thio daunosamine were successfully prepared from D-ristosamine which upon hydrolysis did not afford the expected 5-thio daunosamine in a pyranose form, but gave the corresponding glycal in moderate yield. Better approaches for this hydrolysis are still under active investigation.
CHAPTER IV
EXPERIMENTAL

General Methods -- Melting points are uncorrected values taken on a Fisher-Johns melting point apparatus. Optical rotations were determined in chloroform on a Perkin-Elmer Model 141 polarimeter and 1-dm cells were used. $^1$H NMR spectra were recorded at 200 MHz on a Bruker WP-200 and at 500 MHz on a Bruker AM-500 spectrometer operating in the Fourier-transform mode at 30°. $^{13}$C NMR spectra were recorded at 50.3 MHz on a Bruker WP-200, at 75 MHz on a Bruker WM-300, and at 125 MHz on a Bruker AM-500 spectrometer operating in the Fourier-transform mode at 30°. The Bruker AM-500 spectrometer was operated by Dr. C. Cottrell. TLC was performed on precoated glass plates (0.2 mm) of silica gel 60F-254, and the zones were detected either by spraying the plates with 10% sulfuric acid followed by heating, or by uv light. Column chromatography was performed with silica gel 60 (particle size 0.040-0.063 mm). High-performance liquid chromatography (HPLC) was performed on a Rainin Instrument Company's Model Rabbit-HPX solvent delivery system equipped with a Jenaer differential refractometer, using an analytical column, (EM SN 01147, 250 mm × 4.6 mm, containing Lichrosorb S160, 5μm) at flow rates of 1.2 mL/min, and a preparative column, (μPorasil, Part. No. 84175) at flow rates of 2.2-2.5 mL/min. Electron impact mass spectra were recorded with a Kratos MS-30 mass spectrometer by Dr. C.R.
Weisenberger. Fast atom bombardment (FAB) mass spectra were recorded with VG 7C-250S mass spectrometer by Dr. David Chang, using either a glycerol matrix or a "magic bullet" matrix. Chemical ionization (C.I.) mass spectra were recorded with a Finnagan 4021 mass spectrometer by Ms. Kathy Ault, using methane as the carrier gas. Infrared spectra were recorded with a Polaris IR-10400 infrared spectrophotometer in the Fourier-transform mode. Microanalyses were performed by Atlantic Microlab Inc., Atlanta, Georgia. $^1$H NMR and $^{13}$C NMR spectral data of the compounds are listed in Tables. Oxolane (THF) was purified by distillation over sodium; ethanol and methanol were purified by distillation over magnesium, and stored over 3Å molecular sieves under an atmosphere of argon; 1,2-dimethoxyethane (glycol dimethyl ether) was purified by distillation over calcium hydride, and N,N-dimethylformamide was purified by stirring overnight with barium oxide and fractionating in vacuo.

Preparation of methyl 2,3:4,6-di-0-benzylidene-α-D- mannopyranoside (2). A mixture of methyl α-D-mannopyranoside 1 (100 g, 516 mmol), α, α-dimethoxytoluene (184 g, 1200 mmol), and anhydrous p-toluenesulfonic acid (1.5 g) in N,N-dimethylformamide (600 mL), in a 2-liter flask fitted with an air condenser attached to a water aspirator was stirred magnetically and heated in an oil bath for 4 h at 65-75°. No starting material 1 remained after this time (t.l.c. 4:1 ether-petroleum ether, $R_f$ 2 = 0.63; $R_f$ 1 = 0.18). The mixture was poured with vigorous mechanical stirring into 2 liters of ice--water containing sodium hydrogencarbonate (60 g).
The resultant precipitate was filtered off, resuspended in ice-water, filtered off again, and dried in air and finally in vacuum over phosphorus pentaoxide; yield 185.3 g (97%), m.p. 120°--160°, \([\alpha]^{23}_D -32^\circ\) (c 1, chloroform).

Preparation of methyl 4,6-O-benzylidene-2-deoxy-\(\alpha\)-\(D\)-erythro-hexopyranosid-3-ulose (3). A solution of the diastereoisomeric mixture of acetals 2 (100 g, 270 mmol) in commercial absolute tetrahydrofuran (1.5 L) under argon was cooled to -40°. Butyllithium in hexane (2.6 M, 230 mL, 500 mmol) was added, and the temperature was kept for 2 h below -30°, during which time the color of the solution turned from yellow to red and all of the starting material disappeared as indicated by t.l.c. monitoring. T.l.c. plates were developed with 1:1 ether-petroleum ether, and the developed plates were heated in vacuum for 15 min at 125° before being sprayed with sulfuric acid for zone detection. The heating step was required for removal of 1-phenyl-1-pentanol, whose R_f value is the same as that of 2. \([R_f 2 = 0.69, R_f 3 = 0.18\) 1:1 ether-petroleum ether]. The solution, still at -30°, was poured with vigorous mechanical stirring into ice-water (2 L) containing ammonium chloride (250 g). The tetrahydrofuran was removed on a rotary evaporator at a bath temperature of -30°. The aqueous slurry remaining was cooled to 0°, and the crystalline deoxy
ketone 3 was filtered off with use of suction and dried; yield 66 g (92.6%).

Recrystallization from ethanol gave pure 3, m.p. 170--171°, \( [\alpha]_D^{22} +150° \) (c 1, ethyl acetate); (lit.\(^{256}\) m.p. 170--171°, \( [\alpha]_D^{22} +153° \) in ethyl acetate).


Preparation of methyl 4,6-O-benzylidene-2-deoxy-\( \alpha-D \)-erythro-hexopyranosid-3-ulose oxime (4).\(^{268}\) Finely powdered \( \text{NH}_2\text{OH-HCl} \) (58.5 g) was dissolved in anhydrous ethyl alcohol (1000 mL) with the aid of a warm water bath. To the above stirred solution, cooled to room temperature, was added a solution of sodium hydroxide (33.5 g) in anhydrous ethyl alcohol (1000 mL). After 15 min. of additional stirring, the precipitated sodium chloride was filtered off and to the resulting solution of neutral hydroxylamine was added the crude glycosulose 3 (40 g, 161.3 mmol) with stirring at room temperature. The oxime began to separate as flakes from the reaction mixture on standing for 24 h. The crystallization was completed by cooling at 0--5°C for an additional 6 h. The precipitate was filtered, washed with cold ethyl alcohol, and dried in vacuo at room temperature to give the oxime 4; m.p. 207--208°, \( [\alpha]_D^{23} +202° \) (c 1, chloroform). (lit.\(^{183}\) m.p. 207--208°, \( [\alpha]_D +200° \) in chloroform).
Preparation of methyl 3-amino-4,6-O-benzylidene-2,3-dideoxy-\(\alpha\)-D-ribo-hexopyranoside (5).

To a suspension of oxime 4 (40 g, 152 mmol) in absolute alcohol (1200 mL) was added activated aluminum amalgam (prepared from 17 g of aluminum) and the mixture stirred at 45–50° for 20 h at which point, only a trace of the starting oxime remained unreacted (\(R_f\) 4 = 0.28, \(R_f\) 5 = 0.04 in 1:1 ether–petroleum ether). The cooled suspension was then filtered with filter aid and washed with 95% ethyl alcohol (2 × 100 mL). The ethanolic solution was evaporated in vacuo to dryness to yield a white crystalline residue, which was recrystallized from ether; yield 25 g (65.2%); m.p. 119–120°, \([\alpha]_D^{23} +140°\) (c 1, chloroform); (lit. m.p. 118–120°, \([\alpha]_D +139°\) in chloroform).
Preparation of methyl 3-acetamido-4,6-0-benzylidene-2,3-dideoxy-α-D-ribo-hexopyranoside (6) and its α-D-arabino analogue (7). In a 3-liter flask equipped with a magnetic stirrer, a Soxhlet extractor, and a reflux condenser was placed lithium aluminum hydride (25.5 g, 67.23 mmol) in ether (2 L); and in the extractor thimble was placed the oxime 4 (50 g, 179.4 mmol). The contents of the flask were stirred and heated under reflux for 24 h, after which time the excess of the reducing agent was decomposed by successively adding water (25 mL), 15% aqueous sodium hydroxide (25 mL), and water (75 mL). The resultant mixture was filtered, and the filtrate evaporated to give a crystalline residue which was dissolved in pyridine (300 mL), and acetic anhydride (150 mL) was added, with cooling to 0°. After 18 h at -25°, the solution was poured into ice--water (600 mL), and the product extracted with dichloromethane (3 x 200 mL). The extract was successively washed with sodium hydrogen carbonate and water, dried (sodium sulfate), and evaporated in vacuo. Pyridine (2 x 100 mL) and toluene (2 x 100 mL) were successively added to and evaporated from the residue. To the semicrystalline residue resulting was added toluene (200 mL) and the mixture was cooled to 0°. The crystalline precipitate was then filtered off with suction, and washed with a small volume of cold toluene, to afford the arabino derivative 7; yield 6.8 g (14.3%). Recrystallized from acetone, it had m.p. 272°C (sublimation); [α]_D^{23} +68° (c 1, chloroform); (lit. m.p. 274--277°, [α]_D +65° in chloroform).
The mother liquor was evaporated to give the syrupy ribo derivative 6; yield 41.8 g (86%); \([\alpha]_D^{23} +60^\circ (c 1.2 \text{ chloroform}); (\text{lit.}^{271} [\alpha]_D^\theta +49.8^\circ \text{ in chloroform and } [\alpha]_D^\theta +56^\circ \text{ in chloroform}).

The products 6 and 7 had \(R_f\) values of 0.64 and 0.59, respectively, in t.l.c. with benzene--ethanol, and it was verified that each product was free from contamination by the other.


Preparation of methyl 4,6-O-benzylidene-2,3-dideoxy-3-trifluoroacetamido-\(\alpha\)-D-ribo-hexopyranoside (8).^{188}

\[
\begin{array}{c}
\text{NH-TFA} \\
\text{O} \\
\text{OMe}
\end{array}
\]

A cooled (0\(^\circ\)) solution of the amine 5 (25 g, 94 mmol) in carbon tetrachloride (1000 mL) and triethylamine (62 mL) was treated by a dropwise addition of trifluoroacetic anhydride (25 mL, 175 mmol) with stirring. After 1.5 h of additional stirring at -25\(^\circ\)C the N-trifluoroacetyl derivative was formed (\(R_f\) 8 = 0.45, 6:1 toluene--acetone). The reaction mixture was washed successively with water (250 mL), 10% sodium hydrogensulfate (250 mL), saturated sodium hydrogencarbonate (250 mL) and water (250 mL), dried over sodium sulfate, and filtered. This solution could be used directly for the next reaction.
A sample of the resulting carbon tetrachloride solution was evaporated in vacuo to yield a syrup, which was chromatographed on a column of silica gel to give 18 as a colorless syrup, \([\alpha]_D^{23} + 8.8^\circ\) (c 1, chloroform), (Lit.\(^{188}\) \([\alpha]_D^{23} + 8.6^\circ\) in chloroform).

Preparation of methyl 3-acetamido-4-\(\text{O}\)-benzoyl-6-bromo-2,3,6-trIDEOxy-\(\alpha\)-\(D\)-ribo-hexopyranoside (9).\(^{48}\)

To a solution of compound 6 (14 g, 45.5 mmol) in dry carbon tetrachloride (400 mL) was added N-bromosuccinimide (10 g, 56.18 mmol) and barium carbonate (15 g). The mixture was boiled under reflux for 2 h under normal room-illumination, during which time, the mixture, originally colorless, became successively yellow, red, and finally pale yellow. The solvent was removed in vacuo, and the residue was extracted with dichloromethane (200 mL); the clear extract was washed successively with sodium sulfite and sodium hydrogencarbonate, dried (sodium sulfate) and evaporated. The resultant, crystalline residue was recrystallized from ethanol to give analytically pure 9; yield 12 g (68.5%); m.p. 173°-175°, \([\alpha]_D^{22} + 76.3^\circ\) (c 1, chloroform); (Lit.\(^{48}\) m.p. 173°, \([\alpha]_D^{22} + 76.5^\circ\)).

Preparation of methyl 3-acetamido-4-\(\text{O}\)-benzoyl-2,3,6-trIDEOxy-\(\alpha\)-\(D\)-erythro-hex-5-enopyranoside (10).\(^{48}\)

A mixture of compound 9 (5 g, 13 mmol) and dry, technical-grade silver fluoride (5 g, 22.1 mmol) in dry pyridine (90 mL) was stirred for 14 h at -25°, after which time, t.l.c. (1:1 benzene--acetone; Rₜ
0.5 for both; the product as well as reactant but the colors were different after spraying with sulfuric acid) showed that all of the 9 had been consumed. The dark solution was poured into ether (500 mL) and the resultant mixture was filtered. The filtrate was evaporated under reduced pressure at ≤ 40°, and then three 25 mL portions of toluene were added to and evaporated from the residue to remove all of the pyridine. The resultant syrup was taken up in ether, and the suspension filtered through a small column (250 x 20 mm) of silica gel to remove residual silver salts. The effluent was evaporated in vacuo to give the pure derivative 10 as a syrup; yield 4 g (100%), [α]_D^23 +54.9° (c 1, chloroform), (Lit. 48 [α](p +55.2° in chloroform).


Preparation of methyl 4-O-benzoyl-6-bromo-2,3,6-trideoxy-3-trifluoroacetamido-α-D-ribo-hexopyranoside (11). The carbon tetrachloride solution of the N-trifluoroacetyl derivative 8 was evaporated under reduced pressure to ~600 mL, and then there was added barium carbonate (30.2 g, 152.8 mmol) and freshly recrystallized N-bromosuccinimide (21.7 g, 121.8 mmol) and the mixture was refluxed for 6 h under normal room illumination. During this time, the color of the reaction mixture changed from yellow to red to pale yellow and all of the starting material had been consumed. (Rf 11 =
0.57, Rf 8 = 0.45, 6:1 toluene--acetone). After cooling down to room temperature, the mixture was filtered and the filtrate was washed successively with water (250 mL), 10% sodium hydrosulfite (250 mL), saturated sodium hydrosulfite (250 mL), and water (250 mL) and after drying over anhydrous sodium sulfate was evaporated in vacuo to yield a brown residue, which was taken up with ether (50 mL) and crystallized by adding hexane (~400 mL) to obtain brownish crystals of 11 (yield 26.9 g, 65%), m.p. 106--108°, [α]_D^{23} +38.1° (c 1, chloroform); (Lit. m.p. 111.5--112°, [α]_D^{20} +39.3° in chloroform).

Preparation of methyl 3-acetamido-2,3,6-trideoxy-α-D-erythro-hex-5-enopyranoside (13). To a solution of compound 10 (5 g, 16.4 mmol) in absolute methanol (30 mL) was added 1 M sodium methoxide (0.5 mL), and the mixture was kept at -25° for 12 h, at which point, t.l.c. (Rf 10 = 0.55, Rf 13 = 0.26; 1:1 toluene--acetone) indicated that saponification was complete. The solution was passed through a small bed (250 × 20 mm) of silica gel in a column, and the effluent was evaporated in vacuo to give 13 as a syrup (yield 3.1 g, 97%). This was subjected, without delay, to the hydrogenation reaction.

An analytical sample free from methyl benzoate was secured by dissolving the syrup in water and washing it twice with dichloromethane, and then freeze-dried. The pure 13 had [α]_D^{23} +75.2° (c 1·2, water); (Lit. [α]_D^{23} +74.5° in water).
Preparation of methyl 3-acetamido-2,3,6-trideoxy-α-L-lyxo-hexopyanoside (14) (methyl N-acetyl-α-daunosaminide). A solution of the unsaturated sugar 13 (1.5 g, 7.46 mmol) in absolute methanol (50 mL) was hydrogenated in the presence of 10% palladium-on-barium sulfate (150 mg) at 35 psi in a Parr-1 hydrogenation apparatus. After 30 min, t.l.c. monitoring (2:3 benzene-acetone, \( R_f = 0.36 \)) showed all of the starting material had been consumed. The catalyst was filtered off, and the filtrate was evaporated in vacuo to give a crystalline, chromatographically homogeneous residue of 14; yield 1.5 g (99%). A small sample was recrystallized from ethyl acetate to give 14 as fine needles; m.p. 208—210° (sublimation); \([\alpha]_D^{23} \approx -27° \) (c 1, water); (Lit. m.p. 208--210°, \([\alpha]_D^{22} \approx -28° \) in water).

Preparation of 3-amino-2,3,6-trideoxy-α-L-lyxo-hexose (daunosamine) hydrochloride (15). A solution of the N-acetylated glycoside 14 (200 mg, 0.99 mmol) and barium hydroxide octahydrate (630 mg, 2 mmol) in water (4 mL) was boiled for 12 h under reflux, after which time, t.l.c. (2:3 benzene--acetone) revealed only a trace of starting glycoside (\( R_f 14 = 0.36, R_f 15 = 0.09 \)). Solid carbon dioxide was added, and the resultant precipitate of barium carbonate was filtered off with suction. The filtrate was then lyophilized to give a solid that was dissolved in absolute ethanol and freed from traces of inorganic material by filtration. The filtrate was evaporated to dryness, and the residue dissolved in 0.5 M hydrochloric
acid (7 mL). The solution was heated for 3 h at 100°, decolorized with activated charcoal, and lyophilized to give a foam that readily crystallized on addition of acetone (3 mL). The crystals were filtered off in an inert atmosphere and dried. Yield 130 mg (83%), m.p. 168--170° dec., $[\alpha]_D^{22} -65.2°$ (equil; c 1, water); (Lit. m.p. 168--170° dec., $[\alpha]_D^{23} -65.4°$ in water at equilibrium).

Preparation of 3-acetamido-2,3,6-trideoxy-$\alpha$-lyxo-hexose (16) (N-acetyl-$\alpha$-daunosamine). A solution of the N-acetylated glycoside 14 (200 mg, 0.985 mmol) in water (5 mL) and acetic acid (2 mL) was boiled for 30 min under reflux, whereupon t.l.c. (10:1 chloroform--methanol) showed that compound 14 ($R_f$ 0.5) had all been converted into the product 16 ($R_f$ 0.1). The solution was evaporated and the residue recrystallized from ethyl acetate to give compound 16 (yield 150 mg, 80%). m.p. 161--162°, $[\alpha]_D^{23} -180°$ (initial, extrapolated) $\rightarrow$ -116° (7 min) $\rightarrow$ -100° (30 min, equil., c 0.5, water).

Preparation of 3-benzyamido-2,3,6-trideoxy-$\alpha$-lyxo-hexose (17) (N-benzoyldaunosamine). To a cold solution (0°) of 15 (100 mg, 0.55 mmol) and potassium hydrogencarbonate (0.85 g) in water (5 mL) was added a cold solution of benzoyl chloride (0.5 mL) in acetone (5 mL), and the mixture was stirred for 3 h
at 0° and 18 h at -25°. T.l.c. (2:3 benzene--acetone) then showed a major product (Rf 0.56) together with two faster migrating components. The solution was deionized with a mixture of Amberlite IR-120 (H⁺) and IRA-400 (OH⁻) resins, lyophilized, and the residue purified by preparative t.l.c. with 2:3 benzene--acetone to give 17 as a syrup that crystallized readily from acetone; the crystals were filtered off, and washed with a little ethyl acetate (yield 50 mg, 37%), m.p. 151--153°; [α]D²³ -107° (c 0.5, ethanol); (Lit. m.p. 154--156°; [α]D -107.5° in ethanol).

Preparation of 3-trifluoroacetamido-2,3,6-trideoxy-α-\[\beta\]-lyxo-hexose (18) (N-trifluoroacetyl-α-daunosamine).\textsuperscript{188} A solution of the N-acetylated glycoside 14 (200 mg, 0.99 mmol) and barium hydroxide octahydrate (630 mg, 2 mmol) in water (4 mL) was boiled for 12 h under reflux, after which time t.l.c. (2:3 benzene--acetone) revealed only a trace of starting glycoside (Rf 14 = 0.36, Rf rxn. mix. = 0.1). Solid carbon dioxide was added, and the resultant precipitate of barium carbonate was filtered off with suction. The filtrate was then lyophilized to give a solid that was dissolved in absolute ethanol and freed from traces of inorganic material by filtration. The filtrate was evaporated to dryness and the residue dissolved in absolute methanol (4 mL). To this solution cooled to 0°C was added trifluoroacetic anhydride (7.7 mL, 5 mmoles) and the mixture was stirred for 1 h at room temperature (-25°). T.l.c. monitoring showed only a trace of the amine (Rf = 1.1, 2:3 benzene--
acetone) as most of it had been converted into the N-trifluoroacetamido derivative \( (R_f = 0.4) \). The mixture was evaporated under diminished pressure and to the residue was added 5 mL of 50% acetic acid. The mixture was refluxed for 4 h, by which time all of the glycoside had been converted into the free sugar, as t.l.c. showed only one spot at the baseline. The solution was then evaporated under diminished pressure at -30° bath temperature, and two 10 mL portions of water were added, and subsequently evaporated to dryness. The residue was recrystallized from ethyl acetate to give N-trifluoroacetyldaunosamine as white needles (yield 107 mg, 45%), m.p. 148--150°, \([\alpha]_D^{23} -133.8°\) (c 0.5, 1,4-dioxane); (Lit.\(^{188}\) m.p. 147--150°; \([\alpha]_D -134°\) in 1,4-dioxane).


Preparation of methyl 4,6-\(\beta\)-benzylidene-2-deoxy-3-C- \ methyl-\(\alpha\)-\(\beta\)-ribo-hexopyranoside (19).\(^{129}\) To freshly prepared Grignard reagent, methylmagnesium iodide (1 g magnesium, 1.4 mL methyl iodide) in ether (25 mL) cooled to -10° was added 1,2-dimethoxyethane (25 mL) to displace the Grignard reagent. To the resulting thick white precipitate was added a solution of ketone 13 (2 g, 8 mmol) in 1,2-dimethoxyethane (100 mL) after which time the temperature was allowed to rise to -25° and the mixture was stirred with a mechanical stirrer for 20 h. At this point, t.l.c. \((R_f 3 = 0.17, R_f 19 = 0.3, 1:1\)
ether—petroleum ether) showed complete disappearance of the starting material. Water (15 mL) was then added to decompose the excess of Grignard reagent and the mixture was filtered. The filtrate was evaporated in vacuo to dryness and the residue was taken up in ethyl acetate (100 mL), washed once with water (50 mL), dried, and evaporated to give a syrup that turned into yellow powdery crystals after scratching. This was recrystallized from petroleum ether giving white fluffy crystals of 19; yield 1.4 g (66%), m.p. 124—126°; [α]D = +120° (c 1, ethanol); (Lit.129 m.p. 125.5—126°; [α]D +121° in ethanol).

To the mother liquor concentrated to one third of its volume was added acetone, whereupon white crystals appeared which were identified as the glycal 20, viz., 4,6-O-benzylidene-3-C-methyl-1,5-arabino-hex-1-enitol, m.p. 129—130°, [α]22 D +26° (c 1, ether); (Lit.205 m.p. 130—131°, [α]20 D +27.2 in ether).

Preparation of methyl-4-O-benzoyl-2,6-dideoxy-3-C-methyl-α-D-erythro-hexopyranoside (21).\(^{204}\)

To a solution of 19 (2 g, 7.14 mmol) in dry carbon tetrachloride (120 mL) was added N-bromosuccinimide (1.5 g, 8.43 mmol) and barium carbonate (2 g) and the mixture was refluxed for 2 h. After filtering off barium carbonate, the solution was washed with 10% sodium hydrogen-sulfite (50 mL), saturated sodium hydrogen carbonate (50 mL) and water (50 mL), respectively; dried (sodium sulfate), and evaporated to give a syrup which on addition of ether and then hexane yielded white crystals of 21 (2 g, 78%). m.p. 71°, \([\alpha]_D^{22} +22.4°\) (c 2, chloroform); (Lit.\(^{204}\) m.p. 71°, \([\alpha]_D^{20} +22.2°\) in dichloromethane).

Methyl 4-O-benzoyl-2,6-dideoxy-3-C-ethyl-α-D-erythro-hex-5-enopyranoside (22). A mixture of 21 (3.5 g, 9.5 mmol) and dry technical-grade silver fluoride (5 g, 22.1 mmol) in dry pyridine (90 mL) was stirred for 5 days at -25°, after which time t.l.c. (15:1 toluene--acetone) showed only a trace of 21 remaining unreacted. The dark mixture was poured into ether (500 mL), filtered, and the filtrate evaporated in vacuo to give a syrup which was put on a column of silica gel (60 g) and eluted with the same solvent system. The product 22 was collected as a white solid which was recrystallized from hexane; yield 1.59 g (60%), m.p. 111--113°, \([a]_D^{23} +153.9°\) (c 1.3, chloroform), \(v_{\text{max}}^{KBr}\) 3700 (OH), 3000 (C=C-H), 1750 (OC=O), 1275 (O-H), 1125 (C=C-O-) and 1040 cm\(^{-1}\) (R\(_3\)C-OH); \(m/\ell\) 279 (7.18, M\(^+\) +
245

1), 261 (1.77, M$^+$ + 1 - H$_2$O), 247 (2.21, M$^+$ + 1 - MeOH), 230 (1.69, M$^+$ + 1 - H$_2$O - OMe), 229 (8.58, M$^+$ + 1 - MeOH - H$_2$O), 185 (3.72, M$^+$ + 1 - MeOH - H$_2$O - H$_2$ - CH$_2$=C=O), 143 (2.54, M$^+$ + 1 - OCOPh - CH$_3$), 141 (1.22, M$^+$ + 1 - PhCO$_2$H), 131 (3.24, M$^+$ + 1 - CH$_2$=C=O - PhCHO), 125 (8.4, M$^+$ + 1 - PhCO$_2$H - MeOH), 106 (8.4, PhCHO), and 105 (100, PhCO).

Anal. Calc. for C$_{14}$H$_{18}$O$_5$ (278.31): C, 64.73; H, 6.52. Found: C, 64.67; H, 6.54.

Methyl 4-O-benzoyl-2,6-dideoxy-3-C-methyl-α-D-ribo-hexopyranoside (24) and methyl 4-O-benzoyl-2,6-dideoxy-3-C-methyl-β-L-lyxo-hexopyranoside (25). A solution of the unsaturated sugar 22 (1.3 g, 4.67 mmol) in absolute methanol (30 mL) was hydrogenated in the presence of Raney-nickel catalyst (17 g) at 45 lb in$^{-2}$ in a Parr-1 apparatus. After 48 h, t.l.c monitoring (8:1 toluene--acetone, R$_f$ 22 = 0.53) showed that all of the starting material had been consumed, yielding two different products. The catalyst was filtered off and the filtrate, when evaporated to dryness, gave a syrup (1.25 g, 98%) which was put on a column of silica gel (40 g) and eluted with the same solvent system. The first fraction collected gave methyl 4-O-benzoyl-2,6-dideoxy-3-C-methyl-α-D-ribo-hexopyranoside (24) as a syrup (0.37 g, 28%) which on cooling to -0° yielded white crystals that were further recrystallized from petroleum ether, m.p. 61--62°, [α]$_D^{23}$ +140.8° (c 1, chloroform); (Lit. 204 m.p. 62-63°; [α]$_D^{18}$ +142.6° in chloroform).
The second fraction collected gave 25 as a white solid on evaporation; yield 0.96 g (69%) which was recrystallized from hexane to give methyl 4-O-benzoyl-2,6-dideoxy-3-C-methyl-β-L-lyxo-hexopyranoside as white needles, m.p. 70-71°, [α]D<sup>22</sup> -2.4° (c 1, chloroform), η<sub>max</sub> 3500 (OH), 2950 (CH aromatic), 1710 (C=O), 1460 (CH), 1380 (CH₃), and 1275 cm⁻¹ (O-H); m/z 264 (1.51, M⁺ + 1 - OH), 263 (10.23, M⁺ + 1 - H₂O), 250 (12.21, M⁺ + 1 - OMe), 249 (86.39, M⁺ + 1 - MeOH), 232 (16.27, M⁺ + 1 - OMe - H₂O), 231 (100, M⁺ + 1 - CH₃CHO - MeOH), 204 (1.24, M⁺ + 1 - HCO₂Me - OH), 203 (9.56, M⁺ + 1 - HCO₂Me - H₂O), 141 (6.27, M⁺ + 1 - PhCO₂H - H₂O), 137 (1.99, PhCO₂CH₃ + 1), 127 (11.28, M⁺ + 1 - PhCO₂H - MeOH), 123 (1.77, PhCO₂H + 1), 110 (6.83, M⁺ + 1 - PhCO₂H - H₂O - OMe), 109 (87.15, M⁺ + 1 - PhCO₂H - H₂O - MeOH), and 105 (10.88, PhCO⁺).


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4-O-Benzoyl-2,6-dideoxy-3-C-methyl-β-L-lyxo-hexose (26). The methyl glycoside 25 (300 mg, 1.1 mmol) was mixed with 25% acetic acid (10 mL) and refluxed for 1 h, when t.l.c. monitoring (6:1 toluene--acetone, R<sub>f</sub> 25 = 0.3, R<sub>f</sub> 26 = 0.1) indicated that all of the starting compound 25 had been consumed. The solution
was evaporated in vacuo to a syrup that was dissolved in dichloromethane (2 mL) and put on a column of silica gel (10 g). On elution with dichloromethane and after discarding the fast moving impurities, 26 was collected as a colorless syrup (240 mg, 80%), \([\alpha]_D^{20} -71.5^\circ (c 0.5, \text{chloroform})\); \(\nu_{\max}^{\text{neat}}\) 3500-3300 (OH), 2980 (CH aryl), 1725-1700 (C=O), 1600 (C=C), 1450 (CH\_3), and 1400-1270 cm\(^{-1}\) (OH bend and C-O str.); \(m/z\) 267 \((8.41, M^+ + 1 - OH)\), 249 \((45.54, M^+ + 1 - H_2O)\), 232 \((6.5, M^+ + 1 - H_2O - OH)\), 231 \((36.76, M^+ + 1 - 2H_2O)\), 205 \((4.94, M^+ + 1 - CH_3CHO - H_2O)\), 203 \((1.03, M^+ + 1 - HCO_2H - H_2O)\), 145 \((3.27, M^+ + 1 - PhCO_2H)\), 127 \((19.41, M^+ + 1 - H_2O - PhCO_2H)\), 126 \((1.08, M^+ + 1 - 2H_2O - COPh)\), 125 \((2.46, M^+ + 1 - 2H_2O - PhCHO)\), 111 \((2.69, M^+ + 1 - H_2O - PhCO_2H - CH_4)\), 110 \((8.2, M^+ + 1 - H_2O - PhCO_2H - \text{OH})\), 109 \((82.47, M^+ + 1 - 2H_2O - PhCO_2H)\), 106 \((11.48, PhCHO)\), 105 \((100, PhCO^+)\), and 93 \((52.7, M^+ + 1 - 2H_2O - PhCO_2H - CH_3 - H)\).

Exact Mass for \(C_{14}H_{19}O_5\) (M + H\(^+\)): Calcd. 267.1232. Found: 267.1245.

1-O-Acetyl-4-O-benzoyl-2,6-dideoxy-3-C-methyl-\(\beta\)-\(\text{\textsuperscript{l}}\)-lyxo-hexopyranose (27). The free sugar 26 (300 mg, 1.13 mmol) was dissolved in pyridine (5 mL) and treated with acetic anhydride (0.3 mL, ~3 mmol) at 0\(^\circ\), and the solution was allowed to warm up to room temperature. After stirring for 3 h, t.l.c. monitoring indicated that the reaction was complete (6:1 toluene--acetone, \(R_f\) 26 = 0.1, \(R_f\) 27 = 0.33). The solution was poured over crushed ice (2 g) and extracted with dichloromethane (2 \(\times\) 5 mL). The organic phase was
successively washed with 5% aqueous hydrochloric acid (5 mL), saturated sodium hydrogen carbonate solution (5 mL) and water (5 mL), dried (sodium sulfate) and evaporated in vacuo. Toluene was added to and evaporated from the residue until it was free from pyridine to give a syrup, which on addition of hexane gave a crystalline solid (0.33 g, 95%) which after filtration was recrystallized from hexane to give white prisms of 27, m.p. 145°, $\left[\alpha\right]_{D}^{22} = -42.4^\circ$ (c 1, chloroform), $\nu_{\text{max}}^\text{Nujol}$ 3450 (OH), 2925 (CH aromatic), 1740 and 1730 (C=O esters), 1460 (CH), 1360 (CH$_3$), and 1260 cm$^{-1}$ (OH); m/z 291 (1.07 $M^+ + 1 - H_2O$), 265 (1.09, $M^+ + 1 - CH_3CHO$), 250 (6.85, $M^+ + 1 - OAc$), 249 (36.06, $M^+ + 1 - AcOH$), 233 (6.62, $M^+ + 1 - H_2O - AcO$), 231 (36.98, $M^+ + 1 - H_2O - AcOH$), 205 (1.64, $M^+ + 1 - CH_3CHO - AcOH$), 186 (1.27, $M^+ + 1 - H_2O - COPh$), 185 (12.22, $M^+ + 1 - H_2O - PhCHO$), 145 (1.67, $M^+ + 1 - OAc - PhCO$), 143 (1.44, $M^+ + 1 - CH_3CHO - PhCO_2H$), 127 (8.33, $M^+ + 1 - PhCO_2H - AcOH$), 123 (4.47, $PhCO_2H + 1$), 111 (3.28, $M^+ + 1 - PhCO_2H - OH - OAc$), 110 (12.45, $M^+ + 1 - PhCO_2H + 1 - H_2O - AcOH$), 106 (11.35, PhCHO$^+$), and 105 (98.73, PhCO$^+$).


4-O-Benzoyl-1,2-di-O-acetyl-3-C-methyl-8-L-lyxo-hexopyranose (28). A. A solution of acetate 27 (100 mg, 0.32 mmol) in pyridine (2 mL) was cooled to 0° and treated with acetic anhydride (0.1 mL, -1 mmol), in the presence of 4-dimethylaminopyridine (78 mg, 0.64 mmol), and stirred for 4 h during which time
the solution was allowed to come to room temperature. T.l.c. monitoring showed the complete disappearance of the monoacetate 27 (8:1 toluene--acetone, \( R_f \) 27 = 0.32, \( R_f \) 28 = 0.52). The solution was poured over crushed ice (2 g) and extracted with dichloromethane (2 x 3 mL). The organic layer was successively washed with 5% aqueous hydrochloric acid (2 mL), a solution of saturated sodium hydrogen carbonate (2 mL) and water (2 mL), dried (sodium sulfate) and evaporated in vacuo to a syrup. Toluene was added to and evaporated from the residue until it was free from pyridine. The resulting syrup was put over a column of silica gel (3 g) and eluted with dichloromethane. The fractions containing 28 were combined and evaporated to give a syrup (yield 102 mg, 91%), \([\alpha]_{D}^{22} = -32.4^\circ\) (c 1, chloroform); \(\nu_{\text{max}}\) neat 3000 (CH aromatic), 1750 (C=O), 1460 (CH), 1365 (OCOCH\(_3\)) and 1280--1200 cm\(^{-1}\) (C-O-C); m/z 307 (1.12, \(M^+ + 1\) - CH\(_3\)CHO), 292 (1.14, \(M^+ + 1\) - OAc), 291 (5.27, \(M^+ + 1\) - AcOH), 233 (1.64, \(M^+ + 1\) - 20Ac), 232 (6.93, \(M^+ + 1\) - AcOH - OAc), 231 (38.33, \(M^+ + 1\) - 2AcOH), 221 (1.59, \(M^+ + 1\) - CH\(_3\)CHO - CH\(_2\)=CHOAc), 205 (1.26, \(M^+ + 1\) - CH\(_3\)CHO - COCH\(_3\) - OAc), 203 (1.10, \(M^+ + 1\) - AcOH - HCO\(_2\)COCH\(_3\)), 185 (1.08, \(M^+ + 1\) - AcOH - PhCHO), 169 (3.22, \(M^+ + 1\) - AcOH - PhCO\(_2\)H), 165 (2.62, PhCO\(_2\)COCH\(_3\) + 1), 163 (1.70, \(M^+ + 1\) - HCO\(_2\)Ac - AcOH - HC\(_2\)CMe), 155 (2.01, \(M^+ + 1\) - PhCO\(_2\)CH\(_3\) - AcOH), 143 (1.75, \(M^+ + 1\) - PhCO\(_2\)H - 2COCH\(_3\)), 141 (6.65, \(M^+ + 1\) - PhCO\(_2\)H - AcOH - CO), 129 (6.69, \(M^+ + 1\) - AcOH - MeCH=CHOBz), 127 (10.85, \(M^+ + 1\) - AcOH - PhCO\(_2\)H - COCH\(_3\)), 123 (6.27, PhCO\(_2\)H + 1), 111 (7.95, \(M^+ + 1\) - AcOH - OBz - OAc), 110 (10.43, \(M^+ + 1\) - PhCO\(_2\)H - AcOH - OAc), 109 (100, \(M^+ + 1\) - PhCO\(_2\)H - 2AcOH) and 105 (72.09, PhCO).
Exact mass for C_{18}H_{22}O_7 (350.36), Calcd: 291.1232 (M+ - OAc).
Found: 291.1214.

B. From the free sugar 26: The same procedure as described above was used with 5 equivalents of acetic anhydride and 3 equivalents of 4-dimethylamino pyridine, to give the diacetate 28 in 90% yield.

Methyl 4-O-benzoyl-2,3,6-trideoxy-3-trifluoroacetamido-α-D-ribo-hexopyranoside (31). To a solution of the 6-bromo derivative 11 (20 g, 45.5 mmol) in dry methanol (100 mL) was added triethylamine (10 mL, 71.9 mmol) and Raney nickel catalyst (-30 g) and the mixture was shaken under hydrogen at 50 lb. in.^-2 for 24 h, whereupon t.l.c. indicated the reaction to be complete (Rf 31 = 0.52, Rf 11 = 0.57 in 6:1 toluene--acetone). The catalyst was removed by filtration, the filtrate evaporated, and the semicrystalline residue was dissolved in dichloromethane (500 mL) and washed twice with water (100 mL) to remove triethylammonium bromide, dried over sodium sulfate and evaporated to give 30 as a syrup (yield 15.1 g, 92%), which crystallized on addition of hexane and freezing. White needles of 31 were filtered off and recrystallized from ethyl acetate--hexane; m.p. 65-66°, [α]_D^{22} +60.7° (C 1, chloroform), ν_{max}^{Nujol} 3350 (NH), 2950 (CH aromatic), 1725 (C=O), 1550 (NH), 1460 (C-H), 1380 (C-F), and 1270 cm^-1 (C-O); m/z 362 (4.85, M+ + 1), 360 (1.27, M+ + 1 - H_2), 331 (10.19, M+ + 1 - OMe), 330 (51.69, M+ + 1 - MeOH), 267 (1.21, M+ + 1 - CH_3CHO - MeOH - HF), 241 (1.02, M+ + 1 - OBz), 226 (1.49, M+ + 1 - PhCO_2CH_3), 217 (2.05, M+ + 1 -
MeOH - NH₂COCF₃, 209 (1.05, M⁺ + 1 - MeOH - OBz), 208 (1.96, M⁺ + 1 - MeOH - PhCO₂H), 207 (3.87, M⁺ + 1 - MeOH - PhCO₂H - H), 197 (1.28, M⁺ + 1 - CH₃CHO - OBz), 182 (1.83, M⁺ + 1 - CH₃CHO - PhCO₂CH₂), 180 (1.24, M⁺ + 1 - HCO₂CH₃ - PhCO₂H), 167 (2.33, M⁺ + 1 - MeOH - CH₃CH=CHOBz - H), 166 (1.09, M⁺ + 1 - PhCO₂CH₃ - HCO₂CH₂), 143 (1.02, M⁺ + 1 - HCO₂F - OBz), 127 (2.17, M⁺ + 1 - NH₂COCF₃ - PhCO₂H), 123 (2.08, PhCO₂H + 1), 115 (9.52, M⁺ + 1 - NH₂COCF₃ - PhCO₂CH₃), 113 (3.27, NH₂COCF₃), 111 (1.39, M⁺ + 1 - MeOH - NH₂COCF₃ - PhCHO), 106 (6.4, PhCHO) 105 (52.68, PhCO), 95 (19.17, M⁺ + 1 - NH₂COCF₃ - MeOH - PhCO₂H), and 93 (100, M⁺ + 1 - NH₂COCF₃ - MeOH - PhCO₂H - H₂).

Anal. Calc. for C₁₆H₁₈F₃NΟ₅ (361.307): C, 53.19; H, 5.02; N, 3.88. Found: C, 53.10; H, 5.02; N, 3.82.

4-O-Benzoyl-2,3,6-trideoxy-3-trifluoroacetamido-β-ribo-hexose (32). A mixture of the glycoside 30 (1 g, 27.7 mmol) and 40% acetic acid (100 mL) was refluxed for 12 h, whereupon t.l.c. indicated that the hydrolysis was complete (Rf 31 = 0.52, Rf 32 = 0.27 in 6:1 toluene--acetone). Evaporation of the solvent gave a dark syrup (0.85 g, 88% yield) which could be used directly for the next step.

An analytically pure sample of 32 was obtained by column chromatography using 4:1 hexane--ethyl acetate as the eluent, which gave 31 as a colorless syrup, [α]D₂² +24.9° (c 0.5, chloroform), νₘₙₐₓ 3550-3200 (OH, NH), 2980 (CH aromatic), 1730-1690 (C=O), 1550 (NH), 1450 (C-H), and 1300-1150 cm⁻¹ (C-F); m/z 348 (4.39, M⁺ + 1), 346 (1.42, M⁺ + 1
- H₂), 234 (1.31, M⁺ + 1 - H₂O - NH₂COF₃), 209 (M⁺ + 1 - H₂O - OCHPh), 208 (2.04, M⁺ + 1 - H₂O - PhCO₂H), 207 (3.51, M⁺ + 1 - H₂O - PhCO₂H - H), 197 (1.51, M⁺ + 1 - COPh - HCO₂H), 192 (1.29, M⁺ + 1 - CH₃CHO - NHCOF₃), 183 (2.21, M⁺ + 1 - CH₃CHO - OCOPh), 181 (1.16, M⁺ + 1 - CH₃CHO - PhCO₂H - H), 180 (1.79, M⁺ + 1 - CH₃CHO - PhCHO - H₂O), 165 (1.34, M⁺ + 1 - CH₃CHO - OCOPh - H₂O), 131 (2.21, M⁺ + 1 - NHCOF₃ - COPh), 130 (1.3, M⁺ + 1 - NH₂COF₃ - COPh), 129 (2.32, M⁺ + 1 - PhCO₂H - COF₃), 128 (1.02, M⁺ + 1 - PhCO₂H - HCOF₃), 115 (9.89, M⁺ + 1 - NHCOF₃ - OCOPh), 114 (2.20, NH₃COF₃), 113 (8.61, NH₂COF₃), 112 (1.55, M⁺ + 1 - PhCO - NH₂COF₃), 111 (2.04, M⁺ + 1 - H₂O - NH₂COF₃ - PhCHO), 106 (13.0, PhCHO), 105 (100, PhCO⁺), 97 (2.36, M⁺ + 1 - H₂O - NHCOF₃ - OCOPh - H₂O), 96 (3.96, M⁺ + 1 - NHCOF₃ - H₂O - PhCO₂H), 95 (30.83, M⁺ + 1 - H₂O - NH₂COF₃ - PhCO₂H), and 93 (71.6, M⁺ + 1 - NH₂COF₃ - PhCO₂H - H₂).

**Anal. Calc. for C₁₅H₁₆F₃NO₅ (347.287):** C, 51.87; H, 4.64; N, 4.03. Found: C, 52.16; H, 4.84; N, 3.98.

1,5-Anhydro-4-0-benzoyl-2,3,6-trideoxy-3-trifluoroacetamide-D-ribo-hex-1-enitol (33). When a sample of the free sugar 32 (50 mg, 0.14 mmol) was distilled under reduced pressure (0.1 mm Hg) at 250° in a Kugelrohr apparatus, the distillate was found to be the corresponding glycal 33 (23 mg, 50% yield) which was obtained as a colorless syrup, [α]D²⁸ +44.5° (< 0.5, chloroform); νmax 3350 (NH), 1725 (CO), 1550 (NH), 1460 (CH₃), 1380 (C-O), and 1250-1100 cm⁻¹ (C=C-O-C, CF₃); m/z 330 (61.47, M⁺ + 1), 218 (1.14, M⁺ + 1 -
Ethanethiolysis of 32 leading to 4-O-benzoyl-2,3,6-trideoxy-3-trifluoroacetamido-\(\alpha\)-ribo-hexose diethyl dithioacetal (34). To a solution of the free sugar 32 (8 g, 23 mmol) in ethanethiol (100 mL), cooled in an ice bath, was added cold, concentrated hydrochloric acid (50 mL) and the mixture was stirred for 2 h at 0°, by which time t.l.c. monitoring indicated that all of the starting material \(R_f\) 32 = 0.25, 8:1 toluene--acetone) had been consumed. Three distinct spots were seen on t.l.c. having \(R_f\) values of 0.32, 0.55, and 0.61. The mixture was poured over crushed ice (200 g) and extracted with dichlormethane (4 x 100 mL). The combined extracts were washed with saturated aqueous sodium hydrogencarbonate solution (100 mL) and water (100 mL); dried (sodium sulfate) and evaporated in vacuo using a trap filled with sodium hypochlorite solution (commercially available Clorox bleach was found suitable for this purpose) in order to oxidize the malodorous ethanethiol. A viscous, pale-brown
syrup was obtained (10 g) which was then put on a column of silica gel
(300 g) and eluted with 4:1 hexane--ethyl acetate. The first fraction
collected was found to be a mixture of the α- and β- 1-thioglycosides of
32, viz., 35 and 36, respectively (yield 2 g, 24%). The next fraction
was also a mixture of two compounds, in the ratio 10:1, corresponding to
the 4-O-benzoyl- and 5-O-benzoyl- diethyl dithioacetals of 32,
respectively; yield 7.8 g (75%).

For analytical purposes, a small amount of each of these compounds
was isolated pure by HPLC and the following data were recorded:

\[
\text{4-O-Benzoyl-2,3,6-trideoxy-3-trifluoroacetamido-}
\text{D-ribo-hexose diethyl dithioacetal (34); syrup, } [\alpha]_D^{25}
\text{ -8.1° (c 1, chloroform); } \nu_{\text{max}} \text{ 3400 (NH), 3200 (OH),}
\text{1725 (C=O), 1550 (NH), 1450 (CH₃), and 1275-1175 cm}^{-1}
\text{(CF); } m/z \text{ 454 (0.09, } M^+ + 1 \text{), 453 (0.47, } M^+ \text{), 392}
\text{(0.41, } M^+ + 1 \text{ - EtSH), 359 (1.34, } M^+ + 1 \text{ - EtSH -}
\text{H₂O - CH₃), 358 (8.15, } M^+ + 1 \text{ - EtSH - H₂O - CH₄), 332 (3.02, } M^+ + 1 \text{ -}
\text{PhCO₂H), 331 (18.5, } M^+ + 1 \text{ - PhCO₂H - H), 330 (100, } M^+ + 1 \text{ - 2EtSH), 272}
\text{(3.69, } M^+ + 1 \text{ - SEt - OCOPh), 270 (4.9, } M^+ + 1 \text{ - EtSH - PhCO₂H), 226}
\text{(1.73, } M^+ + 1 \text{ - PhCO - EtSH - SEt), 217 (1.53, } M^+ + 1 \text{ - 2EtSH -}
\text{NH₂COCF₃), 157 (1.01, } M^+ + 1 \text{ - PhCO₂H - EtSH - NHCOCF₃), 123 (4.79,}
\text{PhCO₂H + 1), 105 (3.91, PhCO), 95 (10.41, } M^+ + 1 \text{ - PhCO₂H - 2EtSH -}
\text{NHCOCF₃).}
\]

\text{Anal. Calc. for } C_{19}H_{26}F_{3}NO₄S₂ (453.527): C, 50.32; H, 5.78; F,
12.57; N, 3.09; O, 14.11; S, 14.14. Found: C, 50.41; H, 5.82; N, 3.08;
S, 14.19.
5-O-Benzoyl-2,3,6-trideoxy-3-trifluoroacetamido-D-ribo-hexose diethyl dithioacetal (35). This compound had $[\alpha]_D^{25} -11.5^\circ$ (c 0.5, chloroform); $\nu_{\text{max}}$ neat 3400 (NH), 3200 (OH), 1725 (CO), 1550 (NH), 1450 (CH$_3$), and 1275-1175 cm$^{-1}$ (CF); m/z 454 (0.12, M$^+$ + 1), 453 (0.66, M$^+$), 392 (4.61, M$^+$ + 1 - EtSH), 391 (0.68, M$^+$ + 1 - EtSH - H$_2$O), 391 (7.26, M$^+$ + 1 - EtSH - H$_2$O - CH$_3$), 331 (17.09, M$^+$ + 1 - OCOPh), 330 (100, M$^+$ + 1 - 2EtSH), 272 (2.78, M$^+$ + 1 - SEt - OCOPh), 244 (1.29, M$^+$ + 1 - CH$_3$CHOCOPh - SEt), 218 (2.69, M$^+$ + 1 - 2EtSH - NHCOCF$_3$), 217 (19.29, M$^+$ + 1 - 2EtSH - NH$_2$COF$_3$), 157 (1.85, M$^+$ + 1 - PhCO$_2$H - EtSH - NHCOF$_3$), and 95 (8.41, M$^+$ + 1 - PhCO$_2$H - 2EtSH - NHCOF$_3$).

Anal. Calc. for C$_9$H$_{26}$F$_3$NO$_4$S$_2$ (453.527): C, 50.32; H, 5.78; F, 12.57; N, 3.09; O, 14.11; S, 14.14. Found: C, 50.37; H, 5.82; N, 3.06; S, 14.06.

Ethyl 4-O-benzoyl-2,3,6-trideoxy-3-trifluoroacetamido-1-thio-α-D-ribo-hexopyranoside (36). This compound was obtained as a syrup from the first fraction of the column and had $[\alpha]_D^{25} +151.5^\circ$ (c 0.5, chloroform); $\nu_{\text{max}}$ neat 3350 (NH), 1730 (CO), 1540 (NH), 1450 (CH$_3$), and 1250-1150 cm$^{-1}$ (CF); m/z 392 (0.04, M$^+$ + 1), 358 (7.9, M$^+$ + 1 - CH$_3$ - F), 331 (17.06, M$^+$ + 1 - SEt), 330 (100, M$^+$ + 1 - EtSH), 270 (1.19, M$^+$ + 1 - PhCO$_2$H), 244 (1.19, M$^+$ + 1 - EtSH - HCOF$_3$ - CH$_4$), 226 (4.1, M$^+$ + 1 - EtSH - OCOPh), 218 (1.46, M$^+$ + 1 - EtSH - NHCOF$_3$), 217 (11.37, M$^+$ + 1 - EtSH - NH$_2$COF$_3$), 208 (4.28, M$^+$
+ 1 - EtSH - PhCO₂H), 157 (1.57, M⁺ + 1 - PhCO₂H - NH₂COCF₃), 133 (4.13, M⁺ + 1 - F₃CCONHCH=CHOBz), 96 (2.43, M⁺ + 1 - EtSH - PhCO₂H - NHCOCF₃), and 95 (31.34, M⁺ + 1 - EtSH - PhCO₂H - NH₂COCF₃).

Anal. Calc. for C₁₇H₂₀F₃NO₄S (391.401): C, 52.16; H, 5.11; N, 3.58; S, 8.19; O, 16.35; F, 14.56. Found: C, 51.5; H, 5.06; N, 3.53; S, 8.06.

Ethyl 4-O-benzoyl-2,3,6-trideoxy-3-trifluoroacetamido-1-thio-β-D-ribo-hexopyranoside (37). This compound was found to have [α]D¹⁰ +10.6° (c 0.5, chloroform); νmax 3420 (NH), 1740-1720 (CO), 1550 (NH), 1450 (CH₃), and 1300-1150 cm⁻¹ (CF); m/z 392 (3.26, M⁺ + 1), 359 (5.33, M⁺ + 1 - 2CH₄ - H), 358 (27.22, M⁺ + 1, M⁺ + 1 - CH₃ - F), 310 (1.15, M⁺ + 1 - EtSH - HF), 279 (1.75, M⁺ + 1 - NH₂COCF₃), 271 (1.12, M⁺ + 1 - OCOPh), 270 (1.28, M⁺ + 1 - PhCO₂H), 245 (1.08, M⁺ + 1 - EtSH - CF₃ - CH₄), 244 (5.78, M⁺ + 1 - EtSH - HCF₃ - CH₄), 235 (3.92, M⁺ + 1 - NH₂COCF₃ - CH₃CHOH), 227 (2.26, M⁺ + 1 - SEt - COPh), 226 (25.67, M⁺ + 1 - EtSH - COPh), 218 (5.84, M⁺ + 1 - EtSH - NHCOCF₃), 217 (43.13, M⁺ + 1 - EtSH - NH₂COCF₃), 208 (2.2, M⁺ + 1 - EtSH - PhCO₂H), 157 (7.63, M⁺ + 1 - PhCO₂H - NH₂COCF₃ - H), and 95 (14.41, M⁺ + 1 - EtSH - PhCO₂H - NH₂COCF₃).

Anal. Calc. for C₁₇H₂₀F₃NO₄S (391.401): C, 52.16; H, 5.11; N, 3.58; S, 8.19; O, 16.35; F, 14.56. Found: C, 52.01; H, 5.15; N, 3.52; S, 8.06.
4-O-Benzoyl-5-O-(p-toluenesulfonyl)-2,3,6-trIDEOXY-3-trifluoroacetamido-\(\beta\)-ribo-hexose diethyl dithioacetal (38). To a mixture of dithioacetals 34 and 35 (0.100 g, 0.22 mmol) in dry pyridine (2 mL) at 0° was added recrystallized p-toluenesulfonic chloride (0.200 g, 1.05 mmol) and stirred, while letting it come to room temperature. After 24 h, t.l.c. analysis (6:1 toluene—acetone) showed a very faint spot for the starting material \((R_f = 0.39)\) giving 38 \((R_f = 0.6)\) as the sole product. The reaction mixture was poured into ice-water (5 mL) and extracted with dichloromethane (2 × 5 mL). The organic phase was then washed successively with 5% hydrochloric acid (2 mL), saturated sodium hydrogencarbonate (2 mL), and water (2 mL), dried over sodium sulfate and evaporated in vacuo to yield a pale-yellow syrup. This was put on a column of silica gel (5 g) and eluted with 4:1 hexane-ethyl acetate solution giving 38 in the first fraction (0.119 g, yield 89%). \([\alpha]_D^{23} +11.10 (\varphi 1.0, \text{chloroform})\); \(v_{\text{max}}\) 3320 (NH), 3000 (C-H aromatic), 1750 (C=O), 1550 (NH), 1450 (C-N), and 1175-1200 cm\(^{-1}\) (C-F); m/z (rel. intensity): 607 (1.26, M\(^+\)), 546 (8.58, M\(^+\) - SC\(_2\)H\(_5\)), 433 (8.46, M\(^+\) - C\(_2\)H\(_5\)SH - NHCOCF\(_3\)), 436 (5.17, M\(^+\) - OTs), 374 (25.27, M\(^+\) - TsOH - SC\(_2\)H\(_5\)), 330 (3.04, M\(^+\) - PhCO\(_2\)H - Ts), 252 (18.1, M\(^+\) - PhCO\(_2\)H - TsOH - SET), 190 (9.79, M\(^+\) - PhCO\(_2\)H - TsOH - 2EtSH), 199 (2.00, CH\(_3\)-CH=OTs), 199 (2.00, M\(^+\) - 2EtSH - TsOH - NHCOCF\(_3\)), 212 (32.09, M\(^+\) - 2EtSH - TsOH - CF\(_3\)CHO - H), 105 (100, +COPh), 155 (16.19, Ts\(^+\)).

**Anal. Calc.** for C\(_{26}\)H\(_{32}\)F\(_3\)NO\(_6\)S\(_2\) (607.707): C, 51.38; H, 5.30; N, 2.30; S, 15.80. **Found:** C, 50.90; H, 5.29; N, 2.20; S, 15.29.
S_N2 Displacement of 5-O-p-tolylsulfonyl derivative 38 leading to the oxazine derivative 39. To a solution of 5-O-p-tolylsulfonyl derivative 38 (60 mg, -0.1 mmol) in N,N-dimethyl formamide (5 mL) was added potassium thioacetate (60 mg, -0.5 mmol) and the mixture was heated to 100° under an atmosphere of nitrogen for 1 h at which point t.l.c. monitoring indicated that the reaction was complete (Rf 38 = 0.6, Rf 39 = 0.9, 6:1 toluene--acetone). The solvent was removed in vacuo and the residue was taken up in dichloromethane (5 mL), and washed with water (2 mL), dried (sodium sulfate) and evaporated in vacuo to a thick dark syrup, which was put on a column of silica gel (3 g) and eluted with 10:1 hexane--ethyl acetate to afford 39 as a red-brown syrup (33 mg, 77% yield). m/z 435 (1.36, M^+), 394 (3.94, M^+ - Set), 330 (3.76, M^+ - COPh), 286 (1.14, M^+ - CH_2CH(SEt)_2), 284 (1.82, M^+ - CH_3CH(SEt)_2 - H), 253 (3.43, M^+ - PhCO_2 - Set), 252 (9.59, M^+ - PhCO_2H - Set), 251 (3.11, M^+ - PhCO_2H - EtSH), 236 (1.18, M^+ - PhCO_2H - EtSH - CH_3), 222 (8.73, M^+ - PhCO_2H - CH_3 - EtSMe), 212 (5.55, M^+ - PhCO_2CH=CHCH_3 - Set), 182 (2.83, M^+ - PhCO_2CH=CHCH_3 - EtSH - Et), 176 (1.22, M^+ - PhCO_2CH=CHCH_3 - COCF_3), 171 (16.78, M^+ - CH_3CH(SEt)_2 - CF_3CO - CH_4 - H), 164 (4.76, M^+ - PhCO_2H - CH_2CH(SEt)_2), 152 (1.54, M^+ - PhCO_2Me - CH_2CH(SEt)_2), 150 (1.97, M^+ - PhCO_2CH=CHCH_3 - EtSH - Set), 149 (2.11, CH_2CH(SEt)_2), 135 (3.22, CH(SEt)_2), 105 (100, PhCO), and 95 (7.58, N≡C-CF_3).

Exact mass for C_{19}H_{24}F_{3}NO_{3}S_{2}, Calcd.: 435.1150 (M^+). Found: 435.1192.
2,3,6-Trideoxy-3-trifluoroacetamido-\(\alpha\)-ribo-hexose diethyl dithioacetal (40). A methanolic solution (50 mL) of dithioacetals 34 and 35 containing 1 M sodium methoxide (4 mL) was stirred for 0.5 h at room temperature. At this point t.l.c. analysis (6:1 toluene--acetone) showed complete disappearance of the starting material 34 and 35 (\(R_f = 0.39\)) giving 40 (\(R_f = 0.1\)) as the sole product. Dowex 50 (H\(^+\)) resin (1 g) was then added and the mixture was stirred for 5 min, after which time it was filtered and the filtrate evaporated to dryness to afford a clear syrup which on addition of ethyl acetate (1 mL) and then hexane (5 mL) yielded white, flaky crystals of 40 (1.4 g, 80\%). This was then recrystallized from ethyl acetate--hexane to give analytically pure 40, m.p. 59–60\(^\circ\), \([\alpha]_D^{23} = -12.0^\circ\) (c 1.0, chloroform); \(\nu_{\text{max}}\) 3450–3400 (NH and OH), 1700 (C=O), 1550 (NH), 1475 (C-N) and 1200–1175 cm\(^{-1}\) (CF); m/z 349 (0.59, M\(^+\)), 288 (1.77, M\(^+\) - SEt), 270 (2.07, M\(^+\) - EtSH - CH\(_3\)CHOH), 226 (100, M\(^+\) - EtSH - SEt), 158 (5.9, M\(^+\) - EtSH - NHCOCF\(_3\) - OH), 113 (25.72, NH\(_2\)COCF\(_3\)), and 95 (4.28, M\(^+\) - EtSH - NH\(_2\)COCF\(_3\) - H\(_2\)O - SEt).

**Anal. Calc.** for C\(_{12}\)H\(_{22}\)F\(_3\)NO\(_3\)S\(_2\) (349.43): C, 41.25; H, 6.35; N, 4.01; S, 18.35. Found: C, 41.33; H, 6.35; N, 3.99; S, 18.34.
Methyl 2,3,6-trideoxy-3-trifluoroacetamido-α- and -β-D-ribo-hexofuranosides (41) and (42). A mixture of dithioacetal 40 (3.3 g, 9.4 mmol) and finely powdered 3Å molecular sieves (5 g) in dry methanol (20 mL) was stirred for 1 h. To this mixture were added yellow mercuric oxide (8.11 g, 37.6 mmol) and mercuric chloride (5.2 g, 18.8 mmol), predried azeotropically with benzene, and the mixture was stirred for 8 h at room temperature. At this point, t.l.c. monitoring indicated that all of the starting material (R_f = 0.26, 14:1 chloroform--methanol) had been consumed. The mixture was filtered through Celite and washed thoroughly with acetone. The combined filtrate and washings were then evaporated from the residue repeatedly until all of the pyridine had been removed. Water was added to the solid residue and the precipitated mercuric chloride--pyridine complex was filtered off and washed with water. The filtrate and washings were combined and evaporated in vacuo to a solid residue; yield 3 g (100%).

This was then applied to a column of silica gel (250 g) that was eluted with chloroform. The first fraction collected was found to be the α-furanoside 41 (yield 0.95 g, 39%), following which the β-furanoside 42 was collected (yield 1.02 g, 42%), as a pale-yellow solid.

Compounds 41 and 42 were recrystallized from ethyl acetate to give white needles, for which the following data were recorded.
Methyl 2,3,6-trideoxy-3-trifluoroacetamido-\(\alpha\)-ribo-hexofuranoside (41); white fluffy needles, m.p. 75--78°, \([\alpha]_D^{22} +45.5°\) (c 1, chloroform); 
\(\nu_{\max}^{\text{Nujol}}\) 3400 (NH), 3300 (OH), 1700 (C=O), 1575 (NH), 1450 (C-N) and 1250-1100 cm\(^{-1}\) (CF); m/z 227 (7.88, M\(^+\) + 1 - OMe), 226 (100, M\(^+\) + 1 - MeOH), 224 (1.89, M\(^+\) + 1 - MeOH - H\(_2\)), 212 (1.43, M\(^+\) + 1 - EtOH), 208 (2.94, M\(^+\) + 1 - MeOH - H\(_2\)O), 183 (1.26, M\(^+\) + 1 - HCO\(_2\)CH\(_3\) - CH\(_3\)), 180 (1.02, M\(^+\) + 1 - MeOH - EtOH), 158 (8.15, M\(^+\) + 1 - H\(_2\)O - HCOCF\(_3\) - H\(_2\)), 141 (2.30, M\(^+\) + 1 - H\(_2\)O - HCOCF\(_3\)), 140 (12.78, M\(^+\) + 1 - H\(_2\)O - HCOCF\(_3\) - H\(_2\)), 127 (1.65, M\(^+\) + 1 - MeOH - HCOCF\(_3\) - H - COC\(_3\)F\(_2\)), 115 (2.65, M\(^+\) + 1 - OMe - NHCOCF\(_3\)), 114 (49.4, M\(^+\) + 1 - MeOH - NHCOCF\(_3\)), 113 (79.6, M\(^+\) + 1 - MeOH - NH\(_2\)COF\(_3\)), 111 (4.64, M\(^+\) + 1 - MeOH - H\(_2\)O - COCF\(_3\)), 101 (1.20, M\(^+\) + 1 - NHCOCF\(_3\) - CH\(_3\)CHOH), 100 (3.91, M\(^+\) + 1 - NH\(_2\)COF\(_3\) - CH\(_3\)CHOH), 99 (1.81, M\(^+\) + 1 - MeOH - NHCOCF\(_3\) - CH\(_3\)), 97 (3.33, M\(^+\) + 1 - MeOH - NH\(_2\)COF\(_3\) - CH\(_3\) - H), and 95 (15.53, M\(^+\) + 1 - MeOH - NH\(_2\)COF\(_3\) - H\(_2\)O).

Anal. Calc. for C\(_9\)H\(_{14}\)NF\(_3\)O\(_4\) (257.207): C, 42.03; H, 5.49; N, 5.45.

Found: C, 41.77; H, 5.50; N, 5.38.

Methyl 2,3,6-trideoxy-3-trifluoroacetamido-\(\beta\)-ribo-hexofuranoside (42). This compound had m.p. 126-128°, \([\alpha]_D^{22} -91.0°\) (c 1, chloroform); 
\(\nu_{\max}^{\text{Nujol}}\) 3400 (NH), 3250 (OH), 1700 (C=O), 1575 (NH), 1450 (C-N), and 1200 cm\(^{-1}\) (CF); m/z 227 (12.86, M\(^+\) + 1 - OMe), 226 (97.95, M\(^+\) + 1 - MeOH), 212 (2.62, M\(^+\) + 1 - EtOH), 208 (3.17, M\(^+\) + 1 - MeOH - H\(_2\)O), 194 (1.95, M\(^+\) + 1 - OMe - CH\(_3\)), 183 (2.4, M\(^+\) + 1 - HCO\(_2\)CH\(_3\) - CH\(_3\)), 180 (2.09, M\(^+\) + 1 - MeOH - EtOH), 158 (27.61, M\(^+\) + 1 - HCOCF\(_3\) - H\(_2\)), 153 (4.44, M\(^+\) + 1 - HCO\(_2\)CH\(_3\) - CH\(_3\)CHOH), 140 (3.04, M\(^+\) + 1 - HCOCF\(_3\) - H\(_2\) - H\(_2\)O), 127 (10.17, M\(^+\) + 1 - MeOH - COF\(_3\) - H\(_2\)), 114 (28.03, M\(^+\) + 1 - MeOH - NHCOF\(_3\)), 13
(100, $M^+ + 1 - \text{MeOH} - \text{NH}_2\text{CCOF}_3$), 111 (1.85, $M^+ + 1 - \text{MeOH} - \text{H}_2\text{O} - \text{CCOF}_3$), 101 (3.76, $M^+ + 1 - \text{NHCCOF}_3 - \text{CH}_3\text{CHOH}$), 100 (9.00, $M^+ + 1 - \text{NH}_2\text{CCOF}_3 - \text{CH}_3\text{CHOH}$), 97 (1.49, $M^+ + 1 - \text{MeOH} - \text{NH}_2\text{CCOF}_3 - \text{CH}_4$), 96 (2.1, $M^+ + 1 - \text{MeOH} - \text{OH} - \text{NH}_2\text{CCOF}_3$), and 95 (26.11, $M^+ + 1 - \text{MeOH} - \text{NH}_2\text{CCOF}_3 - \text{H}_2\text{O}$).

Anal. Calc. for $\text{C}_{49}\text{H}_{14}\text{F}_3\text{NO}_4$ (257.207): C, 42.03; H, 5.49; N, 5.45. Found: C, 42.09; H, 5.51; N, 5.42.

Methyl 2,3,6-trideoxy-3-trifluoroacetamido-5-0-(p-tolylsulfonyl)-a-D-ribo-hexofuranoside (43). The furanoside 41 (1 g, 3.9 mmol) was dissolved in dry pyridine (10 mL) and cooled to 0° with an ice bath. To the cold solution was added p-toluenesulfonyl chloride (1.5 g, 8 mmol), and the solution was allowed to come to room temperature while stirring. The stirring was continued for 30 h at room temperature, at which point t.l.c. monitoring indicated that all of the starting material 41 ($R_f = 0.43$, 14:1 chloroform-methanol) had been consumed. The solution was poured over crushed ice (5 g) and extracted with dichloromethane (3 x 25 mL). The combined extracts were successively washed with 5% hydrochloric acid (25 mL), saturated sodium hydrogencarbonate (25 mL), and water (25 mL), dried (anhydrous sodium sulfate), and evaporated in vacuo to a syrup. Toluene was added to and evaporated from the residue until it was free from pyridine. To the resulting syrup was added ethyl acetate (2 mL) and hexane (5 mL) and the solution was cooled to 0° when white needles appeared. The crystallization was allowed to complete by keeping the
mixture overnight in the freezer, after which time it was filtered and washed with cold hexane, to give white needles of 43 (yield 1.5 g, 93%). This was then recrystallized from ethyl acetate--hexane to give analytically pure 43, m.p. 51°, $[\alpha]_D^{23} 47.40$ (c 0.5, chloroform); $\nu_{\text{max}}^\text{Nujol}$ 3400 (NH), 1730 (C=O), 1550 (NH), 1440 (C-N), 1360 (S=O), and 1200-1175 cm$^{-1}$ (CF); m/z 412 (1.57, M$^+$ + 1), 392 (2.53, M$^+$ + 1 - HF), 381 (9.44, M$^+$ + 1 - OMe), 380 (63.87, M$^+$ + 1 - MeOH), 360 (1.21, M$^+$ + 1 - HF - MeOH), 267 (4.96, M$^+$ - MeOH - NHCOCF$_3$), 241 (2.72, M$^+$ + 1 - OTs), 240 (29.57, M$^+$ + 1 - TsOH), 212 (7.98, M$^+$ + 1 - CH$_3$CH-OTs), 208 (18.98, M$^+$ + 1 - TsOH - MeOH), 183 (1.88, M$^+$ - CH$_3$CH(OTs)CHO), 182 (1.87, M$^+$ + 1 - CH$_3$CH-OTs - OMe), 173 (2.02, TsOH$_2$), 157 (1.05, TsOH - CH$_3$), 101 (1.54, M$^+$ + 1 - CH$_3$CH-OTs - NHCOCF$_3$), 96 (9.33, M$^+$ + 1 - MeOH - NH$_2$COCF$_3$ - OTs) and 95 (100, M$^+$ + 1 - MeOH - NH$_2$COCF$_3$ - TsOH).

Anal. Calc. for C$_{16}$H$_{20}$F$_3$N$_{0.6}$S (411.39): C, 46.71; H, 4.9; N, 3.40; S, 7.79. Found: C, 46.64; H, 4.95; N, 3.33; S, 7.86.

Methyl 2,3,6-trideoxy-3-trifluoroacetamido-5-O-(p-tolylsulfonyl)-$\beta$-D-ribo-hexofuranoside (44). The furanoside 41 (1 g, 3.9 mmol) was dissolved in dry pyridine (10 mL) and cooled to 0° with an ice-bath. To the cold solution was added p-toluenesulfonyl chloride (1.5 g, 8 mmol) and the solution was allowed to come to room temperature while stirring. The stirring was continued for 30 h at room temperature at which point t.l.c. monitoring indicated that all of the starting material 41 ($R_f = 0.4$, 14:1 chloroform--methanol) had been consumed. The solution was poured over crushed ice
(5 g) and extracted with dichloromethane (3 x 25 mL). The combined extracts were successively washed with 5% hydrochloric acid (25 mL), saturated sodium hydrogencarbonate (25 mL), and water (25 mL), dried (anhydrous sodium sulfate), and evaporated in vacuo to a syrup. Toluene was added to and evaporated from the residue until it was free from pyridine. The resulting syrup was put on a column of silica gel (40 g) and eluted with dichloromethane to give the tosylate 44 as a thick, colorless syrup (yield 1.35 g, 96.5%).

A small amount of this syrup was further purified by high performance liquid chromatography and the following data were recorded.

\[ [\alpha]_D^{23} = -45^\circ (c 0.5, \text{chloroform}), \nu_{\text{max}}^{\text{neat}} 3400 (\text{NH}), 1730 (\text{C=O}), 1550 (\text{NH}), 1440 (\text{C-N}), 1360 (\text{S=O}), \text{and} 1200-1175 \text{ cm}^{-1} (\text{CF}); m/z 412 (0.7, M^+ + 1), 381 (1.97, M^+ + 1 - \text{OMe}), 380 (10.03, M^+ + 1 - \text{MeOH}), 240 (1.55, M^+ + 1 - \text{TsOH}), 226 (3.26, M^+ + 1 - \text{CH}_3\text{CHOTs}), 208 (4.24, M^+ + 1 - \text{TsOH} - \text{MeOH}), 183 (M^+ + 1 - \text{CH}_2\text{CH(OTs)} - \text{CHOH}), 182 (3.89, M^+ + 1 - \text{CH}_3\text{CHOTs} - \text{OMe}), 157 (1.77, \text{TsOH} - \text{CH}_3), 155 (5.97, \text{Ts}^+), 101 (4.44, M^+ + 1 - \text{CH}_3\text{CHOTs} - \text{NHCOCF}_3), 96 (4.55, M^+ + 1 - \text{MeOH} - \text{NH}_2\text{COCF}_3 - \text{OTs}), 95 (43.95, M^+ + 1 - \text{MeOH} - \text{NH}_2\text{COCF}_3 - \text{TsOH}), 93 (100, M^+ + 1 - \text{MeOH} - \text{NH}_2\text{COCF}_3 - \text{TsOH} - \text{H}_2).

Anal. Calc. for $C_{16}H_{20}F_3N_6O_6S$ (411.39): C, 46.71; H, 4.9; N, 3.40; S, 7.79. Found: C, 46.57; H, 5.21; N, 3.29; S, 7.56.
Methyl 5-S-acetyl-2,3,6-trideoxy-3-trifluoroacetamido-5-thio-α-L-lyxohexofuranoside (45). The crystalline 5-O-tosyl furanoside 43 (0.5 g, 1.2 mmol) was dissolved in dry N,N-dimethylformamide (50 mL). Potassium thioacetate (0.4 g, 3.6 mmol) was added to the solution and the mixture was heated for 4 h, at 100°C while keeping it under an atmosphere of nitrogen. At that point, t.l.c. monitoring showed that all of the starting material 43 had been consumed (Rf 43 = 0.45, 8:1 toluene--acetone). The solvent was then removed in vacuo and the residue partitioned between dichloromethane (75 mL) and water (50 mL). The organic layer was dried (anhydrous sodium sulfate), filtered and evaporated in vacuo to a thick dark syrup which was put over a column of silica gel (20 g) and eluted with 4:1 hexane--dichloromethane. The first fraction collected after discarding the fast moving impurities gave 45 as a syrup after evaporation (yield 0.23 g, 61%), [α]_D^{23} +75.7° (c 0.5, chloroform); ν_{max}^{neat} 3350 (NH), 2950 (CH aliphatic), 1725 (C=O), 1685 (C=O SAC), 1550 (NH), 1450 (CH₃) and 11200-1100 cm⁻¹ (C-F); m/z 316 (10.19, M⁺ + 1), 314 (11.29, M⁺ + 1 - H₂), 300 (1.96, M⁺ + 1 - CH₄), 285 (12.51, M⁺ + 1 - OMe), 284 (100, M⁺ + 1 - MeOH), 241 (2.65, M⁺ + 1 - SAC), 240 (8.42, M⁺ + 1 - AcSH), 226 (1.71, M⁺ + 1 - AcSCH₃), 225 (2.01, M⁺ + 1 - AcS - CH₄), 224 (13.69, M⁺ + 1 - AcSH - CH₄), 212 (12.4, M⁺ + 1 - EtSCOCH₃), 208 (7.2, M⁺ + 1 - AcSH - MeOH), 206 (6.12, M⁺ + 1 - AcSH - MeOH - H₂), 203 (1.22, M⁺ + 1 - NHCOCF₃), 202 (1.02, M⁺ + 1 - MeCOCF₃), 183 (9.9, M⁺ + 1 - CH₃CH(SAc)CHOH), 182 (12.38, M⁺ + 1 - CH₃CH(SAc)CH₂OH), 180 (6.81, M⁺ + 1 - EtSAC - MeOH), 171 (49.84, M⁺ + 1 - NH₂COCF₃ - MeOH), 129 (22.78, M⁺
+ 1 - NHCOCF<sub>3</sub> - SAc), 127 (22.34, M<sup>+</sup> + 1 - NH<sub>2</sub>COCF<sub>3</sub> - AcSH), 111 (30.3, M<sup>+</sup> + 1 - NH<sub>2</sub>COCF<sub>3</sub> - AcSH - H<sub>2</sub>), 101 (14.42, M<sup>+</sup> + 1 - CH<sub>3</sub>CHSAc - NHCOCF<sub>3</sub>), 99 (24.05, M<sup>+</sup> + 1 - CH<sub>3</sub>CH<sub>2</sub>SAc - NH<sub>2</sub>COCF<sub>3</sub>), and 95 (91.47, M<sup>+</sup> + 1 - AcSH - MeOH - NH<sub>2</sub>COCF<sub>3</sub>).

Exact mass for C<sub>11</sub>H<sub>16</sub>F<sub>3</sub>NO<sub>4</sub>S (315.311), Calcd.: 284.0568 (M<sup>+</sup> - OCH<sub>3</sub>). Found: 284.0656.

The compound following immediately after 45 (R<sub>f</sub> = 0.4, 6:1 toluene--acetone), was collected from the next fraction which on evaporation gave a syrup (37 mg, 10% yield). This was found to be the 5-epimer of the thioacetate 45, viz., methyl 5-S-acetyl-2,3,6-trideoxy-3-trifluoroacetamide-<i>α</i>-ribo-5-thiohexofuranoside (47). An analytically pure sample of 47 was obtained by HPLC using 4:1 hexane--ethylacetate as the eluent, and the following data were recorded, [α]<sup>23</sup> <sub>D</sub> +51.5° (c 0.5, chloroform); ν<sub>max</sub> neat 3350 (NH), 2950 (CH<sub>3</sub>, aliphatic), 1725 (C=O), 1685 (C=O SAc), 1550 (NH), 1450 (CH<sub>3</sub>), and 1120-1100 cm<sup>-1</sup> (CF<sub>3</sub>); m/z 316 (4.07, M<sup>+</sup> + 1), 285 (12.70, M<sup>+</sup> + 1 - OMe), 284 (100, M<sup>+</sup> + 1 - MeOH), 241 (2.50, M<sup>+</sup> + 1 - SAc), 240 (6.27, M<sup>+</sup> + 1 - AcSH), 226 (2.24, M<sup>+</sup> + 1 - AcSCH<sub>3</sub>), 225 (3.17, M<sup>+</sup> + 1 - AcSH - CH<sub>3</sub>), 224 (22.14, M<sup>+</sup> + 1 - AcSH - CH<sub>3</sub> - H), 212 (5.18, M<sup>+</sup> + 1 - EtSCOCH<sub>3</sub>), 208 (7.23, M<sup>+</sup> + 1 - AcSH - MeOH), 206 (3.91, M<sup>+</sup> + 1 - AcSH - MeOH - H<sub>2</sub>), 203 (1.12, M<sup>+</sup> + 1 - NHCOCF<sub>3</sub>), 202 (1.12, M<sup>+</sup> + 1 - CH<sub>3</sub> - HCOCF<sub>3</sub>), 183 (6.80, M<sup>+</sup> + 1 - CH<sub>3</sub>CH(SAc)CHOH), 182 (8.18, M<sup>+</sup> + 1 - CH<sub>3</sub>CH(SAc)CH<sub>2</sub>OH), 180 (4.57, M<sup>+</sup> + 1 - EtSAc - MeOH), 171 (14.29, M<sup>+</sup> + 1 - NH<sub>2</sub>COCF<sub>3</sub> - MeOH), 129 (14.30, M<sup>+</sup> + 1 - NHCOCF<sub>3</sub> - SAc), 127 (20.1, M<sup>+</sup> + 1 - NH<sub>2</sub>COCF<sub>3</sub> -...
Methyl 5-S-acetyl-2,3,6-trideoxy-3-trifluoroacetamido-5-thio-α-L-lyxohexofuranoside (46). The 5-O-tosyl furanoside 44 (0.8 g, 1.9 mmol) was dissolved in dry N,N-dimethylformamide (100 mL). Potassium thioacetate (0.65 g, 5.7 mmol) was added and the mixture was heated to 100°C for 8 h, during which time it was kept under an atmosphere of nitrogen, when t.l.c. monitoring showed that all of the starting material 44 had been consumed (Rf 44 = 0.36, 14:1 chloroform--methanol). The solvent was then removed in vacuo and the residue was taken up in dichloromethane (100 mL), and washed with water (50 mL). The organic phase after separation was dried (anhydrous sodium sulfate), filtered and evaporated in vacuo to a thick, dark syrup, which was passed through a column of silica gel (30 g) in order to remove the fast-moving coloring impurities using 1:1 hexane--dichloromethane as the eluent. The fraction following immediately after removal of the impurities rendered white crystals of 46 after evaporation. this was recrystallized from hexane to give pure white prisms of the thioacetate 46; yield 0.39 g (65%), m.p. 72-73°C, [a]D 23 -65° (c .5, chloroform); νmax 3350 (NH), 2950 (CH aliphatic), 1725 (C=O), 1685 (C=O SAc), 1550 (NH), 1450 (CH3), and 1200-1100 cm⁻¹ (C-F); m/z
(relative intensity) 285 (10.66, M+ + 1 - OCH3), 284 (100, M+ + 1 - MeOH), 242 (2.05, M+ + 1 - OCH3 - COCH3), 225 (1.5, M+ + 1 - AcSH - CH3), 224 (18.1, M+ + 1 - AcSH - CH4), 212 (3.72, M+ + 1 - CH3CH2SCOCH3), 208 (1.79, M+ + 1 - AcSH - MeOH), 202 (2.00, M+ + 1 - NH2COCF3 - H), 183 (1.37, M+ + 1 - CH3CHSAcCHOH), 180 (1.31, M+ + 1 - EtSAC - MeOH), 171 (11.27, M+ + 1 - NH2COCF3 - MeOH), 129 (2.31, M+ + 1 - NHCOCF3 - SAC), 127 (2.15, M+ + 1 - NH2COCF3 - AcSH), 114 (5.18, NH2COCF3 + 1), 113 (1.27, NH2COCF3), 101 (1.76, M+ + 1 - CH3CHSAc - NHCOCF3), and 95 (19.74, M+ + 1 - AcSH - MeOH - NH2COCF3).


5-S-Acety1-2,3,6-trideoxy-3-trifluoroacetamido-5-thio-L-ly xo-hexofuranose (48). A mixture of the methyl glycoside 46 (50 mg, 0.16 mmol) and 40% acetic acid (5 mL) was refluxed for 1 h, whereupon t.l.c. monitoring indicated that the hydrolysis was complete (RF 46 = 0.4, RF 48 = 0.17 in 6:1 toluene--acetone). The solution was evaporated to dryness in vacuo to afford 48 as a syrup (40 mg, 85% yield) which was purified by column chromatography using dichloroethane as the eluent. An analytically pure sample of 48 was obtained by HPLC which gave 48 as a colorless syrup that crystallized on addition of hexane, m.p. 90-92°, [α]d23 +16.5° → +41.5° eq. (c 0.5, methanol); νmax

$\text{Nujol}$ 3450 (NH), 3320 (OH), 2950 (CH aliphatic), 1700 (CO), 1570 (NH), 1450 (CH3), 1380 (COCH3) and 1210-1150 cm$^{-1}$ (C-F); m/z (relative intensity) 302 (2.24, M+ + 1), 285 (12.50, M+ + 1 - OH), 284
(100, M\(^+\) + 1 - H\(_2\)O), 242 (4.25, M\(^+\) + 1 - \(\cdot\)OH - COCH\(_3\)), 198 (2.57, M\(^+\) + 1 - EtSAc), 180 (3.95, M\(^+\) + 1 - EtSAc - H\(_2\)O), 173 (1.60, M\(^+\) + 1 - NHCOCF\(_3\) - \(\cdot\)OH), 171 (17.30, M\(^+\) + 1 - NH\(_2\)COCF\(_3\) - H\(_2\)O), 129 (19.36, M\(^+\) + 1 - AcSH - COCFCF\(_3\)), 127 (8.25, M\(^+\) + 1 - AcSH - HCOCF\(_3\) - \(\cdot\)H), 113 (6.36, NH\(_2\)COCF\(_3\)), 111 (33.38, M\(^+\) + 1 - AcSH - COCF\(_3\) - \(\cdot\)OH), 101 (6.02, M\(^+\) + 1 - EtSAc - COCF\(_3\)), 97 (11.19, COCF\(_3\)), 96 (8.35, M\(^+\) + 1 - AcSH - H\(_2\)O - NHCOCF\(_3\)), and 95 (81.86, M\(^+\) + 1 - AcSH - H\(_2\)O - NH\(_2\)COCF\(_3\)).

1-O-Acetyl-5-S-acetyl-2,3,6-trideoxy-3-trifluoroacetamido-5-thio-\(\alpha\)- and \(\beta\)-\(\alpha\)-lyxo-hexofuranoses (49 and 50). The furanose derivative 48 (50 mg, 0.17 mmol) was dissolved in pyridine (5 mL) and treated with dropwise addition of acetic anhydride (0.5 mL) at 0° and the mixture was allowed to come to room temperature.

After stirring for 2 h at -25°, t.l.c. monitoring indicated that the acetylation was complete giving two products, 49 and 50 (R\(_f\) 48 = 0.17, R\(_f\) 49 = 0.39, R\(_f\) 50 = 0.48, 6:1 toluene--acetone). The mixture was poured over crushed ice (2 g) and extracted with dichloromethane (2 x 5 mL). The combined extracts were successively washed with 5% hydrochloric acid (5 mL), saturated sodium hydrogencarbonate (5 mL) and water (5 mL), dried (sodium sulfate), and evaporated in vacuo. Toluene was added to and evaporated from the residue until it was free from pyridine. The resultant syrup was purified by preparative TLC using the same solvent system to afford pure 49 (41 mg, 70% yield) and 50 (14 mg, 24% yield) as syrups. Analytically pure samples of 49 and 50 were obtained.
by HPLC using 4:1 hexane--ethylacetate as the eluent, and the following
data were recorded:

1-O-5-S-Diacetyl-2,3,6-trIDEOxy-3-trifluoroacetamido-
5-thio-α-L-lyxo-hexofuranose (49). This compound was
isolated as a syrup, [α]_D^{23} +90 (c 0.5, chloroform),
ν_{max} ^{neat} 3410 (NH), 1760-1725 (CO), 1550 (NH), 1460
(CH_3), 1380 (COCH_3) and 1250-1150 cm^{-1} (CF_3); m/z
(relative intensity) 344 (0.4, M^{+} + 1), 285 (12.21,
M^{+} + 1 - OAc), 284 (100, M^{+} + 1 - AcOH), 268 (2.19, M^{+} + 1 - SAc), 267
(1.37, M^{+} + 1 - AcSH), 242 (3.64, M^{+} + 1 - OAc - COCH_3), 241 (1.32, M^{+} +
1 - AcOH - COCH_3), 224 (23.15, M^{+} + 1 - AcSH - HCOCH_3), 208 (3.92, M^{+} +
1 - EtSAC - AcOH), 171 (17.97, M^{+} + 1 - NH_2COCF_3 - AcOH), 155 (4.56, M^{+} +
1 - AcSH - NH_2COCF_3), 129 (10.42, M^{+} + 1 - CH_3CHSAC - NHOCOF_3), 111
(28.71, M^{+} + 1 - AcSH - AcOH - COCF_3), and 95 (66.71, M^{+} + 1 - AcSH -
AcOH - NH_2COCF_3).

Exact mass for C_{12}H_{16}F_3NOS (343.291), Calcd.: 284.0568, (MH^{+} -
OAc). Found: 284.0547.

1-O-5-S-Diacetyl-2,3,6-trIDEOxy-3-trifluoroacetamido-
5-thio-α-L-lyxo-hexofuranose (50). This compound was
isolated as a syrup, [α]_D^{23} -37.2 (c 0.5, chloro-
form), ν_{max} ^{neat} 3410 (NH), 1760-1725 (CO), 1550 (NH),
1460 (CH_3), 1370 (COCH_3), and 1250-1150 cm^{-1} (CF_3); m/z
(relative intensity) 344 (0.58, M^{+} + 1), 285
(12.42, $M^+ + 1 - OAc$), 284 (100, $M^+ + 1 - AcOH$), 268 (2.27, $M^+ + 1 - Sac$), 267 (1.58, $M^+ + 1 - AcSH$), 242 (3.43, $M^+ + 1 - OAc - COCH_3$), 241 (2.52, $M^+ + 1 - AcCH - COCH_3$), 224 (27.43, $M^+ + 1 - AcSH - HCOCH_3$), 208 (7.97, $M^+ + 1 - AcSH - AcCH$), 180 (3.78, $M^+ + 1 - EtSAc - AcCH$), 171 (19.75, $M^+ + 1 - NH_2COF_3 - AcCH$), 155 (2.96, $M^+ + 1 - AcSH - NH_2COF_3$), 129 (12.95, $M^+ + 1 - CH_3CHSAC - NHCOF_3$), 111 (31.13, $M^+ + 1 - AcSH - AcOH - COF$), and 95 (80.27, $M^+ + 1 - AcOH - AcOH - NH_2COF_3$).

Exact mass for $C_{12}H_{16}F_3N_0_5S$ (343.291). Calcd.: 284.0568 ($MH^+ - OAc$). Found: 284.0540.

1,5-Anhydro-3-N,4-O-diacetyl-5-thio-2,3,6-trideoxy-L-lyxo-hex-1-enitol (51). The furanoside thioacetate derivative 46 (10 mg, 0.03 mmol) was dissolved in dry methanol purged with argon and potassium cyanide (10 mg, 0.15 mmol) was added. The mixture was stirred overnight at room temperature by which time all of the starting thioacetate 46 had been consumed ($R_f = 0.55$, 14:1 chloroform--methanol). Acetic acid (1 mL) was added and the mixture was evaporated to dryness. The residue was taken up in acetic acid (50%, 3 mL) and the mixture was refluxed for 4 h after which it was again evaporated from the residue, which was then taken up in pyridine (2 mL) and treated with acetic anhydride (0.2 mL, -2 mmol) at 0°. The mixture was stirred overnight at room temperature, poured over crushed ice (1 g) and extracted with dichloromethane (2 x 3 mL). The combined extracts were washed successively with 5% hydrochloric acid (3 mL), saturated sodium hydrogen carbonate (3 mL) and water (3 mL), dried (sodium
sulfate) and evaporated in vacuo to give a dark syrup which was put on a column of silica gel (3 g) and eluted with 40:1 chloroform--methanol. After dissolving the fast-moving impurities, 51 was collected (Rf 51 = 0.5, 14:1 chloroform--methanol) in the next fraction which was evaporated to afford 51 as a yellow syrup (1.7 mg, 25% yield), m/z 230 (48.74, M⁺ + 1), 229 (2.77, M⁺), 215 (1.66, M⁺ + 1 - CH₃), 214 (3.70, M⁺ + 1 - CH₃ - H), 204 (3.73, M⁺ + 1 - C₂H₂), 186 (7.69, M⁺ + 1 - HCOCH₃), 172 (8.31, M⁺ + 1 - NHAc), 171 (16.37, M⁺ + 1 - OAc), 170 (19.18, M⁺ + 1 - AcOH), 156 (6.13, M⁺ + 1 - AcOME), 155 (4.23, M⁺ + 1 - AcOH - Me), 130 (4.86, M⁺ + 1 - MeCH=CHOAc), 129 (16.26, M⁺ + 1 - NHAc - COCH₃), 128 (14.12, M⁺ + 1 - OAc - COCH₃), 127 (12.05, M⁺ + 1 - AcOH - COCH₃), 112 (14.33, M⁺ + 1 - NHAc - AcOH), 111 (100, M⁺ + 1 - NH₂COCH₃ - AcOH), 101 (5.64, CH₃CH₂CH=OCHOCH₃), 97 (7.57, M⁺ + 1 - NH₂COCH₃ - AcOME), 96 (7.44, M⁺ + 1 - NH₂COCH₃ - CH₃CH=CHOAc), and 70 (10.94, M⁺ + 1 - NH₂COCH₃ - CH₃CH=CHOAc).

Exact mass for C₁₀H₁₅NO₃S (229.0773), Calcd.: 230.0851 (MH⁺).
Found: 230.0870.

7-O-(4-O-Benzoyl-2,6-dideoxy-3-C-methyl-a-L-lyxohexopyranosyl)daunomycinone (52). To a solution of 1-O-acetyl derivative 27 (10 mg, 0.03 mmol) in dry dichloromethane (5 mL) was added daunomycinone (10 mg, 0.025 mmol) and 4Å molecular sieves (2 mg) and the mixture was stirred at -25° for 1 h under an atmosphere of argon. After cooling it to -5°, trimethylsilyl trifluoromethanesulfonate (.01 mL, -0.06 mmol) was added to this mixture and the
temperature was kept between -5°--0° for 4 h after which t.l.c. monitoring showed no further progress in the reaction (R_f daunomycinone = 0.3, 3:1 toluene--acetone). Saturated sodium hydrogencarbonate (1 mL) was added to the mixture, and the organic layer was separated. After extracting the aqueous layer with dichloroemthane (2 mL), the combined extracts were washed with water (2 mL), dried (sodium sulfate) and evaporated to dryness. The residue was purified by preparative TLC using the same solvent system. Extraction of the red band corresponding to R_f = 0.5 with acetone afforded 52 as red crystals (-5.2 mg, 32% yield). The band corresponding to R_f = 0.3 was isolated, extracted with acetone and evaporated to dryness to recover the unreacted daunomycinone (3 mg, 28%). The following data were recorded for the coupled product 52. m.p. 108°--112°; UV (CHCl_3) \lambda_{\text{max}} 194 nm (\epsilon_0 \times 10^{-3} 8.8), 198 (5.0), 204 (6.7), 210 (20.0), 216 (5.6), 228 (7.7), 236 (6.1), 254 (37.5), 288 (14.3), 486 (16.8), 500 (16.8), 656 (1.14); m/z 537 (1.05, M^+ + 1 - \text{CH}_3 - \text{HCOCH}_3 - \text{CH}_3), 435 (2.74, M^+ + 1 - \text{PhCO}_2\text{Me} - \text{H}_2\text{O} - \text{CH}_3 - \text{COCH}_3), 417 (1.53, M^+ + 1 - \text{PhCO}_2\text{Me} - 2\text{H}_2\text{O} - \text{CH}_3 - \text{COCH}_3), 398 (3.19, M^+ + 1 - \text{glycon}), 382 (7.75, M^+ + 1 - \text{Oglycon}), 381 (1.59, M^+ + 1 - \text{HOglycon}), 364 (2.64, M^+ + 1 - \text{Oglycon} - \text{H}_2\text{O}), 363 (8.62, M^+ + 1 - \text{HOglycon} - \text{H}_2\text{O}), 347 (4.44, M^+ + 1 - \text{Oglycon} - \text{H}_2\text{O} - \text{OH}), 339 (5.34, M^+ + 1 - \text{Oglycon} - \text{COCH}_3), 338 (3.72, M^+ + 1 - \text{HOglycon} - \text{COCH}_3), 337 (6.27, M^+ + 1 - \text{HOglycon} - \text{HCOCH}_3), 321 (26.26, M^+ + 1 - \text{Oglycon} - \text{H}_2\text{O} - \text{COCH}_3), 249 (9.00, M^+ + 1 - \text{aglycon}), 231 (10.42, M^+ + 1 - \text{aglycon} - \text{H}_2\text{O}), 155 (13.29, M^+ + 1 - \text{PhCO}_2\text{CH}_3 - \text{aglycon} - \text{H}), and 105 (100, PhCO_2).
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