THE USE OF 2,3,4-EPoxyALCOHOL DERIVATIVES
IN CARBOHYDRATE SYNTHESIS

RICHARD JAMES BROWN

B.S., University of Wisconsin-Madison

(1979)

SUBMITTED TO THE DEPARTMENT OF CHEMISTRY IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY IN ORGANIC CHEMISTRY

at the

MASSACHUSETTS INSTITUTE OF TECHNOLOGY

September 1983

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Signature of Author .........................................................

[Signature]

Department of Chemistry
September 8, 1983

Certified by .................................................................

William R. Roush
Thesis Supervisor

Accepted by .................................................................

Glenn A. Berchtold
Chairman, Department Committee

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THE USE OF 2,3,4-EPOXYALCOHOL DERIVATIVES

IN CARBOHYDRATE SYNTHESIS

by

RICHARD JAMES BROWN

Submitted to the Department of Chemistry on
September 8, 1983 in partial fulfillment of the
requirements for the Degree of Doctor of Philosophy
in Organic Chemistry

In connection with a proposed generalized scheme for the
synthesis of 2,6-dideoxyhexoses, the neighboring group assisted
α-ring opening reactions of a series of acylated 2,3,4-epoxy
alcohols were investigated. The phenylurethane group proved
to be ideal for the delivery of oxygen nucleophilic species
to the α-epoxide position. This group is more reactive than
acetate or methylcarbonate neighboring groups and the resulting
trio1 functionality is liberated in a protected, differentiated
form. Problems of competitive attack by nucleophiles at the
β-position or acyl transfer isomerization of the carbonate
after the ring opening were encountered with a number of
substrates, but could be suppressed or eliminated entirely
by judicious choice of reaction conditions.

Using the information gained in the studies of the
behavior of acylated 2,3,4-epoxyalcohols, highly diastereo-
selective syntheses of five 2,6-dideoxyhexoses were developed.
The syntheses of (+)-digitoxose (4), (+)-olivose (17), (+)-
cymarose (19) and (+)-oliose (20) are short (four to seven
steps), relatively efficient (14-22%) and enantioselective.
These syntheses feature the kinetic resolution-enantioselective
epoxidation of racemic allylic alcohols 114 and 117 and the
highly regioselective ring opening reactions of erythro-
epoxyalcohols (+)-73, (+)-115 and (-)-115. Syntheses of
racemic 17 and bovinose 5 from threeo-epoxyalcohol 109 are
also described.

Extensions of the methodology developed for the syntheses
of 2,6-dideoxyhexoses to the synthesis of aminosugars were also
examined. They include the regioselective β-ring opening of
epoxide (+)-73, leading to a protected form of the 2,3,6-tri-
deoxy-3-aminohexose, D-ristosamine (+)-11. The delivery of
nitrogen nucleophiles to the epoxide α-position under basic
reaction conditions was noted for urethanes such as 79a.
In addition, a preliminary investigation of the epoxidation of acylated allylic amines 150 and 170 was conducted.

Thesis Supervisor:  Dr. William R. Roush

Title: Firmenich Associate Professor of Natural Products Chemistry
ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to Professor William R. Roush for the guidance and assistance provided throughout my thesis research. His patience and understanding allowed me to develop as a chemist at my own pace and his high standards of excellence will be models of quality throughout my professional life.

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BIOGRAPHICAL NOTE

The author was born on May 13, 1957 in Rhinelander, Wisconsin. Following graduation from Rhinelander High School, he entered the University of Wisconsin-Madison. While attending that institution, he majored in chemistry and participated in Freshman Honors research with Dr. John Walters and Senior Honors research with Dr. Stephen Nelsen. Mr. Brown graduated with Honors, receiving a B.S. degree in Chemistry in June, 1979.

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Mr. Brown is a member of the American Chemical Society, Phi Eta Sigma and Sigma Xi societies.
ABBREVIATIONS

THF  tetrahydrofuran
MCPBA m-chloroperbenzoic acid
DMSO dimethylsulfoxide
TBHP tert-butylhydroperoxide
DIPT diisopropyltartrate
acac acetylacetone
TMS trimethylsilane
TBDMS tert-butyldimethylsilyl
Bn benzyl
DET diethyltartrate
e.e. enantiomeric excess
eq equivalents
p-TsOH p-toluenesulfonic acid
DIBAL diisobutyl aluminumhydride
DEAD diethylazodicarboxylate
DNPBA dinitroperbenzoic acid
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To my parents
CHAPTER I
INTRODUCTION
Many natural products with physiological activity consist of two parts: a hydrophobic nucleus known as an aglycone and a hydrophilic carbohydrate portion. The function of these hydrophilic sugars in the biological activity of the antibiotics may simply be in transport phenomena such as facilitating passage through membranes, or may be more subtle, involving, for example, recognition factors at the site of activity. Chemists interested in organic synthesis have often, in the past, ignored the sugar portions of these molecules, concentrating instead solely on the synthesis of the aglycones. In many cases, however, these sugars are important and often essential to the physiological activity of the antibiotics, making them important synthetic targets in their own right. In addition, they offer a rich arena for structural modification of the antibiotics, with many stereochemical variations and branch points available. As our knowledge of structure-activity relationships improves, pharmaceutical agents will evolve from natural product leads that happen to produce a physiological response to unnatural products designed to promote the same response with more highly controlled results and fewer side effects.

There has also been a continuing interest in the use of functionalized monosaccharides as intermediates in the synthesis of more complicated molecules. The use of sugars in organic synthesis has been limited by the often lengthy manipulations
required to transform a readily available sugar such as glucose into the specific intermediate needed. Chiral intermediates of this type would be much more useful if they could be prepared more directly. For these reasons the field of carbohydrate chemistry recently has begun to receive more attention from organic synthesis chemists.³

A wide variety of sugars are found in nature, either in free or combined form. The currently known naturally occurring monosaccharides range in length from three to nine carbon atoms.⁴ Sugars are found to occur in protein, lipid and nucleotide structures as well as antibiotic natural products.⁵ Unlike common sugars such as glucose or fructose, many of the sugars found in antibiotics are so-called "rare sugars" having structural variations such as deoxy or 6-deoxy amino sites and, sometimes, chain branching.

Figure 1 shows a few examples of some deoxysugars which have been isolated from natural sources.⁶ The majority of these sugars are 6-deoxysugars; many also have additional deoxygenation. D-Mycinose ¹ and L-mycarose ² are found in various macrolide antibiotics such as tylosin and erythromycin, the aglycones of which have received a great deal of attention from synthesis chemists.⁷,⁸ The pattern of deoxygenation varies widely: mycinose is a 6-deoxysugar, and chalcosie ³ is a 4,6-dideoxysugar. Many 2,6-dideoxysugars, three of which are shown here occur in the cardiac glycosides. More heavily 6-deoxyxgenated sugars are also known. Branched sugars⁹ like
mycarose are frequently found, as are methyl-blocked sugars (D-chalcose). Sometimes, both D- and L-enantiomers of a given sugar are isolated from natural sources.

Some aminosugars are shown in Figure 2. Aminosugars have even more avenues for structural variation than the deoxysugars, since the amino group can build different regio- as well as stereoisomers into the carbon framework. D-Desosamine 7, of the macrolide antibiotics, and L-daunosamine 8, of the anthracyclines, are found in two very important classes
of antibiotics. The three 2,6-dideoxy aminosugars, daunosamine 8, holacosamine 9, and ristosamine 11, and the 4,6-dideoxysugar desosamine 7 illustrate the variability inherent in aminosugars. The regiochemical placement of the nitrogen atom can vary as well as the deoxygenation. Holacosamine is a 4-aminosugar; the others are all 3-aminosugars. As in the deoxysugars, methyl blocking is common; the nitrogen may be unsubstituted, monomethylated or dimethylated. Branched aminosugars also occur. L-Vancosamine 10 and L-ristosamine 11 of the glycopeptide antibiotics vancomycin and ristomycin, respectively, differ only by the presence of the 3-C methyl
group in vancosamine.

While far from inclusive, Figures 1 and 2 serve to illustrate the widely varied structures of the sugars found in natural products. Almost every possible regio- and stereo-chemical substitution pattern allowed by the length of the carbon chain has been observed. Discussion of every sugar-containing antibiotic is beyond the scope of this work. One group of antibiotics, the aureolic group,\textsuperscript{11,12} and olivomycin A (\textsuperscript{12}, Figure 3) in particular, will be discussed in some detail. The synthesis of olivomycin A has been an object of the Roush research group for several years.
FIGURE 3

Olivomycin A(12)
$R_1=H, R_2=(CH_3)_2CHCO$

Chromomycin A$_3$(13)
$R_1=CH_3, R_2=CH_3CO$

Aureolic Acid(14)
The Aureolic Acid Antibiotics

Olivomycin A (12) is a representative of the aureolic acid class of antitumor antibiotics, which aside from the olivomycins,\textsuperscript{13} includes the chromomycins,\textsuperscript{14} such as chromomycin A\(_3\) (13) and aureolic acid (14) (also known as mithramycin).\textsuperscript{15} First isolated as antibiotic NSC-A649 in 1960\textsuperscript{16} and again in 1962 in the Soviet Union,\textsuperscript{17} the olivomycins are produced by 

\textit{Streptomyces olivoreticuli}. The major component, olivomycin A, which accounts for up to 80\% of the total antibiotic mixture, is a yellow crystalline compound, m.p. 164-166°C.\textsuperscript{13a} The structure of olivomycin A (12), determined by Berlin and co-workers,\textsuperscript{13c, d} is shown in Figure 3. It contains a tricyclic aglycone known as olivin,\textsuperscript{15}, consisting of a 1,6,8-tri hydroxy napthalene fused to a third, ketonic ring. In addition, a

![Olivin and Chromomycinone structures](image)

Olivin(15) \(R=H\)

Chromomycinone(16) \(R=CH_3\)

heavily oxygenated acyclic chain is attached to the partially saturated C ring. The aglycone of the chromomycins and mithramycins, chromomycinone (16), differs from olivin only in that a methyl group is substituted at C-7. Aside from that difference,
members of the class differ in the nature and number of carbohydrate residues attached to the aglycones. In olivomycin A, a disaccharide moiety is attached at the phenolic position of C-6, while a trisaccharide is attached to the hydroxyl at C-2.

The aureolic acid group, as a class, is strongly active against Gram-positive bacteria and DNA viruses, but is inactive against Gram negative bacteria, RNA viruses and fungi. More importantly, many of these antibiotics show useful antitumor activity. Members of this class are highly toxic to HeLa cells in culture and have shown some activity against experimental tumors in animals. These results have prompted the use of the aureolic acid antibiotics as antitumor agents. Aureolic acid (14) is currently marketed by Pfizer under the proprietary name Mithracin. It is used in the treatment of testicular tumors and is also useful in treating hypercalcemia and hypercalciuria associated with some advanced neoplasms. Chromomycin A3 (13) is commercially available in Japan from Takeda Chemical Industries under the name of Toyomycin and is currently under investigation by the National Cancer Institute in Phase I and Phase II studies. Olivomycin A (12) has been reported to be an important antitumor agent in the U.S.S.R., being particularly effective against testicular and tonsilar tumors. A comparative study of these three agents against the leukemia L1 in mice was used to determine a therapeutic index for each compound. The results are
summarized in Table 1. Olivomycin A, with a particularly high LD$_{50}$, had the best chemotherapeutic index. Chromomycin A$_3$ was second best, while aureolic acid was the poorest.

TABLE 1$^{21}$

Comparative Activities Against Leukosis La in Mice.$^a$

<table>
<thead>
<tr>
<th>Compound $^b$</th>
<th>LD$_{50}$ (mg/kg)</th>
<th>Dose for 125% survival prolongation (mg/kg)</th>
<th>Chemotherapeutic Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olivomycin A</td>
<td>12.5</td>
<td>0.11</td>
<td>103.5</td>
</tr>
<tr>
<td>Chromomycin A$_3$</td>
<td>1.25</td>
<td>0.039</td>
<td>32.0</td>
</tr>
<tr>
<td>Olivomycin B</td>
<td>37.5</td>
<td>2.25</td>
<td>16.7</td>
</tr>
<tr>
<td>Chromomycin A$_2$</td>
<td>0.4</td>
<td>0.024</td>
<td>16.7</td>
</tr>
<tr>
<td>Aureolic Acid</td>
<td>3.0</td>
<td>0.84</td>
<td>3.6</td>
</tr>
</tbody>
</table>

$^a$ Determined in C$_{57}$Bl mice. $^b$ See TABLE 3 and FIGURE 4 for structures.
The mode of antibiotic action of this group of compounds is primarily binding to DNA with subsequent inhibition of RNA synthesis. When tested against the synthesis of RNA in a cell-free system, olivomycin was found to have no effect on the initiation of RNA chains, but their average length dropped from 5500 to 420 nucleotides.\textsuperscript{22}

Some experimental work has been performed on the nature of the binding of aureolic acid compounds to DNA. It has been found that a maximum interaction with DNA is obtained when a 1:1 mole ratio of Mg\textsuperscript{+2} and antibiotic is used. The Mg\textsuperscript{+2} binds to the ring carbonyl and the adjacent phenolic oxygen and it may serve to counteract the repulsion between the negatively charged DNA and the anionic sites on the antibiotics.\textsuperscript{23} It has also been found that there is a specificity of binding to GC base pairs,\textsuperscript{23} guanine being the required base.\textsuperscript{24} While the properties of the DNA-aureolic acid complex and the planar nature of the aglycone suggest that intercalation of the antibiotic with DNA may be occurring, the currently accepted theory is that it does not. It is believed, however, that the predominant magnesium-dependent interaction involves complexation in the minor groove of the DNA double helix.\textsuperscript{25}

Since their mode of action is the inhibition of DNA-dependent RNA synthesis, the aureolic acid-group antibiotics affect normal cells as well as tumors. Acute toxicity, and such side affects as anorexia, emesis, anemia, and bleeding occur in aureolic acid chemotherapy,\textsuperscript{25} greatly limiting their
use as antitumor agents.

The promising antitumor activity, yet relatively high toxicity of the aureolic acid-group antibiotics make them attractive candidates for the development of analogs with improved chemotherapeutic indices. The structure-activity relationships among the set of naturally-occurring analogs show that even small changes in the aglycones or the sugar portions can result in significant changes in biological activity. For example, olivomycin A differs from chromomycin A₃ primarily in its unmethylated chromophore, yet it has a significantly better chemotherapeutic index (see Table 1).

Large portions of these molecules consist of carbohydrate regions, and it is clear from structure-activity correlations that at least five carbohydrate residues are necessary for maximum activity. Table 2 lists some of aureolic acid antibiotics and compares their antibacterial activity and suppresssion of RNA synthesis.²⁷ The number of sugar residues present in each antibiotic is also listed. As the number of sugars decreases, the activity also drops; the aglycones themselves are virtually inactive. Acetylation of the 3-hydroxyl group of the oliose residue (vide infra) tends to improve activity (compare olivomycin A and chromomycin A₃ to olivomycin C and deacetylchromomycin A₃).

A number of semisynthetic analogs of olivomycin A have been prepared by chemical modification of the aglycone portion of the molecule without disturbing the carbohydrate regions.²⁸ After screening these analogs, it was found that the C.2'
<table>
<thead>
<tr>
<th>Compound</th>
<th>Concentration (μM) inducing 100% suppression of B. subtilis growth</th>
<th>50% suppression of RNA synthesis</th>
<th>no. of sugars</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olivomycin A</td>
<td>0.01</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Olivomycin B</td>
<td>0.03</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Olivomycin C</td>
<td>0.2</td>
<td>2.6</td>
<td>5</td>
</tr>
<tr>
<td>Olivomycin D</td>
<td>0.6</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Olivin</td>
<td>&gt;10</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>Chromomycin A₂</td>
<td>0.01</td>
<td>1.3</td>
<td>5</td>
</tr>
<tr>
<td>Chromomycin A₃</td>
<td>0.01</td>
<td>1.5</td>
<td>5</td>
</tr>
<tr>
<td>Deacetylchromomycin A₃</td>
<td>0.1</td>
<td>2.6</td>
<td>5</td>
</tr>
<tr>
<td>Chromomycin A₄</td>
<td>0.6</td>
<td>3.4</td>
<td>4</td>
</tr>
<tr>
<td>Chromomycinone</td>
<td>&gt;10</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>Aureolic acid</td>
<td>0.005</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Demycarosylaureolic acid</td>
<td>0.23</td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td>2-Olivosylchromomycinone</td>
<td>&gt;10</td>
<td>-</td>
<td>1</td>
</tr>
</tbody>
</table>

aFor structures, see TABLE 3 and FIGURE 4. bAntibacterial activities determined by the serial dilution method. cInhibition of E. coli RNA polymerase acting on a phage T2 DNA template.
methoxime prepared from the side-chain carbonyl group had a wider dose range and greater potency than olivomycin A.

Despite the activity and clinical uses of these compounds for antitumor therapy, only limited effort has been devoted to their synthesis. Weinreb\textsuperscript{29} has reported several studies directed toward the synthesis of olivomycin which concentrated on establishing the proper carbon framework. Franck\textsuperscript{30} has used carbohydrate-derived dienophiles to test the Diels-Alder reaction as a method for attaching the acyclic side chain to the rest of the aglycone. The Roush group\textsuperscript{31} has developed a simple, enantiospecific synthesis of the side chain and has begun to investigate the elaboration of the aglycone from those intermediates. Thiem\textsuperscript{32} has reported a synthesis of the olivin side chain from D-threose.

Thiem has also reported extensive studies on the synthesis of di- and trisaccharides\textsuperscript{33} and has, in some cases, been able to confirm or correct earlier assignments of the linkages between the various monosaccharides by spectroscopic comparisons between synthetic di- and trisaccharides and the natural products.\textsuperscript{33b,i;34}

A listing of the sugar molecules in a number of the aureolic acid group antibiotics is presented in Table 3, together with the structures of each (Figure 4). The first eight entries in Table 3 represent four pairs of antibiotics differing within each pair only in the presence or absence of the C.7 methyl group of the aglycone. Apart from the different aglycones, the olivomycins and chromomycins as a group differ only
<table>
<thead>
<tr>
<th>Name</th>
<th>Aglycone</th>
<th>( C^2 )</th>
<th>( C^6 )</th>
</tr>
</thead>
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<tr>
<td>Chromomycin A&lt;sub&gt;2&lt;/sub&gt;</td>
<td>C</td>
<td>17-17-27</td>
<td>21-18</td>
</tr>
<tr>
<td>Olivomycin A</td>
<td>O</td>
<td>17-17-27</td>
<td>21-18</td>
</tr>
<tr>
<td>Chromomycin A&lt;sub&gt;3&lt;/sub&gt;</td>
<td>C</td>
<td>17-17-25</td>
<td>21-18</td>
</tr>
<tr>
<td>Olivomycin B</td>
<td>O</td>
<td>17-17-25</td>
<td>21-18</td>
</tr>
<tr>
<td>Deacetylcromomycin A&lt;sub&gt;2&lt;/sub&gt;</td>
<td>C</td>
<td>17-17-27</td>
<td>20-18</td>
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<tr>
<td>Olivomycin C</td>
<td>O</td>
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<td>20-18</td>
</tr>
<tr>
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<td>17-17</td>
<td>21-28</td>
</tr>
<tr>
<td>Olivomycin D</td>
<td>O</td>
<td>17-17</td>
<td>21-18</td>
</tr>
<tr>
<td>Propionyldeacetyl-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>chromomycin A&lt;sub&gt;2&lt;/sub&gt;</td>
<td>C</td>
<td>17-17-27</td>
<td>22-18</td>
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<tr>
<td>Propionyldeacetyl-</td>
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<td>chromomycin A&lt;sub&gt;3&lt;/sub&gt;</td>
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<td>21-18</td>
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<td>Mithramycin</td>
<td>C</td>
<td>17-17-23</td>
<td>20-17</td>
</tr>
<tr>
<td>Variamycin</td>
<td>C</td>
<td>17-17-19</td>
<td>20-17</td>
</tr>
</tbody>
</table>

<sup>a</sup> O=Olivin, C=Chromomycinone.  <sup>b</sup>Numbers refer to the compound identification numbers in FIGURE 4 and represent the monosaccharides appearing in sequence from the aglycone at positions C.2 and C.6. The specific linkage pattern and the stereochemistry of the linkages can be ascertained from FIGURE 3.
FIGURE 4

D-Olivose 17

D-Olivomose 18

D-Variose 19

D-Oliose, R=H 20

D-Acetyloliose,
R=COCH₃ 21

D-Propionyloliose,
R=COCH₂CH₃ 22

D-Mycarose 23

L-Olivomycose, R=H 24

L-Acetylolivomycose,
R=COCH₃ 25

L-Propionylolivomycose,
R=COCH₂CH₃ 26

L-Isobutyrylclivomycose,
R=COCH(CH₃)₂ 27
in the short chain esters attached to the sugars. The sequence and connection of all the sugar molecules are identical (chromomycin A₄ and olivomycin D are missing the terminal olivomycose unit of the C.2 carbohydrate residue). The mithramycins, aureolic acid and variamycin, show different patterns of sugar substituents from the other antibiotics of this family and have no esterified positions on the sugars. Variamycin differs from aureolic acid only in that the mycarose residue is replaced by a sugar known as variose.³⁵ The isolation of this sugar as a methyl furanoside resulted in some initial controversy as to its structure;³⁶ recently, variose has been determined to be identical to D-cymarose.³⁷

Examination of Figure 4 reveals that the sugars found in the aureolic acid antibiotics are all 2,6-dideoxyhexoses such as olivose ¹⁷ and oliose ²⁰. Two branched sugars, D-mycarose ²³ and L-olivomycose ²⁴, are also found. D-mycarose is the antipode of the sugar found in various macrolide antibiotics.
Synthetic Considerations

As part of the Roush group's effort toward the total synthesis of olivomycin A and related antibiotics, sufficient amounts of some of the sugars shown in Figure 4 were needed to investigate methods of forming glycosidic linkages and eventual coupling to the aglycone. Needless to say, although all these sugars are structurally similar, the different methylation and acylation patterns manifested render the synthesis of every sugar in this list a formidable undertaking.

In the past, most of these and other "rare sugars" have been synthesized from the readily available group of common sugars. Because the number of suitable "chiral pool" precursors (sugars, terpenes, naturally occurring acids or amino acids, etc.) is limited, syntheses of rare sugars from one of the available group are often cumbersome, involving many steps, and can become lengthy exercises in blocking and deblocking. An example of an efficient synthesis of a rare sugar is Durette's recent synthesis of methyl 2,6-dideoxy-α-D-arabino-pyranoside 31 (methyl α-D-olivoside)\textsuperscript{38} which begins with 2-deoxy-D-glucose 28, itself available in four steps from D-glucose.\textsuperscript{39} This synthesis (Figure 5) represents a "best case", in that the configuration of olivosine is the same as that found in glucose, requiring no inversions or protection/deprotection sequences. Moreover, glucose is the most common natural sugar and is readily available at extremely low cost. Note, however, that this synthesis requires a total of seven
FIGURE 5

steps from glucose. This route would be totally useless, though, of one wished to prepare large quantities of the L-enantiomer of olivose, since L-glucose is not readily available. L-Rhamnose (6-deoxy-L-mannose) is available, but is much more expensive than D-glucose.

Use of a similar sequence would also not be convenient, for example, for the synthesis of D-cymarose, 19, whose analogous precursor: "parent" sugars, D-altrose or D-allose, are not readily available. Synthesis of cymarose from the more available sugar glucose requires an inversion of configuration at C.3. Synthesis of branched sugars or aminosugars would also require additional synthetic steps to effect the introduction of the
amino group or the branching alkyl group at the correct position in the carbon chain.

Until recently syntheses of monosaccharides from nonchiral-pool precursors, on the other hand, generally led to racemic products and often suffered from low stereoselectivity. Most syntheses are based on one of three approaches: oxidation of acetylenic or olefinic precursors, Diels-Alder reactions, or elaboration of furan or pyran derivatives. Of these approaches, the first depends on acyclic stereocontrol while the latter two use cyclic stereocontrol. An example of an acyclic synthesis is Woodward's synthesis (Figure 6) of DL-mycarose (±2) and DL-epimycarose (DL-olivomycose ±24). It demonstrates

**FIGURE 6**

![Chemical structure and reactions](attachment:image.png)

32 → 33 → 34

34 $\xrightarrow{K\text{MnO}_4, \text{aq. NaOH, } 0^\circ}$

35 $\xrightarrow{\text{CH}_3\text{OH, HCl}}$ 37 $R=\text{CH}_3$

36 $\xrightarrow{\text{CH}_3\text{OH, HCl}}$ 38 $R=\text{CH}_3$
the simplicity with which the carbon skeleton can be generated and the flexibility of the intermediates for the synthesis of isomeric compounds. The acetylene can be reduced either to an E- or Z-olefin depending on the reduction method; selective methods for obtaining either cis- or trans-hydroxylation of either olefin isomer thus allow the formation of any stereoisomer. In the Woodward synthesis, however, the cis-hydroxylation of Z-olefin proceeded with very poor stereoselectivity. The resulting mixture of triols was cyclized to methyl-DL-mycaroside and methyl-DL-epimycaroside which were separated at this stage. The free sugars (R=H) were formed in subsequent hydrolysis steps. The lack of stereoselectivity exhibited in the oxidation step is a major disadvantage to this type of synthesis. It should be noted, however, that since this synthesis was undertaken as a proof of structure for mycarose, the epimer was useful in confirming the identification of the synthetic and natural sugars.

Although sufficient supplies of the monosaccharides needed for the synthesis of olivomycin A could have been obtained by synthesis from other more common carbohydrates by known procedures, we felt that such syntheses were often lengthy and cumbersome. In addition, as indicated previously, these syntheses were not generally applicable from one target to the next. From the standpoint of modern organic synthesis, these factors made such an approach less than totally satisfactory. In addition the common structural features found in the aureolic acid group sugars - all are 2,6-dideoxyhexoses -
seemed to demand a more unified approach.

While we were impressed by the potential flexibility of synthetic routes based on non-carbohydrate precursors, the lack of stereochemical and enantioselective control of the previously reported non-carbohydrate based syntheses severely limited their utility. We felt, however, given recent advances in enantioselective synthetic methods and acyclic stereocontrol,\textsuperscript{42} that these problems could be solved. If this were indeed possible, carbohydrate synthesis could be placed on a more generalized, systematic basis. The results of our endeavors in this area are reported in the following chapters.
CHAPTER II

REGIOCHEMICAL CONTROL OF NUCLEOPHILIC RING OPENING OF ACYLATED 2,3,4-EPoxyalcohols
In classical carbohydrate synthesis, the cyclic form of sugars has been used to predict and control the stereo- and regiochemical outcome of many reactions. For example, a number of transformations of sugar epoxides has been observed\(^{44}\) which depend on the steric and conformational relationships among the substituents on the pyranose systems. Mills\(^{45}\) has suggested that the results of the sugar epoxide reactions could be explained by the Fürst-Plattner rule.\(^{46}\) This rule, originally formulated for steroid epoxides, states that ring opening occurs stereospecifically to give the trans-diaxial alcohol as the major product. This stereospecificity is demonstrated by the formation of methyl 4,6-benzylidene-\(\alpha\)-D-altropyranoside \(^{41}\) from alkaline hydrolysis of both methyl 2,3-anhydro-4,6-0-benzylidene-\(\alpha\)-D-allopyranoside \(^{39}\) and \(\alpha\)-D-mannopyranoside \(^{40}\). The former undergoes nucleophilic attack at the 2-position while the latter is attacked at C.3.\(^{47}\) Other

**FIGURE 7**

![Chemical structures](image-url)
selective transformations which rely on well-defined conformational properties of pyranosides include the reactions of keto-derivatives with hydride reducing agents or organo-metallic reagents and the catalytic hydrogenation of exomethylene derivatives.

Although cyclic stereochemical control has been used to good advantage in many carbohydrate syntheses, the same property can also cause problems. If the conformation required for a given transformation is disfavored, the desired reaction may be very sluggish, poorly selective, or not occur at all. Thus, it may be necessary to perform further operations to force the system to adopt the necessary conformation.

Recently, the topic of acyclic stereocontrol has attracted a great deal of attention among organic synthesis chemists. When viewed in their open-chain form, sugars are almost ideal targets for testing methods of acyclic stereocontrol, since they contain a relatively high percentage of stereocenters on a small carbon chain. While early acyclic syntheses of carbohydrates usually suffered from low stereoselectivity, the ease with which one could generate a number of sugars from a common precursor appealed to us. Since the sugars necessary for the aureolic acid antibiotics are all of a particular structural type, such a generalized approach seemed quite useful.

Assuming that the aldehyde moiety, in latent or protected form, provides no complications, a synthesis of a 2,6-dideoxy-
hexose becomes a synthesis of a 2,3,4-triol system. The basis of our approach is illustrated in Figure 8. For many years, it has been known\textsuperscript{51} that acid-catalyzed solvolysis of epoxy-

\textbf{FIGURE 8}

alcohols (or ethers) results in selective nucleophilic attack at the carbon $\beta$ to the hydroxyl group with inversion of configuration at that center. This result is primarily due to the presence of the hydroxyl group which inductively deactivates the epoxide $\alpha$-carbon.\textsuperscript{52}

When the hydroxyl group is acylated, solvolysis results in opening at the $\alpha$-carbon. This reversal of reactivity arises because the acyl group acts as a neighboring group\textsuperscript{53} - an intramolecular nucleophile - which opens the epoxide in competition with external nucleophilic species. Apparently the smaller entropy of activation associated with an intramolecular process counterbalances the inductive effect which disfavors $\alpha$-opening in bimolecular substitution processes. This dichotomy between selective $\alpha$- and $\beta$-openings of epoxy-alcohols and their derivatives has been exploited in several syntheses. An examination of the literature, for example, revealed that the opening of carbohydrate (mostly pyranose
forms), cyclitol and steroidal epoxides with acetate,\textsuperscript{54} carbonate,\textsuperscript{55} and urethane\textsuperscript{56} neighboring groups were known. For our purposes, however, we wished to examine the solvolysis of \textit{acyclic} epoxy alcohols.
Synthetic Strategy

Figure 9 shows the four possible 2,3,4-epoxyalcohol stereoisomers and the triols resulting from solvolysis of each. The descriptors ribo, arabino, lyxo, and xylo are used according to the rules of carbohydrate nomenclature.\textsuperscript{57} Although these descriptors are also completely adequate to define a given epoxyalcohol, we wish to emphasize the geometry of each more explicitly. Thus the descriptors E and Z designate the geometry of the olefin precursor of each epoxide and the terms erythro and threo refer to the stereochemical relationship between C.2 and C.3 of the epoxyalcohol. For example, we refer to a 3,4-anhydro-lyxo-epoxyalcohol as an E-erythro-epoxyalcohol. These descriptors will be used routinely throughout the text.

Examination of Figure 9 shows that each 2,3,4-triol can be prepared in either of two ways. Thus, for example, the ribo triol can be obtained by a nucleophilic opening at the \( \beta \)-position of an E-erythro-epoxyalcohol or from an \( \alpha \)-opening of an E-threo-epoxide. Similarly, the arabino configuration arises from a \( \beta \)-opening of an E-threo epoxyalcohol. The lyxo and xylo configurations can be obtained by proper nucleophilic opening of Z-threo and Z-erythro-epoxyalcohols. It should be noted as well that the lyxo and arabino triols, both containing syn, anti\textsuperscript{58} relationships among the three stereocenters, can be interrelated by exchanging the terminal \( R \) groups.

As indicated in Figure 9, each triol can be prepared in more than one way. Although on the surface this analysis seems somewhat trivial, in practice it may be quite important.
FIGURE 9\textsuperscript{a,b}

\textbf{Erythro-Epoxide Series}

\begin{align*}
\text{3,4-Anhydro-Lyxo} & \quad \text{(E-Erythro)} \\
\text{42} & \\
\alpha & \\
\beta & \\
\text{3,4-Anhydro-Xylo} & \quad \text{(E-Threo)} \\
\text{43} & \\
\alpha & \\
\beta & \\
\text{Arabino} & \quad \\
\text{45} & \\
\text{Lyxo} & \quad \\
\text{46} & \\
\alpha & \\
\beta & \\
\text{3,4-Anhydro-Ribo} & \quad \text{(E-Erythro)} \\
\text{48} & \\
\alpha & \\
\beta & \\
\text{3,4-Anhydro-Arabino} & \quad \text{(E-Threo)} \\
\text{47} & \\
\alpha & \\
\beta & \\
\text{Xylo} & \\
\text{49} & \\
\end{align*}

\textsuperscript{a}Nucleophilic attack at C.3 and C.4 of the oxirane is depicted here as "\(\alpha\)" and "\(\beta\)" opening reactions, respectively.

\textsuperscript{b}We use the terms \textit{threo} and \textit{erythro} in reference to the stereochemical relationships between C.2 and C.3 of the epoxyalcohols and the prefixes "E" and "Z" in reference to the configuration of the olefin from which the epoxides were prepared. All descriptors are used according to the rules of carbohydrate nomenclature (see reference 57).
Experimental results indicate that the preference for β-opening of the epoxyalcohol is small, and that the inductive effect can be overwhelmed by factors such as steric bulk or other inductive effects. If \( R_2 \) contains a branched alkyl group, poor selectivity may result, with increased amounts of attack at the α-position. This point is illustrated by the solvolysis of the cyclohexyl substituted epoxyalcohol 50, which afforded a 3:4:1 mixture of xylo (β-opened) 51 and arabino (α-opened) 52 products. 59

**FIGURE 10**

If the epoxyalcohol system contains an alkoxy or hydroxyl substituent at the γ-position (C.5 in \( R_2 \)), a situation that may arise frequently in carbohydrate synthesis, the inductive effects from the two groups flanking the epoxide would cancel and the product distribution would be governed largely by steric factors. In the example cited in Figure 7, the epoxide 40 is opened mainly at the α-position (because of the stereo-electronic requirement for diaxial opening) despite the greater inductive effect of the C.1 acetal group compared to
the C.4 substituent. Therefore, the use of \(\beta\)-opening reactions may be limited to cases where \(R_2\) is a simple alkyl chain, and it may be desirable to construct triol isomers by using only \(\alpha\)-opening procedures.

Although many examples of neighboring group-assisted openings of 2,3,4-epoxyalcohol derivatives by a variety of acyl groups have been recorded for cyclic structures such as steroids or cyclitols, very few examples of acyclic substrates had been reported. In cyclic systems, the neighboring group is required by stereochemical constraints to be \text{trans}\ to the epoxide group. In addition, the preference for diaxial opening of epoxides in cyclic systems has already been noted. In acyclic systems, the relatively free rotation of the carbon chains imposes fewer restrictions upon the substrates, making it difficult to draw analogies from the results of cyclic cases cited previously. Because of the lack of information on the behavior of acyclic epoxyalcohols, we found it necessary to examine the solvolytic behavior of some of these substrates, particularly examples of those illustrated in Figure 9.
2,3,4-Epoxyalcohol Isomers

Although not crucial for the initial solvolysis studies, our goal of using epoxyalcohol derivatives in carbohydrate synthesis required that two problems be solved. The first was that the synthesis of the necessary epoxyalcohols be effected with good stereoselectivity and in high yield. This was related primarily to our desire for efficiency and ease of operation, and will be discussed immediately following. The second problem was the discovery of the best neighboring group and appropriate solvolysis conditions for highly regioselective opening of the epoxyalcohol substrates. This was, of course, the fundamental reason for conducting the solvolysis studies.

Shown in Figure 11 are two selected secondary allylic alcohols and a summary of methods used for epoxidation, including peracid epoxidations and metal-catalyzed systems. Epoxidation of Z-allylic alcohol 53 with peracids such as m-chloroperbenzoic acid affords epoxyalcohols with a very good threo:erythro selectivity (95:5). Metal-catalyzed epoxidations using tert-butylhydroperoxide as the oxidant also show a preference for threo selectivity. Of these, Ti(0^1Pr)_4 without added ligands gives a result as good as that with MCPBA. With added ligands such as diisopropyltartrate, the selectivity reverses to a predominance of erythro epoxide. This, however, is not a general result and is highly dependent on the individual substrate. 62h
FIGURE 11

\[
\begin{array}{ccc}
\text{CH}_3 \\
\text{CH} = \text{CH} \text{OH} & \xrightarrow{\text{MCPBA}} & \text{OCH} \text{CH}_3 \\
53 & & 54 \\
\end{array}
\]

- MCPBA: 95
- Ti\(^{+4}\), TBHP: 95
- Mo\(^{+6}\), TBHP: 84
- V\(^{+5}\), TBHP: 75
- Ti\(^{+4}\), DIPT, TBHP: 19

*not general

\[
\begin{array}{ccc}
\text{CH}_3 \\
\text{CH} = \text{CH} \text{OH} & \xrightarrow{\text{MCPBA}} & \text{OCH} \text{CH}_3 \\
56 & & 57 \\
\end{array}
\]

- MCPBA: 64
- Al\(^{+3}\), TBHP: 64
- Ti\(^{+4}\), TBHP: 63
- Mo\(^{+6}\), TBHP: 62
- V\(^{+5}\), TBHP: 29
- Ti\(^{+4}\), DIPT, TBHP: 3

\[
\begin{array}{ccc}
\text{CH}_3 \\
\text{CH} = \text{CH} \text{OH} & \xrightarrow{\text{MCPBA}} & \text{OCH} \text{CH}_3 \\
58 & & 55 \\
\end{array}
\]
With E-allylic alcohol 56 both peracid and metal-catalyzed epoxidations exhibit a three:erythro preference of roughly 2:1. With V$^+$ catalysis, the results are reversed: the erythro product is favored by about 7:3. The last entry shows an even more dramatic result. Epoxidations using tert-butylhydroperoxide with Ti$^{4+}$ catalysis with the added chiral ligand diisopropyltartrate give an erythro:three ratio of 97:3. Even more importantly, the epoxylcohol produced can be obtained in high enantiomeric purity from a racemic allylic alcohol precursor. This result, an example of the now well-known Sharpless kinetic resolution asymmetric epoxidation, is very important when one wishes to prepare chiral molecules such as sugars. This technique will be discussed in greater detail in Chapter III.

The selectivity of the various epoxidation methods can be explained by an examination of the geometries of the substrate (Figure 12). In peracid epoxidations, the results indicate that the preferred orientation of the allylic alcohol substrate in the transition state is such that the dihedral angle between the hydroxyl and the olefin is roughly $120^\circ$, forcing either the hydrogen or the alkyl group $R_1$ to eclipse the double bond. With Z-olefins, the sterically less demanding hydrogen is heavily favored to be in the eclipsed position. The hydroxyl group directs the peracid onto the olefin from the top face, presumably by hydrogen bonding (the "Henbest effect"). With E-olefins, in which $R_3$ = hydrogen, the steric crowding in the eclipsed position is less severe, allowing a greater percentage of the erythro product to be formed. Instead of a hydrogen-
 bonded delivery of an oxidizing agent, in metal-catalyzed epoxidations, the substrates form discrete oxygen-metal bonds to an active metal complex. The preferred dihedral angle will change depending on the specific complex, since oxidation levels of the metal and the number and size of the ligands on the complex can vary widely. The preferred dihedral angle for $V^{+5}$-catalyzed epoxidations is believed to be about $50^\circ$, leading to a greater percentage of erythro products.\textsuperscript{63} 

Thus, two of the four stereoisomers of the epoxyalcohols illustrated in Figure 9 can be obtained by direct epoxidation of their allylic alcohol precursors: the $Z$-threo and the $E$-erythro epoxides. The two remaining types cannot be prepared
efficiently in this manner. Several alternatives exist for their synthesis.

The first method was developed concurrently by Oshima\textsuperscript{62d} and Narula.\textsuperscript{62e} Figure 13 shows two additional allylic alcohol substrates and the results of various epoxidation experiments.\textsuperscript{62} A $\beta,\beta$-disubstituted allylic alcohol \textsuperscript{59} can be epoxidized in highly \textit{threo}-selective fashion by peracids or Mo$^{\text{+6}}$ catalysis. This selectivity results for the same reason as that of \textit{Z}-allylic alcohols: the alkyl group at $R_3$ (Figure 12) sterically inhibits the conformation leading to the \textit{erythro} product. Similarly, an $\alpha$-substituted allylic alcohol \textsuperscript{62} can be epoxidized with V$^{\text{+5}}$ catalysis with high \textit{erythro} selectivity because the steric repulsion between $R_1$ and $R_2$ (Figure 12) disfavors the conformation leading to the \textit{threo} product. In both cases, the steric repulsions noted prove to be the dominant factors leading to high selectivity. If allylic alcohols with bulky, yet easily removable groups at these positions are epoxidized by the appropriate method, followed by removal of the directing groups, \textit{E-threo-} and \textit{Z-erythro-}epoxyalcohols should result. One possibility for such a removable directing group is the trialkyl silyl group,\textsuperscript{65} which is removable by fluoride ion with retention of epoxide stereochemistry.\textsuperscript{66} The results of Oshima, shown in Figure 14, demonstrate that this method can provide the desired alcohols.\textsuperscript{62d,67}

Although this method does provide the requisite epoxy-alcohols, it necessitates synthesis of a different set of
FIGURE 13

59

MCPBA
Mo$^{6+}$, TBHP
V$^{+5}$, TBHP

T
95
5

59

60

E
5

60

61

MCPBA
Mo$^{6+}$, TBHP
V$^{+5}$, TBHP

T
45
55

62

63

E
5

63

64

MCPBA
Mo$^{6+}$, TBHP
Al$^{3+}$, TBHP
V$^{+5}$, TBHP

T
45
55

64

64

E
5

64

E
95

64
allylic alcohols. For simplicity and generality, it would be desirable to have all four epoxyalcohol isomers generated from common intermediates. We examined a second alternative in an attempt to effect such a synthesis. By making use of the highly selective epoxidation methods listed in Figure 11, and then inverting the stereocenter at C.2, only two sets of intermediates needed to be synthesized: a Z-olefin and an E-olefin. The inversion of the hydroxyl groups was accomplished by using the methodology developed by Mitsunobu
(Figure 15). The Z-threo-epoxide 71a and the E-erythro-

FIGURE 15

epoxide 73, prepared by standard procedures (vide infra) were treated with triphenylphosphine, diethylazodicarboxylate, and p-nitrobenzoic acid, followed by basic methanolysis, to provide the Z-erythro and E-threo epoxides (72 and 74 respectively) in good yield. The epoxides were unaffected by either the initial inversion or the basic conditions employed to transesterify the intermediate p-nitrobenzoyl esters.
Solvolysis Reactions

With suitable syntheses of the four epoxyalcohol isomers mapped out, we were ready to begin examining some solvolysis reactions. Allylic alcohol 76 was prepared by quenching the lithium anion of 1-benzyloxy-3-butyne 75\textsuperscript{71} with acetaldehyde, followed by hydrogenation over Lindlar catalyst (Figure 16). Epoxidation of 76 by using MCPBA afforded the Z-threo-epoxyalcohol 71a in good yield. Treatment of 71a with a 3:1 mixture of dimethyl sulfoxide and dilute sulfuric acid, followed by peracetylation provided an authentic sample of the xylo-triacetate 77. The solvolysis conditions were well preceded to result in β-ring opening;\textsuperscript{51} confirmation of this

FIGURE 16

75

\[ \text{BnO} \quad \rightarrow \quad \text{BnO} \]

1) n-BuLi, -78°C
2) CH\textsubscript{3}CHO
3) H\textsubscript{2}, Lindlar 79%

76

\[ \text{HO} \quad \rightarrow \quad \text{HO} \quad \rightarrow \quad \text{CH}_3 \]

4) MCPBA
5) CH\textsubscript{2}Cl\textsubscript{2}, 0°C 78%

71a

77

\[ \text{AcO} \quad \rightarrow \quad \text{BnO} \quad \rightarrow \quad \text{AcO} \]

1) 3:1 DMSO/2N H\textsubscript{2}SO\textsubscript{4}
2) Ac\textsubscript{2}O, pyridine 51%
assignment was accomplished by correlations with compounds subsequently described.

The acetate 71b when treated with aqueous acetic acid, followed by peracetylation, gave a 2:1 ratio of arabino (α-opened) and xylo (β-opened) triacetates 78 and 77, respectively. Although a preference for α-opening was observed, the low ratio was disappointing (Figure 17, Entry 2).

A second neighboring group, methyl carbonate, was next examined. We felt that the carbonate would be a better participating group than an acetate since the carbonyl group is substituted with two electron releasing substituents, which should weaken the carbonyl double bond, thereby making the carbonyl oxygen atom more nucleophilic. The percentage of α-opening, however, actually decreased when 71c was treated with aqueous acetic acid (Entry 3). When an even stronger (HClO₄) protic acid was used, β-attack proved to be the sole mode of ring opening (Entry 4). It appeared that the β-opened products could have arisen from competitive external nucleophilic attack by water. At least in this stereochemical series, it seemed probable that the acetate and carbonate groups were not capable of competing successfully with external β-attack. We felt that performing the neighboring group assisted α-opening reaction under nonaqueous Lewis acid-catalyzed conditions might eliminate the β-opening pathway. With the neighboring group isolated as the only nucleophile in the system, we expected to observe the products of attack by that group alone. We
FIGURE 17

\[
\begin{align*}
\text{Conditions} & \quad \text{specified below} \\
1) \quad \text{Ac}_2\text{O}, \text{pyridine} & \\
\end{align*}
\]

\chem{\begin{align*}
\text{BnO} & \quad \text{RO} \quad \text{CH}_3 \quad \text{AcO} \\
\text{BnO} & \quad \text{OAc} \quad \text{OAc} \\
\text{BnO} & \quad \text{OAc} \\
\end{align*}}

\chem{\begin{align*}
\text{R} & = \text{H} \\
\text{R} & = \text{CH}_3\text{CO} \\
\text{R} & = \text{CH}_3\text{OCO} \\
\end{align*}}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>Hydrolysis conditions</th>
<th>Combined yield</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>71a</td>
<td>75% DMSO, H\textsubscript{2}O, H\textsuperscript{+}, 23°C</td>
<td>51%</td>
<td>only 77</td>
</tr>
<tr>
<td>2</td>
<td>71b</td>
<td>4:1 HOAc, H\textsubscript{2}O, 100°C</td>
<td>&gt;95%</td>
<td>33:67\textsuperscript{a}</td>
</tr>
<tr>
<td>3</td>
<td>71c\textsuperscript{b,c}</td>
<td>4:1 HOAc, H\textsubscript{2}O, 100°C</td>
<td>71%</td>
<td>79:21\textsuperscript{d}</td>
</tr>
<tr>
<td>4</td>
<td>71c\textsuperscript{e,c}</td>
<td>5% HClO\textsubscript{4}, CH\textsubscript{3}CN, 23°C</td>
<td>95%</td>
<td>only 77</td>
</tr>
<tr>
<td>5</td>
<td>71c\textsuperscript{f,c}</td>
<td>BF\textsubscript{3}·Et\textsubscript{2}O, Et\textsubscript{2}O, 0°C</td>
<td>60%</td>
<td>only 78</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Ratio was determined by \textsuperscript{1}H NMR spectroscopy. \textsuperscript{b}A mixture of 80a, 86(\textit{vide infra}) and a third, unidentified compound was obtained from this reaction. No dihydroxy methyl carbonate was observed in the \textsuperscript{1}H NMR spectrum. Though we cannot rule out neighboring group attack at the \(\beta\)-position, we believe in light of subsequent observations that the \textit{xylo}-product arises from attack of H\textsubscript{2}O on 71c. The presence of 86 in the mixture indicates that acyl transfer occurred under the reaction conditions. \textsuperscript{c}The crude mixture was transformed to the corresponding triols (cat. NaOMe, MeOH) prior to acetylation. \textsuperscript{d}Ratio was determined by isolation by preparative TLC. \textsuperscript{e}A mixture of 86 and the aforementioned unidentified compound was obtained from this reaction. \textsuperscript{f}A mixture of 80a(minor) and 81a(major) was obtained.
were gratified to find that α-opened products were obtained exclusively when carbonate 71c was treated with BF₃·Et₂O in diethyl ether. Although complete control of neighboring group assisted reaction was accomplished under these conditions, the extreme sluggishness and low yield of this reaction prompted us to examine another neighboring group.

We thus turned to an investigation of the phenylurethanes 73a and 73b. We reasoned that the nitrogen atom, being less electronegative than an oxygen atom, would better enhance the nucleophilicity of the carbonyl oxygen by electron donation into the carbonyl group. In this series too, however, external nucleophilic attack proved to be a problem under strongly acidic and/or nucleophilic conditions (Figure 18). Treatment of 73a and 73b with 48% aqueous HBr in acetone resulted in clean conversion to the xylo bromides 82a and 82b, respectively, in very good yield. No products arising from neighboring group assisted processes were observed. When 73a and 73b were treated with aqueous HClO₄ in acetonitrile, significant amounts of xylo diols were isolated, although the neighboring group process was now the major reaction pathway. Use of aqueous acetic acid virtually eliminated β-attack. As expected from our results obtained on carbonate 71c, solvolysis of the phenylurethanes 73a and 73b under nonaqueous Lewis acid-mediated conditions also resulted in exclusive α-attack. These results confirmed our expectation that the phenylurethane would be more effective as a neighboring group than either the acetate or carbonate groups. We elected to use this group for the rest
### FIGURE 18

![Chemical Structures]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>Conditions</th>
<th>Arabino (80:81)</th>
<th>Xylo (82)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>79a</td>
<td>HBr, acetone, 23°C</td>
<td>-</td>
<td>98% (X=Br)</td>
</tr>
<tr>
<td>2</td>
<td>79b</td>
<td>HBr, acetone, 23°C</td>
<td>-</td>
<td>94% (X=Br)</td>
</tr>
<tr>
<td>3</td>
<td>79a</td>
<td>5% HClO₄, CH₃CN, 23°C</td>
<td>61% (5:1)</td>
<td>29% (X=OH)</td>
</tr>
<tr>
<td>4</td>
<td>79b</td>
<td>5% HClO₄, CH₃CN, 23°C</td>
<td>86% (6:1)</td>
<td>9% (X=OH)</td>
</tr>
<tr>
<td>5</td>
<td>79a</td>
<td>4:1 HOAc, H₂O, 100°C</td>
<td>90% (1:6)</td>
<td>trace (X=OH)</td>
</tr>
<tr>
<td>6</td>
<td>79b</td>
<td>4:1 HOAc, H₂O, 100°C</td>
<td>98% (3:7)</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>79a&lt;sup&gt;e&lt;/sup&gt;</td>
<td>BF₃·Et₂O, CH₂Cl₂, 23°C</td>
<td>71% (1:4)</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>79b&lt;sup&gt;e&lt;/sup&gt;</td>
<td>BF₃·Et₂O, CH₂Cl₂, 23°C</td>
<td>95% (1:5)</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>79a&lt;sup&gt;e&lt;/sup&gt;</td>
<td>BF₃·Et₂O, Et₂O, 0°C</td>
<td>80% (10:1)</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>79b&lt;sup&gt;e&lt;/sup&gt;</td>
<td>BF₃·Et₂O, Et₂O, -20°C</td>
<td>89% (&gt;20:1)</td>
<td>-</td>
</tr>
</tbody>
</table>

*Notes on following page.*
The yields of products isolated by chromatography; the yields listed under the *arabino* heading are the combined yields of acyl transfer isomers 80 and 81. \(^{b}\) The values in parentheses refer to the ratio of *arabino* carbonates 80 and 81, respectively. \(^{c}\) *Arabino* carbonates 80a and 81a were correlated with *arabino* triacetate 78 by trans-esterification (NaOMe, MeOH) and acylation (Ac\(_2\)O, pyridine). \(^{d}\) *Xylo* diol 82a was correlated with *xylo*-triacetate 77 by reduction (LiAlH\(_4\), THF, reflux, 63% yield) and peracetylation (Ac\(_2\)O, pyridine, >95% yield). \(^{e}\) All Lewis acid induced epoxide openings were worked up with mild acid treatment (two phase hydrolysis using 1N H\(_2\)SO\(_4\)) to hydrolyze the intermediate iminocarbonate (see reference 74).
of this study.

Even though these conditions were very effective in favoring internal α-attack over external β-attack, the large amount of acyl transfer from the cis carbonate 80a or b to the more stable trans carbonate 81a or b which occurred was bothersome. Many situations could be envisioned when a neighboring group assisted α-opening might be used not only to control the regioselectivity of epoxide opening but also to effect differentiation of the resulting hydroxyl functionalities. It was therefore desirable to find conditions which would suppress this side reaction. Significant acyl transfer occurred when the urethanes were treated with BF₃•Et₂O in methylene chloride, but this process was effectively suppressed when the ring opening was conducted with BF₃•Et₂O in diethyl ether. Control experiments had indicated that the acyl transfer occurred during the initial Lewis acid-catalyzed ring opening, rather than in the subsequent two-phase hydrolysis step. The major difference between diethyl ether and methylene chloride was that a Lewis acid-substrate (product?) complex precipitated from ether but remained in solution in CH₂Cl₂. Presumably, once out of solution, the deleterious acyl transfer process could not occur.

The observation that all three of the neighboring groups discussed failed to compete successfully with external nucleophiles in strongly acidic, protic conditions was unexpected. The explanation for this behavior lies in the unfavorable steric interactions between the C.5 methylene and the methyl
group on the carbinol carbon which develop as the acyloxy carbonyl group adopts the orientation (A) necessary for backside displacement at C.3 (Figure 19). Consideration of nonbonded interaction leads one to conclude that the protonated forms of

![FIGURE 19](image)

\[ 71b, \text{ R=CH}_3 \]
\[ 71c, \text{ R=OCH}_3 \]
\[ 79a, \text{ R=NHC}_6\text{H}_5 \]

71b,c and 79a will exist predominantly in conformation B, in which the neighboring group occupies an unreactive orientation. Both conformations A and B, however, are still susceptible to external nucleophilic attack at the β-position. Assuming that the two modes of reaction (internal α or external β) may have different pH rate profiles, it is not surprising that the product distributions exhibit higher percentages of xylo (β-opened) products as the pH decreases.

We suspected that the problem of β-opening might be most pronounced in the epoxyalcohol systems represented by 79a and 79b. Examination of the three remaining diastereomeric epoxy alcohol series (Figure 20) led us to suspect that each
one could easily adopt a conformation in which the acyloxy group is properly oriented for attack on C.3.

FIGURE 20

The lowest energy conformation of an epoxyalcohol system should be one in which the smallest substituent of the carbinol carbon atom eclipses the plane occupied by the epoxide ring system (Figure 21). This conformation minimizes the nonbonded interactions between substituents on C.2 and C.4. Although conformation i is the most stable one for threeo-epoxyalcohols, neighboring group reactions must occur via conformation iii, the least stable conformation. In erythro-epoxyalcohols, however, neighboring group reactions proceed via conformation iv, the lowest energy conformation available in this series. These equilibria clearly favor i and iv more when the epoxyalcohol is derived from a Z-olefin rather than an E-olefin.

It is clear from the foregoing analysis that for erythro-epoxide derivatives 83 and 85 the reactive conformation corresponds
FIGURE 21

**Threo** epoxyalcohol

**Erythro** epoxyalcohol

To the most stable one. For the remaining **threo**-epoxide 84, the reactive conformation has a destabilizing interaction between the C.4-H and the methyl group. This interaction is clearly less severe than the one present in the **z-threo**-epoxides such as 79. We felt, therefore, that the epoxide-opening reactions of these remaining substrates would exhibit greater regioselectivity than that exhibited in our first substrate. This, indeed, proved to be the case.

Significant quantities of β-ring opened products resulted from these substrates only when the ring opening reactions were conducted with aqueous HBr in acetone (Figures 22,23,24).
**FIGURE 22**

Yields

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Xylo(86)$^a$</th>
<th>Arabino(87)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HBr, acetone, 23°C</td>
<td>48%</td>
<td>36% (X=Br)</td>
</tr>
<tr>
<td>2</td>
<td>5% HClO$_4$, CH$_3$CN, 23°C</td>
<td>87%</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>4:1 HOAc, H$_2$O, 100°C</td>
<td>94% (1.6:1)$^b$</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>BF$_3$·Et$_2$O, Et$_2$O, -20°C</td>
<td>73%</td>
<td>-</td>
</tr>
</tbody>
</table>

$^a$Xylo carbonate 86 was correlated with triacetate 77 by transesterification (NaOMe, MeOH) and acetylation (Ac$_2$O, pyridine).

$^b$A 1.6:1 mixture of 86 and its 3,4-acyl transfer isomer was obtained.
**FIGURE 23**

![Chemical structures](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Ribo(88)</th>
<th>Lyxo(89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HBr, acetone, 23°C</td>
<td>11%</td>
<td>67%(X=Br)</td>
</tr>
<tr>
<td>2</td>
<td>5% HClO4, CH3CN, 23°C</td>
<td>74%</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>4:1 HOAc, H2O, 100°C</td>
<td>74%</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>BF3·Et2O, -20°C</td>
<td>82%</td>
<td>-</td>
</tr>
</tbody>
</table>
**FIGURE 24**

```
85  \[\begin{array}{c}
\text{O} \\
\text{O} \\
\text{NHCH₃} \\
\end{array}\] \\
85
```

```
90  \[\begin{array}{c}
\text{OH} \\
\text{CH₃} \\
\end{array}\] \\
90
```

```
91  \[\begin{array}{c}
\text{O} \\
\text{O} \\
\text{HO} \\
\text{CH₃} \\
\end{array}\] \\
91
```

```
92  \[\begin{array}{c}
\text{X} \\
\text{O} \\
\text{NHCH₃} \\
\end{array}\] \\
92
```

### Yields

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Lyxo(90)</th>
<th>Ribo(92)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HBr, acetone, 23°C</td>
<td>41%</td>
<td>41% (92, X=Br)</td>
</tr>
<tr>
<td>2</td>
<td>5% HClO₄, CH₃CN, 23°C</td>
<td>85%</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>4:1 HOAc, H₂O, 100°C</td>
<td>95%</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>BF₃·Et₂O, Et₂O, 0°C</td>
<td>&gt;95%</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>Et₂AlCl, Et₂O, 0°C</td>
<td>95%</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>SnCl₄, Et₂O, 0°C</td>
<td>only'</td>
<td></td>
</tr>
</tbody>
</table>

---

\(^a\) A 30:1 mixture of 90 and 91 was obtained from this experiment (NMR analysis).  \(^b\) A 16:1 mixture of 90 and 91 was obtained (NMR analysis).
These conditions provide a useful qualitative measure of the competition between the two reaction pathways (bimolecular β versus intramolecular α opening). The results parallel the trend which one would predict on the basis of the conformational preferences of the epoxyalcohol substrates discussed above - (79 > 84 > 83 ≈ 85). All other sets of reaction conditions, with one important exception, resulted in clean conversion to the expected α-opened carbonate derivatives without detectable quantities of β-opened diols.

Solvolytic of the erythro epoxide 85 (Figure 24) which we expected to be the least troublesome substrate for neighboring group assisted reactions, resulted in the formation of small amounts of the δ-ribo-carbonate 91. Similar results were obtained in the solvolyis of isomeric epoxyurethane 93 (Figure 25). In both cases, the minor ribo carbonate arose not from external nucleophilic attack followed by transacylation, but from intramolecular attack of the neighboring group on the β-position. This interpretation is necessitated by the fact that 91 was obtained under anhydrous conditions (BF₃•Et₂O in CH₂Cl₂ or Et₂O) and conditions in which protic impurities such as water would be rapidly consumed (Et₂AlCl). In addition, δ-ribo carbonate 91 was not observed in reactions that produced γ-ribo carbonate 88 (see Figure 23), which might have isomerized to 91. Therefore, it is unlikely that 91 could have resulted from transacylation of the undetected 92 (X=OH) under the reaction conditions specified in Figure 24.
Yields

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Arabino((+)-81b)</th>
<th>Ribo(94)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HBr, acetone, 23°C</td>
<td>35%</td>
<td>45%</td>
</tr>
<tr>
<td>2</td>
<td>BF$_3$·Et$_2$O, CH$_2$Cl$_2$, 23°C</td>
<td>&gt;95%(4:1)$^a$</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>BF$_3$·Et$_2$O, Et$_2$O, 0°C</td>
<td>88%(10:1)$^a$</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Et$_2$AlCl, Et$_2$O, -20°C</td>
<td>95%(60:1)$^a$</td>
<td>-</td>
</tr>
</tbody>
</table>

$^a$Ratio of 81b to 91 (NMR analysis).
The alternative explanation is that 91 results from a kinetically controlled attack of the neighboring group at the \( \beta \)-position of the epoxide. This situation is not specifically defined by Baldwin's rules for ring closure.\textsuperscript{76} However, a precedent for such a reaction pathway does exist in the steroid literature.\textsuperscript{54e} In addition, attempts to extend this methodology to the branched sugars present in the aureolic acid antibiotic group also provide data in support of this hypothesis.

The epoxyurethane 95, a potential precursor of mycarose, \textsuperscript{23} was treated with a variety of Lewis acids (BF\(_3\)·Et\(_2\)O, SnCl\(_4\), Et\(_2\)AlCl, etc.) to afford mixtures of triols ranging from 10:1 to 1:2 of 96:97 (Figure 26).\textsuperscript{77} The best results were obtained with Et\(_2\)AlCl in Et\(_2\)O at \(-20^\circ\text{C}\). Triol 96 was produced from 95 by attack of the neighboring group on the \( \beta \)-position of the epoxide (the 2,4-carbonate derivative of 96 could be isolated from the mixture before treatment with NaOMe). Exposure of 98 to either aqueous or Lewis acids afforded exclusively tetrahydrofuran 99 in good yield (up to 75\%). In every case, a significant percentage of \( \beta \)-opened products was obtained.

It is likely that protic or Lewis acid promoted epoxide openings proceed with substantial carbonium ion character at the site undergoing substitution. Because of this, it may not be necessary that the angle of nucleophilic approach be coincident with the C-O bond axis of the epoxide. Instead, nucleophilic attack might occur along an approach vector which is almost perpendicular to the epoxide C-C bond axis, coincident
FIGURE 26

\[
\begin{array}{c}
\text{95} \\
\text{96 (β-opened)} \\
\text{97 (α-opened)}
\end{array}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Yield</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BF$_3$·Et$_2$O, CH$_2$Cl$_2$, -20°C</td>
<td>52%</td>
<td>10:1</td>
</tr>
<tr>
<td>2</td>
<td>BF$_3$·Et$_2$O, Et$_2$O, -20°C</td>
<td>62%</td>
<td>2:1</td>
</tr>
<tr>
<td>3</td>
<td>SnCl$_4$, CH$_2$Cl$_2$, -20°C</td>
<td>35%</td>
<td>2:1</td>
</tr>
<tr>
<td>4</td>
<td>Et$_2$AlCl, Et$_2$O, -20°C</td>
<td>62%</td>
<td>1:2</td>
</tr>
</tbody>
</table>

TBDMSO

\[
\begin{array}{c}
\text{98} \\
\text{99}
\end{array}
\]
with the developing p-orbital of the electrophilic carbon atom. Examination of molecular models indicate that such an

\[ \text{H}_2\text{O}^+ \]
\[ \text{H}_2\text{O}^- \]

approach is possible for the internal attack of the carbonyl oxygen on the β-epoxide carbon. The high percentage of β-opened products in the reactions of 95 and 98 is the result of the fact that these substrates can more readily accept the development of positive charge (3° - carbonium ion character) at the β-position.

These results were clearly in opposition to our goal of controlling the neighboring group reaction to effect exclusive α-opening. We observed that for the solvolysis of 79a,b increased acid strength tended to promote larger amounts of β-opened products. Although one must be cautious in discussions of the relative strengths of different Lewis acids in several solvents,78 Figures 24,25,26 show that the percentages of β-opened products can be reduced by the appropriate choice of conditions. Switching from solvolysis of 93 with BF$_3$·Et$_2$O in CH$_2$Cl$_2$ to BF$_3$·Et$_2$O in diethyl ether effected a decrease in the amount of β-opened product from 20% to 10%. Even better results were obtained when Et$_2$AlCl, generally considered a weaker Lewis acid than BF$_3$·Et$_2$O,78 was used, virtually eliminating
the β-opening pathway. This has become the reagent of choice for the α-ring opening of substrates like 85 and 93. Unfortunately, use of Et₂AlCl for the neighboring group reaction of 95 provided a predominance of α-opening, but did not eliminate β-opening.

If such an intramolecular β-ring opening process is available, why was it not observed in the other epoxyalcohol series? For substrate 85 the methyl, allyl, and Lewis acid coordinated alkoxy groups all move into equatorial positions about the intermediate iminocarbonate ring system 100 as the β-ring opening reaction occurs (Figure 27). Substrates 79, 83, 84, on the other hand, would require one or both of the alkyl groups to assume an axial orientation along the reaction coordinate leading to the intramolecular β-opened product. The transition states must reflect the nonbonded interactions that these axial substituents experience along the reaction coordinate. These interactions are apparently of sufficiently high energy that the β-opening is not competitive with the dominant α-opening pathway. 79

FIGURE 27
The preceding results indicate that the opening of acyclic epoxyalcohol derivatives are dependent on the stereochemistry of the epoxyalcohol, the nature of the acyl derivatives and the particular solvolysis conditions used. Geometries of allylic alcohols which favor highly selective epoxidations, ironically, tend to disfavor selective ring opening processes. However, in most cases, suitable solvolysis conditions were found to promote exclusive α-opening. Best results were obtained when a urethane was used as the neighboring group. Thus, neighboring group assisted α-ring opening reactions of acylated 2,3,4-epoxyalcohol derivatives are now available for a range of secondary epoxyalcohols which are of interest for use in syntheses of polyhydroxylated natural products. Applications of this methodology to the synthesis of several 2,6-dideoxyhexoses appear in the following chapter.
Stereochemical Correlations

Arabino-triacetate 78 was correlated with carbonates 80b and 81b as outlined in Figure 28. The stereochemistry of 80b/81b is known unambiguously by virtue of the conversion of these compounds to 2,6-dIDEOXY-arabino-hexose. A similar sequence was used to correlate xylo-triacetate 77 with triol 102, which has been transformed into 2,6-dIDEOXY-xylo-hexose.

Methanalysis (NaOMe, MeOH) of 88 and 91 afforded the corresponding ribo-triol which is an intermediate in the synthesis of 2,6-dIDEOXY-ribo-hexose. Carbonate 90 has also been correlated with a sugar, 2,6-dIDEOXY-lyxo-hexose. The syntheses of all four of these sugars are described in Chapter III.
FIGURE 28

1) $\text{H}_2$, Pd/C
2) $\text{Ac}_2\text{O}$, pyridine

1) $\text{NaOCH}_3$, CH$_3$OH
2) $\text{Ac}_2\text{O}$, pyridine
3) $\text{O}_3$, $\text{NaBH}_4$ workup
4) $\text{Ac}_2\text{O}$, pyridine

1) $\text{H}_2$, Pd/C
2) $\text{Ac}_2\text{O}$, pyridine

1) $\text{Ac}_2\text{O}$, pyridine
2) $\text{O}_3$, $\text{NaBH}_4$ workup
3) $\text{Ac}_2\text{O}$, pyridine
CHAPTER III
SYNTHESES OF 2,6-DIDEOXYHEXOSES

Armed with the information obtained in the studies described in Chapter II, we were now ready to apply this methodology to the synthesis of a number of 2,6-dideoxyhexoses. The only problem remaining to be addressed was the form of latent or protected aldehyde best suited for our synthetic scheme. Preliminary experiments indicated that the benzyl ether function which we used in our initial substrate 71a (see Figure 29) was not appropriate as a latent aldehyde. The benzyl group could be easily removed from carbonate 81a by catalytic hydrogenation to provide the primary alcohol 104a. Selective oxidation of the primary hydroxyl group of 104a or 104b proved difficult, however, in the presence of one or more secondary alcohols in the molecule. Though the complicating hydroxylic functionality of 104a,b could be protected, in principle, before taking steps necessary to convert the benzyl-oxy carbinol center into an aldehyde, we concluded that such a sequence would be too lengthy to be practical. It was also apparent that use of an acetal to protect the aldehydic function would not be feasible because of the acidic conditions employed both in the neighboring group-assisted ring-opening step and in the hydrolysis of the intermediate iminolactones. We turned, therefore, to the use of a vinyl group as a latent aldehyde equivalent. The aldehyde could be easily liberated in the correct oxidation state by ozonolysis at an appropriate
stage of the synthesis without disturbing other functionalities present in the molecules.

FIGURE 29

71a → 81a → 104a \( R_1=R_2=\text{CO} \)

104b \( R_1=R_2=\text{H} \)

104a or 104b

105a \( R_1=R_2=\text{CO} \)

105b \( R_1=R_2=\text{H} \)
Synthesis of Racemic Olivose (17) and Boivinose (5)

Aside from the aureolic acid antibiotics (vide supra), 2,6-dideoxy-D-arabino-hexose 17 (D-olivose; also known as canarose and chromose C) is found in the cardiac glycosides, 83 flambamycin, 84 the eveminomycins, 85 chromocyclomycin, 86 oxamicetin, 87 and chlorothricin. 88 A number of syntheses of olivose have been reported. 82,89 The D-isomer can be obtained from D-glucose 89a-d and the L-isomer from L-rhamnose. 89g-i Several syntheses of the racemic sugar have been reported, 82,89j,k as well as some non-carbohydrate-based syntheses. 82,89f

\[ \text{17} \]
Olivose

\[ \text{5} \]
Boivinose

D-Boivinose 5, 2,6-dideoxy-D-xylo-hexose, can be found as a component of the cardiac glycosides 83b,90 and in coloroside. 91 The D-isomer can be prepared from D-galactose 92b or from 5-deoxy-D-xylose; 92a the L-isomer has been synthesized from D-glucose. 92c Some non-sugar syntheses have also been reported. 82,89f,j

Our synthesis of DL-olivose (Figure 30) originated from 3-butyn-2-ol, 106, which was treated with excess allyl chloride and catalytic CuCl in aqueous methanol maintained between pH 7.5-8.5 to give hept-1-en-4-yn-6-ol 107. This procedure, adapted from
FIGURE 30

106

ClCH₂CH=CH₂, CuCl
H₂O, CH₃OH, 70°
ph=7.5-8.5
95%

107

xs Zn-Cu, CH₃OH
sealed tube
120°
67-73%

108

1) Ti(O^t-Pr)₄ (1.0 eq)
TBHP (1.1 eq), CH₂Cl₂
-20°, 80%
2) C₆H₅NCO, pyridine
23°, 89%

108

109 R=H

79b R=CONHC₆H₅

80b

1) BF₃·Et₂O
Et₂O, -20°
2) 1N H₂SO₄
workup
89%

81b

80b/81b

NaOCH₃ (catalytic), CH₃OH
23°, 24 h.
98%

110

O₃, CH₃OH, -20°
(CH₃)₂S workup
85%

(±)-17
that of Kurtz,\textsuperscript{93} afforded 107 in 95% distilled yield. The acetylene was reduced cleanly in 67-73% yield to the Z-olefin 108 by using Zn-Cu couple\textsuperscript{94} in methanol (120\degree, sealed tube). Attempts to reduce 107 by using H\textsubscript{2} and Lindlar catalyst resulted in partial (ca. 30%) hydrogenation of the vinyl group. Use of P-2 nickel\textsuperscript{95} also was unsuccessful for this reduction. Epoxidation of 108 with tert-butylhydroperoxide and titanium tetraiso-propoxide in CH\textsubscript{2}Cl\textsubscript{2} at -20\degree C afforded epoxide 109 with high threo selectivity (19:1).\textsuperscript{62h} Treatment of 109 with phenyl isocyanate in pyridine\textsuperscript{96} afforded the phenylurethane 79b in 70% overall yield from 108. Solvolytic epoxide opening of 79b with BF\textsubscript{3}•Et\textsubscript{2}O in Et\textsubscript{2}O at -20\degree C, followed by hydrolysis of the intermediate iminocarbonate, resulted in a 20:1 mixture of the isomeric carbonates 80b and 81b (89% yield). When this reaction was performed with BF\textsubscript{3}•Et\textsubscript{2}O in CH\textsubscript{2}Cl\textsubscript{2}, 81b was the major product. Basic methanolysis accomplished the removal of the carbonate, affording the racemic arabinoa-triol 110 in quantitative yield. The triol was converted to DL-olivose 17 by ozonolysis in 80-85% overall yield from 80b/81b.

The epoxide 109 was also used in a synthesis of DL-bovinose 5 (Figure 31). Hydrolysis of 109 with 20% aqueous HClO\textsubscript{4}

\textbf{FIGURE 31}
in THF afforded xylo-triol 102 in 65% yield. None of the isomeric arabino-triol resulting from α-opening was detected in this reaction mixture. When the sulfuric acid-DMSO conditions used in the conversion of 71a to 77 (Chapter II) were employed here, the yield of triol 102 was much lower due to the formation of ketonic products (determined by IR spectroscopy). Presumably, the oxidation occurs through an intermediate of the type shown below:

![Chemical Structure](image)

Ozonolysis (90% yield) of 102 completed this five step synthesis of DL-bovinose (+)-5. The yield of (+)-5 from 3-butyln-2-ol 106 was 30-33%.
**Enantioselective syntheses**

Our original plan for the synthesis of optically active 17 was to modify the route shown in Figure 30 by using optically active 107, which could be prepared by enantioselective reduction of the corresponding propargyl ketone.98 The advent of the Sharpless asymmetric epoxidation procedures,99 however, obviated this plan. The kinetic resolution-enantioselective epoxidation procedure,62h which appeared to offer a convenient route to chiral secondary epoxyalcohols, seemed particularly suited to our purposes. Although a detailed discussion of the mechanism and development of the kinetic resolution technique is beyond the scope of this work, some brief comments are appropriate.

The Sharpless asymmetric epoxidation technique, as originally reported,99 allowed the introduction of a chiral epoxide functionality onto a wide range of prochiral allylic alcohols. The method gives uniformly high, and predictable, asymmetric induction. Since esters of both tartrate enantiomers are readily available at reasonable cost, one can easily prepare either epoxyalcohol enantiomer by choosing the appropriate tartrate ester.

If the allylic alcohol is not a primary (prochiral) alcohol but is instead a secondary allylic alcohol (racemate), two additional effects need to be considered. As noted in Figure 11 (Chapter II), the titanium alkoxide-tartrate catalyst exhibits a strong tendency for erythro epoxidation. In addition, the extra alkyl group at the carbinol position
adds a steric barrier to the epoxidation complex. For a racemic alcohol such as cyclohexyl propenylcarbinol \textbf{111} when epoxidized with a \((+)-\)tartrate-modified reagent, these two effects are consonant for the \((S)\)-enantiomer, but dissonant for the \((R)\)-enantiomer (Figure 32). If the rate of epoxidation of the fast-reacting enantiomer is sufficiently larger than that of the slow-reacting enantiomer, only the fast-reacting enantiomer will be consumed (epoxidized) at partial conversion leading to a mixture of epoxide product and allylic alcohol enriched in the slow-reacting enantiomer. This process is known as a kinetic resolution.\textsuperscript{100a}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure32.png}
\caption{Figure 32}
\end{figure}
For the example described in Figure 32, the (S)-enantiomer reacts 104 times faster than the R-enantiomer, with an *erythro*: *threo* selectivity of 98:2 for the epoxide products. The (R)-enantiomer, however, preferentially gives the *threo* product—apparently the enantiofacial preference of the chiral reagent dominates the tendency for *erythro* selectivity in the matched pair. This *threo* selectivity for the slow-reactivity enantiomer may also arise from epoxidation by the small amount of titanium-TBHP complex without ligated tartate which is present at equilibrium (see Figure 11). These relative rates and selectivity patterns are generally true for all secondary E-allylic alcohols. Significantly, if the epoxidation of an E-allylic alcohol is stopped short of 50% conversion, one can obtain the *erythro*-epoxyalcohol in high purity and very good enantiomeric excess. This is best accomplished by using 0.4-0.45 equivalents of TBHP in the epoxidation system. The *erythro*: *threo* selectivity and optical purity of the *erythro*-epoxyalcohol will, of course, diminish in direct proportion to the extent of reaction beyond 50% conversion.

On the other hand, Z-allylic alcohols are less ideal substrates for the kinetic resolution procedure. The *erythro* selectivity for the titanium alkoxide-tartrate catalyst is at best about 4:1, and the relative rate between the fast- and slow-reacting enantiomers is less than twenty. In addition, *erythro* selectivity is not general for Z-secondary allylic alcohols. The selectivity in these systems decreases as the size of the
(Z)-β-vinyl substituent increases. The latter problem could be overcome by using the Sharpless procedure to resolve a Z-secondary allylic alcohol, which could then be epoxidized with an achiral, three selective reagent (see Figure 11) in a subsequent step. The maximum yield from this procedure, however, is 30–35% since the kinetic resolution would need to proceed to 65–70% conversion in order to prepare >95% e.e. allylic alcohol (assuming a relative epoxidation rate of <20 for the two enantiomers). Thus, we concluded that the kinetic resolution process would not be useful for the preparation of chiral epoxides from racemic Z-allylic alcohols.

A reexamination of Figure 9 shows that the ribo-, lyxo-, and arabino-triols can all be prepared from E-erythro-epoxy-alcohols, and ultimately from E-allylic alcohols, which we expected would be excellent substrates for the kinetic resolution procedure. Only the xylo-triol, which must arise from a Z-allylic alcohol, could not be easily produced by this method. Enantioselective syntheses of xylo-triol derivatives, therefore, might be better accomplished by alternative enantioselective methods or by classical resolution of synthetic intermediates. Since bovinose was of only marginal interest to the olivomycin A synthetic effort, a synthesis of optically active xylo-triol or D-bovinose (+)-5 was not attempted.
Enantioselective Syntheses of D-Digitoxose (4) and D-Olivose (17)

The Sharpless kinetic resolution technique is a resolution and therefore is limited to a maximum of 50% yield of the chiral epoxide. As far as synthetic operations are concerned, this is a serious drawback since one would like to use material as efficiently as possible. This disadvantage can be minimized if both enantiomers of the epoxide can be used. The syntheses of D-digitoxose (4) and D-olivose (17) discussed below illustrate this principle.

![Structural formulas of Digitoxose and Olivose](image)

D-Digitoxose, 2,6-dideoxy-D-ribo-hexose, 4, is a component of the cardiac glycosides \(^{83b,90}\) and is also found in α-lipomycin, \(^{103}\) oleficin, \(^{104}\) and sinapolyglucoerysinoside, a metabolite isolated from *Erysimum marschallium*. \(^{105}\) The L-isomer is a component of kijanimicin \(^{106}\) and the closely related antibiotics, the tetrocarcins \(^{107}\) and antlermicins. \(^{108}\) It is also found in several polyene macrolide antibiotics. \(^{109}\) A number of syntheses have been reported. \(^{82,89f,j;110}\) The D-isomer can be obtained from D-glucose \(^{110a-c}\) via methyl 2,3-anhydro-4-6-O-benzylidene-α-D-allo-pyranoside \((39, Figure 7)\) \(^{47}\)
or from L-rhamnose\textsuperscript{110d} via D-allomethylose.\textsuperscript{111} Both of these routes involve at least one stereochemical inversion. The L-isomer is available from L-rhamnose.\textsuperscript{110e}

The E-allylic alcohol 114 (Figure 33), readily prepared from crotonaldehyde and allylmagnesium bromide,\textsuperscript{112} served as the starting material for the syntheses of D-olivose 17 and D-digitoxose 4. Treatment of 114 with 1.0 equivalents of titanium tetraisopropoxide and 1.5 equivalents of (-)-diisopropyl tartrate ((-) -DIPT) and 0.42 equivalents of TBHP in CH\textsubscript{2}Cl\textsubscript{2} at -20°C produced, after chromatography and distillation of the individual fractions, erythro-epoxide (+)-115 (27-33%}

\textbf{FIGURE 33}

\begin{align*}
(+)-114 & \xrightarrow{\text{CH}_3\text{Ti(O}^\text{Pr})_4(1.0 \text{ eq})} \xrightarrow{(-)-\text{DIPT}(1.5 \text{ eq})} \xrightarrow{\text{TBHP}(0.4 \text{ eq}), \text{CH}_2\text{Cl}_2, -20^\circ} \frac{27-33\% \text{ of } (+)-115}{33-38\% \text{ of } (-)-114} + \xrightarrow{\text{CH}_3\text{Ti(O}^\text{Pr})_4(1.0 \text{ eq})} \xrightarrow{(-)-\text{DIPT}(1.5 \text{ eq})} \xrightarrow{\text{TBHP}(0.8 \text{ eq}), \text{CH}_2\text{Cl}_2, -20^\circ} \frac{75\%}{72\% \text{ e.e.}} \text{ (+)-115 (>95\% e.e.)} \text{ (-)-114 (72\% e.e.)}
\end{align*}

\begin{align*}
(-)-114 & \xrightarrow{\text{CH}_3\text{Ti(O}^\text{Pr})_4(0.2 \text{ eq})} \xrightarrow{(-)-\text{DIPT}(0.37 \text{ eq})} \xrightarrow{\text{TBHP}(0.8 \text{ eq}), \text{CH}_2\text{Cl}_2, -20^\circ} \frac{75\%}{92\% \text{ e.e.}}\text{ (-)-115 (92\% e.e.)}
\end{align*}
yield; 67-76% based on TBHP), partially resolved \(-\)-114 (33-38% yield; 72% e.e.) and recovered \(-\)-DIPT. Mosher ester analysis\(^{114}\) determined that \(+\)-115 was greater than 95% optically pure. The kinetically resolved \(-\)-114, which contained 86% of the S-enantiomer, was treated with 0.2 equivalents of Ti\((\text{OiPr})_4\), 0.37 equivalents of \(+\)-diethyl tartrate ((+)-DET) and 0.8 equivalents of TBHP in \(\text{CH}_2\text{Cl}_2\) at -20°C to afford erythro-epoxide \(-\)-115 (92% e.e.) in 75% yield (94% based on TBHP). The overall result of these transformations is a double kinetic resolution, producing each of the enantio-meric epoxides cleanly in 25-35% yield and at least 92% optical purity.\(^{115}\)

Acid-catalyzed opening of \(-\)-115 with 3:1 DMSO in \(\text{H}_2\text{SO}_4\) afforded the crystalline ribo-triol 116 in 89% yield (Figure 34). Ozonolysis of the vinyl group, as in the previous syntheses,

FIGURE 34

\[
\begin{align*}
\text{(-)-115} & \xrightarrow{3:1 \text{ DMSO/1N H}_2\text{SO}_4, 23^\circ} \text{89%} \\
& \xrightarrow{\text{O}_3, \text{CH}_3\text{OH}, -20^\circ} \text{(CH}_3)_2\text{S workup 79%} \\
& \xrightarrow{} \text{116} \quad \text{(+)-4}
\end{align*}
\]

afforded D-\(+\)-digitoxose (\(+\)-4) in 79% yield. The synthetic sugar, identical in all respects to a commercial sample, was obtained in five steps from crotonaldehyde. Of course, if in the initial resolution of racemic 114 (+)-DIPT were used rather than (-)-DIPT, the sequence would be one step shorter. Indeed,
epoxide (-)-115 (>95% e.e.) was obtained in 37% yield from racemic 114 when (+)-DIPT was used as the chiral auxiliary. 116 In this manner the overall yield of (+)-4 was 22% for the four step sequence from crotonaldehyde. 117

The synthesis of D-olivose from (+)-115 requires an α-opening of the epoxide. Thus, crystalline urethane 93, mp 57-57.5°C, was prepared from (+)-115 in 71% yield (Figure 35). When treated with Et₂AlCl in Et₂O at -20°C, 93 was converted into carbonate (+)-8lb (93-95% yield). Less than 3% of the isomeric ribo-δ-carbonate ent-91, resulting from attack of the urethane carbonyl oxygen at the epoxide β-position, was observed under these conditions. Carbonate (+)-8lb was converted to (+)-17 by using the two step sequence developed in the synthesis of racemic 17. The overall yield of the optically pure sugar, which was identical in all respects to an authentic sample prepared from D-glucose, 89 was 14-17% for this six step synthesis from crotonaldehyde. 117
FIGURE 35

\[ (+)-115 \xrightarrow{\text{C}_6\text{H}_5\text{NCO}} \text{pyridine, } 23^\circ \text{C} \xrightarrow{71\%} \]

\[ \begin{align*}
\text{CH}_3 & \quad \text{O} \\
\text{OCONHCH}_3 & \quad \text{Et}_2\text{AlCl} \\
& \quad \text{Et}_2\text{O}, -20^\circ \text{C} \\
& \quad \text{1N } \text{H}_2\text{SO}_4 \text{ workup} \\
& \quad 95\% \\
\end{align*} \]

\[ (+)\text{-8lb} \]

\[ (+)-8\text{lb} \xrightarrow{1) \text{NaOCH}_3 \text{(catalytic)}} \text{CH}_3\text{OH}, 23^\circ \text{C, 24 h.} \xrightarrow{98\%} \]

\[ \begin{align*}
\text{HO} & \quad \text{O} \\
\text{OH} & \quad \text{CH}_3 \\
& \quad \text{OH} \\
2) \text{O}_3, \text{CH}_3\text{OH, -20}^\circ \text{C} \\
& \quad \text{(CH}_3\text{)}_2\text{S workup} \\
& \quad 85\% \\
\end{align*} \]

\[ (+)-17 \]

\[ \begin{align*}
\text{HO} & \quad \text{O} \\
\text{NO} & \quad \text{O} \\
& \quad \text{CH}_3 \\
\text{ent-9}\text{l} \end{align*} \]
Enantioselective Synthesis of D-Oliose 20 and D-Cymarose 19

Aside from its occurrence in the aureolic acid antibiotics (vide supra), D-oliose 20 (also known as Chromose A), 2,6-dideoxy-lyxo-hexose, can be found in the cardiac glycosides, and in the antibiotics oleandomycin and chromocyclomycin. The L-isomer has been found as a constituent of the rhodomyccins, cinerubins A and B, and the macrolide antibiotic azalomycin-B. The D-isomer can be prepared from D-galactose, and the L-isomer from L-fucose. The L-isomer can also be prepared from D-glucose or by a chemical synthesis. A synthesis of the racemate is also known.

![Structural formulas](figures)

D-Cymarose, 19, 3-O-methyl-2,6-dideoxy-D-ribo-hexose, has recently been identified as D-variose. It also occurs in the cardiac glycosides and in sibiricosides D and E, pregnane glycosides isolated from Cynanchum sibiricum. The D-isomer has been synthesized from D-glucose via methyl 4,6-O-benzylidene-2,3-anhydro-allo-pyranoside (Figure 7) and the L-isomer can be prepared from L-rhamnose. A synthesis of the racemate has also been reported.
Our syntheses of these sugars originate from propargylic alcohol 107, which was reduced stereospecifically\textsuperscript{127} to the E-allylic alcohol 117 with LiAlH\textsubscript{4} in 82-84% yield (Figure 36). Epoxidation of 117 was accomplished by using 0.13 equivalents of Ti(O\textsuperscript{3}Pr\textsubscript{4}), 0.20 equivalents of (-)-DIPT, and 0.45 equivalents of TBHP, which afforded (+)-73 and kinetically resolved (-)-117 in 40% and 39% yields, respectively. Mosher ester analysis\textsuperscript{114} revealed that the optical purity of each was 90% e.e. The Mosher ester\textsuperscript{114} of (-)-73, which was prepared from (-)-117 by using (+)-DIPT as the chiral auxiliary in the oxidation step (92% e.e.), was useful in confirming the optical purity of the (+)-enantiomer.

**FIGURE 36**

\[
\text{CH}_3 \quad \text{LiAlH}_4, \text{ THF, reflux, 4h.} \quad 82-84\%
\]

\[
\begin{array}{c}
\text{OH} \\
\text{CH}_3 \\
\text{Ti(O}^3\text{Pr})_4(0.13 \text{ eq}) \\
\text{(-)-DIPT}(0.21 \text{ eq}) \\
\text{TBHP}(0.45 \text{ eq}) \\
\text{CH}_2\text{Cl}_2, -20^\circ \\
40\% \text{ of (+)-73} \\
39\% \text{ of (-)-117} \\
\end{array}
\]

\[
\text{OH} \\
\text{CH}_3 \\
\]

\[
\begin{array}{c}
\text{OH} \\
\text{CH}_3 \\
\text{Ti(O}^3\text{Pr})_4(0.13 \text{ eq}) \\
\text{(+)-DIPT}(0.21 \text{ eq}) \\
\text{TBHP}(0.8 \text{ eq}) \\
\text{CH}_2\text{Cl}_2, -20^\circ \\
76\% \\
\end{array}
\]

\[
\text{OH} \\
\text{CH}_3 \\
\]

\[
\begin{array}{c}
\text{OH} \\
\text{CH}_3 \\
\end{array}
\]
This synthesis of (+)-73 illustrates the use of catalytic (rather than stoichiometric) Ti(0\textsuperscript{4}Pr\textsubscript{4}) in the kinetic resolution-enantioselective epoxidation procedure. We have observed that the isolated yields of epoxide and kinetically resolved allylic alcohol are generally greater when the catalytic system is employed. This tendency is probably related to the ease of separating smaller amounts of the tartrate ester from the product mixtures. Epoxidation of 117 with 1.0 equiv. of Ti(0\textsuperscript{4}Pr\textsubscript{4}), 1.5 equiv. of (-)-DIPT, and 0.4 equiv. of TBHP afforded 30% of (+)-73 (90% e.e.) and 37% of (-)-117, while the catalytic conditions afforded 40% and 39%, respectively, of these compounds. Similar results were obtained in the epoxidation of 114. A disadvantage of the catalytic system is that the optical purity of the epoxide produced is sometimes lower than when stoichiometric reagents are employed.\textsuperscript{62h}

This problem can be rectified, however, by crystallization of intermediates, such as the derived phenyl urethanes, later in the synthesis.

Conversion of (+)-73 to the crystalline phenyl urethane (+)-85, m.p. 55.5-56.0°C, was effected by treatment with phenyl isocyanate and pyridine (Figure 37).\textsuperscript{96} The urethane (+)-85 was treated with Et\textsubscript{2}AlCl in Et\textsubscript{2}O at -20°C to yield carbonate (+)-90 quantitatively. Standard methanolysis and ozonolysis steps transformed (+)-90 into D-oliose, (+)-20, in 78% yield. This efficient, seven step synthesis provided (+)-20 in 18-20% overall yield.\textsuperscript{117}
D-Cymarose, (+)-119, was prepared by solvolysis of (+)-73 in methanol, followed by ozonolysis of the resulting diol 119 (Figure 38). This methanolysis reaction was highly regioselective and resulted in 119 in up to 84% yield. Presumably other alcohols such as benzyl alcohol or 2,2,2-trichloroethanol could be used in similar fashion to effect the synthesis of diol ethers analogous to 119. Such ethers, consisting of easily removable protecting groups, would allow differentiation of the triol system for other synthetic problems. The overall yield of D-cymarose (+)-119 for the present five step synthesis was 17-20%.117
The preceding syntheses have provided a useful demonstration of our general strategy for the synthesis of 2,6-dideoxyhexoses based on regioselective epoxide ring openings. The syntheses range in length from four to seven steps, and, generally, are shorter than classical syntheses which originate from the parent hexoses. The availability of highly enantioselective and diastereoselective epoxidation procedures\textsuperscript{62,99} has allowed these syntheses to be carried out enantioselectively, as well. The syntheses described are easily adaptable for preparation of the L-enantiomers by the selection of the appropriate tartrate enantiomer for the epoxidation. Only \textsuperscript{x}xylo-triol derivatives (e.g., bovinose, \textsuperscript{5}) cannot be prepared readily by the Sharpless techniques, and may be better prepared by alternative enantioselective techniques\textsuperscript{98,100} or by classical resolution of synthetic intermediates.\textsuperscript{101}
CHAPTER IV

APPROACHES TO AMINOSUGARS
In Chapters II and III, we reported our studies on the synthesis of 2,6-dideoxyhexoses by use of regioselective ring openings of 2,3,4-epoxyalcohol derivatives. In connection with these studies, we investigated several extensions of this methodology towards the synthesis of aminosugars. The extensions explored include β-openings of epoxyalcohols with nitrogen nucleophiles, α-openings of epoxyalcohol derivatives by intramolecular processes, and epoxidation of allylic amine derivatives. These investigations were preliminary and were not carried through to completion. Although no aminosugars were actually synthesized, the results of these investigations are included here to provide a full record of our work. Some of these investigations will be examined further at a later date.
β-Opening of Epoxyalcohols

A number of aminosugars have been synthesized from sugar epoxides by the nucleophilic attack of nitrogen-containing nucleophiles on an epoxide ring. The favored mode of opening in epoxypyranoose systems was that leading to a trans-diaxial arrangement of the nucleophile and the oxygen atom of the oxirane precursor, as would be predicted by the Fürst-Plattner rule. The most common nitrogen nucleophiles used in such syntheses were ammonia and azide anion. As we noted in Chapter II, however, the behavior of cyclic systems has only limited predictive value for acyclic systems of the type we were investigating. Therefore, we felt that an examination of the behavior of nucleophilic nitrogen species toward some of the epoxyalcohols which we had prepared would be appropriate.

We chose as our first target 2,3,6-trideoxy-3-amino-ribo-hexose. L-Ristosamine is a constituent of ristomycin A. A number of syntheses have appeared. The L-isomer has been prepared from L-rhamnose while the D-isomer has been prepared by D-mannose or D-glucose.
The starting material for our approach to D-ristosamine was epoxyalcohol (+)-73 (Figure 39). β-Opening of (+)-73 by a

![Chemical Structure]

(Figure 39)

(+)-73  120a, R=H  D-11
120b, R=Ac

nitrogen nucleophile would lead to the ribo-configuration found in ristosamine. Treatment of (+)-73 with NaN₃ in the presence of NH₄Cl afforded azide 120a in 78% yield. Analysis by 250 MHz ¹H NMR of the azidodiacetate 120b (prepared in 54% yield from (+)-73 by acetylation of 120a) revealed that only one isomer was formed in the ring-opening reaction. The yield of 120a was much lower when the Prinzbach conditions were employed (NaN₃, MgCl₂, CH₃OH, reflux), but here again β-opening was the sole mode of attack. Since the cyclohexyl ketals of the lyxo-, xylo- and arabino-isomers of 120a have previously been transformed to the respective 2,3,6-trIDEOXY-3-AMINOHEXOSE DERIVATIVES, we expect that analogous transformations would provide the ribo-sugar as well. This pro forma conversion, however, was not attempted.

Alternatively, other nitrogen species could also be used. Treatment of a series of 1-phenoxy-2,3-epoxides with secondary
amines indicated that ring opening occurred at the position β to the ether.\textsuperscript{134} Similarly, aminodiol 121 was obtained in 91% yield when (+)-73 was heated to 145°C with benzylammine in the presence of catalytic phenol (Figure 40).\textsuperscript{134b,135} Conversion of 121 to the cyclic urethane 123 was accomplished by sequential treatment with methyl chloroformate and \( \text{K}_2\text{CO}_3 \) in \( \text{CH}_2\text{Cl}_2 \) at 23°C, followed by further treatment with \( \text{K}_2\text{CO}_3 \) in refluxing toluene. A compound believed to be the δ-urethane 124 was also isolated (9% yield) from this reaction. The conversion of 121 to 123 could be accomplished without isolation of the intermediate urethane 122, but reaction times and yields were not reproducible (some 122 was normally recovered).

Ozonolysis followed by acetal formation (HC(\( \text{OCH}_3 \))\textsubscript{3}, \( \text{CH}_3\text{OH} \), p-TsOH, 23°C) afforded 125b as a mixture of anomers. Cleavage of the benzyl protecting group with Na/liquid \( \text{NH}_3 \) provided 126, a protected form of D-ristosamine in 90% yield. The overall yield of 126 was 16% for the nine step sequence from 3-butyn-2-ol 106.\textsuperscript{117} This material has not been correlated to an authentic sample of ristosamine.
FIGURE 40

(+)-73

121

122

122 → K₂CO₃

K₂CO₃, toluene, Δ

73% of 123
9% of 124

123

125a, R=H

125b, R=CH₃

124

Na/NH₃, THF

-78°

96%

126
\(\alpha\)-Opening of Epoxyalcohols

In Chapter II, we reported that the phenyl urethane functionality was ideal for the delivery of oxygen nucleophiles to the epoxide \(\alpha\)-position of 2,3,4-epoxyalcohol derivatives. Amides, urethanes and ureas, however, have two nucleophilic centers. Under acidic or neutral conditions attack by the carbonyl oxygen is usually favored, while under basic conditions the amide anion serves as the nucleophile. For example, under neutral conditions, the iminolactone hydrobromide 128 was formed from 4-bromo-N-cyclohexylbutyramide 127 (Figure 41).\(^{136}\) Yet when fused with alkali, 127 was converted to the pyrrolidone 130. The relative rates of participation by amido, ureido and urethano neighboring groups have been investigated.\(^{137}\) It is

\[\text{FIGURE 41}\]

\[\begin{align*}
\text{127} & \quad \text{128} \\
\end{align*}\]

\[\begin{align*}
\text{127} & \quad \text{129} \\
\end{align*}\]
not surprising that the phenylurethane group was also useful for delivering nitrogen nucleophiles to the epoxide _α_-position.\textsuperscript{138,139}

We have examined the application of this chemistry to the 2,3,4-epoxyalcohol derivative 79a (Figure 42). When treated with NaH in THF at room temperature, 79a afforded urethane 131

![Figure 42](image_url)

in 92% yield. The cis-γ-urethane initially formed by α-attack on the epoxide isomerized under the reaction conditions to the trans-γ-urethane 131. It has been discovered\textsuperscript{140} that conversion of epoxyalcohols to the urethane followed by α-opening of the epoxide by the urethane nitrogen can be accomplished in one step. A few examples are shown in Figure 43.

While β-opening of 2,3,4-epoxyalcohols by nitrogen nucleophiles leads to aminodiol derivatives in which the amino group occupies the outside position of the three contiguous carbon atoms, α-opening affords aminodiol derivatives with the amino group in the center position. Thus, application of the intramolecular α-opening with urethanes may provide a route to 2,3,6-trideoxy-4-aminosugars such as holacosamine (9, Figure 2).\textsuperscript{141} This avenue, however, has not yet been investigated.
FIGURE 43

\[
\text{C}_{18}\text{H}_{31}\text{O} \xrightarrow{\text{PhCH}_2\text{NCO, NaH}} \text{C}_{18}\text{H}_{31}\text{O} + \text{C}_{18}\text{H}_{31}\text{O} \quad 1:1
\]

\[\text{88-94\%} \quad \text{THF, reflux, 2h.}\]

\[
\text{132} \quad 133 \quad 134
\]

\[
\text{81\%} \quad \text{OH}
\]

\[
\text{135} \quad \text{136} \quad 1:1 \quad \text{137}
\]

\[
\text{TBDMSO-CH}_2\text{CH}_3\text{O} \xrightarrow{\text{50\%}} \text{TBDMSO-CH}_2\text{CH}_3\text{O} \quad \text{PhN}
\]

\[
\text{138} \quad 139
\]
Epoxidation of Allylic Amine Derivatives

For secondary allylic alcohols, epoxidation by peracids is directed by the "Henbest effect." The hydrogen bonding of the alcohol to the peracid leads to nearly exclusive formation of threeo-epoxyalcohols for Z-allylic alcohols (vide supra). Acylamino groups can exert a similar syn-directing influence on epoxidation. The cis-epoxide was formed exclusively by treatment of 140 with peracetic acid (Figure 44). Compound 142 was converted to 143, showing that the stereo-selective influence of an allylic acetamido group outweighs the combined influence of an allylic plus a homoallylic hydroxyl group. In contrast to the attention that the epoxidation of acyclic allylic alcohols has received, to the best of our

FIGURE 44

\[
\begin{align*}
\text{NHCOCH}_3 & \quad \xrightarrow{\text{H}_3\text{CO}_2\text{H}} \quad \text{NHCOC}_6\text{H}_5 \\
\text{140} & \quad \text{141}
\end{align*}
\]

\[
\begin{align*}
\text{NHCOCH}_3 & \quad \xrightarrow{\text{MCPBA}} \quad \text{NHCOC}_6\text{H}_5 \\
\text{142} & \quad \text{143}
\end{align*}
\]
knowledge no work has been reported on the stereochemistry of epoxidations of acyclic allylic amine derivatives. To investigate the epoxidation of such substrates, we prepared two model compounds: a Z-allylic amine and an E-allylic amine.

The synthesis of Z-allylic amine 148 is outlined in Figure 45. Phenylacetaldehyde 144 was treated with propynyl-lithium in THF at -78°C to afford the propargylic alcohol 145 in 88% yield. Replacement of the hydroxyl group by phthalimide according to the Mitsunobu methodology provided 146 in 61% yield. Removal of the phthalimido protecting group afforded propargylic amine 147, which was converted to the Z-allylic amine 148 by hydrogenation over Lindlar catalyst.

**FIGURE 45**
Synthesis of the E-allylic amine 153 started with the Wittig-coupling of 144 with 1-triphenylphosphoranylidene-2-propanone to yield the sensitive α,β-unsaturated ketone 149 in 89% yield (Figure 46). Enone 149 was reduced with DIBAL-H in ether to yield allylic alcohol 150 (95% yield). Conversion of 150 to the trichloroacetamide 152a was accomplished in 68% yield by the two step procedure of Overman. Chiral E-allylic amides of this type can be prepared from chiral E-allylic alcohols (possibly prepared by a Sharpless kinetic resolution) since the rearrangement occurs suprafacially with complete (>97%) transfer of chirality. Removal of the trichloroacetyl group completed the synthesis of E-allylic amine 153 in 62% yield.

Amido, urethano, and ureido derivatives of 148 and 153 were prepared and submitted to treatment by the peracids MCPBA or 3,5-dinitroperbenzoic acid (3,5-DNPBA). The results of these experiments are tabulated in Figures 47 and 48. Attempted epoxidations of these substrates by using metal catalyzed procedures (Ti(OiPr)4, TBHP with 154a and VO(acac)2, TBHP with 152a) failed to form any epoxide products.

The structures for the epoxide products 155, 156, 157 and 158 were tentatively assigned as indicated in Figures 47 and 48 on the assumption that the known directing effects of acyl-amino groups for the cyclic structures discussed earlier (Figure 44) were also operating in these acyclic structures. In addition, the product distributions for these substrates roughly paralleled those of the analogous Z- and E-allylic alcohols.
FIGURE 46

144 \[ \text{PhCH}_2\text{CHO} \xrightarrow{(\text{Ph})_3\text{P}=\text{CHCOCH}_3} \text{Ph} \quad \text{THF, } 0^\circ \quad 89\% \]

149 \[ \text{Ph} \quad \text{CH}_3 \xrightarrow{\text{DIBAL-H}} \text{Ph} \quad \text{Et}_2\text{O} \quad -78^\circ \text{C} \quad 95\% \]

150 \[ \text{Ph} \quad \text{CH}_3 \quad \text{OH} \]

150 \[ 1) \text{KH, THF} \quad 2) \text{Cl}_3\text{CCN, Et}_2\text{O} \quad 94\% \]

151 \[ \text{Ph} \quad \text{CH}_3 \quad \text{NH} \quad \text{CCl}_3 \quad \text{O} \quad \text{xylene, } \Delta \quad 72\% \]

152a

152a \[ 1:1 \text{ 5N NaOH/EtOH} \quad 23^\circ \quad 62\% \]

153
FIGURE 47

\[
\begin{align*}
154a, \ R &= \text{C}_6\text{H}_5 \\
154b, \ R &= \text{OCH}_3 \\
154c, \ R &= \text{NHC}_6\text{H}_5
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>Conditions</th>
<th>155:156&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>Yield&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>154a</td>
<td>MCPBA, CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;, 0°C</td>
<td>&gt;95:5</td>
<td>72%</td>
</tr>
<tr>
<td>2</td>
<td>154b</td>
<td>MCPBA, CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;, 0°C</td>
<td>&gt;95:5</td>
<td>67%</td>
</tr>
<tr>
<td>3</td>
<td>154c</td>
<td>MCPBA, CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;, 0°C</td>
<td>&gt;95:5</td>
<td>75%</td>
</tr>
</tbody>
</table>

<sup>a</sup>Product ratios determined by 250 MHz <sup>1</sup>H NMR analysis of the crude products.  
<sup>b</sup>155 and 156 are tentatively assigned the structures shown (see text).  
<sup>c</sup>28% of 154a was recovered in this reaction.
FIGURE 48

\[
\begin{align*}
\text{152a, } R &= \text{CCl}_3 \\
\text{152b, } R &= \text{OCH}_3 \\
\text{152c, } R &= \text{NHCH}_5
\end{align*}
\]

\[
\begin{align*}
\text{157a}  \\
\text{157b}  \\
\text{157c}  \\
\text{158a}  \\
\text{158b}  \\
\text{158c}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>Conditions</th>
<th>\text{157:158}^{a,b}</th>
<th>Yield \text{157:158}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>152a</td>
<td>MCPBA, CH\textsubscript{2}Cl\textsubscript{2}, 0\textdegree C</td>
<td>76:24</td>
<td>62:15\textsuperscript{d}</td>
</tr>
<tr>
<td>2</td>
<td>152a</td>
<td>3,5-DNPBA, CH\textsubscript{2}Cl\textsubscript{2}, 0\textdegree C</td>
<td>78:22</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>152a</td>
<td>MCPBA, benzene, 0\textdegree C</td>
<td>78:22</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>152a</td>
<td>3,5-DNPBA, CH\textsubscript{2}Cl\textsubscript{2}, -20\textdegree C</td>
<td>76:24</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>152b</td>
<td>MCPBA, CH\textsubscript{2}Cl\textsubscript{2}, 23\textdegree C</td>
<td>78:22</td>
<td>79\textsuperscript{e}</td>
</tr>
<tr>
<td>6</td>
<td>152c</td>
<td>MCPBA, CH\textsubscript{2}Cl\textsubscript{2}, 0\textdegree C</td>
<td>60:40\textsuperscript{c}</td>
<td>46:42\textsuperscript{f}</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Product ratios determined by 250 MHz H\textsuperscript{1} NMR analysis of the crude products. \textsuperscript{b}157 and 158 are tentatively assigned the structures shown (see text). \textsuperscript{c}The ratio reported is for the major product, tentatively assigned as 157c, and several minor products which appear to be the result of epoxide opening. \textsuperscript{d}Entries 1-4 were combined prior to chromatography. \textsuperscript{e}Combined yield of 157b and 158b. \textsuperscript{f}The yields reported are for 157c and an epoxide-opened product.
53 and 56 (Figure 11, Chapter II). Since epoxidation of allylic alcohols by peracids is known to be *threo*-selective, a Henbest-like directing effect of allylic acylamines should also lead to *threo*-selection. Thus, the major products have been assigned to be *threo*-epoxyamides. It must be stressed that these structural assignments are provisional - no rigorous structural proof has been carried out - and are subject to revision.

Despite the uncertainty of the current structural assignments for the epoxidation products, two conclusions can be drawn from these preliminary experiments. The epoxidation of Z-allylic acylamines with peracids is highly stereoselective. The major epoxide product is formed in synthetically useful yields and a variety of acyl groups can be used. The product distribution for E-allylic acylamine epoxidations exhibits a stereoselectivity marginally better than that of the corresponding E-allylic alcohols and does not vary for a number of different acyl derivatives or epoxidation conditions. The results of this preliminary study seem to warrant further investigation.
CHAPTER V

EXPERIMENTAL SECTION
\( ^1H \) NMR spectra were measured at 250 and 270 MHz on Bruker 250 and 270 instruments. Chemical shifts are reported in \( \delta \) units relative to internal Me\(_4\)Si. \( ^{13}C \) NMR spectra were measured at 62.8 MHz on a Bruker 250 instrument; carbon resonances are reported in \( \delta_c \) units calibrated against the 77.0 ppm line of CDCl\(_3\). Infrared spectra were measured on a Perkin-Elmer Model 283B Infrared Spectrophotometer and were calibrated with the 1601 cm\(^{-1}\) absorption of polystyrene. Mass spectra were measured at 70 ev on a Varian MAT 44 instrument. High resolution mass spectra were provided by the Facility supported by NIH Grant RR00317 (principal investigator, Professor K. Biemann) from the Biotechnology Resources Branch, Division of Research Resources, and were obtained on a CEC 21-110B high resolution mass spectrometer equipped with a PDP-1145 based computer system to process data recorded on photographic plates. Melting points were recorded on a Fisher-Johns hot stage melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 144 polarimeter using a 1 cm\(^3\) capacity quartz cell (10 cm path length). Elemental analyses were performed by Robertson Laboratories, Florham Park, NJ.

All reactions were conducted in oven-dried (120\(^\circ\)C) or flame-dried glassware under atmospheres of dry argon or nitrogen. All solvents were purified before use: ether, THF, and DME were distilled from Na-benzophenone ketyl; CH\(_2\)Cl\(_2\) and Me\(_2\)SO were distilled from CaH\(_2\); toluene was distilled from sodium metal. Preparative thin-layer chromatography (TLC) was performed using
20 x 20 cm plates coated with 0.5- and 2-mm thicknesses of silica gel containing PF 254 indicator (Analtech). Unless indicated otherwise, compounds were eluted from the adsorbents with ether or ethyl acetate. Column chromatography was performed using activity I Woelm silica gel. Flash chromatography was performed as described by Still.\textsuperscript{151} All chromatography solvents were distilled prior to use.
Experimental Procedures for Chapter II

The epoxyalcohol derivatives reported in the Experimental Sections are named using the descriptors arabino, ribo, lyxo and xylo according to the rules of carbohydrate nomenclature (reference 57).

(Z)-6-Benzylxoyhex-3-en-2-ol (76)

To a solution of 5.0 g (30 mmol) of 1-benzylxoybut-3-yne in 200 mL of THF at -78°C (dry ice/acetone) was added 22 mL (35 mmol) of 1.6M n-BuLi in hexane. The mixture was stirred for 30 min and then 4 mL (71 mmol) of acetaldehyde was added via syringe. The reaction mixture was stirred at -78°C for 1 h and then quenched with 10 mL of methanol. The mixture was warmed to room temperature, 30 mL of 2N HCl was added, and the mixture was stirred for 10 min. The layers were separated and the aqueous phase was extracted with CH$_2$Cl$_2$ (3x). The combined organic layers were dried (Na$_2$SO$_4$), filtered, and concentrated in vacuo to give the crude product. This material was flash chromatographed on a 50-mm x 150-mm column of silica gel using 3:1 hexane-ether as eluent to afford 352 mg (7%) of recovered acetylene and 5.24 g (82%, R$_f$ 0.44, 1:1 hexane-ether) of the product. A portion was further purified by Kugelrohr distillation (150°C, 2.5 mm): $^1$H NMR (CDCl$_3$) δ 7.3 (s, 5H, aromatic), 4.53 (s, 2H, benzylic CH$_2$), 4.49 (br quintet, 1H, H$_2$),
3.55 (t, J = 7 Hz, 2H, H₆), 2.51 (td, J = 2.2, 6.8Hz, 2H, H₅), 2.0 (broad, 1H, –OH), 1.40 (d, J = 6.6 Hz, 3H, H₁); ¹³C NMR (CDCl₃) δ 134.0, 124.4, 123.7, 79.6, 76.9, 74.6, 64.3, 44.2, 20.5, 16.1; IR (neat) cm⁻¹ 3100-3700 (broad OH), 2240, 1080, 690; mass spectrum m/e 204 (parent ion). Anal. Calcd. for C₁₃H₁₆O₂: C, 76.44; H, 7.90. Found: C, 76.65; H, 8.15.

A suspension of 2.20 g (10.8 mmol) of the above propargylic alcohol and 260 mg of Lindlar catalyst in 30 mL of reagent grade CH₃OH was stirred under an atmosphere of H₂ for 19 h at room temperature. The reaction mixture was then filtered through Celite and concentrated in vacuo to give 2.20 g of crude 76. This material was purified by bulb-to-bulb distillation (110°C, 0.8 mm) to give 2.12 g (96%) of pure 76: ¹H NMR (CDCl₃) δ 7.3 (s, 5H, aromatic), 5.35-5.6 (m, 2H, olefin), 4.54 (br quintet, 1H, H₂), 4.46 (s, 2H, benzylic), 3.35-3.5 (m, 2H, H₆), 3.2 (broad, 1H, –OH), 2.15-2.6 (m, 2H, H₅), 1.19 (d, J = 6.4 Hz, 3H, H₁); ¹³C NMR (CDCl₃) δC 138.2, 136.7, 128.3, 127.6, 126.7, 73.0, 69.4, 63.1, 28.3, 23.3; IR (neat) cm⁻¹ 3100-3700 (broad, OH), 3020, 1100, 690; mass spectrum m/e 188 (M⁺-H₂O). Anal. Calcd. for C₁₃H₁₈O₂: C, 75.69; H, 8.80. Found: C, 75.83; H, 9.00.

**Lyxo-6-Benzyloxy-3,4-epoxyhexan-2-ol (71a)**

A solution of 821 mg (3.99 mmol) of 76 in 30 mL of CH₂Cl₂ was cooled to 0°C and treated with 1.1 g of commercial 85% m-chloroperbenzoic acid. After
3 h a white precipitate had formed and all starting material had been consumed. The precipitate was removed by filtration and the filtrate was washed with saturated NaHSO₃, saturated NaHCO₃ (2x), then saturated NaCl. The combined aqueous layers were extracted with CH₂Cl₂ (2x). The combined organic layers were dried (Na₂SO₄), filtered, and concentrated in vacuo to afford 1.04 g of crude product. This material was flash chromatographed over 160 g of silica gel using 3:1 hexane-ether as eluant to yield 47 mg (5%) of erythro epoxide 72 (Rf 0.27 1:1 hexane-ether; identical in all respects to the sample subsequently described) and 694 mg (78%) of three epoxide 71a (Rf 0.22): ¹H NMR (CDCl₃) δ 7.3 (s, 5H, aromatic), 4.52, 4.50 (AB, JAB = 12.3 Hz, benzylic), 3.55-3.7 (m, 3H, H₆ and H₂), 3.17 (dt, J = 4.4, 6.8 Hz, 1H, H₄), 2.9 (dd, J = 4.4, 7.9 Hz, 1H, H₃), 2.5 (broad, 1H, -OH), 1.7-2.0 (m, 2H, H₅), 1.21 (d, J = 6.4, 3H, H₁); ¹³C NMR (CDCl₃) δC 138.3, 128.4, 127.6, 73.1, 67.4, 66.3, 61.4, 55.3, 28.9, 19.2; IR (neat) cm⁻¹ 3100-3700 (broad OH), 1260, 1100, 690; mass spectrum m/e 159 (M⁺-C₂H₂O₂). Anal. Calcd. for C₁₃H₁₈O₃: C, 70.25, H, 8.16. Found: C, 70.45; H, 7.91.

Lyxo-6-Benzyloxy-3,4-epoxyhex-2-yl Acetate (71b)

A solution of 36 mg (0.16 mmol) of 71a in 0.1 mL of pyridine was treated with 1 mL of acetic anhydride and allowed to stand overnight at room temperature. The reaction was quenched by the addition of 2 mL of H₂O and 15 mL of ether. The layers were separated and the organic phase was washed with 5 mL of 3N HCl,
and then saturated NaHCO₃ (2x). The ethereal extracts were dried (Na₂SO₄), filtered, and concentrated to afford 45 mg of crude product. This material was combined with 71 mg of additional product obtained in a separate experiment and chromatographed on a 0.5-mm preparative silica gel plate using 1:1 hexane-ether as the eluent to yield a total of 95 mg of the acetate (Rₓ 0.52): ¹H NMR (CDCl₃) δ 7.25 (s, 5H, aromatic), 4.66 (dq, J = 6.6, 8.8 Hz, 1H, H₂), 4.44 (s, 2H, benzylic), 3.56 (dd, J = 5, 7 Hz, 2H, H₆), 3.11 (dt, J = 4.5, 7.2 Hz, 1H, H₄), 2.96 (dd, J = 4.5, 8.8 Hz, 1H, H₃), 1.99 (s, 3H, acetate), 1.65-1.96 (m, 2H, H₅), 1.19 (d, J = 6.6 Hz, 3H, H₁); IR (neat) cm⁻¹ 2980, 2860, 1735, 1450, 1370, 1240, 805, 735, 690; mass spectrum m/e 264 (parent ion).

Methyl Lyxo-6-Benzylloxy-3,4-epoxyhex-2-yl Carbonate (71c)

A 0°C solution of 222 mg (1 mmol) of 71a in 7 mL of CH₂Cl₂ and 1 mL of pyridine was treated with 0.2 mL of methyl chloroformate. The cooling bath was removed after 2.5 h and the reaction was continued at 23°C for 1 h. The reaction was quenched by the addition of 20 mL of H₂O. The layers were separated and the aqueous phase extracted with CH₂Cl₂ (3x). The combined organic layers were dried (Na₂SO₄), filtered, and concentrated in vacuo to afford 298 mg of yellow oil. This material was bulb-to-bulb distilled (183°C, 3.4 mm) to yield 261 mg (93%) of pure 71c: ¹H NMR (CDCl₃) δ 7.3 (s, 5H, aromatic), 4.60 (m, J = 6.5, 8.5 Hz, 1H, H₂), 4.5 (s, 2H, benzylic), 3.76 (s, 3H, -OCH₃), 3.63 (dd, J = 5.1, 7.1 Hz, 2H, H₆), 3.18 (dt, J =
4.4, 7.2 Hz, 1H, H₄), 3.04 (dd, J = 4.4, 8.6 Hz, 1H, H₃), 1.7-2.0 (m, 2H, H₅), 1.31 (d, J = 6.5 Hz, 3H, H₁); ¹³C NMR (CDCl₃) δc 155.2, 138.4, 128.4, 127.7, 74.3, 73.2, 67.3, 58.1, 54.6, 54.3, 29.0, 16.8; IR (neat) cm⁻¹ 3030, 2860, 1745, 1435, 1250, 1100; mass spectrum m/e 280 (parent ion).

Ribo-6-Benzyllox-3,4-epoxyhexan-2-ol (72)

To a solution of 582 mg (2.62 mmol) of 71a and 816 mg (3.11 mmol) of triphenylphosphine in 15 mL of toluene was added 525 mg (3.14 mmol) of p-nitrobenzoic acid. Diethyl azodicarboxylate (0.5 mL, 550 mg, 3.1 mmol) was then added by syringe. As the p-NBA dissolved, a new precipitate separated from the yellow solution. The reaction mixture was stirred at room temperature for 45 min, and then all volatile components were removed in vacuo to give 2.87 g of a yellow oil. This material was dissolved in 1:1 ether-hexane and filtered through 13 g of silica gel. The resulting crude p-nitrobenzoate (1.37 g) was chromatographed by using the flash procedure (180 g silica gel, 4:1 hexane-ether) to afford 763 mg (78%; Rf 0.73, 1:1 hexane-ether) of pure ester: ¹H NMR (CDCl₃) δ 8.1-8.3 (m, 4H, p-NO₂-benzoate), 7.3 (s, 5H, aromatic), 4.99 (dq, J = 6.4, 8.2 Hz, 1H, H₂), 4.47, 4.44 (AB, J_AB = 12 Hz, 2H, benzylic), 3.62 (t, J = 6 Hz, 2H, H₆), 3.24 (dt, J = 4, 8.7 Hz, 1H, H₄), 3.12 (dd, J = 3.9, 8.2 Hz, 1H, H₃), 1.8-2.1 (m, 2H, H₅), 1.56 (d, J = 6.4, 3H, H₁); IR (neat) cm⁻¹ 2860, 1728, 1610, 1525, 1350, 1270, 1100; mass spectrum m/e 371 (parent ion).
The p-nitrobenzoate (757 mg, 2.04 mmol) prepared above was dissolved in 5 mL of 0.2N NaOMe in MeOH. A precipitate formed after a few minutes, and the reaction was worked up after a total of 25 min. The suspension was diluted with methanol until a clear solution was obtained. This was then passed through 10 cm$^3$ of DOWEX 50W-X8 H$^+$ ion-exchange resin which was pretreated with methanol. The solvent was removed in vacuo to afford 910 mg of crude product, which was purified by flash chromatography (180 g silica gel, 2:1 hexane-ether). In this manner 349 mg (95%) of methyl p-nitrobenzoate (R$_f$ 0.72) and 377 mg (83%) of 72 (R$_f$ 0.27, 1:1 hexane-ether) were obtained. A 562 mg sample was distilled (Kugelrohr, 180°C, 6 mm) to yield 499 mg (88%) of pure 72: $^1$H NMR (CDCl$_3$) $\delta$ 7.3 (s, 5H, aromatic), 4.53 (s, 2H, benzylic), 3.78 (broad, 1H, OH), 3.4-3.7 (m, 3H, H$_6$ and H$_2$), 2.97 (dt, J = 3.8, 10.2 Hz, 1H, H$_4$), 2.79 (dd, J = 4, 8.7 Hz, 1H, H$_3$), 2.10 (dq, J = 14.7, 3.3 Hz, 1H, H$_{5a}$), 1.72 (m, 1H, H$_{5b}$), 1.31 (d, J = 6.2 Hz, 3H, H$_1$); $^{13}$C NMR (CDCl$_3$) 137.0, 128.6, 128.1, 73.6, 66.6, 64.7, 60.1, 55.5, 28.3, 20.1; IR (neat) cm$^{-1}$ 3100-3700 (broad OH), 3040, 2980, 1100, 950, 815; mass spectrum 177 (parent-C$_2$H$_5$O).

Anal. Calcd. for C$_{13}$H$_{18}$O$_3$: C, 70.25; H, 8.16; Found, 70.07; H, 7.89.

Xylo-3,4-Epoxypyhept-6-en-2-ol (74)

Epoxyalcohol 73 (vide infra) ([α]$^D_{30}$ = -2.4° (c = 12.6, CH$_2$Cl$_2$); 92% e.e.) was converted via the inverted p-nitrobenzoate ester (90% yield from 73; $^1$H NMR (CDCl$_3$) $\delta$ 8.25 (m, 4H, aromatic), 5.77
(m, 1H, H₆), 5.15 (m, 2H, H₇), 5.0 (quint, J = 6.4 Hz, 1H, H₂), 3.0 (m, 2H, H₃ and H₄), 2.37 (m, 2H, H₅), 1.44 (d, J = 6.5 Hz, 3H, H₁); IR (neat) cm⁻¹ 3120, 3080, 2990, 1735, 1640, 1610, 1530, 1350, 1270, 1100; mass spectrum m/e 236 (M⁺-C₃H₅); [α]D²⁹ = -40.1 (c = 4.06, CH₂Cl₂) into 74 in 76% overall yield using the procedure described above for the synthesis of 72. Data for 74: bp (Kuglerohr) 100-105°C (20-mm); ¹H NMR (CDCl₃) δ 5.76 (m, 1H, H₆), 5.10 (m, 2H, H₇), 3.55 (br quint, J = 6 Hz, H₂), 2.95 (dt, J = 2.2, 5.5 Hz, 1H, H₄), 2.73 (dd, J = 2.2, 5.2 Hz, 1H, H₃), 2.2-2.5 (m, 3H, OH and H₅), 1.23 (d, J = 6.5 Hz, 3H, H₁); ¹³C NMR (CDCl₃) δ 132.9, 117.4, 67.5, 62.3, 55.3, 35.7, 19.4; IR (neat) cm⁻¹ 3100-3700, 3080, 2980, 1640, 925; mass spectrum m/e 128 (parent ion); [α]D²⁸ = -23.2° (c = 4.35, CH₂Cl₂).

Lyxo-6-Benzylxyloxy-3,4-epoxy-2-O-(N-phenylcarbamoyl)-hexane (79a)

A solution of 2.45 g (11.0 mmol) of 71a in 80 mL of CH₂Cl₂ and 20 mL of pyridine was treated with 3.0 mL of (3.3 g, 27 mmol) of phenyl isocyanate. The reaction mixture was stirred at room temperature for 15 h and then all volatile components were removed in vacuo. The residue was dissolved in acetone and 10 mL of water was added. The mixture was stirred vigorously leading to the formation of a white precipitate. The solvents were removed in vacuo, the residue was taken up in CHCl₃ and the insoluble portion removed by filtration. The solvent was evaporated to give 4.3 g of crude product. This material was
purified by flash chromatography (185 g silica gel, 2:1 hexane-ether) to give chromatographically homogeneous 79a which was crystallized from acetone-hexane to give 3.24 g (84%) of pure 79a: mp 77.5-78°C; $^1$H NMR (CDCl$_3$) δ 7.2-7.4 (m, 9H, aromatic), 7.04 (tt, J = 1.5, 7.3 Hz, 1H, p-H of urethane), 6.64 (broad, 1H, -NH), 4.74 (dq, J = 6.3, 8.8 Hz, 1H, H$_2$), 4.52 (s, 2H, benzylic), 3.65 (dd, J = 5.3, 7.0 Hz, 2H, H$_6$), 3.22 (dt, J = 4.4, 7.4 Hz, 1H, H$_4$), 3.05 (dd, J = 4.4, 8.8 Hz, 1H, H$_3$), 1.77-2.0 (m, 2H, H$_5$), 1.33 (d, J = 6.3 Hz, 3H, H$_1$); IR (CH$_2$Cl$_2$) cm$^{-1}$ 3440, 1740, 1600, 1515, 1440, 1200, 690; mass spectrum m/e 341 (parent ion).

Anal. Calcd. for C$_{20}$H$_{21}$NO$_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.43; H, 6.91; N, 4.18.

Lyxo-3,4-Epoxy-2-O-(N-phenylcarbamoyl)-hept-6-ene (79b) was prepared from 109 (vide infra) in 89% yield using the procedure described above for preparation of 79a. Data for 79b: mp 55.5-56°C; $^1$H NMR (CDCl$_3$) δ 7.2-7.4 (m, 4H, aromatic), 7.0 (broad t, J = 7 Hz, 1H, p-H), 6.67 (broad, 1H, -NH), 5.85 (m, 1H, H$_6$), 5.2 (m, 2H, H$_7$), 4.8 (m, J = 6.3, 8.5, 1H, H$_2$), 3.16 (dt, J = 4.4, 6.6 Hz, 1H, H$_4$), 3.08 (dd, J = 4.4, 8.5 Hz, 1H, H$_3$), 2.35 (m, 2H, H$_5$), 1.39 (d, J = 6.3 Hz, 3H, H$_1$); $^{13}$C NMR (CDCl$_3$) δ 153.1, 138.3, 133.0, 128.8, 123.1, 118.8, 117.5, 70.7, 58.4, 55.6, 32.4, 17.4; IR (CH$_2$Cl$_2$) cm$^{-1}$ 3440, 2980, 1730, 1640, 1600, 1525, 1440, 905; mass spectrum m/e 247 (parent ion).

Anal. Calcd. for C$_{14}$H$_{17}$NO$_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.10; H, 6.96; N, 5.35.
Ribo-6-Benzylxoy-3,4-epoxy-2-0-(N-phenylcarbamoyl)-hexane (83) was prepared in 93% yield from 72 using the procedure described for 79a. Data for 83: $^1$H NMR (CDCl$_3$) $\delta$ 7.2-7.4 (m, 9H, aromatic), 7.03 (broad t, J = 6.8 Hz, 1H, p-H of urethane), 6.65 (broad, 1H, -NH), 4.66 (m, 1H, $H_2$), 4.48, 4.45 (AB, $J_{AB} = 12$ Hz, 2H, benzylic), 3.59 (t, J = 6 Hz, 2H, $H_6$), 3.18 (dt, J = 4, 8 Hz, 1H, $H_4$), 2.94 (dd, J = 4, 8.3 Hz, 1H, $H_3$), 1.7-2.1 (m, 2H, $H_5$), 1.41 (d, J = 6.4 Hz, 3H, $H_1$); IR (CH$_2$Cl$_2$) cm$^{-1}$ 3420, 2920, 1740, 1600, 1525, 1400, 1210; mass spectrum m/e 341 (parent ion).

Anal. Calcd. for C$_{20}$H$_{23}$NO$_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.43; H, 6.81; N, 3.87.

Xylo-3,4-Epoxic-2-0-(N-phenylcarbamoyl)-hept-6-ene (84) was prepared in 95% yield from 74 using the procedure described for 79a: mp <23°C (waxy solid); $^1$H NMR (CDCl$_3$) $\delta$ 7.2-7.4 (m, 4H, aromatic), 7.04 (br t, J = 7.1 Hz, 1H, p-H), 6.72 (broad, 1H, -NH), 5.78 (m, 1H, $H_6$), 5.15 (m, 2H, $H_7$), 4.84 (m, 1H, $H_2$), 2.98 (dt, J = 2.1, 5.4 Hz, 1H, $H_4$), 2.90 (dd, J = 2.1, 5.3 Hz, 1H, $H_3$), 2.34 (m, 2H, $H_5$), 1.35 (d, J = 6.6 Hz, 3H, $H_1$); IR (CH$_2$Cl$_2$) cm$^{-1}$ 3420, 2985, 1730, 1640, 1590, 1520, 1440, 1210; mass spectrum m/e 247 (parent ion); $[\alpha]_{D}^{22} = +5.3$ (c = 3.9, CH$_2$Cl$_2$).

Anal. Calcd. for C$_{14}$H$_{17}$NO$_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.06; H, 7.30; N, 5.57.

Arabino-3,4-Epoxy-2-0-(N-phenylcarbamoyl)-hept-6-ene (85) was prepared in 78% yield from 73 (vide infra) ($[\alpha]_{D}^{30} = +2.8^\circ$ (c=12.5,
\( \text{CH}_2\text{Cl}_2 \): 90\% e.e) using the procedure described for 79a: mp 55.5-56°C; \(^1\text{H} \text{NMR} (\text{CDCl}_3) \delta 7.2-7.4 \text{ (m, 4H, aromatic), 7.05 (broad } t, J = 7.1 \text{ Hz, 1H, p-H), 6.59 (broad, 1H, } \text{NH}, 5.79 \text{ (m, 1H, H}_6\text{), 5.15 (m, 2H, H}_7\text{), 4.87 (dq, J = 4.6, 6.5 Hz, 1H, H}_2\text{), 3.03 (dt, J = 2.1, 5.4 Hz, 1H, H}_4\text{), 2.86 (dd, J = 2.1, 4.6 Hz, 1H, H}_3\text{), 2.32 (broad } t, J = 6 \text{ Hz, 2H, H}_5\text{), 1.29 (d, J = 6.5 Hz, 3H, H}_1\text{); IR (CH}_2\text{Cl}_2 \text{ cm}^{-1} 3420, 2980, 1735, 1640, 1520, 1440, 1210; \text{mass spectrum } m/e 247 \text{ (parent ion); } \left[\alpha\right]_{D}^{22} = +27^\circ (c = 4.25, \text{CH}_2\text{Cl}_2). \textbf{Anal. Calcd. for } \text{C}_{14}\text{H}_{17}\text{NO}_3: \text{ C, 68.00; H, 6.93; N, 5.66. Found: C, 68.14; H, 7.13; N, 5.72.}

Lyxo-2,3-Epoxy-4-O-(N-phenylcarbamoyl)-hept-6-ene (93) was prepared from \((+)-\text{lyx}o-2,3\text{-epoxyhept-6-en-2-ol } ([\alpha]_{D}^{22} = +3.0^\circ \text{(c=7.2, CH}_2\text{Cl}_2), (95\% \text{ e.e.) in 71\% yield using the procedure described for 79a: mp 57-57.5°C; } \text{H NMR} (\text{CDCl}_3) \delta 7.2-7.4 \text{ (m, 4H, aromatic), 7.05 (broad } t, J = 7.2 \text{ Hz, 1H, p-H), 6.59 (broad, 1H, NH), 5.82 \text{ (m, 1H, H}_6\text{), 5.15 \text{ (m, 2H, H}_7\text{), 4.74 (broad } q, J = 5 \text{ Hz, 1H, H}_4\text{), 3.08 (dq, J = 2.0, 5.4 Hz, 1H, H}_2\text{), 2.76 (dd, J = 2.0, 5.5 Hz, 1H, H}_3\text{), 1.96 \text{ (m, 2H, H}_5\text{), 1.30 \text{ (d, J = 5.4, 3H, H}_1\text{); IR (CH}_2\text{Cl}_2 \text{ cm}^{-1} 3420, 3040, 2985, 1740, 1640, 1600, 1540, 1210; mass spectrum } m/e 247 \text{ (parent ion); } \left[\alpha\right]_{D}^{23} = +24^\circ (c = 1.08, \text{CH}_2\text{Cl}_2). \textbf{Anal. Calcd. for } \text{C}_{14}\text{H}_{17}\text{NO}_3: \text{ C, 68.00; H, 6.93; N, 5.66. Found: C, 67.85; H, 6.89; N, 5.44.}

Arabino-6-Benzylxyhexa-2,3,4-triol Triacetate (78)

A solution of 37 mg (0.13 mmol) of carbonate 71c in 4 mL of
ether was cooled in an ice bath and was treated with 20 µL of BF₃•Et₂O. The solution was kept at 0°C for 2 h and then was warmed to 23°C for another hour. TLC analysis of the reaction mixture revealed that 71c was still present, so a second 30 µL portion of BF₃•Et₂O was added. Two hours later the reaction was quenched by the addition of 3 mL of water; the resulting two-phase system was stirred for 2 h. The solution was diluted with CH₂Cl₂ (20 mL), and the aqueous layer was extracted with additional portions of CH₂Cl₂ (2x). The combined extracts were dried (Na₂SO₄), filtered, and the solvents evaporated to yield 39 mg of crude product (a mixture of carbonates 80a and 81a). This material was dissolved in 5 mL of 0.2N NaOMe in MeOH and the solution was kept at 23°C for 48 h. The solution was then passed through 6 cm³ of DOWEX 50W-X8, H⁺ ion exchange resin and the solvent was removed in vacuo to give 31 mg of crude arabino-triol. This material was dissolved in 5 mL of ether and treated with 0.5 mL of pyridine and 2 mL of acetic anhydride. The reaction was worked up after 18 h by dilution with 15 mL of ether and extraction with 3N HCl and then saturated NaHCO₃ (3x). The organic extracts were dried (Na₂SO₄), filtered, and concentrated to give 44 mg of crude 78. This material was purified by preparative TLC on a 0.25-mm silica gel plate using 1:1 hexane-ether as the eluent to yield 29 mg (60% overall yield) of pure 78 (Rf 0.45, 1:1 hexane-ether): bp 180°C (3.3 mm; Kuglerohr); ¹H NMR (CDCl₃) δ 7.3 (s, 5H, aromatic), 5.37 (m, 1H, H₄), 5.08 (dd, J = 3.5, 7.8 Hz, 1H, H₃), 4.95 (m, 1H, H₂), 4.45,
4.43 (AB, J<sub>AB</sub> 12 Hz, 2H, benzylic), 3.45 (m, 2H, H<sub>6</sub>), 2.10 (s, 3H, acetate), 2.00 (s, 3H, acetate), 1.99 (s, 3H, acetate), 1.80 (m, 2H, H<sub>5</sub>), 1.16 (d, J = 6.4 Hz, 3H, H<sub>1</sub>); 13C NMR (CDCl<sub>3</sub>) 169.9, 138.4, 128.4, 127.9, 74.7, 73.3, 68.5, 67.5, 66.3, 31.6, 20.6, 16.2; IR (neat) cm<sup>-1</sup> 3020, 2860, 1740, 1370, 1220, 840; mass spectrum m/e 366 (parent ion). *Anal.* Calcd. for C<sub>19</sub>H<sub>26</sub>O<sub>7</sub>: C, 62.28; H, 7.15. Found: C, 62.40; H, 7.23.

**Xylo-6-Benzylxyhexa-2,3,4-triol Triacetate (77)**

A solution of 102 mg (0.46 mmol) of 71a in 3 mL of DMSO and 1 mL of 2N H<sub>2</sub>S<sub>4</sub> was stirred at 23°C for 3 h. The solution was diluted with 20 mL of methanol and passed through 9 cm<sup>3</sup> of DOWEX 1X-8 ion exchange resin (pretreated with 5N NaOH and then methanol). The solvents were concentrated in vacuo and the slightly colored residue was purified by flash chromatography on 55 g of silica gel using 2:1 ethyl acetate-hexane as eluant. In this manner 56 mg (51%) of the *xylo* triol was obtained: 1H NMR (CDCl<sub>3</sub>, D<sub>2</sub>O exchange) δ 7.3 (s, 5H, aromatic), 4.49 (s, 2H, benzylic), 3.88 (m, 2H, H<sub>2</sub> and H<sub>4</sub>), 3.67 (m, 2H, H<sub>6</sub>), 3.14 (t, J = 3 Hz, 1H, H<sub>3</sub>), 1.9-2.05 (m, 1H, H<sub>5a</sub>), 1.7-1.8 (m, 1H, H<sub>5b</sub>), 1.19 (d, J = 6.3 Hz, 3H, H<sub>1</sub>); IR (CH<sub>2</sub>Cl<sub>2</sub>) cm<sup>-1</sup> 3100-3700 (broad -OH), 3040, 2920, 1600, 1250, 1090; mass spectrum m/e 240 (parent ion).

The triol prepared above was converted by the standard acylation procedure (Ac<sub>2</sub>O, pyridine, Et<sub>2</sub>O) to afford, in quantitative yield, *xylo* triacetate 77 (R<sub>f</sub> 0.4, 1:1 hexane-ether): bp 185°C (3
mm; Kuglerohr); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.3 (s, 5H, aromatic), 5.28 (m, 1H, H\(_4\)), 5.05 (m, 2H, H\(_2\) and H\(_3\)), 4.40 (s, 2H, benzyl), 3.40 (m, 2H, H\(_6\)), 2.04 (s, 3H, acetate), 1.97 (s, 3H, acetate), 1.94 (s, 3H, acetate), 1.78 (q, J = 6 Hz, 2H, H\(_5\)), 1.13 (d, J = 6.1 Hz, 3H, H\(_1\)); IR (neat) cm\(^{-1}\) 3020, 2860, 1740, 1370, 1240; mass spectrum m/e 366 (parent ion). Anal. Calcd. for C\(_{19}\)H\(_{26}\)O\(_7\): C, 62.28; H, 7.15. Found: C, 62.35; H, 7.40.

Representative Procedures for Urethane Solvolysis Reactions

The physical, analytical, and spectroscopic data for the products of the solvolysis reactions of 79a, 79b, 83, 84, 85, and 93 are tabulated in the section immediately following these representative procedures. The product distributions and yields of isolated (chromatographed) products obtained from individual experiments are summarized in Figures 17, 18, 22, 23, 24, and 25.

1. \(\text{HBr in Acetone}\)

A solution of 54 mg (0.22 mmol) of 84 in 4 mL of acetone was treated with 0.2 mL of 48% HBr at 23°C for 2 h. The reaction mixture was diluted with 8 mL of H\(_2\)O and was extracted with CH\(_2\)Cl\(_2\) (4 x 8 mL). The combined extracts were dried (Na\(_2\)SO\(_4\)), filtered, and concentrated in vacuo. The crude product was chromatographed on a 0.5-mm silica gel plate using 1:1 hexane-ether as eluent (two developments) to give bromohydrin 89 (48 mg, 67%; \(R_f = 0.59\)) and carbonate 88 (4 mg, 11%; \(R_f = 0.28\)) from the well-resolved bands.

2. Aqueous Perchloric Acid

To a solution of 63 mg (0.19 mmol) of urethane 79a in 3 mL of acetonitrile was added 1 mL of 5% aqueous HClO\(_4\). The cloudy
solution was stirred for 19 h at room temperature and then was diluted with 15 mL of CH₂Cl₂ and water. The aqueous phase was extracted with two additional portions of CH₂Cl₂. The combined organic extracts were dried (Na₂SO₄), filtered, and concentrated in vacuo to give 72 mg of crude product. A portion which was insoluble in CHCl₃ was removed by filtration, and the remainder (60 mg) was chromatographed on a 0.5 mm silica gel plate using 95:5 toluene-.moves BuOH as eluent. Although carbonates 80a and 81a are separable by TLC (Rf=0.44 for 80a; Rf=0.33 for 81a, in this experiment the mixture of 80a and 81a (5:1, respectively, as determined by ¹H NMR analysis) was isolated as a single band (30 mg, 61% yield). The slower moving band (Rf=0.26) afforded 19 mg (29%) of dihydroxyurethane 82a (X = OH). A sample of 63 mg of 82a (combined from several experiments) was recrystallized from ethyl acetate-hexane to give 50 mg (79%) of amorphous, white crystals: mp 128-129°C. A pure sample of 80a was obtained by chromatography of mixtures of 80a and 81a. Attempted Kugelrohr distillation of 80a (213°C, 2 mm) resulted in nearly complete isomerization to the more stable isomer 81a.

3. Aqueous Acetic Acid

A solution of 61 mg (0.18 mmol) of 83 in 2 mL of 4:1 HOAc:H₂O was heated at 100°C for 45 min, at which time the reaction was judged complete by analytical TLC. The volatile components of the mixture were removed in vacuo and the crude product (89 mg) was purified by flash chromatography (20 g silica gel, 95:5 toluene-moves BuOH). In this manner 27.5 mg (58%) of xylo carbonate
86 (Rf=0.44) and 17 mg (36%) of its 3,4-carbonate acyl transfer isomer 86' (Rf=0.39) were obtained.

4. BF$_3$·Et$_2$O in Et$_2$O

To a solution of 500 mg (2.02 mmol) of 93 in 40 mL of dry Et$_2$O at 0°C was added 0.27 mL (2.2 mmol) of BF$_3$·Et$_2$O. A precipitate formed immediately. The mixture was stirred at 0°C for 75 min and then 40 mL of 1N H$_2$SO$_4$ was added (precipitate redissolved). The ice bath was removed and the two-phase system was stirred at room temperature for 5 h. The aqueous layer was separated and extracted with CH$_2$Cl$_2$ (4 × 20 mL). The combined extracts were dried (Na$_2$SO$_4$) and concentrated in vacuo. The crude product was purified by flash chromatography (50-mm × 6 in. silica gel pad; 2% MeOH-CH$_2$Cl$_2$) to give 306 mg (88%) of (+)81b (Rf=0.33; 4% MeOH-CH$_2$Cl$_2$) slower moving fractions containing 91 (Rf=0.24, 4% MeOH-CH$_2$Cl$_2$) were not recovered from this experiment. Ribo-carbonate 91 was, however, isolated from several experiments using BF$_3$·Et$_2$O in CH$_2$Cl$_2$ (see Figure 25 and reference 75).

5. Et$_2$AlCl in Et$_2$O

A solution of 281 mg (1.14 mmol) of 85 in 40 mL of Et$_2$O was cooled to 0°C and treated with 0.75 mL of 25% Et$_2$AlCl in hexane. The reaction was judged complete by TLC analysis after 30 min. The solution was removed from the ice bath and 20 mL of 1N H$_2$SO$_4$ was added. The two-phase system was stirred for 1.5 h and then the aqueous phase was extracted with CH$_2$Cl$_2$ (5x). The combined extracts were dried (Na$_2$SO$_4$), filtered, and concentrated to
afford 215 mg of crude product which was purified by flash chromatography (55 g silica gel, 1:1 EtOAc-hexane; 25 mL fractions). Fractions 5-9 were combined and concentrated to give 185 mg (94%) of lyxo carbonate 90.

Arabino-6-Benzylxyhexa-2,3,4-triol-2,3-Carbonate (80a)

$^1$H NMR (CDCl$_3$) $\delta$ 7.3 (s, 5 H, aromatic), 4.84 (br quintet, 1H, H$_2$), 4.50 (s, 2H, benzylic), 4.39 (dd, J = 2.0, 7.8 Hz, H$_3$), 4.02 (br d, J = 9.3 Hz, 1H, H$_4$), 3.6-3.8 (m, 2H, H$_6$), 3.25 (br, 1H, -OH), 2.0 (br m, 1H, H$_5$a), 1.7 (d of quintets, J = 14.7, 3 Hz, 1H, H$_{5b}$), 1.56 (d, J = 6.4 Hz, 3H, H$_1$); $^{13}$C NMR (CDCl$_3$) $\delta$ 155.3, 137.8, 128.5, 127.9, 81.2, 76.2, 73.3, 68.4, 68.0, 33.1, 14.1; IR (neat) cm$^{-1}$ 3100-3600 (-OH), 2920, 2860, 1790, 1190, 1090, 695.

Carbonates 80a and 81a were correlated with arabino triacetate 78 by transesterification (NaOMe, MeOH) and acetylation (Ac$_2$O, pyridine, Et$_2$O); see procedure for preparation of 78.

Arabino-6-Benzylxyhexa-2,3,4-triol 3,4-Carbonate (81a)

$^1$H NMR (CDCl$_3$) $\delta$ 7.3 (s, 5H, aromatic), 4.82 (br q, 1H, H$_4$), 4.48 (s, 2H, benzylic), 4.20 (dd, J = 4.8, 5.8 Hz, 1H, H$_3$), 3.94 (broad m, J = 4.8, 6.4 Hz, 1H, H$_2$), 3.62 (t, J = 5.9 Hz, 2H, H$_6$), 2.68 (broad d, J = 4.8 Hz, 1H, -OH), 2.01 (q, J = 6.0 Hz, 2H, H$_5$), 1.20 (d, J = 6.4 Hz, 3H, H$_1$); $^{13}$C NMR (CDCl$_3$) $\delta$ 155.0, 138.1, 128.6, 127.9, 84.5, 75.9, 73.5, 66.9, 65.7, 35.0, 18.1; IR
(CH₂Cl₂) cm⁻¹ 3200-3700 (-OH), 1800, 1190, 1080; mass spectrum m/e 266 (parent ion). Anal. Calcd. for C₁₄H₁₈O₅: C, 63.15; H, 6.81. Found: C, 63.21; H, 7.02.

Arabino-Hept-6-en-2,3,4-triol 2,3-Carbonate (80b)

H NMR (CDCl₃) δ 5.73 (m, 1H, H₆), 5.18 (m, 2H, H₇), 4.87 (m, 1H, H₂), 4.47 (dd, J = 1.6, 7.7 Hz, 1H, H₃), 3.81 (broad t, H₄), 2.52 (broad, 1H, -OH), 2.38 (m, 2H, H₅), 1.54 (d, J = 6.6 Hz, 3H, H₁); ¹³C NMR (CDCl₃) δc 155.2, 133.1, 119.4, 80.0, 76.1, 68.3, 38.4, 14.3; IR (CH₂Cl₂) cm⁻¹ 3200-3700 (-OH), 3060, 2940, 1800, 1640, 995; mass spectrum m/e 131 (parent-C₃H₅).

Transesterification of 5b or 6b (NaOMe, MeOH) afforded arabino-hept-6-en-2,3,4-triol³b in 95% yield. The correlation of this compound with 78 (via101) is outlined in Figure 28 and is described in detail in a subsequent procedure.

Arabino-Hept-6-en-2,3,4-triol 3,4-Carbonate (81b)

¹H NMR (CDCl₃) δ 5.73 (m, 1H, H₆), 5.2 (m, 2H, H₇), 4.70 (q, J = 5.4 Hz, 1H, H₄), 4.12 (dd, J = 3.9, 5.4 Hz, 1H, H₃), 4.0 (broad m, 1H, H₂), 3.1 (broad, 1H, -OH), 2.49 (m, 2H, H₅), 1.15 (d, J = 6.8 Hz, 3H, H₁); ¹³C NMR (CDCl₃) δc 154.8, 130.3, 120.5, 83.2, 76.7, 66.7, 38.6, 18.1; IR (CH₂Cl₂) cm⁻¹ 3300-3700 (-OH), 3060, 2975, 1800, 1640, 1375, 1180, 1060; mass spectrum m/e 131 (parent-C₃H₅); [α]D²³ = +59.4°(c = 8.8, CH₂Cl₂). Anal. Calcd. for C₈H₁₂O₄: C, 55.81; H, 7.03. Found: C, 55.54; H, 7.35.
Xylo-6-Benzyloxy-4-Bromo-2-O-(N-phenylcarbamoyl)-hexan-3-ol (82a), X=Br

$^1$H NMR (CDCl$_3$) δ 7.2-7.4 (m, 9H, aromatic), 7.10 (tt, J = 1.5, 7.0 Hz, 1H, p-H of urethane), 6.70 (br, 1H, -NH), 5.15 (m, 1H, H$_2$), 4.54, 4.53 (AB, J$_{AB}$ = 11.5 Hz, 2H, benzylic), 4.38 (dt, J = 3, 7 Hz, 1H, H$_4$), 3.7 (m, 2H, H$_6$), 3.50 (td, J = 2.9, 7 Hz, 1H, H$_3$), 2.74 (d, J = 7.7, 1H, -OH), 2.25 (m, 2H, H$_5$), 1.33 (d, J = 6.3, 3H, H$_1$); IR (CH$_2$Cl$_2$) cm$^{-1}$ 3100-3700 (-OH), 3420, 3020, 1720, 1595, 1520, 1440; mass spectrum m/e 421, 423 (parent ions).

Anal. Calcd. for C$_{20}$H$_{22}$BrNO$_4$: C, 56.88; H, 5.73; N, 3.32. Found: C, 57.09; H, 5.88; N, 3.05.

Xylo-4-Bromo-2-O-(N-phenylcarbamoyl)-hept-6-en-3-ol (82b, X = Br)

$^1$H NMR (CDCl$_3$) δ 7.2-7.4 (m, 4H, aromatic), 7.04 (broad t, J = 7.2 Hz, 1H, p-H of urethane), 6.90 (broad, 1H, -NH), 5.80 (m, 1H, H$_6$), 5.0-5.2 (m, 3H, H$_2$ and H$_7$), 4.06 (dt, J = 3.4, 6.9 Hz, 1H, H$_4$), 3.51 (dd, J = 3.4, 6.4 Hz, 1H, H$_3$), 2.65-2.9 (m, 3H, OH and H$_5$), 1.30 (d, J = 6.4 Hz, 3H, H$_1$); IR (CH$_2$Cl$_2$) cm$^{-1}$ 3500-3700 (-OH), 3420, 3040, 2980, 1730, 1640, 1600, 1520, 1440, 1210; mass spectrum m/e 327, 329 (parent ions).

Xylo-6-Benzyloxy-2-O-(N-phenylcarbamoyl)-hexane-3,4-diol (82a, X = OH)

mp 128-129 C; $^1$H NMR (CDCl$_3$) δ 7.2-7.4 (m, 9H, aromatic), 7.03 (broad t, J = 7.3 Hz, 1H, p-H of urethane), 6.9 (broad, 1H, -NH), 5.05 (dq, J = 4.9, 6.4 Hz, 1H, H$_2$), 4.49 (s, 2H, benzylic), 3.87 (broad m, J = 3.9 Hz, 1H, H$_4$), 3.68 (m, 2H, H$_6$), 3.41 (broad t, 1H, H$_3$), 3.31 (broad, 1H, -OH), 3.13 (broad, 1H, -OH), 1.8 (m, 2H, H$_5$), 1.34 (d, J = 6.4 Hz, 3H, H$_1$); IR (CH$_2$Cl$_2$) cm$^{-1}$ 3100-3700
(-OH), 3040, 2920, 1730, 1600, 1520, 1440, 1210, 1090; mass spectrum m/e 359 (parent ion). \textbf{Anal. Calcd.} for \(\text{C}_{20}\text{H}_{25}\text{NO}_{5}\): C, 66.84; H, 7.01; N, 3.90. \textit{Found:} C, 66.94; H, 6.97; N, 4.03.

Xylo-2-0-(N-phenylcarbamoyl)-hept-6-en-3,4-diol (82b, \(X = \text{OH}\))

\(\text{mp 105-107 C; } {^1}\text{H NMR (CDCl}_3\text{)} \delta 7.2-7.4 (m, 4H, aromatic), 7.04 (m, 2H, \text{-NH and p-H of phenyl}), 5.80 (m, 1H, \text{H}_6), 5.0-5.2 (m, 3H, \text{H}_2 \text{ and H}_7), 3.70 (m, 1H, \text{H}_4), 3.44 (t, J = 4.5 Hz, 1H, \text{H}_3), 2.35-2.65 (m, 2H, \text{H}_5), 1.34 (d, J = 6.5 Hz, 3H, \text{H}_1); IR (\text{CH}_2\text{Cl}_2) \text{ cm}^{-1} 3200-3700 (-\text{OH}), 3420, 2930, 1730, 1640, 1600, 1520, 1440, 1210; \text{mass spectrum m/e 265 (parent ion).}

Xylo-6-Benzylxylohexa-2,3,4-triol 2,3-Carbonate (86)

\(\text{\text{H NMR (CDCl}_3\text{)} \delta 7.3 (m, 5H, aromatic), 4.75 (quint, J = 6.3 Hz, 1H, H}_2), 4.50, 4.49 (AB, J_{AB} = 10 Hz, 2H, benzylic), 4.10 (dd, J = 2.8, 6.3 Hz, 1H, \text{H}_3), 3.86 (m, 1H, \text{H}_4), 3.7 (m, 2H, \text{H}_6), 3.42 (d, J = 4.7 Hz, 1H, \text{-OH}), 1.7-2.0 (m, 2H, \text{H}_5), 1.41 (d, J = 6.4 Hz, 3H, \text{H}_1); } {^{13}\text{C NMR (CDCl}_3\text{)} \delta} 154.7, 137.5, 128.3, 127.7, 84.8, 74.8, 73.1, 68.8, 67.4, 32.0, 19.5; IR (\text{CH}_2\text{Cl}_2) \text{ cm}^{-1} 3200-3700 (-\text{OH}), 3040, 2935, 1800, 1380, 1365, 1180, 1080; \text{mass spectrum m/e 266 (parent ion). \textbf{Anal. Calcd.} for C}_{14}\text{H}_{18}\text{O}_5: C, 63.15; H, 6.81. \textit{Found:} C, 62.92; H, 6.79.

Xylo-6-Benzylxylohexa-2,3,4-triol 3,4-Carbonate (86')

\(\text{\text{H NMR (CDCl}_3\text{)} \delta 7.3 (s, 5H, aromatic), 4.74 (q, J = 6.3 Hz, 1H, \text{H}_4), 4.47 (s, 2H, benzylic), 4.24 (dd, J = 3.4, 6.3 Hz, 1H,}\)
H₃), 3.78 (broad dq, J = 3.4, 6.6 Hz, 1H, H₂), 3.63 (t, J = 5 Hz, 2H, H₆), 2.32 (broad, 1H, −OH), 2.03 (m, 2H, H₅), 1.21 (d, J = 6.6 Hz, 3H, H₁); ¹³C NMR (CDCl₃) δ 154.5, 137.7, 128.5, 127.8, 84.5, 73.5, 66.9, 65.5, 34.3, 18.5; IR (CH₂Cl₂) cm⁻¹ 3300-3700 (−OH), 3040, 2945, 1800, 1600, 1540, 1175, 1090; mass spectrum m/e 266 (parent ion).

Carbonates 86 and 86' were correlated with xylo-triacetate 77 by using the procedure described above for the correlation of 80a and 81a with 78.

Arabino-6-Benzyloxy-4-bromo-2-o-(N-phenylcarbamoyl)-hexan-3-ol (87)

¹H NMR (CDCl₃) δ 7.2-7.4 (m, 9H, aromatic), 7.05 (broad t, J = 7.1 Hz, 1H, p-H of urethane), 6.78 (broad, 1H, −NH), 4.93 (m, 1H, H₂), 4.49-4.60 (m, 3H, benzylic and H₄), 3.59-3.73 (m, 3H, H₆ and H₃), 3.47 (broad d, J = 7.4 Hz, 1H, −OH), 2.16-2.22 (m, 2H, H₅), 1.40 (d, J = 6.2 Hz, 3H, H₁); IR (CH₂Cl₂) cm⁻¹ 3100-3700 (−OH), 3420, 3040, 1735, 1600, 1520, 1440, 1210; mass spectrum m/e 421, 423 (parent ions).

Ribo-Hept-6-en-2,3,4-triol 2,3-Carbonate (88)

¹H NMR (CDCl₃) δ 5.79 (m, 1H, H₆'), 5.16 (m, 2H, H₇), 4.90 (m, 1H, H₂), 4.38 (dd, J = 7.2, 9.3 Hz, 1H, H₃), 3.84 (broad m, 1H, H₄), 2.58 (d of multiplets, J = 14.3 Hz, 1H, H₅a), 2.36 (d, J = 4.5 Hz, 1H, −OH), 2.21 (td, J = 8.2, 14.3 Hz, 1H, H₅b), 1.46 (d, J = 6.7 Hz, 3H, H₁); ¹³C NMR (CDCl₃) δ 154.4, 132.5, 120.0,
79.9, 76.5, 67.4, 38.8, 14.8; IR (CH$_2$Cl$_2$) cm$^{-1}$ 3580, 3040, 2920, 1802, 1640, 1180, 1085, 1015; mass spectrum m/e 131 (parent-C$_3$H$_5$); [α]$^D_{29}$ = +19° (c = 4.1, CH$_2$Cl$_2$). Anal. Calcd. for C$_8$H$_{12}$O$_4$: C, 55.81; H, 7.02. Found: C, 55.67; H, 7.22.

Trans-esterification of 88 using the usual procedure (NaOMe, MeOH, 95% yield) afforded ribo-hept-6-en-2,3,4-triol (vide infra).

**Lyxo-4-Bromo-2-O-(N-phenylcarbamoyl)-hept-6-en-3-ol (89, X = Br)**

$^1$H NMR (CDCl$_3$) δ 7.35 (m, 4H, aromatic), 7.07 (broad t, J = 7 Hz, 1H, p-H), 6.92 (broad, 1H, NH), 5.91 (m, 1H, H$_6$), 5.37 (dq, J = 2.8, 6.5 Hz, 1H, H$_2$), 5.2 (m, 2H, H$_7$), 4.05 (dt, J = 3.7, 8 Hz, 1H, H$_4$), 3.72 (dd, J = 2.8, 7.9 Hz, 1H, H$_3$), 2.4-2.95 (m, 3H, -OH and H$_5$), 1.37 (d, J = 6.5 Hz, 3H, H$_1$); IR (CH$_2$Cl$_2$) cm$^{-1}$ 3200-3700 (-OH), 3040, 2980, 1730, 1640, 1595, 1520, 1440, 1210; mass spectrum m/e 327, 329 (parent ions).

**Lyxo-Hept-6-en-2,3,4-triol 2,3-Carbonate (90)**

$^1$H NMR (CDCl$_3$) δ 5.78 (m, 1H, H$_6$), 5.2 (m, 2H, H$_7$), 4.80 (quint, J = 6.3 Hz, 1H, H$_2$), 4.06 (t, J = 6 Hz, 1H, H$_3$), 3.87 (m, 1H, H$_4$), 2.14-2.4 (m, 3H, H$_5$ and -OH), 1.47 (d, J = 6.3 Hz, 3H, H$_1$); $^{13}$C NMR (CDCl$_3$) δ $^1$C 55.0, 132.8, 119.0, 84.3, 75.1, 69.9, 37.0, 20.3; IR (CH$_2$Cl$_2$) cm$^{-1}$ 3300-3700 (-OH), 3040, 1800, 1640, 1180, 920; mass spectrum m/e 131 (parent-C$_3$H$_5$); [α]$^D_{26}$ = +37.9° (c = 3.6, CH$_2$Cl$_2$). Anal. Calcd. for C$_8$H$_{12}$O$_4$: C, 55.81; H, 7.02. Found: C, 56.09; H, 7.05.
Ribo-Hept-6-en-2,3,4-triol 2,4-Carbonate (91)

$^{1}H$ NMR (CDCl$_3$) $\delta$ 5.8 (m, 1H, $H_6$), 5.2 (m, 2H, $H_7$), 4.25 (m, $H_2$ and $H_4$), 3.48 (dt, J = 5.4, 9.3 Hz, 1H, $H_3$), 2.94 (broad d, J = 5 Hz, 1H, $-$OH), 2.4-2.7 (m, 2H, $H_5$), 1.43 (d, J = 6.3 Hz, 3H, $H_1$); IR (CH$_2$Cl$_2$) cm$^{-1}$ 3100-3700 (-OH), 3040, 2920, 1750, 1640, 1245, 1200, 1080. Trans-esterification (NaOMe, MeOH) of 91 afforded a triol which was identical to that prepared by trans-esterification of ribo-carbonate 88. Carbonates 91 prepared from (+)-85 and (+)-93 are enantiomeric.

Ribo-4-Bromo-2-O-(N-phenylcarbamoyl)-hept-6-en-3-ol (92)

$^{1}H$ NMR (CDCl$_3$) $\delta$ 7.2-7.4 (m, 4H, aromatic), 7.06 (broad t, J = 7.1 Hz, 1H, p-H), 6.70 (broad, 1H, NH), 5.86 (m, 1H, $H_6$), 5.1-5.27 (m, 3H, $H_2$ and $H_7$), 4.0 (m, 2H, $H_3$ and $H_4$), 2.4-2.9 (m, 3H, $-$OH and $H_5$), 1.34 (d, J = 6.2 Hz, 3H, $H_1$); IR (CH$_2$Cl$_2$) cm$^{-1}$ 3500-3700 (-OH), 3420, 3040, 2980, 1733, 1640, 1600, 1520, 1440, 1210; mass spectrum m/e 327, 329 (parent ions); $[^{28}]D = +13.7^\circ$ (c = 1.15, CH$_2$Cl$_2$).

Ribo-2-Bromo-4-O-(N-phenylcarbamoyl)-hept-6-en-3-ol (94)

(Prepared in 45% yield by treatment of 93 with HBr in acetone; 35% of carbonate 81b was also obtained); mp 77-77.5°C; $^{1}H$ NMR (CDCl$_3$) $\delta$ 7.2-7.4 (m, 4H, aromatic), 7.06 (broad t, J = 7.1 Hz, 1H, p-H), 6.73 (broad, 1H, $-$NH), 5.82 (m, 1H, $F_6$), 5.1-5.2 (m, 2H, $H_7$), 5.00 (dt, J = 3.8, 7.5 Hz, 1H, $H_4$), 4.32 (dq, J = 3.7, 6.7 Hz, 1H, $H_2$), 3.97 (dd, J = 3.7, 7.5 Hz, 1H, $H_3$), 2.39-2.70 (m, 3H, $-$OH and $H_5$), 1.70 (d, J = 6.7 Hz, 3H, $H_1$); IR (CH$_2$Cl$_2$) cm$^{-1}$ 3500-3700 (-OH), 3420, 3040, 2980, 1735, 1640, 1595, 1520, 1440, 1205; mass spectrum m/e 327, 329 (parent ions); $[^{28}]D = +18.8^\circ$ (c = 2.4, CH$_2$Cl$_2$). Anal. Calcd. for C$_4$H$_{18}$BrNO$_3$: C, 51.23; H, 5.53; Br, 24.35. Found: C, 51.36; H, 5.85; Br, 24.35.
Correlation of Urethane 82a (X = OH) with Xylo-Triacetate 77

A solution of 19 mg (0.53 mmol) of 82a (X=OH) in 5 mL of THF was treated with 6 mg (0.16 mmol) of LiAlH₄ and the resulting suspension was heated to reflux for 5 h. The reaction was quenched by the addition of 2 mL of H₂O which was followed by 2 mL of 1N NaOH. The resulting precipitate was removed by filtration through a Celite pad and was washed with several portions of ether. The aqueous phase was separated from the filtrate and was extracted with CH₂Cl₂ (5x). The combined organic phases were concentrated in vacuo to afford 30 mg of crude material which was purified by flash chromatography (15 g silica gel; EtOAc as eluent) to yield 8 mg (63%) of the xylo triol. This material was acylated by the usual procedure (see preparation of 78) to afford 77 in quantitative yield.

Correlation of 78 with 81b via Arabino-Hex-2,3,4,6-yl Tetraacetate (101)

A solution of 20.3 mg (0.055 mmol) of 78 in 7 mL of reagent grade MeOH was hydrogenated over 10.1 mg of 5% Pd/C under an atmosphere of H₂. The reaction mixture was stirred for 4 h and was then filtered and concentrated in vacuo. The crude product (8.8 mg, 65%) was purified by chromatography on a 0.5 mm silica gel plate using 3:1 ether-hexane as eluent giving 7.7 mg (55%) of the desired primary alcohol. This material was then acylated according to the conditions described previously (Ac₂O, pyridine, Et₂O) to give 7.5 mg (78%) of 101 following chromatographic purification (0.25-mm silica gel preparative plate, 2:1 ether-hexane).
Tetraacetate 101 prepared in this manner was identical to a sample prepared from carbonate 81b. Thus, 37 mg (0.21 mmol) of 81b was treated with NaOMe in MeOH and the crude triol (which was also prepared from 80b) was acylated with acetic anhydride and pyridine in Et₂O according to the procedure described previously for the synthesis of 78 from 80a and 80b. The triacetate (35 mg) was isolated in 60% overall yield by chromatography (0.5-mm silica gel plate, 3:1 ether-hexane). A portion of this product (26 mg, 0.096 mmol) was dissolved in 20 mL of MeOH and cooled to -78 C. A stream of dry O₃/O₂ was passed through the solution until it developed a deep blue color. The solution was then purged with O₂ to remove excess O₃ and was quenched with 3 mL of Me₂S. The reaction mixture was then allowed to warm to room temperature and was stirred for 19 h. To this mixture was then added 10.8 mg (3 equiv.) of NaBF₄. The solution was stirred for 1 h and then was diluted with 11 mL of 0.1N HCl. The mixture was extracted with CH₂Cl₂ (4x), and the extracts were dried (Na₂SO₄), filtered and concentrated in vacuo. The crude product was chromatographed (0.5-mm silica gel plate, 3:1 ether-hexane) to give 19.8 mg of crude primary alcohol. This intermediate was acylated as described above to give 14.5 mg (45%) of 101: ¹H NMR (CDCl₃) δ 5.3 (dt, J = 3.4, 6.4 Hz, 1H, H₁), 5.1 (dd, J = 7.5, 3.4 Hz, 1H, H₃), 4.95 (dt, J = 7.5, 6.4 Hz, 1H, H₂), 4.05 (t, J = 6.4 Hz, 2H, H₆), 2.11 (s, 3H, acetate), 2.03 (s, 3H, acetate), 2.02 (s, 3H, acetate), 2.00 (s, 3H, acetate), 1.84 (m, 2H, H₅), 1.17 (d, J = 6.4 Hz, 3H, H₁); IR (CH₂Cl₂) cm⁻¹ 2960, 1740, 1368,
1228, 1042, 677; mass spectrum m/e 303 (M⁺ - CH₃).

Correlation of 77 with 102 via Xylo-Hex-2,3,4,6-yl Tetraacetate (103)

Xylo-triacetate 77 and xylo-triol 102 (vide infra) were transformed into xylo-tetraacetate 103 by using procedures exactly analogous to those described above for the synthesis of arabino-tetraacetate 101. Data for 29: ¹H NMR (CDCl₃) δ 5.24 (dt, J = 8.0, 4.6 Hz, 1H, H₄), 5.10 (m, 2H, H₂ and H₃), 4.07 (t, J = 6.3 Hz, 2H, H₆), 2.12 (s, 3H, acetate), 2.09 (s, 3H, acetate), 2.06 (s, 3H, acetate), 2.05 (s, 3H, acetate), 1.88 (dt, J = 6.3, 8.0 Hz, 2H, H₅), 1.24 (d, J = 6.0 Hz, 3H, H₁); IR (CH₂Cl₂) cm⁻¹ 2920, 1732, 1424, 1327, 1230; mass spectrum m/e 303 (M⁺ - CH₃).
Experimental Procedures for Chapter III

Hept-1-en-4-yn-6-ol (107) 93

A 1000 mL 3-neck flask equipped with a magnetic stirrer, two dropping funnels, and a reflux condenser was charged under a nitrogen atmosphere with a solution of 2.0 g (20 mmol) of CuCl dissolved in 320 mL of saturated aqueous NaCl containing 2 mL of concentrated HCl. 3-Butyn-2-ol 106 (19.7 g, 22 mL, 280 mmol) was then added. From one dropping funnel was added dropwise 40% NaOH solution until the pH, monitored by a pH-meter, reached 8.5. The resulting suspension containing a bright yellow-orange precipitate was heated to 70-75°C, and then a solution of allyl chloride (40 mL, 490 mmol) in 40 mL of methanol was added dropwise over a 1.5 h interval. Sufficient NaOH solution was added periodically to maintain the pH between 7.5 and 8.5. After the addition was complete and the uptake of NaOH ceased, an aliquot was worked up (as below) and analyzed by 1H NMR which indicated that the reaction was ca. 50% complete. A fresh portion of CuCl (1.0 g) was added, followed by additional allyl chloride (approximately 40 mL) and NaOH until the orange precipitate no longer formed upon further addition of base. The resulting dark orange solution was cooled and acidified to pH 1 by the addition of concentrated HCl. The organic phase was separated and the aqueous layer extracted with CH₂Cl₂ (4×75 mL). The combined organic extracts were dried (Na₂SO₄), filtered, and concentrated and distilled to give 28.2 g of pure 107 (b.p. 114-115°C, 80-85 mm Hg; lit. 13 b.p. 73°C, 15 mm Hg). Redistillation of the fore-run resulted in the recovery of an additional
1.1 g of \textsuperscript{107} for a total yield of 29.3 g (95%): \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \delta 5.7-5.9 (m, 1 H, H\textsubscript{2}), 5.3 (dd, J=1.8, 16.9 Hz, 1 H, H\textsubscript{1E}), 5.1 (dd, J=1.8, 10.3 Hz, 1 H, H\textsubscript{1Z}), 4.55 (broad quartet, J=6 Hz, 1 H, H\textsubscript{6}), 3.0 (dd, J=1.5, 5.1 Hz, 2 H, H\textsubscript{3}), 2.07 (broad, 1 H, -OH), 1.45 (d, J=6.6 Hz, 3 H, H\textsubscript{7}); IR (neat) cm\textsuperscript{-1} 3100-3700 (-OH), 3080, 2980, 2240, 1640, 1150, 1070; mass spectrum m/e 110 (parent ion).

(2)-Hepta-1,4-dien-6-ol (108)

A solution of 1.28 g (11.6 mmol) of \textsuperscript{107} in 15 mL of absolute MeOH was transferred to a resealable tube under N\textsubscript{2} and treated with the zinc-copper couple\textsuperscript{94} prepared from 370 mg of CuSO\textsubscript{4} and 5.54 g of Zn dust in 11 mL of H\textsubscript{2}O. The reaction vessel was purged with Ar, sealed, and heated to 110\degree C for 11 h. Analysis of the reaction mixture by GC (10 ft 5% SE-30 column, 130-140\degree C temperature program (10\degree C/min ramp rate), R\textsubscript{t} (108)=0.9 min, R\textsubscript{t} (107)=1.1 min) indicated that the reduction had proceeded to approximately 50% conversion. A second batch of Zn/Cu couple (as above) was added and the reaction mixture was heated at 100-110\degree C until all \textsuperscript{107} had been consumed (40 h in this run). The spent reagent was then removed by filtration. The filtrate was diluted with 50 mL of CH\textsubscript{2}Cl\textsubscript{2} and washed with 10 mL of saturated aqueous NH\textsubscript{4}Cl, which was back-extracted with CH\textsubscript{2}Cl\textsubscript{2} (2X). The combined extracts were dried (Na\textsubscript{2}SO\textsubscript{4}), filtered, concentrated, and distilled (kugelrohr, 100\degree C, 80 mm Hg) to afford 958 mg (73%) of
pure 108: $^1$H NMR (CDCl$_3$) $\delta$ 5.7-5.9 (m, 1 H, H$_2$), 5.4-5.6 (m, 2 H, H$_4$ and H$_5$), 5.0-5.1 (m, 2 H, H$_1$) 4.63 (d quartet, J=6.2, 7.4 Hz, 1 H, H$_6$) 2.85 (broad t, 2 H, J=6 Hz, H$_3$), 1.83 (broad, 1 H, -OH), 1.24 (d, J=6.2 Hz, 3 H, H$_7$); $^{13}$C NMR (CDCl$_3$) $\delta_{c}$ 136.5, 135.0, 127.6, 115.1, 63.7, 31.7, 23.8; IR (neat) cm$^{-1}$ 3100-3700 (-OH), 3080, 3010, 1635, 910; mass spectrum m/e 112 (parent ion). High resolution mass spectrum. Calcd for C$_7$H$_{12}$O: 112.08881. Found: 112.09031.

Lyxo-3,4-Epoxyhept-6-en-2-ol (109)

To a solution of 1.15 g (10 mmol) of 108 in 100 mL of dry CH$_2$Cl$_2$ under argon cooled in a dry ice/CCl$_4$ bath was added 3 mL (10 mmol) of titanium tetraisopropoxide and 2.2 mL of 5 M tert-butyl hydroperoxide (11 mmol) in CH$_2$Cl$_2$.$^{63}$ This mixture was stirred for 30 min and then placed in a -20°C freezer for 18 h. The solution was diluted with 100 mL of acetone and 3 mL of H$_2$O. The resulting mixture was stirred at room temperature for 1 h and then the resulting precipitate was removed by filtration through a pad of Celite. The solvents were removed in vacuo and the crude product distilled (kugelrohr, 100°C, 25 mm Hg) to give 1.02 g (80%) of pure 109: $^1$H NMR (CDCl$_3$) $\delta$ 5.8 (m, 1 H, H$_6$), 5.1 (m, 2 H, H$_7$), 3.65 (broad quintet, J=6.3 Hz, 1 H, H$_2$), 3.10 (d of t, J=4.4, 8.8 Hz, 1 H, H$_4$), 2.90 (d of d, J=4.4, 8.3 Hz, 1 H, H$_3$), 2.59 (broad, 1 H, OH) 2.3 (m, 2 H, H$_5$), 1.22 (d, J=6.3 Hz, H$_1$); $^{13}$C NMR (CDCl$_3$) $\delta_{c}$ 133.4, 117.3, 66.0, 61.5, 56.0, 32.6, 19.5; IR (neat) cm$^{-1}$ 3100-3700, 3080, 2972, 1640, 990, 915, 820; mass
spectrum m/e 128 (parent ion). *Anal.* Calcd. for C$_7$H$_{12}$O$_2$: C, 65.60; H, 9.44. Found: C, 65.43; H, 9.36.

**Arabino-Hept-6-en-2,3,4-triol (110)**

Epoxyalcohol 109 was converted to urethane 79b (89%; mp 55.5-56°C (EtOAc hexane)) as described above. Conversion of 79b to carbonates 80b and/or 81b (89-95% yield) is summarized in Figure 18.

A solution of 346 mg (2.01 mmol) of a mixture of racemic carbonates 80b and 81b (combined from a number of solvolytic ring openings of 79b) in 20 mL of 0.2 N NaOMe in MeOH was stirred at room temperature for 5 h. The solution was then passed through a column containing 14 cm$^3$ (wet volume) of Dowex 50W-X8, H$^+$ ion exchange resin which had been pretreated with methanol. A total of 100 mL of MeOH was used to ensure that the triol 110 had eluted from the column. Concentration of the eluate in vacuo afforded 288 mg (98%) of triol as a pale yellow oil: $^1$H NMR (CDCl$_3$, D$_2$O exchanged) δ 5.82 (m, 1 H, H$_6$), 5.2 (m, 2 H, H$_7$), 3.95 (m, 2 H, H$_2$ and H$_4$), 3.34 (dd, J=2.6, 4.0 Hz, 1 H, H$_3$), 2.4 (m, 2 H, H$_5$), 1.26 (d, J=6.6 Hz, 3 H, H$_1$); $^{13}$C NMR (CDCl$_3$) δ$_C$ 134.5, 117.8, 75.4, 70.1, 69.5, 38.0, 18.8; IR (CH$_2$Cl$_2$) cm$^{-1}$ 3100-3700 (broad-OH), 3040, 2920, 1640, 1245, 1060, 990, 915; mass spectrum m/e 146 (parent ion). High resolution mass spectrum. Calculated for C$_7$H$_{12}$O$_2$ (m-H$_2$O): 128.08343. Found: 128.08372.

By an analogous procedure, 667 mg of (+)-81b (prepared as described subsequently) was transformed to 560 mg (99% yield) of
(+)-arabino-triol 110 ([α]_{D}^{22} = + 5.5° (C=4.7, CH_{2}Cl_{2})), the spectroscopic properties of which are identical in all respects to the data summarized above for the racemic material.

2,6-Dideoxy-D-arabino-hexose ((+)-17)

A solution of 560 mg (3.84 mmol) of the (+)-arabino triol 110 described above in 50 mL of absolute methanol was cooled to -20°C (dry ice, CCl_{4}) and treated with a stream of O_{3} in O_{2} until the triol was consumed (TLC analysis). The solution was purged with O_{2} to remove excess O_{3} before 5 ml of Me_{2}S was added. The solution was warmed to room temperature and stirred for 18 h. All volatile components were then removed in vacuo to give 711 mg of crude sugar. This material was chromatographed (130 g of silica gel, 10% EtOH in CH_{2}Cl_{2}) to give 485 mg (85%) of pure (+)-17, [α]_{D}^{22} = + 19.4° (c=2.9, H_{2}O, equilibrated). An authentic sample of (+)-17 prepared from D-glucose had [α]_{D}^{25} = + 19.5° (c=1.6, H_{2}O, equilibrated). Rotations of +20° and -18° were reported for the D- and L-enantiomers, respectively.\textsuperscript{89d,89g} \textsuperscript{1}H NMR (D_{2}O), a 60:40 mixture of α- and β-pyranose structures; β-anomer: δ 4.67 (dd, J=2.2, 9.7 Hz, 1 H, H_{1}), 3.42 (ddd, J=5.3, 9.3, 11.9 Hz, 1 H, H_{3}), 3.17 (d quartet, J=6.2, 9.3 Hz, 1 H, H_{5}), 2.81 (t, J=9.3 Hz, 1 H, H_{4}), 2.01 (ddd, J=2.2, 5.3, 11.9 Hz, 1 H, H_{2e}), 1.26 (dt, J=9.7, 11.9 Hz, 1 H, H_{2a}), 1.04 (d, J=6.2 Hz, 3 H, H_{6}); α-anomer: δ5.07 (broad d, J=4 Hz, 1 H, H_{1}), 3.6 (m, 2 H, H_{3} and H_{5}), 2.86 (t, J=9.3 Hz, 1 H, H_{4}), 1.88 (ddd, J=1.3, 5.3, 13.3 Hz, 1 H, H_{2e}), 1.46 (ddd, J=4.0, 11.9, 13.3 Hz, 1 H, H_{2a}),
1.02 (d, J=6.2 Hz, 3 H, H₆). ¹³C NMR (D₂O) β anomer: δₐ 93.9, 77.0, 68.5 (2 carbons), 40.6, 17.8; α anomer: δₐ 91.8, 77.7, 72.5, 71.0, 38.4, 17.8.

Racemic 17, prepared by ozonolysis of the racemic triol in 89% yield, crystallized when stored at 0°C for several months: mp 125.5 –127°C. We have been unsuccessful in all attempts to induce the optically active sugar to crystallize.

**Xylo-6-Hepten-2,3,4-triols (102)**

A solution of 178 mg (1.39 mmol) of epoxyalcohol 109 in 4 mL of THF was treated with 1 mL of 20% aqueous perchloric acid at room temperature. All of _ was consumed after 18 h. The solution was thus diluted with 20 mL of methanol and passed through a column containing approximately 10 cm³ (wet volume) of Dowex 1-X8 ion-exchange resin, which had been pretreated with 5N NaOH. The resin was washed with 100 mL of methanol to ensure complete elution of the product. All volatile components of the mixture were removed in vacuo to give 244 mg of a thick syrup. This material was chromatographed on 110 g of silica gel using 4:1 EtOAc-hexane as eluent (25 mL fractions). Fractions 8-30 were combined and evaporated to yield 133 mg (65%) of pure 102: ¹H NMR (CDCl₃-D₂O exchange) δ 5.65-5.8 (m, 1 H, H₆), 5.0-5.1 (m, 2 H, H₇), 3.8 (d quartet, J=4.4, 6.6 Hz, 1 H, H₂), 3.63 (dt, J=2.2, 6.6 Hz, 1 H, H₄), 3.14 (dd, J=2.2, 4.4 Hz, 1 H, H₃), 2.27 (broad t, J=6.6 Hz, 2H, H₅), 1.14 (d, J=6.6 Hz, 3H, H₁); ¹³C NMR (CDCl₃) δc 134.6, 117.8, 75.9, 72.5, 69.5, 38.7, 19.8; IR (CH₂Cl₂)
cm⁻¹ 3100–3700 (broad OH), 3080, 2920, 1640, 1380, 1060, 995, 920; mass spectrum m/e 146 (parent ion).

2,6-Dideoxy-xylo-hexose (racemic boivinose, 5)

A solution of 175 mg (1.2 mmol) of racemic 102 in 5 mL of methanol was ozonized using the procedure described for preparation of (+)-17. The crude product was purified by flash chromatography (40 g silica gel, 20% EtOH in CH₂Cl₂) to give 160 mg (90%) of racemic boivinose as a syrup (Rᵢ=0.2 in EtOAc); ¹H NMR (DMSO-d₆, D₂O exchanged) ~80% β-pyranose anomer (the remainder being a mixture of the α- and the furanose anomers): δ 4.75 (dd, J=2.5, 9.8 Hz, 1 H, H₁), 3.74 (broad quartet, J=6.2 Hz, 1 H, H₅), 3.7 (m, 1 H, H₃), 2.95 (m, fine coupling, 1 H, H₄), 1.58 (ddd, J=3.1, 9.8, 13.2 Hz, 1 H, H₂a), 1.42 (dt, J=3.1 Hz, 13.2 Hz, 1 H, H₂e), 1.02 (d, J=6.2 Hz, 3 H, H₆); ¹³C NMR (D₂O) δc 92.6, 69.9 (2 carbons), 69.3, 34.7, 16.7. These ¹³C NMR data are in good agreement with literature values for racemic boivinose. 89j

(E)-1,5-Heptadien-4-ol (114)

A 2-L 3-neck flask equipped with a mechanical stirrer, reflux condenser, and two 500 mL dropping funnels was charged with 50 g (2 mol) of Mg turnings, 130 mL of anhydrous ether, and a few I₂ crystals. A solution of 58 mL (670 mmol) of allyl bromide in 650 mL of anhydrous Et₂O was transferred to the addition funnels. A small portion of this solution was added to the reaction vessel to initiate the Grignard formation. The
remainder of the allyl bromide solution was added dropwise at a rate such that gentle reflux was maintained. The solution was heated to reflux for an additional hour. The heating bath was removed and then 40 mL (490 mmol) of distilled crotonaldehyde was added dropwise over one hour. After being stirred for an additional hour, the reaction mixture was poured through a glass wool plug into 800 mL of ice water. Magnesium salts were dissolved by the careful addition of 160 mL of 9N H₂SO₄. The two phases were separated and the aqueous layer extracted with CH₂Cl₂ (4x100 mL). The combined organic extracts were dried (Na₂SO₄), filtered, concentrated in vacuo, and distilled to give 47.6 g of 114 (bp 71° C, 25 mm Hg). An additional 3.0 g of product was obtained by redistillation of the fore-run bringing the total yield of 114 to 50.6 g (92%): ¹H NMR (CDCl₃) δ 5.6-5.9 (m, 2 H; H₆ and H₂), 5.49 (dd, J=7, 16.4 Hz, 1 H, H₃), 5.1 (m, 2 H, H₇), 4.08 (quartet, J=6.5 Hz, H₄), 2.2 (m, 2 H, H₅), 1.71 (broad, 1 H, -OH), 1.67 (d, J=6.3 Hz, H₁); IR (neat) cm⁻¹ 3100-3600 (broad-OH), 3080, 2910, 1675, 1640, 1440, 1030, 960, 910; mass spectrum m/e 112 (parent ion).

(+)-Lyxo-2,3-Epoxyhept-6-en-4-ol ((+)-115): Kinetic Resolution of Racemic 114

A solution of 30 mL (100 mmol) of titanium tetraisopropoxide and 31.5 mL (150 mmol) of D-(−)-diisopropyl tartrate in 1 L of dry CH₂Cl₂ was cooled to −20° C (CCl₄, dry ice bath) under argon. The resulting pale yellow solution was stirred for 15 min and
then 11.2 g (100 mmol) of racemic 114 and 8.5 mL of 4.96 M tert-butyl hydroperoxide in CH₂Cl₂ (42 mmol) were added. The reaction vessel was then stored in a -20°C freezer for 18 h, after which the reaction mixture was poured into a prechilled (-20°C) mixture of 30 mL of H₂O in 1000 mL of acetone. The resulting precipitate was removed by filtration through a pad of Celite, and the solvents evaporated in vacuo to yield 46.5 g of crude product. This mixture was separated by chromatography using a Waters Prep 500 liquid chromatograph (four equal sized portions, one silica gel cartridge, 3:7 EtOAc-hexane as the eluent). Allylic alcohol (-)-114 elutes first (t_R=12 min, 100 mL/min), followed by DIPT (t_R=18 min), and epoxide (+)-115 (t_R=23 min). Similar fractions were combined, evaporated, and distilled (kugelrohr) to give 3.38 g (30% of (-)-114 (bp 68°C, 25 mm Hg; [α]D²⁵⁻ = -8.9° (c=9.4, CH₂Cl₂); 72% ee by Mosher ester analysis), 3.50 g (27%) of (+)-115 (bp 90°C, 25 mm Hg; [α]D²³⁺ = 3.0° (c=7.2, CH₂Cl₂), 95% ee by Mosher ester analysis), and 25 g of recovered DIPT (71%).

A simplified work up procedure was developed for the kinetic resolution of racemic 114 to produce (-)-115. (The two phase hydrolytic procedure recommended by Sharpless for removal of the tartrate ester, or a modification using NaOH in saturated NaCl solution, leads to partial (ca. 10%) Payne rearrangement of 115). Thus, 9.95 g (88.8 mmol) of 114 was epoxidized by using 8.9 mmol of Ti (OPr)₄, 14.3 mmol of L-(+)-diisopropyl tartrate, and 37.3 mmol (0.42 equiv.; 6.3 mL of 5.93 M TBHP solution) in
500 mL of \( \text{CH}_2\text{Cl}_2 \) (-20° C, 43 h). Ether (200 mL) and 5-10 mL of saturated \( \text{Na}_2\text{SO}_4 \) solution were then added at 25° C and the mixture stirred vigorously for 2 h at room temperature. The white precipitate was removed by filtration through a pad of Celite, and the solvents evaporated in vacuo. The residue was dissolved in 50 mL of ether and washed with saturated \( \text{Na}_2\text{SO}_3-\text{NaCl} \) solution, dried (MgSO₄), filtered, and again concentrated in vacuo. The crude product was distilled through a short-path apparatus (25 mm Hg, 90-110° C) to give 7.8 g of a mixture of (+)-114 and (-)-115, contaminated with a small amount of (+)-DIPT. The pot residue (ca. 10 mL) was Kugelrohr distilled (115° C, 25 mm Hg) to give 2.9 g of essentially pure (-)-115, leaving (+)-DIPT in the distillation pot. The mixed fraction was separated by chromatography (\( \text{CH}_2\text{Cl}_2-\text{Et}_2\text{O}, 16:1, 500 \text{ g silica gel} \)). Similar fractions were combined (the above, distilled, epoxide was combined with the chromatographically homogeneous fractions), concentrated and redistilled (Kugelrohr) to give 4.17 g (37%) of (-)-115 ([\( \alpha \)] D²⁰ = -2.8° (c=4.9, \( \text{CH}_2\text{Cl}_2 \)), 95% ee by Mosher ester analysis), and 4.58 g (46%) of kinetically resolved (+)-114 ([\( \alpha \)] D²⁰ = +10.3° (c=3.1, \( \text{CH}_2\text{Cl}_2 \)), [\( \alpha \)] D²⁰ = +12.3° (c=2.8, \( \text{CHCl}_3 \)), 68% ee by Mosher ester analysis).

Data for (+)-115: \(^1\text{H NMR} \text{(CDCl}_3 \)) \( \delta \) 5.8 (m, 1 \( \text{H}, \text{H}_6 \)), 5.1 (m, 2 \( \text{H}, \text{H}_7 \)), 3.7 (broad m, 1 \( \text{H}, \text{H}_4 \)), 3.0 (dq, \( \text{J}=2.5, 5.5 \text{ Hz}, 1 \text{ H}, \text{H}_2 \)), 2.66 (dd, \( \text{J}=2.5, 4.4 \text{ Hz}, 1 \text{ H}, \text{H}_3 \)), 2.44 (broad, 1 \( \text{H}, -\text{OH} \)), 2.3 (m, 2 \( \text{H}, \text{H}_5 \)), 1.24 (d, \( \text{J}=5.5 \text{ Hz}, 3 \text{ H}, \text{H}_1 \)); \(^{13}\text{C NMR} \text{(CDCl}_3 \)) \( \delta \) 133.5, 117.0, 68.5, 61.1, 51.4, 37.9, 16.7; IR (neat) cm⁻¹
3100-3700 (broad OH), 3070, 2990, 1640, 1430, 1375, 995, 910; mass spectrum m/e 128 (parent ion). Anal. Calcd. for \( C_7H_{12}O_2 \): C, 65.60; H, 9.44. Found: C, 65.37; H, 9.65.

**General Procedure for Mosher Ester Analyses**

A solution of 10-20 mg of the alcohol in 50 \( \mu L \) of \( CC_4 \) and 10-20 \( \mu L \) of pyridine was treated with 1.2 equiv. of the acid chloride of (-)-\( \alpha \)-methoxy-\( \alpha \)-(trifluoromethyl)phenylacetic acid ((-)-MPTA-Cl). After 12 h at room temperature the reaction was quenched with 1 mL of water and extracted with 20 mL of ether. The organic extract was washed with dilute HCl and saturated NaHCO\(_3\). The sample was dried (\( Na_2SO_4 \)), filtered, and concentrated in vacuo. The NMR analysis was performed on the crude esters. Diastereomeric ratios were calculated from integrations of signals in the 250 or 270 MHz \(^1H\) spectra.

Tabulated below are the relevant signals of the MTPA esters used in the diastereomer analyses.

**MTPA ester of Racemic** 114: \(^1H\) NMR (CDCl\(_3\)) \( \delta \) 3.53 (s, with fine coupling, -OCH\(_3\)), 1.70 (dd, \( J=1.5 \), 6.3 Hz, \( H_1 \) for the (S)-isomer), 1.66 (dd, \( J=1.5 \), 6.3 H, \( 3 H \), \( H_1 \) for the (R)-isomer); the signal for \( H_4 \) of both isomers is obscured by \( H_7 \) in the vinyl group).

**MTPA ester of (+)-115:** \( \delta \) 4.96 (ddd, \( J=4.4 \), 5.9, 7.9 Hz, \( 1 H \), \( H_4 \)), 3.53 (s, with fine coupling, -OCH\(_3\)), 2.93 (d quartet, \( J=2.0 \),
5.4 Hz, 1 H, H₂), 2.64 (dd, J=2.0, 6 Hz, 1 H, H₃), 1.21 (d, J=5.4 Hz, 3 H, H₁).

**MTPA ester of (-)-115**: δ 3.52 (s, with fine coupling, -OCH₃), 3.00 (d quartet, J=2.9, 5.4 Hz, 1 H, H₂), 2.78 (dd, J=2.0, 5.0 Hz, 1H, H₃), 1.26 (d, J=5.4 Hz, 3 H, H₁); the signal for H₄ is obscured by H₇.

**MTPA ester of racemic 117**: δ 3.52 (s, with fine coupling, -OCH₃), 1.39 (d, J=6.4 Hz, 3 H, H₁ of (R)-isomer); 1.32 (d, J=6.2 Hz, 3 H, H₁ of (S)-isomer); the resonances for H₂ of both isomers are obscured by olefinic signals.

**MTPA ester of (+)-118**: δ 3.54 (s, with fine coupling, -OCH₃), 2.91 (dt, J=2.0, 5.4 Hz, 1 H, H₄), 2.74 (dd, J=2.0, 5.2 Hz, 1 H, H₃), 1.39 (d, J=6.6 Hz, 3 H, H₁); the signal for H₂ overlaps with H₇.

**MTPA ester of (-)-118**: δ 3.53 (s, with fine coupling, -OCH₃), 3.00 (dt, J=2.0, 5.4 Hz, 1 H, H₄), 2.85 (dd, J=2.0, 5.0 Hz, 1 H, H₃), 1.31 (d, J=6.6 Hz, 3 H, H₁); the signal for H₂ overlaps with H₇.

(-)-Lyxo-2,3-Epoxyhept-6-en-4-ol ((-)-115): Kinetic Resolution of Partially Resolved (-)-114

A solution of 1.5 mL (5.0 mmol) of Ti (O^iPr)₄ and 1.3 mL
(7.5 mmol) of (+)-diethyl tartrate in 200 mL of dry CH₂Cl₂ was cooled to -20°C. The pale yellow solution was stirred for 15 min, and then 2.24 g (20 mmol) of 72% ee (-)-114 and 3.2 mL of 4.96 M TBHP in CH₂Cl₂ (15.8 mmol, 0.80 equiv.)⁶³ were added. The reaction mixture was stored in a -20°C freezer for 52 h, and then was worked up using the procedure described above for the preparation of (+)-115. The crude product (3.3 g) was distilled in vacuo to give 2.55 g of volatile products ((-)-115 and residual 114) and 1.48 g of recovered DET (94%). The mixture containing (-)-115 was purified by flash chromatography (170 g silica gel, 2:1 hexane-ether, 25 mL fractions). Fractions 18-30 afforded 393 mg (17%) of recovered 114 and fractions 31-70 afforded 1.91 g (75%) of chromatographically homogeneous (-)-115 (92% ee by Mosher ester analysis).

Lyxo-2,3-Epoxy-4-O-(N-phenylcarbamoyl)-hept-6-ene (93)

A solution of 4.7 g (36.7 mmol) of (+)-115 (containing 5% of the three-epoxide isomer)⁶³ in 40 mL of pyridine and 200 mL of dry CH₂Cl₂ was treated with 5 mL (47 mmol) of phenyl isocyanate at 23°C. Starting material was still present after 20 h by TLC analysis, so an additional portion of phenyl isocyanate (4 mL) was added. Ten hours later all volatile components were removed in vacuo and the residue dissolved in 50 mL of acetone and 14 mL of water. The solution was again evaporated, dissolved in CHCl₃, and filtered to remove insoluble diphenyl urea. The crude product was then chromatographed (200 g of silica gel, 1:1 hexane
ether) to give 9.1 g of urethanes. Crystallization of this material from ether-hexane afforded 6.55 g (72%) of pure 93, mp 57-57.5 °C, \( [\alpha]_D^{23} = +24^\circ \) (c=1.08, \( \text{CH}_2\text{Cl}_2 \)). Spectroscopic and combustion analytical data for this compound are reported above.

Additional quantities of 93 can be obtained by chromatography of the mother liquors from the above crystallization. For example, recrystallized 93 was obtained in 71% yield from a 4 mmol scale experiment. Careful chromatography to remove the threeo urethane (\( R_f = 0.56 \) vs. \( R_f = 0.62 \) for 93 in 1:1 hexane-ether) afforded an additional 18% of 93 for a total yield of 86%.

**Arabino-Hept-6-en-2,3,4-triol 3,4-Carbonate ((+)-81b)**

A solution of 5.30 g (21.5 mmol) of (+)-93 in 350 mL of dry \( \text{Et}_2\text{O} \) was cooled to -20°C (\( \text{CCl}_4 \), dry ice bath) and treated with 24 mL of 1M diethyl aluminum chloride in hexane. Starting material was completely consumed after 45 min (TLC analysis). The mixture was warmed to 23°C and 200 mL of 1N \( \text{H}_2\text{SO}_4 \) was added. The resulting two-phase mixture was stirred vigorously for 2 h, and then the layers were separated. The aqueous phase was extracted with \( \text{CH}_2\text{Cl}_2 \) (5x70 mL). The combined extracts were dried (\( \text{Na}_2\text{SO}_4 \)), filtered, concentrated in vacuo, and chromatographed (300 g silica gel, 1:1 ether-hexane) to give 3.43 g (93%) of pure (+)-81b (\( [\alpha]_D^{23} = +59.4^\circ \) (c = 8.8, \( \text{CH}_2\text{Cl}_2 \))). Spectroscopic and combustion analytical data for this compound are reported above.
Ribo-Hept-6-en-2,3,4-triol (116)

A solution of 644 mg (5.03 mmol) of (-)-115 in 30 mL of Me₂SO was treated with 10 mL of 1N H₂SO₄ for 20h at 23°C. The solution was diluted with 40 mL of methanol and filtered through a column of 40 cm³ (wet volume) of DOWEX 1-X8 ion exchange resin (pretreated with 5N NaOH and washed with methanol). An additional 100 mL of methanol was used to ensure that all of 116 had been removed from the column. The filtrate was concentrated in vacuo (high vacuum used to remove Me₂SO) to give 1 g of crude product. This material was purified by flash chromatography (170 g silica gel, 3:1 EtOAc-hexane, Rf 0.08 with 1:1 EtOAc-hexane as eluent) to give 660 mg (89%) of white solid: m.p. 54-55°C; [α]²²D = -19.3° (c=5.15, acetone); lit. rotation for (+)-15, [α]²⁰D = +20.1° (c=1, EtOH); H NMR (CDCl₃, D₂O exchange) δ 5.85 (m, 1 H, H₆), 5.2 (m, 2 H, H₇), 3.95 (quintet, J=6.4 Hz, 1 H, H₂), 3.69 (dt, J=2.9, 6.4 Hz, 1 H, H₄), 3.44 (t, J=6.4 Hz, 1 H, H₃), 2.57 (d multiplet, J=14.6 Hz with fine splitting, 1 H, H₅), 2.2 (ddd, J=6.3, 8.8, 14.2 Hz, 1 H, H₅), 1.25 (d, J=6.4 Hz, 3 H,H₁), IR (CH₂Cl₂) cm⁻¹ 3100-3600 (broad OH), 3080, 2960, 1640, 1050, 990, 920. High resolution mass spectrum (no parent ion observed).


2,6-Dideoxy-D-ribo-hexose (digitoxose, (+)-4)

A solution of 317 mg (2.17 mmol) of ribo-triol 116 in 50 mL of methanol was ozonized using the procedure described for preparation of (+)-17. The crude product was purified by flash
chromatography (200 g silica gel, 10% EtOH in CH₂Cl₂) to yield 254 mg (79%) of pure, crystalline digitoxose. After recrystallization from EtOAc and drying over P₂O₅ the sample had m.p. 102-103°C and [α]²²_D = + 48.8° (c=1.3, H₂O, equilibrated). An authentic sample obtained from commercial sources had mp 105-106°C and [α]²⁵_D = + 47.3° (c=1.3, H₂O). The following values have previously been reported for natural digitoxose:¹¹⁰ mp 110°C and [α]²⁰_D = + 46.3°; mp 108-110°C and [α]¹⁹_D = + 50.2°; and mp 105-108°C and [α]²²_D = + 47.8°. Spectroscopic data: ¹H NMR (D₂O, a 2:1 mixture of pyranose β and α anomers plus minor amounts of furanose anomers); β-anomer: δ 4.91 (dd, J=2.5, 9.8 Hz, 1 H, H₁), 3.9 (m, 1 H, H₃), 3.64 (d quartet, J=6.1, 9.8 Hz, 1 H, H₅), 3.12 (dd, J=3.1, 9.8 Hz, 1 H, H₄), 1.86 (ddd, J=2.5, 3.6, 13.5 Hz, 1 H, H₂a), 1.53 (ddd, J=3.1, 9.8, 13.5 Hz, 1 H, H₂e), 1.03 (d, J=6.1 Hz, 3 H, H₆); α-anomer: δ 4.97 (t, J=3 Hz, 1 H, H₁), 3.9 (m, 1 H, H₃), 3.6 (m, 1 H, H₅), 3.19 (dd, J=3.1, 8.5 Hz, 1 H, H₄), 1.9 (m, 1 H, H₂a), 1.69 (d, fine coupling, J=14 Hz, 1 H, H₂e), 0.98 (d, J=7.3 Hz, 3 H, H₆).¹³C NMR (D₂O) β anomer: δc 92.1, 73.1, 70.1, 68.2, 39.2, 18.2; α anomer: δc 91.6, 72.7, 70.9, 65.6, 39.6, 17.8.

(E)-Hepta-1,4-dien-6-ol (117)

To a 0°C suspension of 12 g (310 mmol) of LiAlH₄ in 275 mL of THF was added dropwise a solution of 11.0 g (100 mmol) of racemic ¹⁰⁷ over a 30 min period. The resulting mixture was then heated to reflux for 4.5 h.¹²⁷ The mixture was then cooled to 0°C
and the reaction terminated by the careful, dropwise addition of 50 mL of H₂O. The pale grey suspension was allowed to warm to 23°C and then 30 mL of 1N NaOH was added slowly, with stirring, to give a grainy, white precipitate. The suspension was filtered through a pad of Celite and washed with five 50 mL portions of Et₂O. The filtrate and washes were dried (MgSO₄), filtered, concentrated in vacuo and distilled to give 9.1 g (82%) of pure 117: bp 78°C, 25 mm Hg; ¹H NMR (CDCl₃) δ 5.7-5.85 (m, 1 H, H₂), 5.4-5.7 (m, 2 H, H₄ and H₅), 4.9-5.05 (m, 2 H, H₁), 4.23 (broad quintet, J=6.4 Hz, 1 H, H₆), 2.73 (broad t, J=6 Hz, 2 H, H₃), 1.94 (broad, 1 H, -OH), 1.21 (d, J=6.4 Hz, 3 H, H₇); IR (neat) cm⁻¹ 3100-3700 (broad OH); 3070, 2960, 1640, 1055, 965, 910; mass spectrum m/e 112 (parent ion); Anal. Calcd. for C₇H₁₂O: C, 74.95; H, 10.78. Found: C, 74.85; H, 11.00.

(+)-Arabino-3,4-Epoxypept-6-en-2-ol ((+)-73). Kinetic Resolution of 117

A solution of 1.6 mL (7.5 mmol) of (-)-DIPT and 1.5 mL (5 mmol) of Ti (O⁻Pr)₄ in 50 mL of dry CH₂Cl₂ was cooled to -20°C and stirred for 10 min before a solution of 4.39 g (39.2 mmol) of racemic 117 in 200 mL of dry CH₂Cl₂ was added. Finally, 5.0 mL of 3.34 M TBHP in CH₂Cl₂ (16.7 mmol, 0.43 equiv.) was added. The reaction mixture was stored at -20°C for 5 days, and then was worked up by being poured into a precooled (-20°C) solution of 5 mL of H₂O in 300 mL of acetone. The resulting precipitate was removed by filtration through a pad of Celite, and the solvents
removed in vacuo to give 6 g of crude product. This material was purified by flash chromatography (300 g silica gel, 7:3 hexane-EtOAc, 50-mL fractions). Fractions 13-21 contained dienol and DIPT and were concentrated to give 2.5 g of material which was distilled (kugelrohr, 90°C, 25 mm Hg) to give 1.71 g (39%) of (-)-117 ([α]$_D^{31}$ = -7.2° (c=12.1, CH$_2$Cl$_2$), 90% ee by Mosher ester analysis) with 524 mg (29%) of DIPT remaining in the pot. Fractions 22-50, which contained epoxyalcohol and DIPT, afforded 3.2 g of material which was dissolved in 75 mL of ether and 75 mL of saturated brine. This mixture was vigorously stirred, cooled to 0°C, and treated with 15 mL of 15% NaOH solution. Two hours later the phases were separated and the aqueous extracted with CH$_2$Cl$_2$ (3x20 mL). The combined extracts were dried (Na$_2$SO$_4$), filtered, concentrated, and distilled (kugelrohr, 95°C, 25 mm Hg) to give 2.03 g, (40%) of (+)-73: [α]$_D^{30}$ = +2.8° (c=12.5, CH$_2$Cl$_2$), 90% ee by Mosher ester analysis; $^1$H NMR (CDCl$_3$) δ 5.75 (m, 1 H, H$_6$), 5.1 (m, 2 H, H$_7$), 3.87 (broad m, J=3 Hz, 1 H, H$_2$), 3.01 (dt, J=2.3, 5.5 Hz, 1 H, H$_4$), 2.73 (t, J=2.3 Hz, 1 H, H$_3$), 2.5 (broad d, J=2.4 Hz, 1 H, -OH), 2.27 (m, 2 H, H$_5$), 1.17 (d, J=6.4 Hz, 3 H, H$_1$); $^{13}$C NMR (CDCl$_3$) δ 132.7, 117.1, 65.1, 61.1, 54.2, 35.4, 18.8; IR (neat) cm$^{-1}$ 3100-3700 (broad OH), 3080, 2980, 1640, 995, 915; mass spectrum m/e 110 (M$^+$-H$_2$O). Anal. Calcd. for C$_7$H$_{12}$O$_2$: C, 65.60; H, 9.44. Found: C, 65.65; H, 9.52.
(-)-Arabino-3,4-Epoxyhept-6-en-2-ol(-)-73. Epoxidation of Partially Resolved (-)-117.

By the usual procedure, 1.52 g (13.6 mmol) of 90% ee (-)-117 was epoxidized by using 650 mg (2.8 mmol) of L-(+)-Dipt, 0.55 mL (1.85 mmol) of Ti (O^tPr)_4 and 3.2 mL of 3.34 M TBHP solution in 80 mL of dry CH_2Cl_2 at -20°C for 90 h. The crude product was dissolved in 60 mL of ether and treated with a mixture of 60 mL of saturated brine and 3 mL of 40% NaOH at 0°C for 45 min with vigorous stirring to hydrolyze the tartrate ester. The aqueous phase was then extracted with CH_2Cl_2 (4x25 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. Chromatography of the crude product (130 g silica gel, 7:3 hexane- EtOAc) afforded 156 mg (10%) of recovered 117 and 1.92 g of (-)-73, which was distilled (kuigelrohr, 95°C, 25 mm Hg) to yield 1.32 g (76%) of (-)-73 ([α]_D^{30} = -2.4° (c=12.6, CH_2Cl_2)). 113 This sample was 92% optically pure as determined by the Mosher ester analysis.

Arabino-3,4-Epoxy-2-0-(N-phenylcarbamoyl)-hept-6-ene (85)

Epoxide (+)-73 (1.84 g, 14.4 mmol, containing approximately 5% of the threo-isomer) 113 was treated with phenyl isocyanate (33 mmol, added in two batches) in 15 mL of pyridine according to the procedure described for preparation of (+)-93. The crude product (5.8 g) was chromatographed on 120 g of silica gel using 2:1 hexane-ether as eluent to give 3.54 g chromatographically homogeneous phenyl urethane. This sample was recrystallized from
ether-hexane (two crops) to give a total of 2.81 g (79%) of pure 85, mp 55.5-56°C; \([\alpha]^{22}_D=+27^\circ\) (c=4.25, CH₂Cl₂). Spectroscopic and combustion analytical data for this compound are recorded above. The mother liquors contained additional 85 (R_f=0.62, 1:1 ether-hexane) along with the three-isomer 84 (R_f=0.60 in the same solvent system).

Lyxo-Hept-6-en-2,3,4-triol 2,3-Carbonate (90)

A solution of 2.40 g (9.72 mmol) of urethane 85 in 200 mL of Et₂O at -20°C was treated with 12 mL of 1M diethylaluminum chloride (12 mmol) in hexane. The reaction was judged complete by TLC analysis after 30 min. The solution was removed from the cooling bath and 200 mL of 1N H₂SO₄ was added. The initially-formed precipitate redissolved after a few minutes and the two-phase system was stirred vigorously for 2 h. The aqueous phase was then extracted with CH₂Cl₂ (5 x 50 mL). The combined extracts were dried (Na₂SO₄), filtered, and concentrated in vacuo to yield 1.73 g of crude 90. This material was purified by flash chromatography on 140 g of silica gel (3:7 hexane-EtOAc; 100 mL fractions) to give 1.66 g (99%) of pure 90 ([\alpha]^{26}_D=37.9°) (c=3.6, CH₂Cl₂) from fractions 4-9. Spectroscopic and combustion analytical data for this compound are reported above.

Lyxo-Hept-6-en-2,3,4-triol (118)

A solution of 622 mg (3.62 mmol) of 90 in 5 mL of 0.2 N NaOMe in MeOH was heated to reflux for 48 h. The reaction
mixture was then passed through 14 cm$^3$ (wet volume) of DOWEX 50W-X8, H$^+$ ion exchange resin. An additional 75 mL of methanol was used to ensure complete elution of the product.

Concentration of the filtrate in vacuo afforded 503 mg (95%) of pure lyxo-triol (118): m.p. 45-46 °C; $[\alpha]_D^{20} = +13.9^\circ$ (c=1.0, EtOH); a value of $[\alpha]_D = -1.4^\circ$ (c=1, EtOH) has previously been reported$^{89f}$ for the L-enantiomer; $^1$H NMR (CDCl$_3$, D$_2$O exchanged) $\delta$ 5.8 (m, 1 H, H$_6$), 5.1 (m, 2 H, H$_7$), 4.0 (d quartet, J=3, 6.4 Hz, 1 H, H$_2$), 3.73 (dt, J=4.2, 8 Hz, 1 H, H$_4$), 3.26 (dd, J=3, 4.2 Hz, 1 H, H$_3$), 2.28 (m, 2 H, H$_5$), 1.18 (d, J=6.4 Hz, 3 H, H$_1$); IR (CH$_2$Cl$_2$) cm$^{-1}$ 3100-3700 (broad OH), 3050, 2990, 2940, 1640, 1250, 990, 920.

2,6-Dideoxy-D-lyxo-hexose ((+)-20 Oliose)

A solution of 460 mg (3.15 mmol) of the lyxo-triol 118 in 40 mL of MeOH was ozonized at -20°C according to the procedure described for preparation of (+)-17. The crude product was chromatographed on 90 g of silica gel using 10% EtOH in CH$_2$Cl$_2$ as eluent to give 380 mg (82%) of pure (+)-20 ($R_f$=0.15): $[\alpha]_D^{23} = +48.8^\circ$ (c=1, H$_2$O, equilibrated); lit.$^{36a}$ $[\alpha]_D^{23} = +46^\circ$ (c=0.7, H$_2$O); lit.$^{36b}$ for the L-enantiomer, $[\alpha]_D^{23} = -51.5^\circ$ (c=1, H$_2$O, equil.); $^1$H NMR (D$_2$O) ~1:1 mixture of $\alpha:\beta$ pyranose anomers: $\beta$-anomer: $\delta$ 4.58 (dd, J=1.6, 9.8 Hz, 1 H, H$_1$), 3.64 (ddd, J=3.0, 4.7, 12.0 Hz, 1 H, H$_3$), 3.44 (broad quartet, J=6.6 Hz, 1 H, H$_5$), 3.35 (s, with fine coupling, 1 H, H$_4$), 1.6 (m, 1 H, H$_{2e}$), 1.41 (dt, J=9.8, 12.0 Hz, 1 H, H$_{2a}$), 1.01 (d, J=6.6 Hz, 3 H, H$_6$); $\alpha$ anomer: $\delta$ 5.12 (broad s, 1 H, H$_1$), 3.90 (broad quartet, J=6.6 Hz, 1 H, H$_5$), 3.86
(ddd, J=2.8, 6.4, 11.3 Hz, 1 H, H₃), 3.45 (broad s, 1 H, H₄), 1.7 (m, 1 H, H₂a), 1.6 (m, 1 H, H₂e), 0.98 (d, J=6.6 Hz, 3 H, H₆).

¹³C NMR (D₂O) β-anomer: δ₉4.3; 71.4; 70.2, 68.9, 35.4, 16.8;  
α-anomer: δ 92.0; 71.2, 67.3, 65.5, 32.4, 16.8.

Ribo-4-Methoxyhept-6-en-2,3-diol (119)

A solution of 44 mg (0.34 mmol) of pure (+)-73 and 5 mg of p-toluenesulfonic acid monohydrate in 2 mL of absolute MeOH was heated to reflux for 24 h. The solvent was removed in vacuo and the crude product was chromatographed on 30 g of silica gel (1% MeOH-CH₂Cl₂, 3 mL fractions). Fractions 65-105 afforded 46 mg (84%) of crystalline 119, mp 54-55°C.

A larger-scale experiment using 698 mg (5.45 mmol) of (+)-73 contaminated with approximately 5% of the threo-epoxide isomer 113 afforded 543 mg (62%) of pure 119. Fractions contaminated with products deriving from the threo-epoxide present in the starting material were also obtained, but were very difficult to separate efficiently by chromatography.

Data for 119: [α]D²² = +37.0° (c=1.28, CH₂Cl₂); ¹H NMR (CDCl₃, D₂O exchange) δ 5.87 (m, 1 H, H₆), 5.0-5.2 (m, 2 H, H₇), 3.88 (d quartet, J=3, 6 Hz, 1 H, H₂), 3.56 (t, J=3 Hz, 1 H, H₃), 3.3 (m, 4 H, H₄ and -OCH₃), 2.3-2.55 (m, 2 H, H₅), 1.20 (w, J=6 Hz, 3 H, H₁); IR (CH₂Cl₂) cm⁻¹ 3200-3700, 3080, 2930, 1640, 1090, 915; mass spectrum m/e 119 (M⁺ - C₃H₅). Anal. Calcd. for C₈H₁₆O₃: C, 59.98; H, 10.19. Found: , 60.13; H, 10.19.
2,6-Dideoxy-3-O-methyl-D-ribo-hexose (19, D-cymarose)

A solution of 522 mg (3.26 mmol) of methoxy diol in 50 mL of methanol was ozonized at -20°C by using the procedure described for preparation of (+)-17. Chromatography of the crude product on 130 g of silica gel (5% EtOH in CH₂Cl₂) afforded 470 mg (89%) of crystalline 19 (Rᵢ=0.61, 10% EtOH-CH₂Cl₂).

Recrystallization of this material from ether-pentane afforded colorless crystals, mp 84-85°C (after being dried over P₂O₅): [α]₂⁰_D = + 48.9° (c=0.7, H₂O, equilibrated), prepared from 90% e.e. [α]¹⁴_D = + 54.9° (c=0.58, H₂O). ¹H NMR (CDCl₃) ~1:1 mixture of α:β pyranose epimers and smaller amounts of furanoses; β-anomer: δ 4.9 (broad d, J=8.5 Hz, 1 H, H₁), 3.9 (m, 1 H, H₂), 3.6 (m, 1 H, H₅), 3.37 (s, 3 H, -OCH₃), 3.17 (dt, J=3.4, 8 Hz, H₄), 2.26 (broad d, J=14 Hz, 1 H, H₂e), 1.47 (ddd, J=2.6, 9.8, 14.1 Hz, 1 H, H₂a), 1.22 (d, J=6.0 Hz, 3 H, H₆); α anomer: δ 5.03 (broad t, 1 H, H₁), 3.9 (m, 1 H, H₃), 3.6 (m, 1 H, H₅), 3.4 (m, 1 H, H₄), 3.30 (s, 3 H, -OCH₃), 2.1 (m, 1 H, H₂a), 1.70 (dt, J=1.7, 14.5 Hz, 1 H, H₂e), 1.15 (d, J=6.0 Hz, 3 H, H₆); ¹³C NMR (D₂O) β anomer: δₗ₉ 88.0, 78.0, 73.1, 67.6, 57.8, 35.4, 18.3; α-anomer: δₗ₉ 92.1, 81.7, 80.9, 68.2, 57.0, 39.0, 18.7.
Experimental Procedures for Chapter IV

Ribo-4-Azidohept-6-en-2,3-diol (120a)

A solution of 97 mg (0.76 mmol) of (+)-73, 275 mg (4.2 mmol) of NaN₃ and 90 mg (1.7 mmol) of NH₄Cl in 8 mL of 8:1 methoxyethanol - H₂O was heated to reflux for 6 h. The dark solution was then cooled, diluted with 3 mL of MeOH, and neutralized with saturated aqueous NaHCO₃ solution. Solvents were removed in vacuo, and the residue dissolved in EtOAc and filtered through 20 g of silica gel. This procedure afforded 120 mg of crude 120a which was used directly in the next experiment. Pure 120a was obtained in 78% yield from a similar experiment following silica gel chromatography: mp 66-67°C; [α]D²³=-62.5°C (c=0.28, CH₂Cl₂); ¹H NMR (CDCl₃, D₂O exchange) δ 5.8 (m, 1 H, H₆), 5.19 (broad d, J=18 Hz, 1 H, H₇E), 5.13 (broad d, J=10 Hz, 1 H, H₇E), 3.90 (d quartet, J=4.1, 6.3 Hz, 1 H, H₂), 3.50 (dd, J=4.1, 7.5 Hz, 1 H, H₃), 3.3 (m, 1 H, H₄), 2.5-2.7 (d with fine splitting, J=14.6 Hz, H₅), 2.35 (dt, J=7.5, 14.6 Hz, 1 H, H₅), 1.15 (d, J=6.3 Hz, 3 H, H₁); IR (CH₂Cl₂) cm⁻¹ 3100-3700 (broad OH), 3080, 2980, 2920, 2100, 1640, 1380, 1065, 990, 920; mass spectrum m/e 171 (parent ion). Anal. Calcd. for C₇H₁₃N₃O₂: C, 49.11; H, 7.65; N, 24.54. Found: C, 49.10; H, 7.51; N, 24.42.

The crude azide from the preceding experiment was dissolved in 15 mL of CH₂Cl₂ and treated with 0.4 mL of pyridine and 1.6 mL of Ac₂O at room temperature for 16 h. Analysis of the crude product by 250 MHz ¹H NMR revealed that only one isomer
was present. The crude product was purified by preparative TLC (0.5-mm silica gel plate, 2:1 hexane-Et$_2$O, two developments, Rf 0.7) to yield 105 mg (54% from 73) of the azido diacetate: $[\alpha]_{D}^{19} = +36.5^\circ$ (c=3.52, CH$_2$Cl$_2$); $^1$H NMR (CDCl$_3$) $\delta$ 5.72 (m, 1 H, H$_6$), 5.0-5.2 (m, 4 H, H$_2$, H$_3$ and H$_7$), 3.43 (ddd, J=4.3, 6.1, 9.2 Hz, H$_4$), 210-2.4 (m, 2 H, H$_5$), 2.04 (s, 3 H, acetate), 1.94 (s, 3 H, acetate), 1.19 (d, J=6.2 Hz, 3 H, H$_1$); IR (CH$_2$Cl$_2$) cm$^{-1}$ 3080, 2940, 2110, 1740, 1640, 1370, 1225, 1020, 920; mass spectrum m/e 256 (N$^+$ + 1).

**Ribo-4-Benzylaminoohept-6-en-2,3-diol (121)**

A resealable Carius tube was charged with 490 mg (3.83 mmol) of (+)-73, 0.42 mL (3.85 mmol) of benzylamine, 32 mg (0.34 mmol) of phenol, and 0.19 mg (0.04 mmol) of BHT. The tube was purged with argon and heated to 145°C for 86 h. The crude product was dissolved in CH$_2$Cl$_2$ and concentrated in vacuo to give 971 mg of crude product. Recrystallization of this sample from Et$_2$O-CCl$_4$ afforded 366 mg, mp 62-64°C, of pure 121 as bulky plates. The mother liquors were chromatographed on 90 g of silica gel (4% MeOH in CH$_2$Cl$_2$) to afford an additional 448 mg (814 mg total, 91% yield) of crystalline 121: $[\alpha]_{D}^{20} = +27^\circ$ (c=1.2, EtOH); $^1$H NMR (CDCl$_3$) $\delta$ 7.3 (s, 5 H, aromatic), 5.76 (m, 1 H, H$_6$), 5.13 (m, 2 H, H$_7$), 3.83, 3.75 (AB, J=12.6 Hz, 2 H, benzylic), 3.76 (m, 1 H, H$_2$), 3.28 (t, J=6.8 Hz, 1 H, H$_3$), 2.89 (dt, J=4.1, 6.8 Hz, 1 H, H$_4$), 2.3-2.6 (m, 2 H, H$_5$), 1.24 (d, J=6.2 Hz, 3 H, H$_1$); IR (CH$_2$Cl$_2$) cm$^{-1}$ 3100-3700 (broad NH and OH), 3070, 3030,
2920, 1640, 1607, 1500, 1455, 1070, 995, 920; mass spectrum m/e 236 (M⁺ + 1). Anal. Calcd. for C₁₄H₂₁NO₂: C, 71.45; H, 8.99; N, 5.95. Found: C, 71.58; H, 8.80; N, 5.95.

**Ribo-4-(N-Carbomethoxy)benzylaminohept-6-en-2,3-diol (122)**

A solution of 613 mg (2.61 mmol) of 121 and 0.22 mL (2.85 mmol) of ClCOOMe in 25 mL of CH₂Cl₂ was treated with 2 g solid K₂CO₃. After 90 min of vigorous stirring at 23°C, the K₂CO₃ was removed by filtration through a Celite pad and the filtrate was concentrated in vacuo to afford 730 mg of crude product. Flash chromatography on 150 g of silica gel (2% MeOH in CH₂Cl₂) provided 629 mg (82% yield) of pure 122: [α]D²⁶ = -10.4° (c=0.97, CH₂Cl₂); ¹H NMR (CDCl₃, D₂O exchange) δ 7.2-7.4 (m, 5 H, aromatic), 5.73 (m, 1 H, H₆), 5.09 (br d, J= 18.3 Hz, 1 H, H₇), 5.03 (br d, J=10.4 Hz, 1 H, H₇'), 4.78 and 4.09 (AB, J=15.4 Hz, 2 H, benzylic ), 3.79 (s, 3 H, OCH₃); 3.56 (m, 2 H, H₂ and H₄), 3.45 (br d, J=6 Hz, 1 H, H₃), 2.79 (m, 1 H, H₅), 2.4 (br dt, J=5, 14.4 Hz, 1 H, H₅'), 1.0 (d, J= 6.2 Hz, 3 H, H₁); IR (CH₂Cl₂) cm⁻¹ 3100-3700 (broad OH), 3080, 2960, 1675, 1640, 1470, 1360, 1235, 990, 920; mass spectrum m/e 293 (parent ion).

**Ribo-2,3-dihydroxy-4-benzylaminohept-6-enyl-3,4-carbamate (123)**

A mixture of 521 mg (1.78 mmol) of 122, 2 g of K₂CO₃ and 50 mL of toluene were heated to reflux for 70 h. The K₂CO₃ was removed by filtration through cotton and the filtrate was concentrated in vacuo to give 448 mg of crystalline material.
Recrystallization of this sample from Et₂O-CCl₄ afforded 297 mg, mp 123-124°C, of pure 123 as fine prisms. The mother liquors were chromatographed on a 1.5 mm silica gel TLC plate (2% MeOH in CH₂Cl₂, 3 developments) to yield an additional 42 mg (339 mg total, 73% yield) of 123 and 43 mg (9% yield) of 124.

Data for 123: [α]D²¹ = +4.1° (c=3.9, CH₂Cl₂); ¹H NMR (CDCl₃) δ 7.2-7.4 (m, 5 H, aromatic), 5.76 (m, 1 H, H₆), 5.15-5.25 (m, 2 H, H₇), 4.84 (A of AB, J=15.3 Hz, 1 H, benzylic), 4.0-4.2 (m, 3 H, H₃, H₄ and H₈), 3.70 (br q, J=5.3 Hz, 1 H, H₂), 2.51 (dd, J=5.3, 6.6 Hz, 2 H, H₅), 1.5-1.8 (broad, 1 H, -OH), 1.35 (d, J=5.3 Hz, 3 H, H₁); IR (CH₂Cl₂) cm⁻¹ 3300-3700 (broad OH), 3030, 2935, 1750, 1640, 1495, 1410, 1060. Anal. Calcd. for C₁₅H₁₉NO₃: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.71; H, 7.06; N, 5.34.

Ribo-2,3-dihydroxy-4-benzylaminohept-6-enyl-2,4-carbamate (124)

Prepared in 9% yield in the procedure above. Data for 124; ¹H NMR (CDCl₃) δ 7.2-7.4 (m, 5 H, aromatic), 5.7 (m, 1 H, H₆), 5.0-5.2 (m, 2 H, H₇), 4.77 (A of AB, J=15.3 Hz, 1 H, benzylic), 4.60 (dq, J=5.0, 6.3 Hz, 1 H, H₂), 4.18 (B of AB, J=15.3 Hz, 1 H, benzylic), 3.83 (dd, J=1.8, 5.3, 7.3 Hz, 1 H, H₄), 3.10 (dd, J=1.8, 5.0 Hz, 1 H, H₃), 2.0-2.2 (m, 2 H, H₅), 1.27 (d, J=6.3 Hz, 3 H, H₁).
N-benzylristosamine-3,4-carbamate (125a)

A solution of 36.5 mg (0.14 mmol) of 123 in 4 mL of absolute MeOH was cooled to -20°C and treated with O₃ for 1 min. Following the standard (CH₃)₂S workup, the solvent was removed in vacuo to afford 63 mg of crude product. Preparative TLC (0.5 mm silica gel, 4% MeOH in CH₂Cl₂, 2 developments, Rf = 0.62) afforded 33 mg (0.125 mmol) of 125a (89% yield). ¹H NMR (CDCl₃) a 1:1 mixture of α- and β-pyranose anomers: β-anomer: δ 7.2-7.4 (m, 5 H, aromatic), 5.12 (ddd, J=3.6, 5.3, 6.7 Hz, 1 H, H₁), 4.79 (A of AB, J=15.2 Hz, 1 H, benzylic), 4.15 (B of AB, J=15.2 Hz, 1 H, benzylic), 4.05 (m, 1 H, H₃), 3.9 (m, 1 H), H₄), 3.6 (m, 1 H, H₅), 1.7-2.2 (m, 2 H, H₂), 1.27 (d, J=6 Hz, 3 H, H₆); α-anomer: δ 7.2-7.4 (m, 5 H, aromatic), 4.95 (ddd, J=2.4, 4.5, 7 Hz, 1 H, H₁), 4.67 (A of AB, J=15.2 Hz, 1 H, benzylic), 4.04 (B of AB, J=15.2 Hz, 1 H, benzylic), 4.05 (m, 1 H, H₃), 3.6 (m, 2 H, H₄ and H₅), 1.7-2.2 (m, 2 H, H₂), 1.29 (d, J=6 Hz, 3 H, H₆); IR (CH₂Cl₂) cm⁻¹ 3100-3700 (broad OH), 3060, 2940, 1755, 1499, 1405, 1310, 1090; mass spectrum m/e 263 (parent ion).

Methyl N-benzylristosaminoside-3,4-carbamate (125b)

A solution of 177 mg (0.68 mmol) of 123 in 10 mL of absolute MeOH was treated with O₃ under the standard conditions. After workup, the crude 125a was dissolved in 5 mL of MeOH and treated with 20 mg of p-TsOH and 100 mg (0.9 mmol) of HC(OMe)₃ for 20h at 23°C. The methanol was removed in vacuo
and the remainder was dissolved in CH₂Cl₂ and filtered through Florisil. Concentration of the filtrate in vacuo afforded 224 mg of crude product. Flash chromatography on 30 g of silica gel (2% MeOH in CH₂Cl₂) afforded 178 mg of 125b (95% yield):

1H NMR (CDCl₃) 1.5:1 mixture of β- and α-anomers: β-anomer: δ 7.2-7.4 (m, 5 H, aromatic), 4.62 (A of AB, J=15.4 Hz, 1 H, benzylic), 4.60 (t, J=5.6 Hz, 1 H, H₁), 4.03 (B of AB, J=15.4 Hz, 1 Hz, benzylic), 4.0 (m, 1 H, H₃), 3.9 (m, 1 H, H₄), 3.6 (m, 1 H, H₅), 3.30 (s, 3 H, -OCH₃), 1.7-2.2 (m, 2 H, H₂), 1.28 (d, J=6 Hz, 3 H, H₆); α-anomer: δ 7.2-7.4 (m, 5 H, aromatic), 4.81 (A of AB, J=12.8 Hz, 1 H, benzylic), 4.47 (dd, J=2.4, 6.6 Hz, 1 H, H₁), 4.17 (B of AB, J=12.8 Hz, 1 H, benzylic), 4.0 (m, 1 H, H₃), 3.6 (m, 2 H, H₄ and H₅), 3.31 (s, 3 H, -OCH₃), 1.7-2.2 (m, 2 H, H₂), 1.30 (d, J=6 Hz, 3 H, H₆); IR (CH₂Cl₂) cm⁻¹ 2940, 1755, 1495, 1405, 1045, 905; [α]D¹⁸ = +69.3° (c=1.0, CH₂Cl₂).

Methyl ristosaminoside-3,4-carbamate (126)

A solution of 27 mg (0.1 mmol) of 125b in 5 mL of THF was cooled to -78°C and 100 mg of Na was added. Liquid NH₃ (20 mL) was condensed into the flask, resulting in a deep-blue solution. After 30 min, the reaction was quenched with solid NH₄Cl and 15 mL of THF. The reaction vessel was brought to 23°C and 10 mL of H₂O was added carefully (vigorous reaction) and the mixture was stirred for 30 min. The layers were separated and the aqueous phase was extracted with 5x10 mL of CH₂Cl₂. The
combined organic extracts were dried (Na$_2$SO$_4$), filtered and concentrated in vacuo to afford 34 mg of crude product.

Preparative TLC (0.25 mm silica gel, 2% MeOH in CH$_2$Cl$_2$, 2 developments) afforded 16.5 mg (92% yield) of 1H NMR (CDCl$_3$) 1.5:1 mixture of β- and α-anomers: β-anomer: δ 6.1 (br d, J=9 Hz, 1 H, NH), 4.67 (t, J=5.6 Hz, 1 H, H$_1$), 4.2 (m, 1 H, H$_3$), 3.9 (m, 1 H, H$_4$), 3.6 (m, 1 H, H$_5$), 3.33 (s, 3 H, -OCH$_3$), 1.7-2.2 (m, 2 H, H$_2$), 1.30 (d, J=6 Hz, 3 H, H$_6$);

α-anomer: δ 6.1 (br d, J=9 Hz, 1 H, NH), 4.3 (m, 1 H, H$_1$), 4.2 (m, 1 H, H$_3$), 3.9 (m, 1 H, H$_4$), 3.40 (s, 3 H, -OCH$_3$), 3.3 (m, 1 H, H$_5$), 1.7-2.2 (m, 2 H, H$_2$), 1.32 (d, J=6 Hz, 3 H, H$_6$).

Arabino-6-Benzylxoxy-2,4-dihydroxy-3-(N-phenylamino)-hexyl 3,4-Carbamate (127)

A solution of 26 mg of (0.076 mmol) of 79a in 5 mL of THF was treated with 9 mg of 50% NaH-oil dispersion. The resulting suspension was stirred at 23°C for 2 h, at which point 8 mL of CH$_2$Cl$_2$ and 3 mL of 15% NH$_4$Cl solution were added. The aqueous layer was separated and extracted with CH$_2$Cl$_2$ (2x). The combined extracts were dried (Na$_2$SO$_4$), filtered and concentrated to afford 33 mg of a pale yellow solid. This crude material was crystallized from CCl$_4$ to yield 24 mg (95%) of white crystals: mp 128-129.5°C; 1H NMR (CDCl$_3$) δ 7.3 (m, 10 H, aromatic), 4.84 (m, 1 H, H$_4$), 4.53, 4.52 (AB, J$_{AB}$ = 12 Hz, 2 H, benzylic), 4.13 (dd, J=2.2, 4.4 Hz, 1 H, H$_3$), 4.05 (broad m, 1 H, H$_2$), 3.73 (t, J=5.9 Hz, 2 H, H$_6$), 2.1 (m, 2 H, H$_5$), 1.70 (d, J=4 Hz, 1 H, -OH), 1.15
(d, J=6.6 Hz, 3 H, H₁); IR (CH₂Cl₂) cm⁻¹ 3200-3700 (-OH), 3020, 2920, 1745, 1595, 1495. High resolution mass spectrum. Calcd. for C₂₀H₂₃NO₄: 341.16271. Found: 341.16389.

1-Phenylpent-3-yne-2-ol (145)

In a 100 mL 3-neck flask, fitted with a magnetic stirrer and a dropping funnel equipped with a dry ice/acetone condenser, 2.6 mL of 3.3 M n-butyllithium in hexane was added to 60 mL of dry THF, with cooling to -78°C. Approximately 5 mL of propyne (dried through CaCl₂ and Dehydrite) was condensed into the dropping funnel and the added dropwise to the cooled butyllithium solution. After the reaction mixture was stirred for 30 min., 1 mL of phenylacetaldehyde (8.1 mmol) was added. The reaction mixture was stirred for 2 h, gradually warming to -20°C. The reaction was quenched by the addition of 10 mL of H₂O. The resulting yellow solution was brought to 23°C and washed with 15 mL of 1N HCl, then 10 mL of water. The combined aqueous washes were extracted with 3x15 mL of CH₂Cl₂. The combined organic phases were dried (Na₂SO₄), filtered and concentrated to yield 1.48 g of crude product. This material was kugelrohr distilled at 107°/1 mm. to afford 1.15 g (88% yield) of viscous liquid, sufficiently pure for use in succeeding reactions. A small portion was further purified by preparative TLC: 290 mg of 145 applied to a 1.5 mm silica gel plate (1:1 ether/hexane, Rₛ=0.59) to yield 128 mg of 145 after kugelrohr distillation.¹H NMR (CDCl₃) δ 7.2-7.4 (m, 5 H, aromatic), 4.5 (t, fine coupling, 6.5 Hz, 1 H, H₂), 2.9 (m, 2 H, H₁), 2.3 (broad, 1 H,
-OH), 1.79 (d, J=2.0 Hz, 3 H, H₂); IR (neat) cm⁻¹ 3100-3600 (broad OH), 3030, 2920, 2235, 1605, 1495, 1455, 1030, 695;

1-Phenyl-2-phthalimidopent-3-yne (146)

To a solution of 1.5 g (9.41 mmol) of 145, 2.66 g (10.2 mmol) of triphenylphosphine, and 1.53 g (10.4 mmol) of phthalimide in 75 mL of dry THF, was added 1.8 mL (11.4 mmol) of diethyl-azodicarboxylate. The resulting yellow solution was allowed to stand for 20 h. The solvent was removed in vacuo to afford 8.9 g of semi-solid material, which was taken up in 1:1 ether/hexane. The resulting precipitate was triturated with several portions of 1:1 ether/hexane. After filtration and removal of the solvent, the filtrate afforded 6g of yellow oil. This material was flash chromatographed on 250 g of silica gel with 2:1 hexane:ether as the eluant to yield 2.88 g solid material, which was recrystallized from ether/hexane to yield 1.66 g (61%) of crystalline 146, mp 96-97°C: ¹H NMR (CDCl₃) δ 7.77 (dd, J=3.2, 5.3 Hz, 2 H, ν-H of phthalimide), 7.65 (dd, J=3.2, 5.3 Hz, 2 H, m-H of phthalimide), 7.17 (s, 5 H, phenyl), 5.21 (m, 1 H, H₂), 3.41 (dd, J=9.2, 13.6 Hz, 1 H, H₁'), 3.32 (dd, J=7.2, 13.6 Hz, 1 H, H₁'), 1.60 (d, J=2.0 Hz, 3 H, H₅); IR (CH₂Cl₂) cm⁻¹ 3050, 2930, 2240, 1780, 1720, 1495, 1470, 1385, 1350, 1100; mass spectrum m/e 289 (parent ion).
l-Phenyl-2-aminopent-3-yne (147)

A solution of 1.53 g (5.28 mmol) of 146 and 0.3 mL (6.18 mmol) of hydrazine hydrate in 45 mL of absolute EtOH was heated to reflux for 3.5 h, resulting in the formation of a white precipitate. The reaction mixture was cooled to 23°C and 6 mL of concentrated HCl was added. The precipitate was removed by filtration and the filtrate was concentrated to a solid residue. This material was taken up in 60 mL of 2:1 EtOH:H₂O. The insoluble portion was removed and the filtrate was brought to pH >10 by the addition of 1N NaOH. The solution was extracted with 7x30 mL of Et₂O. The combined extracts were dried (Na₂SO₄), filtered, and concentrated in vacuo to afford 820 mg of inhomogeneous material. Bulb-to-bulb distillation at 110°/0.7 mm afforded 708 mg (84% yield) of slightly colored liquid: ¹H NMR (CDCl₃) δ 7.2-7.3 (m, 5 H, aromatic), 3.75 (m, 1 H, H₂), 2.92 (dd, J=6.0, 13.2 Hz, 1 H, H₁), 2.77 (dd, J=7.2, 13.2 Hz, 1 H, H₁'), 1.78 (d, J=2.0 Hz, 3 H, H₅), 1.47 (broad, 2 H, -NH₂); IR (neat) cm⁻¹ 3100-3700 (broad NH₂), 3030, 2920, 2220, 1605, 1495, 1455, 695; mass spectrum m/e 159 (parent ion).

Z-1-phenyl-2-aminopent-3-ene (148)

A suspension of 481 mg of 147 and 26 mg of Lindlar catalyst in 25 mL of absolute MeOH was stirred vigorously under 1 atmosphere of hydrogen gas. After 110 min, GC analysis (9' 5% SE-30 on Chrom G, 52 psi, 150°C) showed no 147 (Tₚₕ=4.4 min) and a new peak corresponding to 148 (Tₚₕ=3.4 min). The
catalyst was removed by filtration through a Celite pad and the solvent was removed in vacuo to yield 487 mg (95% yield) of 148: $^1$H NMR (CDCl$_3$) $\delta$ 7.2-7.3 (m, 5 H, aromatic), 5.5 (dq, J=6.7, 17.4 Hz, 1 H, H$_4$), 5.35 (ddd, J=1.4, 7, 17.4 Hz, 1 H, H$_3$), 3.93 (broad q, J=7 Hz, 1 H, H$_2$), 2.7 (d, J=6.8 Hz, 2 H, H$_1$), 1.49 (dd, J=1.4, 6.7 Hz, 3 H, H$_5$); IR (neat) cm$^{-1}$ 3100-3700 (broad NH$_2$), 3020, 2920, 1650, 1600, 1495, 1455, 695.

E-1-phenylpent-2-en-4-one (149)$^{147}$

A suspension of 2.39 g (19.9 mmol) of phenylacetaldehyde and 7 g (22 mmol) of 1-triphenylphosphoranylidene-2-propanone in 250 mL of dry THF was stirred at 0°C for 135 h. The solvent was removed in vacuo and the solid residue was triturated with several portions of hexane. The hexane triturates were evaporated to yield 3.94 g of crude product. This material was flash chromatographed on 230 g of silica gel with 7:3 hexane:ether as the eluent to yield 2.83 g (89%) of 149: $^1$H NMR (CDCl$_3$) $\delta$ 7.2-7.4 (m, 5 H, aromatic), 6.96 (dt, J=6.8, 16.0 Hz, 1 H, H$_2$), 6.12 (d, fine coupling, J=16.0 Hz, 1 H, H$_3$), 3.59 (broad d, J=6.8 Hz, 2 H, H$_1$), 2.29 (s, 3 H, H$_5$); IR (CH$_2$Cl$_2$) cm$^{-1}$ 3030, 2920, 1670, 1625, 1605, 1495, 1450, 1360, 980; mass spectrum m/e 160 (parent ion).

E-1-phenylpent-2-en-4-ol (150)

A solution of 2.67 g (16.7 mmol) of 149 in 150 mL of dry Et$_2$O was cooled to -78°C and 19 mL of 1M DIBAL in hexane was added. After 30 min, the reaction mixture was brought to
23°C and stirred for 1 h. The reaction was quenched by the addition of 30 mL of MeOH. Then, just enough 6N HCl was added to dissolve the precipitate that had formed. The phases were separated and the aqueous phase was extracted with 3x30 mL of CH₂Cl₂. The combined extracts were dried (Na₂SO₄), filtered and concentrated to afford 2.57 g (95% yield) of 150: ¹H NMR (CDCl₃) δ 7.2-7.4 (m, 5 H, aromatic), 5.82 (ddt, J=0.9, 6.8, 15.2 Hz, 1 H, H₂), 5.61 (ddt, J=1.3, 6.4, 15.2 Hz, 1 H, H₃), 4.29 (quintet, J=6.4 Hz, 1 H, H₄), 3.40 (broad d, J=6.8 Hz, 2 H, H₁), 2.06 (broad, 1 H, -OH), 1.30 (d, J=6.4 Hz, 3 H, H₅); IR (CH₂Cl₂) cm⁻¹ 3100-3600 (broad OH), 3030, 2970, 1670, 1605, 1495, 1450, 1060, 970, 695; mass spectrum m/e 162 (parent ion).

E-1-phenylpent-2-enyl-4-trichloroacetimidate (151)

A solution of 2.34 g (14.4 mmol) of 150 in 16 mL of dry THF was treated with approximately 110 mg of KH (prepared from 310 mg of 35% KH in mineral oil by washing 3X with hexane). After 5 min, the dark orange solution was transferred by canulation into a solution of 1.6 mL (16 mmol) of trichloroacetonitrile in 16 mL of dry Et₂O which had been cooled to 0°C. The reaction mixture was maintained at 0°C for 1.5 h, then warmed to 23°C over 1 h. The solvent was removed and the residue was taken up in 60 mL of pentane and 0.16 mL of MeOH. The mixture was stirred vigorously for 10 min and the precipitate was removed by filtration. The solvent was evaporated to
afford 4.14 g (94% yield) of golden liquid: $^1$H NMR (CDCl$_3$)

8.29 (broad, 1 H, NH), 7.2-7.4 (m, 5 H, aromatic), 5.97 (ddt, J=0.8, 6.8, 15.2 Hz, 1 H, H$_2$), 5.65 (ddt, J=1.4, 6.3, 15.2 Hz, 1 H, H$_3$), 5.51 (quintet, J=6.3 Hz, 1 H, H$_4$), 3.40 (d, J=6.8 Hz, 2 H, H$_1$), 1.44 (d, J=6.3 Hz, 3 H, H$_5$); IR (neat) cm$^{-1}$ 3340, 3030, 2980, 1660, 1605, 1495, 1450, 1285, 1080, 965, 695, 645; mass spectrum m/e 305, 306, 307, 308 (parent ions).

E-1-Phenyl-2-amino(N-trichloroacetylpent-3-ene (152a)

A solution of 943 mg (3.1 mmol) of 151 in 10 mL of xylene was heated to reflux for 8 h. After cooling to 23°C, the brown solution was filtered through 7g of silica gel which had been packed with toluene. The silica gel was eluted with further portions of toluene until all of the product was removed. After removal of the solvents in vacuo, 1.3 g of dark gold liquid remained. This liquid was kugelrohr distilled, first at 50°/1.5 mm to remove the remaining solvent, then at 160-165°/1.1 mm to yield 771 mg (82% yield) of slightly colored liquid which solidified on cooling. The solid was recrystallized from hexane to afford 676 mg (72% yield) of white needles, mp 73-74°C: $^1$H NMR (CDCl$_3$) δ 7.2-7.4 (m, 5 H, aromatic), 6.50 (broad, 1 H, NH), 5.63 (ddq, J=0.9 Hz, 6.4, 15.2 Hz, 1 H, H$_4$), 5.41 (ddq, J=1.4, 6.2, 15.2 Hz, 1 H, H$_3$), 4.62 (m, 1 H, H$_2$), 2.96 (dd, J=6.4, 13.7 Hz, 1 H, H$_1$), 2.87 (dd, J=6.5, 13.7 Hz, 1 H, H'), 1.67 (d, fine coupling, J=6.4 Hz, 3 H, H$_5$); IR (CH$_2$Cl$_2$) cm$^{-1}$ 3410, 3040, 2920, 1715, 1505, 1440, 1245, 965, 815; mass
spectrum m/e 305, 306, 307, 308 (parent ions). Anal. Calcd. for C_{13}H_{14}Cl_{3}NO: C, 50.92; H, 4.60; N, 4.57. Found: C, 51.02; H, 4.70; N, 4.77.

**E-1-Phenyl-2-aminopent-3-ene (153)**

A solution of 1.06 g (3.44 mmol) of 152a in 16 mL of EtOH was treated with 20 mL of 5N NaOH for 3 h. The reaction mixture was diluted with 30 mL of Et_{2}O and the layers were separated. The aqueous phase was extracted with 4x20 mL of CH_{2}Cl_{2}. The combined extracts were dried (Na_{2}CO_{3}), filtered, and concentrated in vacuo to afford 505 mg of viscous oil. This material was distilled bulb-to-bulb at 90-95°/1.0 mm to give 344 mg (62% yield) of colorless 153: ^1H NMR (CDCl_{3}) 6 7.2-7.4 (m, 5 H, aromatic), 5.45-5.66 (m, 2 H, H_3 and H_4), 3.6 (m, 1 H, H_2), 2.83 (dd, J=5.1, 13.3 Hz, 1 H, H_1), 2.59 (dd, J=8.4, 13.3 Hz, 1 H, H_1), 1.70 (d, J=5.3, 3 H, H_5).

**Z-1-Phenyl-2-amino(N-benzoyl)pent-3-ene (154a)**

A solution of 45 mg (0.38 mmol) of 148 in 4 mL of CH_{2}Cl_{2} and 0.4 mL of pyridine was treated with 65 μL (0.56 mmol) of benzoyl chloride. After 14 h, 2 mL of H_{2}O was added and the result in mixture was stirred for 10 min. The mixture was diluted with 15 mL of CH_{2}Cl_{2} and the phases were separated. The organic phase was washed with 2x5 mL of 1N HCl. The combined washes were extracted with 5 mL of CH_{2}Cl_{2}. The combined organic phases were dried (Na_{2}SO_{4}), filtered and
concentrated in vacuo to yield 123 mg of crude product. The crude material was chromatographed on a 0.5 mm silica gel TLC plate (2:1 hexane:ether, 2 developments, \( R_f = 0.5 \)) to yield 81 mg of thick liquid, which was crystallized from ether/hexane to yield 53 mg (72% yield) of fine needles, mp 100.5-101.5°C: \(^1\)H NMR (CDCl\(_3\)) \( \delta \) 7.2-7.7 (m, 10 H, aromatic), 6.0 (broad d, J=10 Hz, 1 H, NH), 5.58 (dq, 6.7, 10.6 Hz, 1 H, H\(_4\)), 5.33 (ddq, J=1.6, 9.0, 10.6 Hz, 1 H, H\(_3\)), 5.16 (m, 1 H, H\(_2\)), 3.08 (dd, J=5.2, 13.3 Hz, 1 H, H\(_1\)), 2.88 (dd, J=7.3, 13.3 Hz, 1 H, H\(_1\)' ), 1.57 (dd, J=1.6, 6.7 Hz, 3 H, \( \beta \)), IR (CH\(_2\)Cl\(_2\)) cm\(^{-1}\) 3440, 3050, 3030, 2920, 1660, 1603, 1580, 1505, 1480, 1255; mass spectrum m/e 265 (parent ion).

**Z-1-Phenyl-2-amino(N-carbomethoxyl)pent-3-ene (154b)**

A solution of 112 mg (0.7 mmol) of 148 in 9 mL of CH\(_2\)Cl\(_2\) and 1 mL of pyridine was treated with 62 \( \mu \)L (0.8 mmol) of methyl chloroformate. After 14 h, 1 mL of H\(_2\)O was added and the resulting mixture was stirred for 15 min. The mixture was diluted with 15 mL of Et\(_2\)O and the phases were separated. The organic phase was extracted with 2x5 mL of 2N HCl, then 5 mL of saturated NaCl solution. The combined aqueous phases were extracted with 10 mL of ether. The organic phases were combined, dried over Na\(_2\)SO\(_4\), filtered and concentrated in vacuo to yield 138 mg of crude product. The crude 154b was chromatographed on a 0.5 mm silica gel TLC plate using 1:1 hexane:ether as the eluent to afford 143 mg of material (\( R_f = 0.46 \)). Further purification by kugelrohr distillation at
140°/1 mm provided 127 mg (83% yield) of pure 1H NMR (CDCl₃) δ 7.2-7.4 (m, 5 H, aromatic), 5.57 (dq, J=6.9, 10.7 Hz, 1 H, H₄), 5.28 (ddq, J=1.6, 9, 10.7 Hz, 1 H, H₃), 4.72 (broad, 2 H, H₂ and NH), 3.69 (s, 3 H, -OCH₃), 2.8 (m, 2 H, H₁), 1.55 (dd, J=1.6, 6.9 Hz, 3 H, H₅); IR (neat) cm⁻¹ 3420, 3030, 2920, 1715, 1605, 1510, 1220, 965, 820; mass spectrum m/e 219 (parent ion). Anal. Calcd. for C₁₃H₁₇NO₂: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.34; H, 8.04; N, 6.41.

Z-1-phenyl-2-amino(N-phenylureido)pent-3-ene (154c)

A solution of 135 mg (0.84 mmol) of 148 in 4 mL of CH₂Cl₂ and 1 mL of pyridine was treated with 125 µL (1.24 mmol) of phenylisocyanate. After 13 h, 1 mL of MeOH was added and the mixture was stirred for 1.5 h. The solvent was removed to afford 370 mg of pale yellow oil. This material was flash chromatographed on 100 g of silica gel using 1:1 hexane:ether as the eluant to afford 276 mg viscous oil. Recrystallization from ether/CCl₄ afforded 238 mg of amorphous solid (>95% yield) which was used in subsequent steps without further purification: 1H NMR (CDCl₃) δ 7.0-7.7 (m, 10 H, aromatic), 6.75 (broad, 1 H, NH), 5.50 (dq, J=6.9, 10.7 Hz, 1 H, H₄), 5.20 (ddq, J=1.6, 9.1, 10.7 Hz, 1 H, H₃), 5.02 (broad d, J=7.1 Hz, 1 H, NH), 4.80 (broad quintet, J=7 Hz, H₂), 2.88 (dd, J=5.9, 13.3 Hz, 1 H, H₁'), 2.71 (dd, J=7.3, 13.3 Hz, 1 H, H₁'; 1.49 (dd, J=1.6, 6.9 Hz, 3 H, H₅); IR (CH₂Cl₂) cm⁻¹ 3100-3400 (broad NH), 3040, 2980, 1670, 1600, 1520, 1495, 1250, 890.
E-1-Phenyl-2-amino(N-carbomethoxy)pent-3-ene (152b)

A solution of 161 mg (1.0 mmol) of 153 in 10 mL of CH₂Cl₂ and 1 mL pyridine was treated with 100 μL (1.3 mmol) of methyl chloroformate. After 15 h, 1 mL of H₂O was added and the mixture was stirred for 15 min and then diluted with 20 mL of Et₂O. The layers were separated and the organic phase was extracted with 2x5 mL 2N HCl and 5 mL of saturated NaCl solution. The combined aqueous extracts were extracted with 10 mL of Et₂O. The combined organic phases were dried (Na₂SO₄), filtered and concentrated to afford 214 mg of crude product. Flash chromatography on 28 g of silica gel (2:1 hexane:ether as eluent) afforded 210 mg colorless oil, which was distilled bulb-to-bulb at 125-130°C/0.7 mm to yield 196 mg (89%) of 154b, mp <35°C: ¹H NMR (CDCl₃) δ 7.2-7.3 (m, 5 H, aromatic), 5.55 (dq, J=6.4, 15.4 Hz, 1 H, H₄), 5.36 (dd, fine coupling, J=5.8, 15.4 Hz, 1 H, H₃), 4.57 (broad, 1 H, NH), 4.37 (broad m, 1 H, H₂), 3.60 (s, 3 H, -OCH₃), 2.80 (broad d, J=6.5 Hz, 2 H, H₁), 1.63 (d, J=6.4 Hz, 3 H, H₅); IR (CH₂Cl₂) cm⁻¹ 3430, 3030, 2940, 1720, 1605, 1505, 1440, 1350, 1250, 965, 890.

E-1-Phenyl-2-amino(N-phenylureido)pent-3-ene (152c)

A solution of 125 mg (0.78 mmol) of 153 in 9 mL of CH₂Cl₂ and 1 mL of pyridine was treated with 100 μL (0.95 mmol) of phenyl isocyanate. After 15 h, 1 mL of MeOH was added and the mixture was stirred for 3 h. The solvent was removed to afford 413 mg of brown oil, which was flash chromatographed on 100 g of
silica gel (2:1 hexane:ether as eluant) to yield 264 mg thick oil. The crude 152c was crystallized from ether/hexane to yield 138 mg (64% yield) white needles, mp 50-55°C. \[^1\text{H}\text{ NMR (CDCl}_3\text{)}\] \(\delta\) 7.94 (broad, 1 H, NH), 7.0-7.4 (m, 10 H, aromatic), 6.00 (broad d, J=8 Hz, 1 H, NH), 5.54 (dq, J=6.1, 15.4 Hz, 1 H, H\text{4}), 5.35 (dd, fine coupling, J=5.3, 15.4 Hz, 1 H, H\text{3}), 4.55 (broad quintet, J=7 Hz, 1 H, H\text{2}), 2.73 (d, J=7 Hz, 2 H, H\text{1}), 1.60 (d, J=6.1 Hz, 3 H, H\text{5}); IR (CH\text{2Cl}_2) cm\(^{-1}\) 3100-3400 (broad NH), 3040, 2980, 1670, 1600, 1570, 1545, 1250, 965, 890.
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70. Base catalyzed epoxide rearrangements have been observed: (a) Payne, G.B., J. Org. Chem. 1962, 27, 3819; (b) Angyal, S.J.; Gilham, P.T. J. Chem. Soc. 1957, 3691; (c) See also reference 51.


72. Kishi (reference 3g) has also noted that methyl carbonates react sluggishly under acidic conditions. Whereas our solution to this problem involved use of phenylurethanes, Kishi achieved satisfactory results by using benzyl carbonates as the neighboring group.

73. Urethanes are well-known to be outstanding neighboring groups. See reference 53 and the following recent papers: (a) Georges, M.; Fraser-Reid, B. Tetrahedron Lett. 1981, 22, 4635; (b) Pauls, H.W.; Fraser-Reid, B. J. Am. Chem. Soc. 1980, 102, 3956; (c) For recent examples of urethane-assisted epoxide solvolyses, see reference 61b.


75. In fact, all attempts to purify 91 by silica gel chromatography resulted in the equilibration of 91 with 88 and the second γ-carbonate acyl transfer isomer.


77. Hagadorn, S.M. unpublished results.

79. We thank Dr. D. Kerkman of Abbott Laboratories for helpful discussions regarding the formation of 91.

80. The exceptions are, of course, those referred to in Figure 26; see also Reference 77.

81. We thank M. DiMare for performing the experiments summarized in Figure 28.

82. (a) Roush, W.R.; Brown, R.J.; J. Org. Chem. 1982, 47, 1373; (b) Roush, W.R.; Brown, R.J.; Ibid. in press.


97. Intermediates of this type have been invoked in acid catalyzed DMSO-solvolyes of epoxides: Khuddus, M.A.; Swern, D. Tetrahedron Lett. 1971, 411.


115. The kinetic resolution-epoxidation sequence is highly erythro selective (19:1). Erythro-epoxides 115 and 73
isolated by chromatography as described in the experimental procedures were usually contaminated with up to 5% of the respective threo-epoxide isomers. These mixtures can be separated by chromatography using 10:1 CH$_2$Cl$_2$-Et$_2$O as the eluant (R$_f$ erythro-115, 0.36, R$_f$ threo-115, 0.29; R$_f$ erythro-73, 0.43; R$_f$ threo-74, 0.35 (two developments in each case)). All optical rotations and Mosher ester analyses were performed on isomerically pure epoxides obtained in this manner. This separation was not routinely performed, however, for preparative scale experiments. In the arabino- and lyxohexose series this separation was accomplished by crystallization at the stage of the phenylurethanes.

116. We thank Ms. Susannah M. Hagadorn for performing this experiment.

117. The maximum theoretical yield for these syntheses is 40-45% -- the amount of TBHP employed in the kinetic resolution -- enantioselective epoxidation step.


128. See references 5 and 51 for leading references.


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139. The cyclizations of glycidyl-derived urethanes had been described before our work was initiated: (a) Farrissey, W.J., Jr.; Nashu, A.M. J. Heterocyclic Chem. 1970, 7, 331; (b) Kishi (ref. 3g) has recently reported additional examples of the intramolecular α-addition of nitrogen nucleophiles to epoxides in 2,3-epoxy urethane systems.


141. For a recent synthesis of holacosamine using a different urethane neighboring group reaction, see reference 73a.


145. All yields reported in this section are unoptimized.


