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EXPLORATORY STUDIES IN FREE RADICAL CHEMISTRY

CHAPTER 1: USE OF BIS(CYCLOPENTADIENYL)TITANIUM(III) CHLORIDE AS A SINGLE ELECTRON REDUCTANT

CHAPTER 2: TITANIUM(III) MEDIATED PENT-4-ENYL RADICAL CYCLIZATIONS

CHAPTER 3: TRIBUTYL Tin MEDIATED HEPT-6-ENYL RADICAL CYCLIZATIONS: SYNTHESIS OF THIONOCARBONATES AND THIOCARBAMATES

DISESSION

Presented in Partial Fulfillment of the Requirements for the Degree

Doctor of Philosophy

in the Graduate School of The Ohio State University

by

Brian Irving Alban Bliss, M.S.

The Ohio State University
2000

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“Science exacts a substantial entry fee in effort and tedium in exchange for its insights.”

Carl Sagan,
Shadows of Forgotten Ancestors, 1992

“Concern for man himself and his fate must always form the chief interest of all technical endeavors...Never forget this in the midst of your diagrams and equations.”

Albert Einstein, 1939
ABSTRACT

This study was a preliminary investigation into new applications of \( \text{Cp}_2\text{Ti(III)Cl} \) (1.55). Reagent 1.55 failed to reduce alkyl bromide 1.107, \( \text{S-methyl dithiocarbonate} \) 1.82a, and also failed to ring open 2-aziridinecarboxylates 1.94 and 1.96. Attempts to induce ketyl formation in aldehyde 1.108 and acyclic ketone 2.41 with 1.55 failed, however, cyclic ketones 1.110 and 1.111 underwent hex-5-enyl cyclization to give the functionalized cyclopentitols 1.113 and 1.114.

We next investigated preparation of functionalized cyclobutanes via 1.55 mediated ring opening of epoxides 2.48 and 2.51. Pent-4-enyl cyclization of radical 2.59 lead to 3-deoxy-3-\( \text{C-\alpha-D-erythrofuranoside} \) 2.57. Further studies involving cyclization of thionocarbonates 2.65, 2.66, and thiocarbamate 2.67 under Barton-McCombie conditions provided 2-deoxy-2-\( \text{C-D-pyranosides} \) 2.68-2.70 by a novel hept-6-enyl cyclization. We recognized this mode of cyclization of thionocarbonates and thiocarbamates might provide a new and general method of preparing \( \text{O- and N-pyranosides} \).

A general route to sugar thionocarbonates and thiocarbamates was developed. The method involved the thioacylation of 6-chloro- and 6-methoxypurines with \( \text{O-pentafluorophenyl chlorothioformate} \) (3.32 and 3.36) followed by selective substitution of the pentafluorophenol moiety by the carbohydrate derivative 2.37 or 2.52 gave the target thiocarbamate 3.37. The mixed thionocarbonates 3.74, and 3.75 were prepared via sugar thiocarbamate 3.60. Cyclization of mixed thionocarbonate 3.75, cyclic thionocarbonates 3.76 and 3.77, and thiocarbamate 3.61 under modified Barton-McCombie conditions yielded carbohydrates 3.94, 3.78, 3.85, and 3.90 respectively. A novel aliphatic variation of the Newman-Kwart Rearrangement was also observed. Ongoing work in our laboratory will concentrate on developing this cyclization for the preparation of \( \text{O- and N-pyranosides and furanosides} \).
To Carolina
ACKNOWLEDGMENTS

As I near the completion of this dissertation, I have come to realize it is impossible to thank everyone who has made a contribution to its content either directly or indirectly. First and foremost, I wish to sincerely thank Prof. T.V. RajanBabu for his guidance during my doctoral studies. A consummate professional who’s enthusiasm and stamina are surpassed only by his dedication to his students. I pledge to repay the debt I owe by ensuring that the skill of the artisan is reflected in the apprentice’s work. I also wish to thank Prof. H. Shechter, who’s door is literally always open, for his helpful discussions and encouragement.

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It’s been my pleasure to get to know so many interesting faculty, staff, and colleagues within the department over the years whose friendship will last a life-time. Special thanks to Branko Radetich for
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Finally, I’d like to acknowledge the part my two sons, Ethan and Joshua (b. 5/29/99) played in making the process of writing this dissertation far more enjoyable than I could have ever imagined.
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<th>Definition</th>
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<tbody>
<tr>
<td>$[^\alpha]_{\text{D}}^{\text{temp}}$</td>
<td>specific rotation</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>AIBN</td>
<td>azobisisobutyronitrile</td>
</tr>
<tr>
<td>APT</td>
<td>attached proton test ($¹³C$-NMR)</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>t-Boc</td>
<td>tert-butoxycarbonyl</td>
</tr>
<tr>
<td>t-Bu or Bu'</td>
<td>tertiary butyl</td>
</tr>
<tr>
<td>c</td>
<td>concentration in grams per deciliter (optical rotation)</td>
</tr>
<tr>
<td>°C</td>
<td>degrees Celsius</td>
</tr>
<tr>
<td>calcd</td>
<td>calculated</td>
</tr>
<tr>
<td>cat.</td>
<td>catalytic</td>
</tr>
<tr>
<td>COSY</td>
<td>H-H correlational spectroscopy (NMR)</td>
</tr>
<tr>
<td>Cp₂TiCl</td>
<td>bis(cyclopentadienyl)titanium(III) chloride</td>
</tr>
<tr>
<td>$\delta$</td>
<td>chemical shift in parts per million (ppm)</td>
</tr>
<tr>
<td>d</td>
<td>doublet (spectral)</td>
</tr>
<tr>
<td>DEAD</td>
<td>diethylazodicarboxylate</td>
</tr>
<tr>
<td>DEPT</td>
<td>distortionless enhancement by polarization transfer ($¹³C$-NMR)</td>
</tr>
<tr>
<td>DIAD</td>
<td>diisopropylazodicarboxylate</td>
</tr>
<tr>
<td>Dibal-H</td>
<td>diisobutylaluminum hydride</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
</tr>
<tr>
<td>DME</td>
<td>dimethoxyethane</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethylformamide</td>
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</table>
DMS  dimethylsulfide
DMSO  dimethylsulfoxide
EI    electron ionization (HRMS)
Et    ethyl
g     grams
h     hours
HETCOR H-C correlational spectroscopy (NMR)
HMDS hexamethyldisilazane
HRMS high resolution mass spectrometry
Hz    hertz
HMPA hexamethylphosphoramide
IR    infrared
J     coupling constant (NMR)
L     liters
LAH  lithium aluminum hydride
LDA  lithium diisopropylamide
m     milli; multiplet (spectral)
µ     micro
m-CPBA meta-chloroperbenzoic acid
Me    methyl
MHz  megahertz
mol  moles
mp   melting point

xix
Ms  methanesulfonyl

m/z  mass to charge ratio (mass spectrometry)

ν  frequency expressed in inverse centimeters (spectral)

NBS  N-bromosuccinimide

NCS  N-chlorosuccinimide

NMR  nuclear magnetic resonance

NOE  nuclear Overhauser effect spectroscopy

PCC  pyridinium chlorochromate

PDC  pyridinium dichromate

Ph  phenyl

PhH  benzene

ppm  parts per million

pyr  pyridine

q  quartet (spectral)

rt  room temperature

s  singlet (spectral)

t  triplet

TBAF  tetrabutylammonium fluoride

TBDMSCI  tert-butyldimethylsilyl chloride

TFA  trifluoroacetic acid

TFAA  trifluoroacetic anhydride

THF  tetrahydrofuran

TLC  thin layer chromatography
TMEDA \( N,N',N^\prime,N^\prime\prime\)-tetramethylethlenediamine

tol toluene

Tr triphenylmethyl

Ts \( p \)-toluenesulfonyl

\( p \)-TsOH \( p \)-toluenesulfonic acid
CHAPTER 1

USE OF BIS(CYCLOPENTADIENYL)TITANIUM(III) CHLORIDE AS A SINGLE ELECTRON REDUCTANT

1.1 Cyclopentitols from Carbohydrates

Carbohydrates, or more precisely saccharides, are polyhydroxylated derivatives of aldehydes and ketones with empirical formula $C_n(H_2O)_x$. In addition to the widespread economic importance of carbohydrate based materials such as sugar cane, honey, milk, starch, cotton, and wood, carbohydrates have more recently held a central place in the fields of biology and chemistry. Although originally viewed as a simple compound of carbon and water (French, hydrates de carbone), Nature's most abundant monosaccharide, D-glucose, is a major source of fuel for most living organisms and a basic monomer for several important polysaccharides including cellulose, starch, and glycogen. Cellulose is the structural component responsible for imparting rigidity in plant cell walls while starch is the principal fuel storage carbohydrate in most plants. Similarly, glycogen is the principal fuel storage carbohydrate in most animals.

The widespread recognition by organic chemists of the enormous synthetic potential carbohydrates possess, however, is a relatively recent phenomenon. Although the field of organic chemistry has benefited greatly from the seminal contributions of almost a century of carbohydrate chemistry, the organic discipline has been slow to fully incorporate carbohydrates into the art and practice of synthesis. For example, the origins of modern asymmetric synthesis can be traced as far back as 1894, to the work of Emil Fischer who first applied the Kiliani cyanohydrin reaction for the preparation of the
entire D-series aldoses. In 1929, Haworth laid the foundations of modern conformational analysis with his recognition of the importance of 3-dimensional structure in carbohydrate chemistry. With the advent of nuclear magnetic resonance spectroscopy, Lemieux demonstrated in 1958 the power of coupling constants for the elucidation of structure. Despite these and many other contributions, the chemistry of carbohydrates continues to be viewed by many as a specialized and often misunderstood sub-discipline of organic chemistry.

Not until the late 1970’s did the realization emerge that carbohydrates were manageable and versatile starting materials for the synthesis of complex natural products. This new way of thinking about carbohydrates was helped by the development of new synthetic methods and the recognition of several carbohydrate like substructures in important natural products. Several excellent reviews and texts in the late 1970’s and early 1980’s, most notably by Hanessian, Fraser-Reid, and others would underscore that Nature provides more carbohydrates than all other organic matter combined and that these compounds provide the synthetic chemist with a relatively cheap, replenishable, pool of chiral synthons or “chirons” with a staggering array of functional, stereochemical, and conformational diversity.

By the late 1980’s the utilization of carbohydrates as starting materials in a wide variety of natural products had progressed beyond complex natural products related to or containing carbohydrates to those employing carbohydrates as chirons to polyhydroxylated cyclohexanes (inositols and carbasugars) and cyclopentanes (cyclopentitols). The first functionalized cyclohexane derived from carbohydrate precursors was prepared in 1948. Although cyclopentitols are not as widespread as inositols in nature, it would take another three decades before the first functionalized cyclopentane was prepared from carbohydrates.

1.2 Naturally Occurring Cyclopentitols

During the last half of the 1980’s, a number of naturally occurring compounds containing cyclopentitols were isolated and later shown to be potent inhibitors of various carbohydrate processing enzymes (Figure 1.1). These cyclopentitols were fundamental departures from existing alkaloid based
glycosidase inhibitors\textsuperscript{17} such as castanospermine (1.1),\textsuperscript{18} 1-deoxynojirimycin (1.2),\textsuperscript{19} l-deoxymannojirimycin (1.3),\textsuperscript{20} and swainsonine (1.4)\textsuperscript{21} (Figure 1.1).

![Chemical structures](image)

**Figure 1.1** Alkaloid based glycosidase inhibitors.

Allosamidin (1.5) containing the aminocyclopentitol allosamizoline (1.6), was isolated in 1986 by Sakuda\textsuperscript{22} and later synthesized by Trost in 1990.\textsuperscript{23} Allosamidin was shown to be a highly potent and selective chitinase inhibitor. Shortly thereafter in 1989, the aminocyclopentitols mannostatin A (1.7) and mannostatin B\textsuperscript{24} (1.8) were isolated by Yamamoto\textsuperscript{25} and shown to be potent inhibitors for glycoprotein processing enzymes.\textsuperscript{26} Their first total synthesis was reported simultaneously in 1991 by Ganem\textsuperscript{27} and Knapp.\textsuperscript{28} In 1990, Merrill Dow researchers prepared the aminocyclopentitol 1.9.\textsuperscript{29} In 1991, Trehazolin (1.10a) was isolated by Ando and Nakamura et al.\textsuperscript{30} and found to contain the aminocyclopentitol trehalamine (1.11a). Trehazolin (1.10a) was first prepared by Shiozaki\textsuperscript{31} and subsequently shown to exhibit strong and specific inhibitory activity toward several trehalases.\textsuperscript{32} Because \textsuperscript{a-glycosidase inhibitors were thought to exert immunoregulatory effects, these new cyclopentitols were promising candidates for antitumor and antiviral screens.}
Concurrent with the rapid growth in the development of new methods to transform simple carbohydrates into cyclitols was a "renaissance" in preparative free radical mediated transformations. Initially seen as unmanageable and capricious, preparative free radical chemistry had matured during the 1980's to provide some of the most versatile reactions in the synthetic chemist's arsenal. Modern free radical chemistry employed mild, neutral conditions which avoided many of the problems which plagued anionic processes (i.e. loss of adjacent stereochemistry, regiospecific anion formation, and β-elimination). Radical mediated processes also exhibited high chemo-, regio-, and stereoselectivity, and often proceeded without the need for protecting groups. Not surprisingly, many of
the early methods developed for the preparation of cyclitols from monosaccharides took full advantage of
the recent developments in preparative free radical chemistry, especially those involving the use of
tributyltin hydride.

1.3.1 Polyhydroxylated Cyclopentitols From Carbohydrates via Radical Reactions

The first radical mediated preparation of a cyclopentitol from carbohydrates was reported in
1985 by Wilcox and Thomasco (Scheme 1.1). Wilcox assembled the desired ethyl 7-bromo-2,3,7-
trideoxy-4,5-O-isopropylidene-D-ribo-hept-2-enoate (1.15) in 5 steps starting from commercially
available D-ribono-γ-lactone.

![Scheme 1.1 Radical Cyclization of unsaturated halo sugars. Reagents and conditions: (a) 2,2-
dimethoxypropane, p-TsOH, DMF. (b) PPh3, NBS, CH2Cl2. (c) Dibal-H, -78 °C; 82% (two steps).]

<table>
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</tr>
<tr>
<td>2</td>
<td>(E)-1.15a</td>
<td>H</td>
<td>80</td>
<td>0.2/1</td>
</tr>
<tr>
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<td>Piv</td>
<td>87</td>
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</tr>
</tbody>
</table>

Table 1.1 Radical cyclization of unsaturated halo sugars.

5
Wittig olefination of 5-bromo-5-deoxy-2,3-O-isopropylidene-D-ribofuranose (1.14) with (carbethoxymethylidene)triphenylphosphorane gave a mixture of (Z)-1.15 and (E)-1.15 in 67% and 13% respectively. Following acylation, both (Z)-1.15 and (E)-1.15 were heated in the presence of tributyltin hydride and AIBN in benzene to afford diastereomeric mixtures of carbasugars 1.16.

The stereochemistry of the isolated products was determined by $^{13}$C-NMR since the ester sidechains residing in an endo orientation are shielded relative to those residing in an exo orientation. The stereocontrol observed in the cyclization was a function of both the C-4 substituent as well as the starting olefin geometry (Table 1.1). The consistently higher stereocontrol exhibited by (Z)-1.15 compared to that of (E)-1.15 was rationalized as originating from the larger van der Waals interaction in the transition state between the ester and the $\gamma$-oxygen of the acetonide in transition state 1.17 as compared with that of the $\gamma$-hydrogen in transition state 1.18 (Figure 1.3).

![Rationalization for $\text{exo}$-1.16 diastereoselectivity during radical cyclization.](image-url)

**Figure 1.3** Rationalization for $\text{exo}$-1.16 diastereoselectivity during radical cyclization.
Radical addition should then occur preferentially on the $si$ face of the double bond (via 1.18) to give $exo$-1.16 diastereoselectively. Since ($E$)-1.15 had a much smaller van der Waals interaction with the acetonide oxygen (1.19 vs 1.20) the diastereoselectivity was lower for $exo$-1.16 from ($E$)-1.15.

![Scheme 1.2 Carba-D-fructofuranose via radical cyclization. Reagents and conditions:](image)

**Scheme 1.2** Carba-D-fructofuranose via radical cyclization. Reagents and conditions: (a) Ph$_3$P=CHCO$_2$Bu', CH$_2$Cl$_2$, 25 °C; 92% ($Z/E = 1.5$). (b) DMSO/(COCl)$_2$, then Et$_3$N; 96%. (c) TFA, CH$_2$Cl$_2$, 0 °C; 93%. (d) 1.0 equiv. LDA (e) CH$_2$Br$_2$; then LDA, -78 °C, CH$_2$N$_2$; 78%. (f) 5.0 equiv. Bu$_3$SnH, AIBN, PhH, 80 °C; 85%. (g) PhMgBr, AcOH; Os/NaBH$_4$; 50%. (h) Pd(OH)$_2$/C, EtOH, H$_2$; 98%.

Wilcox later applied this new methodology to the preparation of analogues of carba-D-fructose (1.21) and 6-phospho-D-fructose (1.22) starting from commercially available 2,3,5-tri-O-benzyI-D-arabinose (1.25) as outlined above.\(^4\)

Of particular interest is the high diastereoselectivity observed in the nucleophilic addition of (dibromomethyl)lithium to the intermediate lithium carboxylate 1.24. This novel one carbon synthon was generated in situ and resulted in a single diastereomer. Initial attempts to add nucleophilic reagents to ketone 1.23 resulted in intramolecular 1,4-addition of the resulting alkoxide to afford the undesired C-glycoside. In practice, nucleophilic additions were performed on carboxylate 1.24 without the interference of unwanted 1,4-additions. Cyclization of the radical generated from reduction of the
intermediate gem-dihalide 1.26 proceeded to give the desired carbocycle 1.27 with high exo-diastereoselectivity. Barbier-Wieland degradation of ester 1.27 followed by debenzylolation provided the desired carba-D-fructofuranose (1.21) in excellent overall yield.

In 1987, RajanBabu reported his results in the transformation of simple carbohydrates into cyclopentitols.\(^\text{43}\) He observed a highly stereoselective 5-hexenyl radical cyclization of cyclic sugar precursors yielding 1,5-cis products preferentially (Scheme 1.3). The protected 2,3,4,6-tetra-O-benzyl-D-glucopyranose was subjected to Wittig olefination followed by thioacylation with 1,1'-thiocarbonyldiimidazole to give the acyclic thiocarbamate 1.28. The thiocarbamate was exposed to tributyltin hydride in refluxing toluene (Barton-McCombie Reaction).\(^\text{44}\) As anticipated, a mixture of diastereomers 1.29-1.31 resulted.

The stereochemical assignments were confirmed by NOE and chemical degradation experiments, and the 1,5-cis product was found to be favored over the 1,5-trans by a ratio of 3:1. This preference for 1,5-cis stereochemistry is well preceded,\(^\text{45}\) and can be rationalized by invoking a chair-like transition state as depicted below in 1.32 where all substituents occupy equitorial positions.

\begin{方案}{1.3} Cyclopentitols from acyclic precursors. Reagents and conditions: \(\text{(a) Bu}_3\text{SnH, AIBN, PhH, reflux.}\)
Figure 1.4 1,5-cis products via chair-like transition state.

However, when the analogous thiocarbamate 1.33 (Scheme 1.4) was prepared from 4,6-
O-benzylidene-2,3-di-O-benzyl-D-glucopyranose and subjected to Barton-McCombie conditions, a single
cyclopentane product 1.34 was isolated resulting from a 1,5-trans cyclization.

Scheme 1.4 Cyclopentitols from cyclic precursors. Conditions: (a) Bu₃SnH, AIBN, PhH, reflux.

This 1,5-trans product could not be explained in terms of the existing chair-like transition state
model 1.35 but instead was rationalized as resulting from a boat-like transition state 1.36 as depicted in
Figure 1.5. Although the difference in energy between the boat-like transition state 1.36 and chair-like
transition 1.35 has been calculated to be as small as 1 kcal/mol, RajanBabu has demonstrated that
adoption of transition state 1.36 is a result of a bulky substituent at C-4, which forces the olefin to adopt a
boat conformation in order to minimize A(1,3)-strain in the transition state. In the absence of a bulky
C-4 substituent, the stereochemistry reverts back to the expected 1,5-cis products.
This new stereocontrol\textsuperscript{49} was applied to the synthesis of the important prostaglandin intermediate, Corey lactone \textsuperscript{1.38}.\textsuperscript{50} 3-Deoxy-D-glucose, available from Barton-McCombie deoxygenation of commercially available 1,2:5,6-di-O-isopropylidene-D-glucopyranose, was used to prepare the desired 1,5-trans cyclopentanoid framework \textsuperscript{1.37}.\textsuperscript{50} Subsequent modification yielded the desired lactone \textsuperscript{1.38}.

\textbf{Scheme 1.5} Corey Lactone (\textsuperscript{1.38}) via 1,5-trans selective hex-5-enyl radical cyclization.

Reagents and conditions: (a) H\textsuperscript{+}, allyl alcohol, PhH. (b) PhCHBr\textsubscript{2}, pyr, \Delta. (c) BnBr, NaH, DMF. (d) [Ir(COD)(PPh\textsubscript{2}Me)\textsubscript{2}]\textsuperscript{PF\textsubscript{6}}, H\textsubscript{2}, then HgCl\textsubscript{2}, HgO, H\textsubscript{2}O, acetone. (e) Ph\textsubscript{3}P=CHOMe, THF. (f) Im\textsubscript{2}C=S, CH\textsubscript{2}ClCH\textsubscript{2}Cl, reflux. (g) Bu\textsubscript{3}SnH, AIBN, toluene, reflux. (h) H\textsubscript{2}, Pd, H\textsuperscript{+}. (i) TsCl, pyr. (j) Ac\textsubscript{2}O, pyr. (k) NaCN, DMF. (l) OH\textsuperscript{-}; H\textsuperscript{+}. (m) Conc. HCl.
Both the Wilcox and RajanBabu procedures highlight the major disadvantages of the tributyltin method of generating a radical; namely that a functional group, either a bromide or alcohol, is lost in the process of generating the radical. The number of synthetically useful procedures for generating a radical are limited, and the loss of a functional group during the radical process reduces further functionalization of the product. Methods specifically addressing these limitations will be discussed later in this chapter.

In 1988, Bartlett employed an oxime ether as the radical acceptor and was the first to prepare aminocyclopentitols from carbohydrate precursors by this method.\textsuperscript{51-53} Oximination of 2,3,4,6-tetra-O-benzyl or tetra-O-methyl-D-glucopyranose (Scheme 1.6) followed by thioacylation gave the corresponding $O$-phenylthionocarbonates \textsuperscript{1.39}.\textsuperscript{54} Exposure of these substrates to tributyltin hydride and AIBN in refluxing benzene yielded diastereomeric mixtures of aminocyclopentitols with predominantly 1,5-cis selectivity\textsuperscript{42} consistent with the acyclic results reported earlier by RajanBabu (Scheme 1.3).

![Scheme 1.6](image)

**Scheme 1.6** Aminocyclopentitols from carbohydrates: oxime ethers as radical acceptors. Reagents and conditions: (a) Bu$_3$SnH, AIBN, benzene, reflux, 14 h.

In 1994, Ingall and Roberts also employed oxime ethers as radical acceptors in investigations into new free radical methods for preparing cyclopentitols related to the mannostatins (Figure 1.2 and Scheme 1.7).\textsuperscript{55} Specifically, Ingall and Roberts recognized that the presence of a thioalkyl side chain in the mannostatins meant that the radical cyclization could be performed using a thioacetal \textsuperscript{1.45} as radical
precursor. Starting from commercially available 1,2:5,6-O-diisopropylidene-α-D-allofuranose (1.43), selective deprotection, oxidation, and oximation yielded the O-methyl oxime 1.44. Simultaneous deprotection of the acetonide followed by thioacetal formation in the presence of ethanethiol and zinc chloride yielded the desired thioacetal radical precursor 1.45 after acetylation. Radical cyclization in the presence of excess tributyltin hydride then gave the desired aminocyclopentitols 1.46a and 1.46b (1,5-cis/1,5-trans = 3).

Scheme 1.7 Preparation of mannostatin analogues: dithioacetals as radical precursor. Reagents and conditions: (a) PhCH2Br, NaH, THF. (b) HCl, MeOH, 25 °C, 12 h. (c) NaIO4, H2O, MeOH. (d) MeONH2·HCl, pyridine, CH2Cl2, 25 °C, 2 h. (e) EtSH, ZnCl2, -10 °C, 1 h. (f) Ac2O, DMAP, pyridine, (g) 40 °C, 18 h. (h) 6 equiv. Bu3SnH, 2.5 equiv. AIBN, toluene, reflux, 1.5 h.

1.3.2 Cyclopentitols from Carbohydrates Involving Reducing and Organometallic Reagents

In 1989, Enholm would take a new approach to preparing cyclopentitols by avoiding the tin hydride method in favor of the one-electron reduction of carbonyls by samarium(II) iodide (Scheme 1.8). The conditions employed to generate the prerequisite ketyls were mild and the residual oxygen functionality remained in the product and available for further modification.
Scheme 1.8 Aldehydes as radical precursors in cyclopentitol synthesis. Reagents and conditions: (a) BnOH, p-TsOH; 63%. (b) acetone, 2,2-dimethoxypropane, p-TsOH; 68%. (c) TBDMSCl, CH₂Cl₂, Et₃N, DMAP. (d) Li, NH₃; 81% (two steps). (e) Ph₃P=CHCO₂Me, CH₂Cl₂, 10 mol% PhCO₂H; 74%. (f) PDC, CH₂Cl₂, 3 Å sieves, 10 mol% AcOH; 73%. (g) Sml₂, THF/MeOH, -78 °C, then TBAF, THF, 0 °C; 69%. (h) BnOH, p-TsOH; 63%. (i) acetone, 2,2-dimethoxypropane, p-TsOH; 68%. (j) TBDMSCl, CH₂Cl₂, Et₃N, DMAP; (k) Li, NH₃; 80% (two steps). (l) Ph₃P=CHCO₂Me, CH₂Cl₂, 10 mol% PhCO₂H; 80% (E/Z = 3). (m) PDC, CH₂Cl₂, 3 Å sieves, 10 mol% AcOH; 80%. (n) Sml₂, THF/MeOH, -78 °C, then TBAF, THF, 0 °C; 64-73%.

Standard protection/deprotection of D-arabinose gave the intermediate lactol which underwent Wittig olefination and oxidation to give aldehyde 1.47. Exposure of aldehyde 1.47 to two equivalent of Sml₂ in THF/MeOH at -78 °C yielded the desired cyclopentitol 1.48 as a single 1,5-cis diastereomer.

Similarly, D-lyxose was exposed to identical conditions to give a mixture of (Z)-1.49 and (E)-1.49. Exposure of these aldehydes to reducing conditions gave products whose stereochemistry was a function of starting material olefin geometry. Cyclization of substrate (Z)-1.49 favored a 1,5-cis product 1.50a, whereas cyclization of substrate (E)-1.49 favored a 1,5-trans product 1.50b. Enholm provided no rationalization for these results.

In the case of 1.48, comparison of the two transition states which lead to product shows that the 1.48 (chair-like) has a bulky C-4 group in an unfavorable axial position with significant A₁³-strain
(Figure 1.6). The 1.48 (boat-like) transition state places the C-3 and C-4 substituents in a lower energy diequitorial orientation. The C-1 substituent adopts an axial orientation anti- to the C-2 acetonide. The C-5 (Z)-olefin adopts an axial orientation to avoid an unfavorable allylic interaction with the axial H-4. It is unlikely that coordination between the ester function and samarium(III) alkoxide is a significant factor in 1.48 (boat-like) since subsequent samarium(II) mediated 4-butenyl cyclizations of esters bearing a C-2 benzyl oxy substituent have provided 1,4-trans products\(^{57}\) (vide infra, Scheme 2.3) Furthermore, the reversibility of the radical addition step leading to epimerization cannot explain these results since the later examples 1.50a and 1.50b (Scheme 1.8) do not epimerize at the C-5 position under identical reaction conditions.

![Diagram](image.png)

**Figure 1.6** Rationalization of 1,5-cis stereochemistry in 1.48.

The high diastereoselectivity for 1,5-cis products from (Z)-1.49 must occur via transition state 1.50a (boat-like) which places the C-2 and C-3 substituents in the preferred di-equitorial orientation and the ester in the axial orientation which minimizes allylic strain with the adjacent C-4 acetonide. However, it is not clear why the C-1 substituent adopts a pseudo-axial orientation cis to the C-4 substituent. Likewise, preferential formation of 1,5-trans products from (E)-1.49 occurs via 1.50b (chair-like) where the (E)-geometry of the olefin could minimize the A\(^{(1,3)}\)-strain encountered when the olefin adopts the preferred pseudo-equitorial orientation.
In 1994, RajanBabu and Nugent reported the results of their efforts to find a low-valent transition metal complex capable of a selective one-electron reduction of an epoxide to give a carbon-centered radical intermediate (Scheme 1.9). Epoxides are versatile intermediates in organic synthesis with numerous means of preparation in both racemic and optically pure form. Their use as radical precursors would greatly expand the options available to the synthetic chemist. After screening several metals, RajanBabu and Nugent found that bis(cyclopentadienyl)titanium(III) chloride (Cp₂TiCl) complex promotes the desired one electron reduction under mild conditions. The paramagnetic Cp₂TiCl complex can most conveniently be thought of as a metal centered radical, which upon coordination with the epoxide oxygen induces C-O homolysis to give the desired carbon-centered radical (vide infra, 1.55, Figure 1.8). The Cp₂TiCl reagent is easily prepared in one step from inexpensive and commercially available titanocene dichloride and a metal reducing reagent such as Zn, Al, or Mg (Scheme 1.10).
RajanBabu and Nugent illustrated this new reagent's potential in cyclopentitol synthesis by cyclizing the epoxide 1.52 to give the desired functionalized cyclopentane 1.53. When a large C-4 substituent is present in 1.52, an exocyclic methyl results from 1,5-trans cyclization. In the absence of a large C-4 substituent, 1,5-cis cyclization results. Unlike the previously discussed tin hydride method, use of this new method leaves a hydroxymethyl fragment after cyclization that is amenable to further elaboration and functionalization. The synthetic potential of this new method was quickly recognized and applied to several natural product syntheses.\(^3\)

1.4 Bis(cyclopentadienyl)titanium(III) chloride

This new method of generating a radical from an epoxide under mild conditions from easily prepared and inexpensive Cp\(_2\)TiCl stimulated further investigation into other applications of this reagent. Specifically, what other functional groups besides epoxides could be used radical precursors, and could this then be applied to cyclopentitol synthesis? Before addressing these questions, the details of this reagent's preparation and reactivity are discussed.

1.4.1 Preparation, Isolation, and Reactivity of Cp\(_2\)TiCl

The most convenient methods of preparing the air sensitive Cp\(_2\)TiCl have been the procedures reported by Green\(^6\) (Eq. 1) and by Coutts and Martin\(^6\)\(^1\) (Eq. 2) as shown below in Scheme 1.10. Each method involves the reduction of titanocene dichloride under conditions involving elemental Zn\(^6\) (Eq. 1)
or Al\textsuperscript{61} (Eq. 2). An alternate procedure has also been reported by Manzer (Eq. 3)\textsuperscript{64} (Eq. 3). In its isolated state, the Cp\textsubscript{2}TiCl reagent exists in dimeric form 1.54. However, on dissolution in a donating solvent such as THF, the complex exists in its monomeric form 1.55.

$$2\text{Cp}_2\text{TiCl}_2 + \text{Zn} \xrightarrow{\text{THF}} 2\text{Cp}_2\text{TiCl} + \text{ZnCl}_2 \quad \text{Eq. 1}$$

$$3\text{Cp}_2\text{TiCl}_2 + \text{Al} \xrightarrow{\text{THF}} 3\text{Cp}_2\text{TiCl} + \text{AlCl}_3 \quad \text{Eq. 2}$$

$$\text{TiCl}_3 + 2\text{Cp}_2\text{Ti} \xrightarrow{\Delta} \text{Cp}_2\text{TiCl} + 2\text{TiCl} \quad \text{Eq. 3}$$

Scheme 1.10. Preparation of bis(cyclopentadienyl)titanium(III) chloride complex.

The hypothesis that one-electron reduction of the epoxide by Cp\textsubscript{2}TiCl occurs to give a carbon-centered radical has been supported by mechanistic probes. For example, it is known that Cp\textsubscript{2}TiCl will deoxygenate epoxides 1.56 to give the corresponding olefin 1.59 (Scheme 1.11). Two electron reductants such as tungsten are known to deoxygenate epoxides with retention of configuration.\textsuperscript{65} When both stereoisomers of 5,6-epoxydecane (1.60) and (1.61) were individually exposed to Cp\textsubscript{2}TiCl, identical mixtures of (E)- and (Z)-dec-5-ene (1.62) were obtained. The loss of stereochemistry in these experiments was rationalized as resulting from the presence of a long-lived, radical intermediate such as 1.57. The presence of this radical intermediate was further confirmed by trapping experiments involving the well studied 5-hexenyl radical cyclization like the ones discussed earlier in Section 1.3. 4,4-Dicarbethoxy-6,7-epoxyhept-1-ene (1.63) was exposed to Cp\textsubscript{2}TiCl to afford the cyclopentane product 1.64 in good yield and in a \textit{cis/trans} ratio of 85:15.
Scheme 1.11 Mechanistic probes to determine the nature of the Cp₂TiCl reagent.

Based in part upon these mechanistic probes, the Cp₂TiCl reagent 1.55 may be conveniently conceptualized as a "loosely solvated transition-metal-centered radical" as depicted below.

Figure 1.8 Conceptual model of Cp₂TiCl complex as a transition metal-centered radical.

1.4.2 Deoxygenation of Epoxides

RajanBabu and Nugent have also shown that in the absence of a suitable radical trap and in the presence of excess reagent, epoxides are cleanly deoxygenated under mild conditions (Scheme 1.12).
For example, this highly selective and mild procedure was employed to prepare the sensitive methyl 3,4-anhydro-1,6-di-O-trityl-α-D-fructofuranoside (1.66) whose synthesis by classical methods had failed in earlier attempts.68

\[
\begin{align*}
\text{TrO} & \quad \text{OTr} \\
\text{O} & \quad \text{OMe} \\
\text{1.65} & \quad \text{1.66}
\end{align*}
\]

Scheme 1.12 Deoxygenations of epoxides involving Cp2TiCl under mild conditions. Reagents and conditions: (a) Cp2TiCl, THF, 25 °C.

It is worth noting that since many vicinal diols are themselves precursors to epoxides via the Mitsunobu reaction, the sequence of epoxidation, deoxygenation with titanium(III), and catalytic hydrogenation provides a useful alternate to double deoxygenation under Barton-McCombie conditions.66

1.4.3 Glycal Formation

In 1995, Schwartz reported a new method of preparing glycals from glycosyl halides involving Cp2TiCl (Scheme 1.13).69,70 Glycals are important synthetic intermediates to oligosaccharides and other O- and C-glycosides. This mild method of glycal formation is attractive since many existing methods of reducing glycosyl halides are incompatible with a number of common protecting groups. Schwartz argues that the Cp2TiCl complex abstracts bromine from an activated glycosyl halide 1.70 to give the stable glucopyranosyl radical 1.71, which undergoes further reduction in the presence of excess Cp2TiCl to form an intermediate glucopyranosyltitanium(IV) species 1.72. This intermediate organotitanium(IV) species
then undergoes β-elimination with loss of bis(cyclopentadienyl)titanium(IV) chloroacetate to give the desired glycal 1.73 in excellent yield.

Scheme 1.13 Glycal formation from glucopyranosyl bromides and Cp₂TiCl.

1.4.4 Summary

By the late 1980's, the use of carbohydrates as chirons in natural product synthesis had become widely established. The emergence of a new class of cyclopentanoid inhibitors of carbohydrate processing enzymes fueled the interest of a growing number of chemists outside the mainstream carbohydrate field to develop new methods to prepare polyhydroxylated carbocycles from simple sugar precursors. Many of these early procedures took advantage of the simultaneous maturation in radical based methodologies involving the tributyltin hydride method. However, limitations in the number of radical precursors, radical acceptors, and the use of tributyltin hydride itself encouraged several researchers to develop new reagents, such as SmI₂ and Cp₂TiCl, and new radical precursors such as simple carbonyls and epoxides.

1.5 Initial Research Plan Involving Cp₂TiCl

In view of the remarkable reactivity Cp₂TiCl displayed in the presence of epoxides, a more thorough investigation of its scope and utility was needed. The initial comparisons of Cp₂TiCl to similar
one-electron reducing reagents such as SmI₂ and other metal-centered radicals such as tributyltin radical were obvious, and prompted an investigation into whether Cp₂TiCl might be a more synthetically useful alternative. Therefore, our initial investigation into further uses of Cp₂TiCl in the preparation of functionalized cyclopentitiols from carbohydrates focused on several broad topics including the ring opening of aziridines, the reduction of bromides and xanthates, and the formation and cyclization of ketyl.

1.5.1 Cp₂TiCl Mediated Ring Opening of Aziridines

The demonstrated ability of Cp₂TiCl to open epoxides regioselectively under mild conditions lead us to consider if the analogous ring opening of aziridines was possible (Scheme 1.14). In a manner analogous to Scheme 1.11, the ring opening of aziridines such as 1.74 would provide another radical precursor and yield a useful methylamino side chain available for further functionalization after cyclization to 1.75.

Scheme 1.14 Proposed Cp₂TiCl mediated ring opening of aziridines to give aminomethylcyclopentitiols.

The facility of the titanium(III) mediated ring opening of epoxides can be understood in terms of titanium’s high oxophilicity and strong Ti-O bond strength (Table 1.2) and relief of ring strain inherent in the epoxide (Table 1.3). Similar analysis would predict that the titanium(III) mediated ring
opening of aziridines would also be favored by a comparable relief of ring strain in the aziridine but would suffer from the reduced strength of the new Ti-N bond.73

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Table 1.2 Bond Dissociation Energies ($D^\circ_{298}$) Of Selected Bonds.73

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<td>115</td>
</tr>
<tr>
<td>NH</td>
<td>27.7</td>
<td>116</td>
</tr>
<tr>
<td>S</td>
<td>17.7</td>
<td>74</td>
</tr>
</tbody>
</table>

Table 1.3 Strain energies of saturated three-membered heterocycles.71,72

The ring opening of aziridines has attracted the attention of synthetic chemists as a means of preparing a number of biologically important compounds.74 When coupled with the existing methods of preparing $N$-activated aziridines stereospecifically,75 regioselective methods of ring opening of aziridines would allow access to stereochemically well defined peptide isosteres and novel amino acids (Scheme 1.15). We anticipated that regio-controlled opening of 2-aziridinecarboxylates 1.76 in the presence of Cp$_2$TiCl would provide a convenient route to $\beta$-amino acid derivatives such as 1.78.
1.5.2 Cp₂TiCl Mediated Ketyl Formation

In light of the ability of Cp₂TiCl to induce C-O₄ homolysis in an epoxide, we initially considered the possibility of the reagent acting like a one-electron reducing reagent and inducing C-O₄ homolysis in carbonyls to provide a ketyl intermediate analogous to that obtained with SmI₂ (Scheme 1.8). If realized, this would be an attractive alternative to SmI₂, since the organotitanium intermediate 1.81 might be alkylated with an electrophile (Scheme 1.16).^[76]
1.5.3 \( \text{Cp}_2\text{TiCl Mediated Reduction of Bromides, Xanthates, Thionocarbonates, Thiocarbamates, and Phosphonates.} \)

As discussed earlier, one of the principal disadvantages of the tributyltin hydride method is the subsequent loss of a functional group, either a halide or an alcohol, in the generation of the carbon-centered radical. Even in those cases where this loss is not an issue, the difficulties involved with the use of tributyltin hydride and the elevated temperatures often used to initiate the radical chain process make a synthetic equivalent to tributyltin hydride a valuable option. In view of the widely accepted mechanism of tin hydride reduction of alkyl bromides, xanthates, thiocarbamates, thionocarbonates, and phosphonates,\(^7\) we wondered if the \( \text{Cp}_2\text{TiCl} \) reagent could induce C=S (or C-Br) homolysis analogous to tributyltin radical. Of course, a hydrogen donor source such as 1,4-cyclohexadiene would have to be provided since the reaction is not a chain process.

![Diagram](image)

**Scheme 1.17** Proposed application of \( \text{Cp}_2\text{TiCl} \) as tributytin radical equivalent.

1.5.4 **Transmetalation and Alkylation of Organotitanium(IV) Intermediates.**

In the initial work on the cyclization of 1,6-heptadiene monoepoxide (1.84) (Scheme 1.18), the putative organotitanium(IV) intermediates 1.85 formed upon epoxide opening was quenched with simple electrophiles, such as a proton source or halogen, resulting in the isolation of products such as 1.86 with terminal methyl and halomethyl side chains. The issue of whether or not organotitanium(IV)
intermediates such as 1.85 could be transmetallated or alkylated with synthetically more useful electrophiles had not been addressed.

![Scheme 1.18 Proposed transmetallation and alkylation of organotitanium(IV) intermediates.](image)

1.6 Discussion of Experimental Results

In the work described in Scheme 1.9, RajanBabu reported that the reactions involving Cp₂TiCl were conducted using isolated (Cp₂TiCl)₂ (1.54), prepared according to the procedure of Manzer⁶⁴ (Eq. 3, Scheme 1.10). However, they found no reason why these transformations could not be conducted more conveniently with Cp₂TiCl generated in situ (Eq 1, Scheme 1.10). From the outset, we decided to look specifically at the Cp₂TiCl mediated ring opening of aziridines, the reduction of bromides, xanthates, and phosphonates, and the formation of ketals from carbonyls using Cp₂TiCl generated in situ.

1.6.1 Preparation of Phosphates, Phosphoramidates and Xanthates and Reaction with Cp₂TiCl

The ability to selectively replace a hydroxyl function with a hydrogen under mild conditions is a synthetic transformation of fundamental importance in natural products and carbohydrate chemistry. There are numerous methods for the deoxygenation of alcohols based upon heterolytic cleavage of the C-O bonds involving the nucleophilic displacement of the corresponding mesyl-, tosyl-, and sulphonate esters or reductive dehalogenation and desulphurization of the corresponding halides or sulphides. However, several alternate routes involving the homolytic cleavage of the C-O bond have also been developed which
take advantage of neutral, non-ionic conditions. One such method involves the radical deoxygenation of S-methyl dithiocarbonates and thiocarbamates in the presence of tributylstannane (Barton-McCombie Reaction)\(^{44,54}\) and another involves the electron transfer reduction of phosphonates and phosphoramidates developed by Ireland and coworkers.\(^{78,79}\) Although both the diethyl phosphonate (DEP) and \(N,N,N',N'^4\)tetramethylphosphorodiamidate (TMPDA) derivatives are reported to be readily prepared and isolated in high yield, several attempts to prepare both the corresponding diphenyl phosphonate (DPP) and TMPDA derivatives of diacetone D-glucose \(1.82d\) and \(1.82e\) yielded only reactions which failed to go to completion or provided mixtures difficult to purify by flash chromatography (Scheme 1.19 and Table 1.4).

\[\text{Scheme 1.19 Initial attempts to prepare phosphonates and phosphoramidates.}\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.2 eq. CIP(O)(OPh)(_2), 1:1 CH(_2)Cl(_2)/pyr, 0→25 °C, 12 h</td>
<td>50% by (^1)H-, (^{31})P-NMR</td>
</tr>
<tr>
<td>2</td>
<td>2.0 eq. CIP(O)(NMe(_2))(_2), 1:1 CH(_2)Cl(_2)/Et(_3)N, 0→25 °C, 24 h</td>
<td>No Reaction</td>
</tr>
<tr>
<td>3</td>
<td>1.0 eq. (n)-BuLi, 4:1 THF/TMEDA, 0 °C, 0.5 h, then 1.2 eq. CIP(O)(NMe(_2))(_2), 0→25 °C, 2 h</td>
<td>Mixture of products</td>
</tr>
<tr>
<td>4</td>
<td>1.5 eq. CIP(O)(OPh)(_2), 1:1 CH(_2)Cl(_2)/pyr, 0→25 °C, 12 h</td>
<td>Mixture of products</td>
</tr>
</tbody>
</table>

\[\text{Table 1.4 Conditions investigated to prepare phosphonates and phosphoramidates.}\]
However, the corresponding S-methyl dithiocarbonate of diacetone glucose 1.82a (Scheme 1.20) was prepared and isolated in fair yield and subsequently exposed to 1.5 equivalents Cp₂TiCl, prepared in situ from activated zinc. To a solution of xanthate 1.82a in THF containing γ-terpinene (a 1,4-cyclohexadiene) as the hydrogen donor, a solution of Cp₂TiCl was added via addition funnel slowly over several minutes.

Following work-up, analysis of the crude reaction product(s) by ¹H-NMR showed only recovered starting material as was indicated by the existence of a singlet at δH = 2.55 characteristic of the starting methyl xanthate.

![Diagram of diacetone-D-glucose](image)

**Scheme 1.20.** Attempt to reduce xanthates with Cp₂TiCl in situ. Reagents and conditions: (a) 1.5 equiv. NaH, THF, cat. imidazole; 3.0 equiv. CS₂; 1.2 equiv. MeI; 62%. (b) Cp₂TiCl₂, activated Zn, (in situ), 4.5 equiv. γ-terpinene, THF, 25 °C, 0.5 h.

Although the preparation of Cp₂TiCl was carried out under oxygen free conditions and its presence indicated by the persistence of the characteristic green color, we decided to confirm its presence and test its reactivity against a model hex-5-enyl cyclization of 1,6-heptadiene monoepoxide 1.87 under standard cyclization conditions (Scheme 1.21 and Table 1.5).

Elemental zinc was activated according to published procedures and the preparation of the Cp₂TiCl was conducted with sonication to ensure a clean metal surface. Rigorous exclusion of oxygen was maintained by a positive atmosphere of nitrogen. In each case, the dark green color characteristic of Cp₂TiCl was observed during its formation and persisted as the reagent was carefully transferred via
syringe or cannula to an addition funnel for subsequent addition to the epoxide solution. The green color was discharged on addition to the epoxide solution to give a light yellow color.

Scheme 1.21 Reactions to test the activity of Cp₂TiCl (in situ).

```
<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Cp₂TiCl (in situ) Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CO₂Et</td>
<td>Cp₂TiCl₂, activated Zn, THF, 3 h</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>Cp₂TiCl₂, activated Zn, THF, sonic., 24 h</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>Cp₂TiCl₂, activated Zn, THF, sonic., 2 h</td>
</tr>
</tbody>
</table>
```

Table 1.5 Conditions investigated to test the activity of Cp₂TiCl (in situ).

Following addition of the titanium(III) reagent and stirring for a specified period of time, the reaction mixture was washed with 10% H₂SO₄, dried over anhydrous MgSO₄, concentrated, and the crude reaction products were analyzed by 'H-NMR. The doublet at δ_H = 0.9 previously reported to be due to the exocyclic methyl of 1.88 was not present in the crude product. Olefin signals were observed (δ_H = 5.7-5.1) although the epoxy signals (δ_H = 3.0 and 2.4) were absent. Analysis of the crude reaction mixture by gas chromatography (GC) gave a signal different from starting epoxide indicating consumption of starting material. The absence of both starting epoxide and signals characteristic of cyclization products lead us to speculate that perhaps the Lewis acid (ZnCl₂) remaining in the reaction following Cp₂TiCl formation lead to formation of chlorohydrin 1.89 or may have facilitated deoxygenation to give diene 1.90 (Scheme 1.21). High resolution mass spectrometric (HRMS) analysis of the reaction product indicated the presence of 1,6-heptadiene 1.90. These initial results involving the use of Cp₂TiCl generated in situ with substrates of
known reactivity lead us to conclude that for best results, isolated (Cp₂TiCl)₂ should be employed in all future reactions.

1.6.2 Reaction of Aziridines With Cp₂TiCl

We also prepared several aziridines for reaction with Cp₂TiCl. Although the dominant feature of aziridine chemistry is their ring opening resulting from the relief of ring strain inherent in three-membered rings, the regiochemistry of the ring opening is controlled by the character of the substituent on nitrogen.¹¹ Nonactivated aziridines are those bearing electron donating groups (N-H, N-alkyl, N-aryl) and a relatively basic nitrogen which favors nucleophilic opening only after pre-coordination by an electrophile. Conversely, activated aziridines are those bearing an electron withdrawing group (N-acyl, N-CO₂R, N-SO₂R) which stabilizes the excess negative charge on nitrogen resulting from direct nucleophilic attack on the aziridine ring.

![Scheme 1.22. Preparation of 2-aziridinecarboxylates. Reagents and conditions:](image)

(a) methylacetoacetate, KOH, MeOH, 25 °C, 5 h; 94%. (b) BnBr, DMF, 25 °C, 24 h; 96%. (c) p-TsOH H₂O, dioxane, 25 °C, 12 h; then Ph₃CCl, CHCl₃, Et₃N, 0→25 °C, 12 h; 74%. (d) SO₂Cl₂, toluene, Et₃N, -50 °C, 1 h; 49%. (e) HCO₂H, MeOH, 0→25 °C, 2 h; 38%. (f) TFA, CHCl₃/MeOH, 0 °C, 0.5 h; Ac₂O, CHCl₃/Et₃N, 0→25 °C, 14 h; 40%. (g) t-Boc₂O, dioxane, NaOH(aq), 0 °C, 1 h; 79%. (h) BnBr, K₂CO₃, DMF, 25 °C, 24 h; 24%. (i) PPh₃, DIAD, THF, 0 °C.

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Therefore, we wanted a convenient route to aziridines bearing radical stabilizing groups on the ring and a route with the flexibility to change the character of the $N$-substituent. Of the many routes available into aziridines, we initially took advantage of the ring closure of 1,2-amino alcohols derived from readily available amino acids. We prepared the known $(2S,3S)$-3-methyl-1-trityl-2-aziridinecarboxylate ester 1.94 (Scheme 1.22) which was available in four steps from L-threonine. The presence of the carboxylate residue would be expected to further facilitate ring opening by stabilizing the adjacent radical center upon C-N homolysis. More importantly, the regio-controlled opening of 2-aziridinecarboxylates at the 2-position would provide access to an important class of $\beta$-amino acid derivatives. Preparation of the intermediate $N$-trityl-L-threonine benzyl ester 1.93 was accomplished by way of a little used "fugitive" $N$-protecting group. Dane and others have reported that condensation of 1,3-dicarbonyl compounds with the potassium salts of amino acids yield hydrogen-bond stabilized enamines such as 1.91. Although too labile for peptide syntheses, these protected potassium salts undergo facile esterification in DMF and the $N$-protecting group can be subsequently removed by mild acidolysis.

Thus, the desired $N$-trityl-L-threonine benzyl ester (1.94) was prepared by initial protection of L-threonine with methylacetoacetate in methanolic KOH to give the intermediate potassium salt 1.91 in 94% yield. The carboxylate was then benzylated to give benzyl ester 1.92 in 96% yield. The enamine was hydrolyzed and the free amine tritylated to give the intermediate benzyl $N$-trityl-L-threonine 1.93 in 74% yield. Aziridination was accomplished by treatment of the protected 1,2-amino alcohol with 1.0 M sulfuryl chloride in toluene at $-50^\circ$C to give an intermediate sulphamidate, which on exposure to base, gave the desired unactivated aziridine benzyl $(2S,3S)$-3-methyl-1-trityl-2-aziridinecarboxylate ester 1.94 in 49% yield.

Attempts to prepare the activated aziridine benzyl $(2S,3S)$-1-Boc-3-methyl-2-aziridinecarboxylate ester 1.98 were unsuccessful due to the failure of the benzyl $N$-Boc-L-threonine to undergo intramolecular cyclization under sulfuryl chloride conditions. The success of this method of aziridination
seems to be dependent on the bulkiness of the \(N\)-substituent and may not be general for all \(N\)-protecting groups.\(^{87}\) Preliminary attempts to cyclize 1.97 under Mitsunobu conditions\(^{89,90}\) (Ph\(_3\)P, DIAD, THF, 0 °C) failed to give aziridine 1.98. Fortunately, the unactivated aziridine (2S,3S)-1-trityl-3-methyl-2-aziridinecarboxylate ester 1.94 could easily be transformed into an activated aziridine by acidolysis of the trityl function followed by acetylation to give the desired (2S,3S)-1-acetyl-3-methyl-2-aziridinecarboxylate ester 1.96 in 40% yield from 1.94.

Further efforts were made to prepare other aziridines. 2-Phenyl-\(N\)-phenylaziridine 1.101 (Scheme 1.23) was chosen since the presence of a phenyl substituent on the ring would provide a stabilized benzyl radical upon C-N homolysis. Aziridine 1.101 was prepared in two steps from benzaldehyde by reaction of \(N\)-benzylidene aniline 1.100 with dimethylsulfoxonium methylide.\(^{91}\) Preliminary attempts to prepare the known 2-phenylaziridine 1.103 from azidohydrin\(^{92}\) 1.102 were unsuccessful under the conditions investigated.\(^{93,94}\)

Scheme 1.23 Preparation of 1,2-diphenylaziridine. Reagents and conditions: (a) PhNH\(_2\), 95% EtOH, 0 °C; 62%. (b) Dimsyl sodium, Me\(_3\)ST, THF, 0 °C; 55%. (c) NaN\(_3\), dioxane, H\(_2\)O, reflux, 24 h; 31%. (d) PPh\(_3\), Et\(_2\)O, 25 °C, 18 h. (e) P(OMe)\(_3\), CH\(_2\)Cl\(_2\), reflux, 24 h.

Having several representative aziridines in hands, attempts to open these aziridines in the presence of isolated (Cp\(_2\)TiCl)\(_2\)\(^{61,64}\) under carefully controlled conditions\(^{95}\) gave the results as summarized in Scheme 1.24 below. In the first two instances, both unactivated 1.94 and activated 2-
aziridinecarboxylates 1.96 yielded only recovered starting materials on $^1$H-NMR analysis of the crude reaction mixtures. In contrast to the apparent lack of reactivity of 2-aziridinecarboxylates, exposure of 2-phenyl-$N$-phenyl aziridine (1.101) to isolated $(\text{Cp}_2\text{TiCl})_2$ under otherwise identical conditions gave a complex mixture of unidentifiable products.

The observation that the 2-phenylaziridines underwent some form of ring opening reaction, and the 2-aziridinecarboxylates did not, is difficult to rationalize. Although it may be argued that the presence of a phenyl group on the ring is better able to stabilize the intermediate radical, and thus lowers the activation barrier to C-N homolysis, this does not explain the complete absence of reactivity in the case of the 2-aziridinecarboxylates.

Scheme 1.24 Reaction of 1,2-diphenylaziridine and 2-aziridinecarboxylates with $\text{Cp}_2\text{TiCl}$. Reagents and conditions: (a) 1.25 equiv. $(\text{Cp}_2\text{TiCl})_2$, THF, 25 °C, 1 h. (b) 1.05 equiv. $(\text{Cp}_2\text{TiCl})_2$, 10 equiv. γ-terpinene, THF, 25 °C, 1 h. (c) 2.2 equiv. $(\text{Cp}_2\text{TiCl})_2$, 15 equiv. ethyl acrylate, THF, 25 °C, 1 h. (d) 1.25 equiv. $(\text{Cp}_2\text{TiCl})_2$, 10 equiv. γ-terpinene, THF, 25 °C, 1 h.

Since $\text{Cp}_2\text{TiCl}$ has a half-filled valence shell and is expected to be Lewis acidic, the observation that activated aziridines are unreactive due to their diminished Lewis basicity may explain why the $N$-acyl aziridinecarboxylates do not react, but fails to explain why the corresponding unactivated $N$-trityl-2-aziridinecarboxylate fails to react. Perhaps the trityl group is too bulky a protecting group and impedes
effective titanium-nitrogen coordination. One other possible explanation may be in the method of preparing the isolated (Cp₂TiCl₂)₂ reagent.

In the preparation of isolated (Cp₂TiCl₂)₂ by either the method of Manzer⁶⁴ or Coutts and Martin⁶¹ (Scheme 1.10), the ether soluble Lewis acid by-products (TICl and AlCl₃ respectively) are removed by repeated rinsing with fresh solvent. No doubt small amounts of Lewis acid remain behind in each procedure. In the case of 2-phenyl-N-phenylaziridine (1.101), the residual AlCl₃ may be a more effective Lewis acid, and therefore may favor an S₆1 type C-N heterolysis over titanium(III) induced C-N homolysis. The TICl conversely, may be a softer and less effective Lewis acid in the case of the 2-aziridinecarboxylates since we see no titanium(III) induced C-N homolysis and no competing side reactions from (Cp₂TiCl₂)₂ isolated by the Manzer procedure.⁶⁴

Any residual Lewis acid could cause competing side-reactions with acid sensitive substrates as well as diminish the activity of the Ti(III) reagent by forming a non-reactive, bimetallic Ti(III) complex 1.104 as originally reported by Coutts and Martin.⁶¹

![Scheme 1.25 Possible Cp₂TiCl contaminant.](image)

**Table 1.6** Representative ⁷¹Al chemical shifts.⁹⁷
In an attempt to confirm the presence of residual AlCl₃ in the isolated Ti(III) dimer, $^{27}$Al-NMR $(I = 5/2)$ was employed to detect any residual AlCl₃. $^{27}$Aluminum has a relative abundance of 100% and thus $^{27}$Al-NMR should provide a qualitative, yet highly sensitive means of detecting trace aluminum. A solution of dimeric Cp₂TiCl in benzene-$d_6$ recorded at 130 MHz gave a broad signal at $\delta_{Al} = 75.6$ relative to a Al(H₂O)₆³⁺ reference standard. Although the exact nature of the species responsible for the observed resonance is unclear, the resonance at $\delta_{Al} = 75.6$ is in the region assigned to tetrahedral Al-bound halides and adducts and is consistent with the presence of the bimetallic titanium(III) complex.

Future studies should focus on aziridine substrates containing an appropriately placed point of unsaturation to facilitate intramolecular reaction (Scheme 1.14 and 1.26). Substrates such as aziridine 1.105 could be prepared in three steps from commercially available 5-hexenol by selective oxidation to the aldehyde, followed by imine formation and aziridination with dimethylsulfonium methylide. $^{91}$

![Scheme 1.26 Proposed modification of aziridine substrates for future study. Reagents and conditions: (a) PCC or PDC oxidation. (b) PhNH₂, abs. EtOH. (c) Dimy sodium, DMSO, Me₂ST.](image)

**1.6.3 Reductive Coupling of Aldehydes and Ketones using Cp₂TiCl**

Based upon Enholm's work cited earlier involving the SmI₂ mediated cyclization of 5-hexenals (Scheme 1.8), we were interested in an efficient route to a simple 5-hexenal and hept-6-en-2-one to determine if (Cp₂TiCl)₂ could induce ketyl formation in aldehydes and ketones. Preparation of both substrates from lactols via Wittig olefination involving stabilized phosphoranes would permit activated olefins to be used as radical acceptors (Scheme 1.16). Our first target substrate was the simple 5-hexenal
1.108 (Scheme 1.27) derived in five steps from methyl α-D-glucopyranoside as reported by Vasella. Reductive dehalogenation of 6-deoxy-6-bromo-2,3,4-tri-O-benzyl-α-D-glucopyranoside 1.107 gave the target 5-hexenal 1.108 in modest yield.

A second substrate similar to that reported by Enholm (1.47, Scheme 1.8) was also prepared. The hept-6-en-2-one 1.110 was prepared from 2-deoxy-D-glucopyranose by a route reported earlier by Masumune and Sharpless as modified by RajanBabu and Nugent (Scheme 1.28).

Scheme 1.27 Preparation of 5-hexenal. Reagents and conditions: (a) PhCH(OMe)₂, cat. p-TsOH, DMF, 100 °C, 75%. (b) KH, DME, BnBr, 78%. (c) LAH, AlCl₃, Et₂O/CH₂Cl₂, reflux; 97%. (d) NBS, PPh₃, CH₂Cl₂, 0 °C-reflux; 83% (e) Zn/Cu couple, n-PrOH/H₂O, reflux; 50%.

Scheme 1.28 Preparation of hex-5-enones. Reagents and conditions: (a) Allyl alcohol, Amberlite IR-120 acidic ion-exchange resin, 4 Å sieves, 40 °C, 24 h; 65%. (b) PhCHBr₂, pyridine, reflux, 1 h; 61%. (c) KH, THF; BnBr, 0→25 °C, 12 h; 73%. (d) Ir[COD(PPhMe₂)₂]⁺PF₆⁻, H₂, THF, 5 h; then HgO, HgCl₂, 10:1 acetone/H₂O, 5 h; 61% (two steps). (e) DME, Ph₃P=CHCO₂Et, 5 mol% PhCO₂H, reflux, 12 h; 39% (f) NCS, DMS, toluene, -25 °C, 2 h, then Et₃N; 47%. (g) Ph₃P=CHCO₂Bu', DME, 25 °C, 36 h; 88%. (h) DMSO, TFAA, CH₂Cl₂, -78 °C, 1 h, then Et₃N, 63%. (i) BnONH₂-HCl, 12:1 MeOH/pyr, reflux, 4 h; 76%; (j) DMSO, TFAA, CH₂Cl₂, -78 °C, 1 h, then Et₃N; 80%.
Thus, 2-deoxy-D-glucopyranose was Fischer glycosylated in the presence of allyl alcohol to give the corresponding allyl glucopyranoside in 64% yield as a mixture of anomers. Because of the presence of an acid-labile allyl protecting group, the glycoside was then protected as its 4,6-O-benzylidene under basic conditions by reaction with benzal bromide in refluxing pyridine in 61% yield. Benzylation of the remaining 3-O position gave the fully protected allyl 4,6-O-benzylidene-3-O-benzyl-D-glucopyranoside in 71% yield. The 4,6-O-benzylidene-3-O-benzyl-D-glucopyranose was obtained, as reported by RajanBabu and Nugent, by isomerization of the fully protected allyl glycoside to the corresponding enol ether in the presence of cationic iridium followed by hydrolysis of the enol ether to give the free glucopyranose in 61% yield. With 4,6-O-benzylidene-3-O-benzyl-D-glucopyranose now available, Wittig olefination of the lactol with stabilized phosphoranes followed by oxidation under either Corey-Kim or Swern conditions provided access to the functionalized hept-6-en-2-ones and needed for further experiments involving \((\text{Cp}_2\text{TiCl})_2\). Furthermore, oximation of the lactol intermediate in 76% yield followed by Swern oxidation in 80% yield provided a route to keto-oxime, which was also of interest as a cyclization substrate.

Since preparation of the 5-hexenal involved the primary bromide (Scheme 1.27), we wondered if \(\text{Cp}_2\text{TiCl}\) would induce dehalogenation of 1.107 and give the 5-hexenal 1.108 and if so, would the intermediate 5-hexenal undergo further reaction? Schwartz has shown that activated glycosyl bromides undergo elimination in the presence of \(\text{Cp}_2\text{TiCl}\) to give the glycals (Scheme 1.12). Although this primary bromide was not activated, the presence of a \(\beta\)-leaving group should eliminate once the titanium organometallic species was produced by homolysis and further electron transfer.

Therefore, both 1.107 and 1.108 were exposed to excess \((\text{Cp}_2\text{TiCl})_2\). In both cases, \(^1\text{H-NMR}\) analysis of the crude reaction products indicated only unreacted starting material remained.
Likewise, exposure of ketones 1.110 and 1.111 to Cp₂TiCl under identical conditions as described for 5-hexenal 1.108 gave results shown in Scheme 1.30. Exposure of the ketone 1.110 to (Cp₂TiCl)₂ gave an oil (37%) which clearly was not starting material, and has been tentatively assigned the bicyclic lactone structure 1.113. This structural assignment was based in part upon the absence of the ketone, vinyl and ethyl signals in both ¹H- and ¹³C-NMR spectra of the product. The cyclization of 1.111 (vide infra, 1.114) also supports this assignment. The presence of a signal in the infrared spectrum (ν = 1758 cm⁻¹) and the absence of a hydroxyl signal (br ca. 3200-3600 cm⁻¹), strongly supports the bicyclic lactone structure 1.113. High resolution mass spectral analysis of the product showed a molecular ion signal consistent with C₂₂H₂₂O₅ ± 1.7 ppm of the calculated value. The stereochemistry of the final product was inferred since the dioxane function would require a 1,2-cis relationship between H-4a, H-7a and the stereochemistry at the H-7a position of the tricycle is fixed from the starting glucose. This inference leads to the relative and absolute stereochemistry shown at positions H-4a and H-5 of 1.113.

Scheme 1.29 Reaction of Cp₂TiCl with an alkyl bromide and 5-hexenal. Reagents and conditions: (a) excess (Cp₂TiCl)₂, THF, 25 °C, 1 h. (b) excess (Cp₂TiCl)₂, THF, 25 °C, 1 h.
Scheme 1.30 Cyclization of ketones with Cp₂TiCl. Reagents and conditions: (a) 1.25 equiv. (Cp₂TiCl)₂, THF, 25 °C, 3 h; 35%. (b) 1.25 equiv. (Cp₂TiCl)₂, THF, 25 °C, 3 h; 47%.

Similarly, keto-acrylate 1.111 also underwent cyclization in the presence of Cp₂TiCl to give the cyclopentane 1.114 in 47% yield. The structural assignment was based in part upon the loss of starting ketone and vinyl signals (δc = 205.4, 143.3 and 126.4) and IR signals (ν = 1736 and 1710 cm⁻¹). Further support for the structure was the presence of a new signal consistent with the ester function at δc = 172.8 and the presence of a broad signal in the infrared at ν = 3483 cm⁻¹. Subsequent analysis by HRMS gave a molecular ion signal consistent with C₂₂H₂₄O₆ (M-C₆H₉)⁺ ± 4.4 ppm of the calculated value. Surprisingly, an attempt to confirm the presence of the hydroxy function by acetylation of the tertiary alcohol failed and only unreacted starting material was recovered.

Definitive stereochemical assignment at H-5 in 1.114 has not been possible. The complexity of the ¹H-NMR spectra of 1.114 prevented stereochemical assignment at position H-5 based upon coupling constant analysis. Furthermore, stereochemical assignment at H-5 based upon NOE difference experiments also failed to show any signal enhancement upon irradiation of both H-7 and H-7a. Our
tentative assignment is based upon the result observed in 1.113 which can be rationalized by examination
of the *endo* products derived from the predicted 1,5-*cis* cyclization.

![Diagram](image)

**Figure 1.9** Rationale for tentative 1,5-*trans* assignment in 1.114.

The transition state leading to the 1,5-*cis* product forces the bulky ester side-chain into the *endo*
face of a sterically congested *cis*-indane framework as shown in transition state 1.115. The 1,5-*trans*
products may reflect kinetic control wherein the congestion of the *endo* products is reflected in the
transition state as a preference for the double bond to adopt a lower energy boat-like transition state as
depicted in transition state 1.116.

![Scheme](image)

**Scheme 1.31** Attempt to use oxime ether as a radical acceptor. Reagents and conditions:
(a) 1.25 equiv. (Cp₂TiCl)₂, 61 THF, 25 °C, 0.5 h; 1.0 M HCl/ Et₂O; Ac₂O, pyridine, DMAP,
25 °C, 12 h.

Likewise, keto-oxime 1.112 was also exposed to Cp₂TiCl under standard conditions with the
exception that following workup, acetylation was attempted to aid in the recovery of all amine products

39
Following flash chromatography, several unidentified compounds were isolated along with material whose spectra was consistent with benzyl acetate. This observation led to some concern about the stability of oxime ethers to the reaction conditions.

1.7 Chapter Summary

The initial aim of this research was a preliminary investigation into new synthetic applications of Cp₂TiCl for the generation of radicals from a variety of different precursors and further application to cyclopentitol synthesis. Our initial tests failed to support the hypothesis that Cp₂TiCl prepared in situ, acting as a transition metal-centered radical, might serve as a functional equivalent to tributytin radicals in the reduction of alkyl bromides and S-methyl dithiocarbonates. Furthermore, our experience with Cp₂TiCl used in situ indicated that the presence of the Lewis acids generated in the reaction may play a complicating role in the reaction and that for the remainder of our studies isolated (Cp₂TiCl₂) prepared by the Manzer procedure⁶⁴ should be used whenever possible to avoid such problems. Although our initial attempts to induce Cp₂TiCl mediated ring opening in 2-aziridinecarboxylates gave only unreacted starting materials, attempts using 2-phenyl-Ν-phenylaziridines were encouraging, yet inconclusive and suggested further studies with modified aziridine substrates were necessary (Scheme 1.26). In reactions designed to test the ability of Cp₂TiCl to induce ketyl formation in aldehydes and ketones, two examples of cyclic ketones bearing activated 4-butenyl sidechains underwent 5-hexenyl radical cyclizations in modest yield to give the anticipated cyclopentanes (Scheme 1.9). Attempts to induce ketyl formation in an aliphatic ketone with subsequent cyclization onto a sidechain bearing an oxime ether radical acceptor gave decomposition products which raised the suspicion that benzyl oximes, and perhaps oxime ethers in general, are cleaved under the reaction conditions (Scheme 1.31).

Faced with these initial results, we decided to turn our attention to epoxides as the radical precursor of choice, and investigate the feasibility of preparing functionalized cyclobutanoids via Cp₂TiCl mediated 4-*exo-trig* radical cyclizations.
CHAPTER 2

TITANIUM(III) MEDIATED PENT-4-ENYL RADICAL CYCLIZATIONS

2.1 Functionalized Cyclobutanoids of Medicinal Interest

The Cp2TiCl mediated opening of epoxides and subsequent 5-hexenyl radical cyclization was a route particularly suited for the preparation of cyclopentitols since the hydroxymethyl sidechain residue remaining after ring opening and annulation was a common feature found in several cyclopentitols of medicinal interest (Figure 1.1). In addition to the several cyclopentitols described earlier, medicinally important natural products containing a hydroxymethyl sidechain include a novel class of cyclobutyl nucleosides possessing powerful antiviral activity (Figure 2.1).

![Figure 2.1 Oxacyclobutyl and cyclobutyl nucleosides of medicinal interest](image)

2.1 Oxetanocin A \( X = O, Y = NH_2, Z = H \)
2.2 Oxetanocin G \( X = O, Y = OH, Z = NH_2 \)
2.3 COXT A \( X = CH_2, Y = NH_2, Z = H \)
2.4 COXT G \( X = CH_2, Y = OH, Z = NH_2 \)
In 1986, Shimada and coworkers isolated the oxacyclobutyl nucleosides oxetanocin A (2.1) and oxetanocin G (2.2) from the bacteria *Bacillus megaterium* NK84-0218. The oxetanocins were later shown to exhibit inhibitory activity against a number of viruses including human cytomegalovirus (HCMV) and hepatitis B virus (HBV), herpes simplex virus (HSV-1) and (HSV-2), and the human immunodeficiency virus (HIV) responsible for the acquired immune deficiency syndrome (AIDS).

The oxetanocins are the only known examples of cyclobutyl nucleosides and preparation of analogues has become a priority. In 1990, the analogous carbocyclic oxetanocins (COXT) A (2.3) and COXT G (2.4) were prepared and shown in some cases to exhibit even greater antiviral activity than their heterocyclic analogues. For example, COXT A has been shown to be 350 times more potent against HBV than adenosine arabinose and COXT G is 2-3 times more potent than the currently prescribed acyclovir against HSV. Despite the immense interest in preparing analogues of the oxetanocins, the preparation of the cyclobutyl backbone in the COXT's has remained a formidable challenge due to the limited number of synthetic methods available for preparing cyclobutanes. The majority of synthetic routes to the COXT's to date have relied upon [2+2] cycloadditions, Wolff rearrangement, intramolecular cyclizations, and others.

We recognized that the Cp2TiCl mediated epoxide ring opening/cyclization could provide one of the necessary hydroxymethyl sidechains found in the COXT analogues and considered whether the

![Figure 2.2 Proposed Cp2TiCl mediated route to functionalized cyclobutanes.](image-url)
analogous Cp₂TiCl mediated 4-pentenyl cyclizations could be used to provide a general route to functionalized cyclobutanes as depicted in Figure 2.2.

At the outset, we recognized the inherent difficulty in preparing cyclobutanes via radical reactions was the reversibility of the 4-exo-trig ring closure to give the methylcyclobutyl radical (2.8) which favors the strain free, acyclic 4-pentenyl radical (2.7). However, we reasoned that the presence of a strategically placed dioxolane and radical stabilizing group might shift the equilibrium toward methylcyclobutane radical 2.8. Although a literature review provided a number of examples where a 4-exo-trig radical cyclization had been employed in the synthesis of β-lactams, the corresponding carbocyclic examples were far less common.

Figure 2.3 Reversibility of carbocyclic 4-pentenyl radical cyclizations.

2.2 Examples of 4-Pentenyl Radical Cyclizations

Although the number of reports were few, the literature precedents for carbocyclic 4-pentenyl cyclizations were encouraging. In 1990, Newcomb performed a kinetic study to determine the cyclization rate constant $k_c$ of 2,2-dimethyl-5-cyano-4-pentenyl radical (2.10) for which he determined the value to be $1.9 \times 10^4 \text{s}^{-1}$. Newcomb then argued that kinetic data from analogous 5-exo and 3-exo cyclizations can be used to reliably predict the effects on 4-exo cyclizations. For example, the Thorpe-Ingold or gem-dimethyl effect is known to increase the rate of 3-butenyl cyclizations by a factor of 333 at 50 °C. Similarly, a radical stabilizing cyano group is known to increase the rate of 5-hexenyl cyclizations by a factor of 275 at 50 °C. These two effects, if additive, would give a predicted 90,000-fold rate increase for a cyclization
employing both moieties. It follows then from the rate data Newcomb determined for the 2,2-dimethyl-5-cyano-4-pentenyl radical (2.10) that the representative 4-pentenyl radical (2.7) would be expected to have a rate constant $k_c$ on the order of 0.2 s$^{-1}$.

\[
\text{CN} \quad \text{Bu}_3\text{SnH} \quad \begin{array}{c}
\text{CN} \\
\text{Br}
\end{array} \\
\text{2.9}
\]

Scheme 2.1 Kinetic studies on ring closure of 4-pentenyl radical.\textsuperscript{122} Reagents and conditions: tributyltin hydride, catalytic AIBN, benzene, reflux.

Since Geise has established a qualitative lower limit of $k_c = 1 \times 10^4 \text{ s}^{-1}$ to be the rate of a synthetically useful intramolecular cyclization,\textsuperscript{119} it follows then from Newcomb's results that the presence of gem-dialkyls or a radical stabilizing group alone would not be expected to influence the rate of 4-pentenyl cyclizations significantly (ca. $k_c = 67 \text{ s}^{-1}$ and $k_c = 55 \text{ s}^{-1}$ respectively). This prediction is in accord with Beckwith's results wherein a 3,3-dimethyl-4-pentenyl radical (2.15) gave only reduced 3,3-dimethyl-4-pentene (2.16) and none of the 2-methyl-5-hexene (2.19) resulting from 4-pentenyl cyclization and rearrangement (Scheme 2.2).\textsuperscript{123}
Scheme 2.2 Results concerning the influence of the Thorpe-Ingold Effect on the rate of 4-pentenyl radical cyclizations.\textsuperscript{123}

Other examples of carbocyclic 4-pentenyl cyclizations also foreshadow its future synthetic potential. In 1992, Ogura reported a single example where a captodative effect\textsuperscript{124} was advantageously used in a 4-pentenyl cyclization to prepare the cyclobutane 2.22 in 48\% along with 34\% of the reduced product 2.21 (Eq. 1, Scheme 2.3).\textsuperscript{125}

\begin{tabular}{|c|c|c|c|c|}
\hline
\textbf{2.23} & \textbf{R} & \textbf{2.24} & \textbf{2.25} & \textbf{Yield} \\
\hline
\textbf{a} & H & 100 & 0 & - \\
\textbf{b} & Me & 2 & 1 & - \\
\textbf{c} & Me & 1 & 9 & - \\
\textbf{d} & OEt & 0 & 100 & 72\% \\
\hline
\end{tabular}

Scheme 2.3 Other examples of 4-\textit{exo-trig} radical cyclizations.
Jung has also reported a variation on the Thorpe-Ingold effect where the presence of gem-alkoxy groups appear to facilitate cyclization over simple gem-dialkyl groups (2.23d, Eq. 2, Scheme 2.3). The first synthetically useful 4-pentenyl cyclization was reported in 1994 by Weinges wherein optically active (E)-6-oxo-hex-2-enoate (2.26) gave the enantiopure ethyl (1S, 3R, 4R)-(−)-[3-(benzyloxy)-4-hydroxy-2,2-dimethylcyclobutyl]acetate (2.27) in 60% yield in the presence of samarium diiodide.\(^\text{57}\)

Scheme 2.4 Weinge's 4-exo-trig route to functionalized cyclobutanes.\(^\text{57}\)

The high diastereoselectivity of the 4-pentenyl cyclization was rationalized as resulting from a model transition state 2.28 analogous to that proposed by Beckwith for the corresponding 5-hexenyl cyclization 2.29 where adjacent sidechains adopt trans orientations.

Figure 2.4 Proposed transition state for 4-exo-trig cyclization.

One additional example to note was that reported by Kocovský where he attempted a 4-pentenyl radical cyclization on a diquinane backbone 2.30 which yielded only reduced product 2.31.\(^\text{126}\) When the
reaction conditions were changed from neutral to ionic, the desired cyclization occurred in good yield to give cyclobutane 2.32 indicating that the geometrical requirement for cyclobutane formation was satisfied and was not a factor in the failure of the 4-pentenyl radical cyclization.

Scheme 2.5  Attempt at 4-pentenyl radical cyclization.

2.3 Synthetic Plan

2.3.1 Preparation of Epoxides via Williamson Ether Synthesis

With this precedent on 4-pentenyl cyclizations, we set out to test our hypothesis and began the synthesis of the target ethyl 6,7-anhydro-2,3-dideoxy-4,5-0-isopropylidene-D-ribo-hept-2-enoate (2.34) (Scheme 2.6). In keeping with our desire to construct functionalized carbocycles from simple carbohydrate precursors, we recognized that disconnection of epoxide 2.34 would yield ethyl 7-bromo-2,3,7-trideoxy-4,5-0-isopropylidene-D-ribo-hept-2-enoate (2.33). Further disconnection of the α,β-unsaturated ester would yield 5-bromo-5-deoxy-2,3-O-isopropylidene-D-ribofuranose which was available in three steps from the commercially available D-ribono-γ-lactone.

Protection of D-ribono-γ-lactone as its isopropylidene derivative was accomplished conveniently in dry acetone/iodine in 89% yield. The 2,3-O-isopropylidene-D-ribono-γ-lactone was then converted to 5-bromo-5-deoxy-2,3-O-isopropylidene-D-ribono-γ-lactone in 75% yield under conditions described by Hanessian. Diisobutylaluminum hydride reduction of the 5-bromo-5-deoxy-2,3-O-isopropylidene-D-ribono-γ-lactone gave 5-bromo-5-deoxy-2,3-O-isopropylidene-β-D-ribofuranose in 95% yield (β/α = 18).
Subsequent Wittig olefination\textsuperscript{129} of 5-bromo-5-deoxy-2,3-\textit{O}-isopropylidene-\textit{D}-ribofuranose with commercially available (carbethoxymethylene)triphenylphosphorane gave the ethyl 7-bromo-2,3,7-trideoxy-4,5-\textit{O}-isopropylidene-\textit{D}-ribo-hept-2-enoate (2.33) in almost quantitative yield as a mixture of isomers \((Z/E = 3)\) which could be separated by careful chromatography.

Scheme 2.6  Synthetic route to target epoxide via halohydrin. Reagents and conditions: 
(a) acetone, \(I_2\), anhydrous \(\text{MgSO}_4\), 25 °C, 12 h; 89%. (b) \(\text{PPh}_3\), NBS, \CH_2Cl_2, 0 °C, 0.5 h; then \(\text{BaCO}_3\), 50 °C, 15 min; 75%. (c) Dibal-H 1.5 M in toluene, \ET_2O, -78 °C, 1 h; 95%. (d) \(\text{Ph}_3\text{P}=\text{CHCO}_2\text{Et}\), DME, 25 °C, 12 h; 97%. (e) NaOEt/EtOH, 25 °C, 2 h. (f) Ag_2O, McCN, 0→25 °C; 62%. (g) LDA, THF, -78→25 °C.

As observed earlier, stabilized Wittig olefination of unprotected lactols gave predominantly \((Z)\) products (Scheme 1.1).\textsuperscript{130} Attempts to prepare epoxide 2.34 under standard Williamson conditions (NaOEt/EtOH) yielded the unwanted ethyl (5-bromo-5-deoxy-2,3-\textit{O}-isopropylidene-\textit{D}-ribofuranosyl)acetate (2.35) resulting from irreversible 5-exo-trig addition of the alkoxide onto the
acylate. This result is consistent with Baldwin's rules\textsuperscript{131} where the rate of cyclization follows the trend $5 > 6 > 3$ and is a general method for preparing 2-(furanosyl)acetates.\textsuperscript{132} Attempts to eliminate the $\beta$-alkoxide of 2.35 and force 3-\textit{exo-tet} epoxidation in the presence of a stronger base such as LDA lead to a complex mixture of products.

Williamson ether synthesis under neutral conditions was then attempted by exposure of the bromohydrin (Z)-2.33 to silver oxide in acetonitrile at 0 °C with the hope of activating the bromide to displacement. The net result was the recovery of isomerized bromohydrin (E)-2.33 exclusively. From these initial results, attempts to prepare epoxide 2.34 from halohydrins bearing an activated 4-pentenyl sidechain were abandoned in favor of other potential routes.

### 2.3.2 Preparation of Epoxides via Displacement of Mesylates

In an attempt to avoid the C-glycoside formation via the highly favored 5-\textit{exo-trig} cyclization, it was hoped that 3-\textit{exo-tet} displacement of ethyl 2,3-dideoxy-6-O-methanesulfonyl-4,5-O-isopropylidene-ribo-hept-2-enoate (2.40) by the vicinal primary alcohol would occur preferentially over the undesired 6-\textit{exo-trig} cyclization under carefully controlled and near neutral reaction conditions (Scheme 2.7).

The fully protected 5-O-\textit{tert}-butyldimethylsilyl-2,3-O-isopropylidene-D-ribo-\gamma-lactone (2.36) was reduced to the lactol and subsequently olefinated as previously described to give (Z)-ethyl 2,3-dideoxy-7-O-\textit{tert}-butyldimethylsilyl-4,5-O-isopropylidene-ribo-hept-2-enoate (2.37) in good yield (two steps, 93%) as a mixture of isomers ($Z/E = 2.3$). Mesylation to give both (Z) and (E)-ethyl 2,3-dideoxy-7-O-\textit{tert}-butyldimethylsilyl-6-O-methanesulfonyl-4,5-O-isopropylidene-ribo-hept-2-enoate (2.38) was accomplished in 76% yield. Desilylation was attempted under a variety of conditions. Since neutral conditions were desired, we initially wished to avoid the basic conditions reported with the use of the TBAF reagent. Desilylation was first attempted in the presence of tetrabutylammonium triphenyldifluorosilicate.\textsuperscript{133} These conditions, however, proved too basic and resulted in 6-\textit{exo-trig} cyclization to give the unwanted ethyl (2,3-O-isopropylidene-4-O-methanesulfonyl-D-ribo.pyranosyl)acetate (2.39) in 69% yield. We next looked to desilylation under acidic conditions.
involving 48% hydrofluoric acid. Our initial concern was whether we could selectively desilylate in the presence of an acetonide under acidic conditions. Kocienski’s monograph warns that such selectivity may be poor. In practice, and on a small scale, 48% hydrofluoric acid at 0 °C was capable of selective desilylation of (Z)-ethyl 7-O-tert-butyldimethylsilyl-2,3-dideoxy-4,5-O-isopropylidene-6-O-methanesulfonyl-ribo-hept-2-enoate (2.38) without loss of the isopropylidene function, but provided only uncyclized (Z)-ethyl 2,3-dideoxy-4,5-O-isopropylidene-6-O-methanesulfonyl-ribo-hept-2-enoate (2.40).

Scheme 2.7 Synthetic route to target epoxide via a mesylate. Reagents and conditions:
(a) Dibal-H 1.5 M in toluene, Et₂O, -78 °C, 1 h; 95%. (b) Ph₃P=CHCO₂Et, DME, 25 °C, 12 h; 98%. (c) MeSO₂Cl, pyridine, 0 °C, 5 h; 72%. (d) Ph₃S₂SiBu₃N⁺, THF, 50 °C, 24 h; 69%. (e) HF 48%, MeCN, 0 °C. (f) TFAA, DMSO, CH₂Cl₂, -78 °C; then Et₃N, 25 °C; 48%. (g) (Cp₂TiCl)₂, THF, 25 °C. (h) HF (48%), MeCN, 0 °C; 59%.
Attempts to scale up the reaction lead to polar products which were undoubtedly the result of loss of the isopropylidene function. This route involving selective displacement of a mesylate to give epoxide 2.34 was also abandoned.

In an attempt to further investigate the potential of Cp₂TiCl to induce ketyl formation from ketones, (Z)-ethyl 7-O-tert-butyldimethylsilyl-2,3-dideoxy-4,5-O-isopropylidene-6-oxo-ribo-hept-2-enoate (2.41) was prepared in 48% yield from alcohol 2.37 via Swern oxidation. Exposure of ketone 2.41 to 1.25 equivalents of (Cp₂TiCl)₂ (1.54) in THF at 25 °C yielded only recovered starting ketone 2.41.

2.3.3 Preparation of Epoxides via Mitsunobu Reaction

It is known that epoxides are available from vicinal diols by way of the Mitsunobu and Mattock reaction. Therefore, we planned to prepare the target diol ethyl 2,3-dideoxy-4,5-O-isopropylidene-ribo-hept-2-enoate (2.42) from commercially available D-ribofuranose. In practice, attempts to prepare 2.42 directly from 2,3-O-isopropylidene-D-ribofuranose under Wittig olefination conditions were complicated by large amounts of unwanted ethyl (2,3-O-isopropylidene-D-ribofuranosyl)acetate formation. We were able to prepare small amounts of diol 2.42 from the desilylation of (Z)-ethyl 2,3-dideoxy-7-O-tert-butyldimethylsilyl-4,5-O-isopropylidene-ribo-hept-2-enoate (2.37) (Scheme 2.7) but eventually decided to prepare the tert-butyl 2,3-dideoxy-4,5-O-isopropylidene-ribo-hept-2-enoate (2.43) instead of the ethyl hept-2-enoate 2.42 since use of (carbtert-butoxymethylene)triphenylphosphoranes had been reported by Clive to reduce the incidence of unwanted C-glycoside formation with unprotected pyranosides during Wittig olefination. With this reduced propensity toward C-glycoside formation, we then looked to see if the tert-butyl 6,7-anhydro-2,3-dideoxy-4,5-O-isopropylidene-D-ribo-hept-2-enoate (2.48) could be prepared via 3-exo-tet displacement of a bromide or a tosylate.

We began with inexpensive D-ribofuranose and prepared 2,3-O-isopropylidene-D-ribose (β/α = 7.1) in 75% yield according to literature procedure. Subsequent Wittig olefination in the presence of (carbtert-butoxymethylene)triphenylphosphorane gave predominantly the (Z)-tert-butyl 4,5-O-
isopropylidene-ribo-hept-2-enoate (2.43) in modest yield along with a small amount of the corresponding 
(E)-2.43.130

Diol (Z)-2.43 was then selectively tosylated to give the (Z)-tert-butyl 2,3-dideoxy-4,5-O-
isopropylidene-7-O-toluenesulfonyl-ribo-hept-2-enoate (2.47) in 40% yield. Exposure of primary tosylate 
(Z)-2.47 to sodium methoxide in methanol gave the desired (Z)-tert-butyl 6,7-anhydro-2,3-dideoxy-4,5-O-
isopropylidene-ribo-hept-2-enoate (2.48) in 24% yield along with unwanted methyl and tert-butyl (2,3-O-
isopropylidene-5-O-toluenesulfonyl-D-ribofuranosyl)acetates in 12% and 26% respectively.

We had also hoped to prepare the desired epoxide 2.48 by way of a modification of the Mattock 
reaction as described by Sharpless.140 It was thought that treatment of the diol under the reaction 
conditions (Scheme 2.8) would generate an 1,3-dioxolan-2-ylium intermediate which would open

\begin{align*}
\text{Scheme 2.8 Synthetic route to target epoxide via diols. Reagents and conditions:} & \\
& \text{(a) 2,2-dimethoxypropane, DMF, 1 mol\% } p\text{-TsOH-H}_2\text{O, 25 °C, 3 h; 75\%. (b) } \text{Ph}_3\text{P}=\text{CHCO}_2\text{Bu}', \text{ DME,} \\
& 12 \text{ h; 60\%. (c) } \text{CH}_3\text{C(OMe)}_3, \text{ cat. } p\text{-TsOH/pyr, CH}_2\text{Cl}_2, 25 \text{ °C, 0.5 h; then AcBr, Et}_3\text{N, CH}_2\text{Cl}_2,} \\
& 25 \text{ °C, 0.5 h; then MeOH, Amberlite basic ion-exchange resin. (d) } \text{TsCl, pyr, CH}_2\text{Cl}_2, \text{ cat.} \\
& \text{DMAP, 0→25 °C, 12 h; 40\%. (e) NaOMe, MeOH, CHCl}_3, 0.5 \text{ h; 24\%. (f) PPh}_3, \text{ DEAD, toluene} \\
& 0→110 \text{ °C, 2 h; 32\%.}
\end{align*}
regioselectively in the presence of halide ion to give the (Z)-tert-butyl 7-O-acetyl-6-bromo-2,3,6-trideoxy-4,5-O-isopropylidene-ribo-hept-2-enoate (2.44). Mild methanolysis of 2.44 would then provide the desired epoxide 2.48 by way of the 3-exo-tet pathway over the unwanted 6-exo-trig.

In practice, however, no epoxide was isolated and a 1:1 mixture of both (Z)-tert-butyl 7-O-acetyl-2,3-dideoxy-4,5-O-isopropylidene-ribo-hept-2-enoate (2.45) and undesired regioisomer (Z)-tert-butyl 6-O-acetyl-7-bromo-2,3,6-trideoxy-4,5-O-isopropylidene-ribo-hept-2-enoate (2.46) was recovered. Diol (Z)-2.43 was next exposed to Mitsunobu conditions to give (Z)-tert-butyl 6,7-anhydro-4,5-O-isopropylidene-ribo-hept-2-enoate (2.48) in 32% along with recovered starting materials. To our surprise, no indication of tert-butyl (2,3-O-isopropylidene-D-ribofuranosyl)acetate formation was detected even under forcing conditions. Despite the low yields obtained from the Williamson and Mitsunobu reactions, enough of the desired epoxide 2.48 was prepared to test our hypothesis.

We also wished to determine the suitability of oxime ethers to participate in the proposed 4-pentenyl cyclizations. Similarly, 2,3-O-isopropylidene-D-ribofuranose was methoximinated to give the corresponding 2,3-O-isopropylidene-D-ribofuranose, O-methyl oxime ether (2.49) in 67% as a mixture of isomers (E/Z = 5). We elected to prepare the O-methyl oximes as opposed to the O-benzyl oximes since the stability of the later in the presence of (Cp₂TiCl)₂ was suspect as previously described (Scheme 1.31). Furthermore, since we did not expect oxime 2.49 to undergo base induced, 5-exo-trig cyclizations as readily as the hept-2-enoates, we decided S₂N₂ displacement of a tosylate was a feasible route to the corresponding epoxides. Diol 2.49 was then selectively tosylated to give 2,3-O-isopropylidene-5-O-toluenesulfonyl-D-ribofuranose, O-methyl oxime ether (2.50) in 62% yield. Intramolecular displacement of the primary tosylate was conducted in the presence of mild base to give the desired 4,5-anhydro-2,3-O-isopropylidene-D-ribofuranose, O-methyl oxime ether (2.51) in 74% yield (E/Z = 3.5). Epoxide 2.51 was also obtained directly from diol 2.49 under Mitsunobu conditions in 30% yield.
A recent report indicating that azides are reduced in the presence of poly(methylhydrosiloxane) and catalytic tributyltin hydride to the corresponding amines by way of an intermediate aminyl radical.\textsuperscript{143} We postulated that this intermediate aminyl radical might be efficiently trapped via 5-exo-trig radical cyclization to give the corresponding heterocycle. We expected sodium azide displacement of (Z)-\textit{tert}-butyl \textit{7-O-tert}-butyldimethylsilyl-2,3-dideoxy-4,5-O-isopropylidene-6-O-toluenesulfonyl-\textit{ribo}-hept-2-enoate (2.53) would give the desired (Z)-\textit{tert}-butyl 6-O-azido-7-\textit{O-tert}-butyldimethylsilyl-2,3,6-trIDEOXY-4,5-O-isopropylidene-\textit{ribo}-hept-2-enoate (2.55) to test this hypothesis. Although the displacement of tosylates by azides has been reported,\textsuperscript{144} several attempts to perform a simple S\textsubscript{N}2 displacement on the secondary tosylate 2.53 by sodium azide failed under a variety of conditions (Scheme 2.10) which yielded only unreacted starting material or decomposition products under forcing conditions.
Having access to tosylate 2.53, we could not resist one last effort to prepare epoxide 2.48. Desilylation of (Z)-tert-butyl 7-O-tert-butyldimethylsilyl-2,3-dideoxy-4,5-O-isopropylidene-6-O-tosyl-ribo-hept-2-enoate (2.53) gave (Z)-tert-butyl-(5-O-tosyl-3,4-O-isopropylidene-D-ribofuranosyl)acetate (2.54) without any detected epoxide formation. This route to epoxides bearing activated olefins was finally laid to rest.

2.4 Cp2TiCl2 Mediated Cyclization of Epoxides: Attempted Cyclobutane Formation.

With (Z)-tert-butyl 6,7-anhydro-2,3-dideoxy-4,5-O-isopropylidene-ribo-hept-2-enoate (2.48) and 4,5-anhydro-2,3-O-isopropylidene-D-ribofuranose, O-methyl oxime ether (2.51) in hand, each was exposed to (Cp2TiCl2) under standard conditions. Isolation of the reaction products from cyclization of epoxide 2.51 yielded only decomposition products while cyclization of epoxide 2.48 yielded an unexpected result.
Scheme 2.11 Cp₂TiCl mediated cyclization of epoxides. Reagents and condition: (a) 1.25 equiv. (Cp₂TiCl)₂, THF, 25 °C.

By ¹H-NMR, the product obtained from cyclization of epoxide 2.48 contained the characteristic signals of a tert-butyl ester and acetonide, yet failed to show the epoxide signals which would indicate unreacted starting material. Interestingly, the olefin geometry was now that of an (E)-olefin (J = 15.8 Hz) as opposed to the (Z)-olefin (J = 11.6 Hz) in the starting material. With a general lack of functionalized cyclobutanes in the literature and commensurate lack of NMR data available, we had few guides in interpreting the NMR. However, simple cyclobutane formation could not be rationalized without the presence of an α-methylene signal of an ester (ca. δH = 2.3) and with the ester unsaturation clearly intact. Further complicating the picture was the complete absence of the expected hydroxyl function as was clear from the infrared spectrum.

We were confident the (Cp₂TiCl)₂ used was active as demonstrated by tests with the standard epoxy olefins as described earlier (Scheme 1.21) and therefore, had little doubt that epoxide ring opening was occurring. Furthermore, trace amounts of side products isolated from the reaction exhibited new olefin signals by ¹H-NMR which suggested the presence of deoxygenation side products. The presence of diene (2.58) was later supported by high resolution mass spectrometry.
From the knowledge that radical cyclizations of 4-pentenyl radicals were reversible as described earlier (Figure 2.3), the presence of deoxygenation side products, and the observation that the double bond had undergone isomerization, we rationalized that the reversibility could entail ring opening of radical 2.60 in one of two ways to give 4-pentenyl radicals 2.59 and 2.61 as depicted in Scheme 2.12 below. The radical 2.61 might then trap chlorine within the reaction mixture to give the highly reactive 2.62, which then undergoes further cyclization to give the observed furanoside products.

Scheme 2.12 Proposed Reaction Pathway to Observed Furanoside Formation.

It quickly became apparent that some form of rearrangement had taken place and that the 3-deoxy-3-C-α-D-erythrofuranoside 2.57 was consistent with the observed one and two-dimensional NMR (COSY, HETCOR, NOESY), HRMS, and elemental analysis data. The absolute stereochemistry in 2.57 was tentatively assigned based upon comparison of vicinal coupling constant data with related furanosides, and the known preference for dioxolane formation from cis-1,2 diols.

It is reasonable to assume that the stereochemistry at position C-5 in epoxide 2.48 (C-2 in 2.57) remains unchanged throughout the rearrangement process and therefore, becomes the foundation for our
Considering the known preference for [3.3.0]octanes and bicyclic 1,3-dioxolanes to prefer a cis ring juncture, intramolecular substitution of the activated chloride in intermediate 2.62 should be expected to give the cis-1,3-dioxolane diastereoselectively as depicted in 2.57.

Table 2.1 Stereochemical comparison of the known α-D-erythrofuranoside 2.63, β-L-threofuranoside 2.64 with novel α-D-erythrofuranoside 2.57.

The relative stereochemistry between the 3-C-side chain and the 1,2-O-isopropylidene was assigned as cis based upon the J\(_{2,3}\) coupling of 4.1 Hz which was consistent with the coupling constants obtained from two related 3-deoxy-3-C-furanoside analogues of 2.57, 3-deoxy-3-C-methyl-1,2-O-isopropylidene-α-D-erythrofuranoside 2.63 and 3-deoxy-3-C-methyl-1,2-O-isopropylidene-β-L-threofofranoside 2.64. As the proton NMR data summarized in Table 2.1 shows, the coupling between H-2 and H-3 in 2.63 and 2.64 clearly differentiates the relative stereochemistry of the two centers. This
cis assignment between H-2 and H-3 was further supported by NOESY data which showed a large through space interaction between H-1 and H-3 of 2.57.

Likewise, our assignment of C-1 and C-2 stereochemistry is corroborated by 2.63 and 2.64. The doublet at $\delta_c = 106.5$ in the DEPT spectra of 2.57 was assigned as the anomeric signal C-1. Final yield calculated for 3-deoxy-3-C-(tert-butoxy-3-oxopropenyl)-1,2-O-isopropylidene-\( \alpha \)-D-erythrofuranoside 2.57 was 10-13%.

This unexpected result was encouraging for several reasons. First, the fact that we isolated furanoside 2.57 with the observed isomerization of the olefin side chain strongly supported the intermediacy of a cyclobutylmethyl radical 2.60 (Scheme 2.12) which would constitute a rare example of carbocyclic 4-pentenyl cyclization. Second, this result suggests that in addition to the rate acceleration expected from the presence of a stabilizing ester function, the presence of a dioxolane ring must also assist the ring closure in a manner similar to that observed by Jung with simple gem-dialkyls (Scheme 2.3). Third, the observed products also suggested that fine tuning the reaction by changing the radical stabilizing group (CN, SO$_2$Tol, etc.) or trapping the intermediate cyclobutylalkyl radical 2.60 with a hydrogen donor (1,3-cyclohexadiene) would further favor cyclobutyl products. Another alternative would be to trap radical 2.60 intramolecularly with an allyl or allyl sulfone moiety. Finally, the isolated product is a rare example of a branched chain sugar containing a 3-carbon side chain. Further understanding of the reaction mechanism might provide a general route to other important branched chain sugars.

When proposing a mechanism for the radical rearrangement, we could not rule out what effect, if any, residual Lewis acid present in the isolated (Cp$_2$TiCl)$_2$ might have had on the reaction mechanism (Scheme 1.25). We would also like to conduct the cyclization without any possible participation or interference by the primary titanium alkoxide generated. In an attempt to better understand the mechanism of this reaction and remove these two issues from consideration, we decided to attempt the 4-pentenyl cyclization under Barton-McCombie conditions using the thiocarboxylic acid derivatives 2.65-2.67 of alcohols 2.37 and 2.52, as shown in Scheme 2.13 below.
2.5 Tributyltin Hydride Mediated Cyclization of Thiocarboxylic Acid Derivatives

2.5.1 Synthesis of Thiocarbonate and Thiocarbamate Precursors

The (Z)-ethyl and (Z)-tert-butyl 7-O-tert-butyldimethylsilyl-2,3-dideoxy-4,5-O-isopropylidene-D-ribo-hept-2-enoate O-phenyl thionocarbonate (2.65) and (2.66) were prepared in 64% and 94% respectively with commercially available O-phenyl chlorothioformate from (Z)-2.37 and (Z)-2.52.54 Similarly (Z)-tert-butyl 7-O-(tert-butyldimethylsilyl)-2,3-dideoxy-4,5-O-(isopropylidene)-D-ribo-hept-2-enoate thiocarbonylimidazole (2.67) was prepared from (Z)-2.52 in 90% with commercially available 1,1'-thiocarboonyldiimidazole.

Scheme 2.13 Preparation of thiocarboxylic acid derivatives. Reagents and conditions:
(a) O-phenyl chlorothioformate, CH₂Cl₂, pyr, 0→25 °C, 12 h; 64%. (b) O-phenyl chlorothioformate, cat. DMAP, CH₂Cl₂, 0→25 °C, 24 h; 94%. (c) Im₂C=S, THF, reflux, 2.5 h: 90%.

2.5.2 Cyclization of Thiocarbonate and Thiocarbamate Precursors.

In an initial experiment, a solution of 1.5 equivalents of tributyltin hydride in toluene containing 0.2 equivalents of AIBN and one equivalent of O-phenyl thionocarbonate 2.65 was immersed in an oil bath at 75 °C.
Scheme 2.14 Tributyltin mediated cyclization of O-phenyl thionocarbonate. Reagents and conditions: 1.5 equiv. Bu₃SnH, 0.2 equiv. AIBN, 2.65 0.05 M in toluene, 75 °C; 25%.

Following standard workup and flash chromatography of the crude reaction product, a single compound was isolated which retained the phenyl signal of the starting thionocarbonate yet lacked the signals characteristic of the thiocarbonyl function (δ_c ≈ 190) and exhibited two signals at δ_c = 171.5 and δ_c = 170.6 suggesting the presence of two ester functions. The unsaturation of the starting ester was no longer detected. Repeated attempts to rationalize the data in terms of the expected mechanism where the secondary radical generated on deoxygenation undergoes 4-exo-trig cyclization onto the unsaturated ester was unproductive. We soon realized that the carbon-centered radical intermediate generated by attack of tributyltin radical onto the C=S functionality (vide infra, Scheme 2.17) was undergoing addition to the olefin resulting in the 2-deoxy-D-altro-5-lactone (2.68) in 25% overall yield. The structure deduced from such a mechanism indeed fit the spectral data including COSY, HETCOR and elemental analysis. No additional products or starting material was isolated.

The stereochemistry of lactone 2.68 has tentatively been assigned the altro- configuration based in part on Wilcox’s results (Scheme 1.1 and Figure 1.3), conformational analysis, coupling constant and NOESY data. Correlation to similar compounds was nearly impossible due to the lack of 2-C-5-lactones reported in the literature. The absolute stereochemistry at positions C-3, C-4, and C-5 of 2.68 are assumed fixed from the known stereochemistry of the starting ribo-hept-2-enoate 2.65. The stereochemistry at position C’-1 of the 2-C sidechain in 2.68 is undefined, even though 2.68 is obtained as
a single diastereomer. The remaining stereochemical issue is the absolute stereochemistry of position C-2 of 2.68.

![Stereochemical assignment of 2.68.](image)

Figure 2.5 Stereochemical assignment of 2.68.

The observed coupling constant $J_{45} = 9.6$ Hz in 2.68 is consistent with trans-diaxial coupling observed for several representative hexopyranosides. The observed coupling constant for the cis H-3/H-4 hydrogens on the dioxolane was found to be $J_{3,4} = 6.7$ Hz also consistent with cis coupling on cyclopentanes (Table 2.2). The remaining coupling constant $J_{2,3} = 6.7$ Hz may be rationalized by examining a molecular model of both allo-2.68 and altr-o-2.68.

<table>
<thead>
<tr>
<th>Cycloalkane</th>
<th>Vicinal Hydrogens</th>
<th>$^1J$ values (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclohexane</td>
<td>axial-axial</td>
<td>8-10</td>
</tr>
<tr>
<td></td>
<td>axial-equitorial</td>
<td>2-3</td>
</tr>
<tr>
<td></td>
<td>equitorial-equitorial</td>
<td>2-3</td>
</tr>
<tr>
<td>Cyclopentane</td>
<td>cis</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>trans</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 2.2 Representative coupling constants for cycloalkanes.

In models of both 2.68 epimers, the cis-fused bicycle adopts a twist boat conformation with the carbonyl deciding either a chair-like or boat-like bias. In allo-2.68a (Figure 2.6), the dihedral angle between the cis H-2 and H-3 approaches zero where the overlap is maximized and the $J_{2,3}$ coupling is expected to be on the order of 3 Hz (Table 2.2). In altr-o-2.68b, the dihedral angle between the cis H-2 and
H-3 increases, which decreases orbital overlap and thus the coupling constant decreases from the expected value of 3 Hz. In addition to the conspicuous torsional strain the large C-2 substituent encounters with the adjacent acetonide, both conformations of \textit{allo-2.68} appear to be inconsistent with the observed J_{2,3} coupling data reported.

\[ I = \text{CH(Ph)CO}_2\text{Et} \]

Figure 2.6 Rationale against \textit{allo-2.68} stereochemical assignment (J_{2,3} = 6.7 Hz).\textsuperscript{153}

The observed coupling data is more conveniently rationalized by an \textit{alto-2.68} configuration. In the \textit{alto-2.68a}, the dihedral angle between \textit{trans} H-2 and H-3 approaches 90° where overlap and coupling constants are at their minima. However, in the \textit{alto-2.68b} conformation, the dihedral angle between \textit{trans} H-2 and H-3 approaches about 150°. Since we would expect \textit{trans} hydrogens at 180°, \textit{alto-2.68b} is in general agreement with the observed J_{2,3} coupling value of 6.7 Hz. Furthermore, our tentative assignment of \textit{alto-2.68} is consistent with Wilcox and Thomasco's previous results (Figure 1.3) where the halo sugar ester sidechain adopted a pseudo-axial orientation in the transition state to avoid significant A\textsuperscript{(1,3)}-strain with the acetonide (Figure 1.3).
Finally, NOESY analysis showed a strong through space interaction between H-2 and H-5 in 2.68 further supporting the *altro-* stereochemical assignment (*vide infra*, Appendix B). A weak through space interaction is also observed between H-2 and adjacent side-chain methylene.

This totally unexpected result lead us to speculate whether this was a general or an isolated example dependant upon the substrate and reaction conditions chosen. We then repeated the reaction under slightly different conditions as described in Table 2.3 and found that regardless of the order of addition, products derived from 6-exo-trig cyclizations were the only products isolated. When the concentration of tributyltin hydride was increased to trap the α-methylene radical before phenyl migration could occur, a change in product distribution was observed. When high levels of tributyltin hydride were employed (0.075 M) only recovered starting alcohol was obtained indicating the suspected triheterosubstituted radical intermediate had been quenched with subsequent loss of the carbonyl function. In one instance, reverse addition of the substrate 2.65 to an excess of tributyltin hydride provided a different result (entry 3, Table 2.3). The first product isolated was 2.68 in 10% yield and identical to material isolated previously.
Table 2.3 Tributyl tin mediated cyclization of O-phenyl thionocarbonates 2.68 and 2.69.

The new product 2.69 was isolated in 65% yield and lacked both the phenyl and ester functions observed in 2.68. The fact that cyclization had taken place was supported by the loss of unsaturation as evidenced by the presence of a new triplet in the DEPT spectra at $\delta_C = 66.1$. The structural assignment was reinforced by both COSY and HETCOR analysis. In light of our earlier data surrounding \textit{allo}-2.68, the initial stereochemical assignment of \textit{allo}-2.69 was reasonable although a much smaller coupling constant $J_{2,3} = 1.6$ Hz suggested a conformation where the H-2/H-3 dihedral angle approaches 90° as shown in \textit{allo}-2.69b (Figure 2.8). Further support for the \textit{allo}-2.69 assignment came from the presence of a relatively large dipole-dipole interaction between H-2 and H-4. Conspicuously absent was a through space correlation between protons H-2 and H-5 in the NOESY of 2.69 (\textit{vide infra}, Appendix B) as had been observed for \textit{allo}-2.68 and expected for an \textit{allo}- assignment. Based upon the coupling constant and NOESY data, an \textit{allo}- configuration for 2.69 has been assigned.
Figure 2.8 Rationale for allo-2.69 stereochemical assignment ($J_{2,3} = 1.6$ Hz).

2.5.3 Cyclization of Thiocarbamate Precursors

Exposure of thiocarbamate 2.67 under similar reverse addition conditions described above (Table 2.3) gave a single compound which was later shown to be 1-$\alpha$-(1,2-dideoxy-2-C-[tert-butoxy-2-oxoethyl]-6-O-tert-butyldimethylsilyl-3,4-O-isopropylidene-D-allopyranosyl)imidazole (2.70) in 37% yield. The compound isolated had a $^1$H-NMR spectrum clearly exhibiting the signals due to an imidazole function and the absence of the starting double bond. More importantly, a signal at $\delta_H = 5.89$ (d, $J_{1,2} = 3.2$ Hz) suggested the presence of an anomeric center. The DEPT spectra supported this suspicion with the presence of a doublet at $\delta_C = 83.2$ which correlated nicely with the reported anomeric $^{13}$C-chemical shift of several representative hexopyranosyl nucleosides.154

Scheme 2.15 6-exo-trig radical cyclization yields novel branched chain $N$-glycoside. Reagents and conditions: 1.5 equiv. Bu$_3$SnH, 0.075 M in toluene, 0.2 equiv. AIBN, 90 °C, 3.5 h, reverse addition by syringe pump; 37%.
Upon standing, the emergence of a new signal at $\delta = 5.68$ (d, $J_{1,2} = 8.54$ Hz) was observed and initially ascribed as resulting from anomeration with an equilibrium ratio of anomers $\alpha/\beta = 72:28$ determined by $^1$H-NMR. The structure 2.70 fit well with our $^1$H- and $^{13}$C-NMR, infrared, and elemental analysis data.

The tentative *allo*-stereochemical assignment of 2.70 was based upon conformation and coupling constant analysis (Table 2.4). As previously noted, we assumed the stereochemistry at position H-3, H-4, and H-5 remained unchanged from the *ribo*-hept-2-enoate 2.67. Initially, we assumed the 2-C sidechain would adopt the axial position to minimize torsional strain as described earlier for the *altro*-2.68 assignment.

![Diagram](image)

<table>
<thead>
<tr>
<th>Atom</th>
<th>2.71 Dihedral Angle$^a$</th>
<th>2.70</th>
</tr>
</thead>
<tbody>
<tr>
<td>H-1</td>
<td>6.18 dd, 1H, $J_{1,2a} = 9.1$</td>
<td>5.89 d, 1H, $J_{1,2} = 3.2$</td>
</tr>
<tr>
<td></td>
<td>$J_{1,2a} = 3.8$</td>
<td>174 ± 6</td>
</tr>
<tr>
<td></td>
<td>$J_{2a,3} = 0.0$</td>
<td>46 ± 1</td>
</tr>
<tr>
<td>H-2</td>
<td>2.50 m, 2H, $J_{2a,3} = 6.9$</td>
<td>2.88 dddd, 1H, $J_{2,3} = 3.6$</td>
</tr>
<tr>
<td></td>
<td>$J_{2a,3} = 0.0$</td>
<td>156 ± 3</td>
</tr>
<tr>
<td>H-3</td>
<td>5.65 dd, 1H, $J_{3,4} = 2.9$</td>
<td>4.31-4.24 m</td>
</tr>
<tr>
<td>H-4</td>
<td>5.16 dt, 1H, $J_{4,5a} = 8.0$</td>
<td>4.31-4.24 m</td>
</tr>
<tr>
<td></td>
<td>$J_{4,5a} = 0.0$</td>
<td>8 ± 2</td>
</tr>
<tr>
<td></td>
<td>$J_{4,5a} = 8.4$</td>
<td>112 ± 2</td>
</tr>
<tr>
<td>H-5</td>
<td>4.03 d, 2H</td>
<td>3.69 ddd, 1H, $J_{5,4} = 8.4$</td>
</tr>
</tbody>
</table>


Dihedral angles derived from Karplus equation, $^3J = A \cos^2\phi - 0.28$, where $A = 8.5$ for $0^\circ \leq \phi \leq 90^\circ$ and $A = 9.5$ for $90^\circ \leq \phi \leq 180^\circ$.

Table 2.4 Support for *allo*-2.70 assignment.
The anomeric center ($\delta_C = 83.2$, doublet) was tentatively assigned as the $\alpha$-configuration by comparison with $^{13}$C-NMR data reported for 9-$\alpha$- and 9-$\beta$-D-arabinopyranosyl adenine having anomeric chemical shifts of $\delta_C = 84.15$ and $\delta_C = 80.40$ respectively. Examination of models showed that the presence of an acetonide in addition to the well known preference for $\alpha$-glycosylamines to adopt an equatorial orientation provided a framework as shown for 2.70 below. Comparison of the $J_{1,2} = 3.2$ Hz coupling constant with Table 2.2 and the data provided for structure 2.71 strongly suggest a cis relationship between H-1 and H-2 analogous to that observed with allo-2.69. Furthermore, glycosylamine 2.70 displays a new anomeric signal on standing with a coupling constant of $J_{1,2} = 8.5$ Hz which is consistent with the trans-diaxial arrangement of H-1 and H-2 in the $\beta$-anomer. No attempt was made to perform 2-D NMR experiments on the anomeric mixture and thus a tentative allo-2.70 assignment was made pending further experimental data.

Although no rationalization is offered for the change in side-chain stereochemistry between compounds altr-o-2.68, allo-2.69 and allo-2.70 from these few experiments, it is interesting to note that Entry 3 of Table 2.3 gave both altr-o-2.68 and allo-2.69 suggesting that the altr-o- configuration may be specific to the mechanism of phenyl transfer and/or unsaturated ester orientation in the transition state.

2.5.4 Related S-exo Cyclizations

Even though these results have some literature precedent, the heterocyclic glycoside formation is novel and of potential value. Indeed, a literature review uncovered the following: in 1986, Clive was attempting a tandem intermolecular-intramolecular annulation sequence initiated by deoxygenation of a secondary thiocarbamate 2.72 to give the expected annulation product 2.74 as shown in Scheme 2.16 below.
Scheme 2.16 First reported example of 5-exo-dig trapping of "Barton intermediate."

Table 2.5 Bachi’s General Route to Thionolactones.159

However, Clive observed and isolated a single thionolactone 2.73 which he rationalized as resulting from intramolecular 5-exo-dig capture of the triheterosubstituted radical intermediate, herein referred to as the “Barton intermediate”.158 He avoided this problem in future reactions by using the corresponding secondary bromide as the radical precursor and did not comment further on this novel reaction except to note that the desired radical annulations could be conducted with thiocarbamates as radical precursors in geometrically favorable cases.
Shortly thereafter, Bachi would observe a similar process. Thionolactone formation following a 5-exo-trig cyclization of the Barton intermediate was observed. Bachi later reported the same phenyl migration as we observed (2.80 and 2.81, Table 2.3), and further demonstrated that 5-exo capture of these Barton-intermediates could be exploited as a general route to thionolactones. The only other report of 5-exo trapping of the Barton intermediate was the observation by Yamamoto that stereocontrol in these cyclizations was in accord with previously established principles.

Figure 2.9 Stereochemical studies of 5-exo cyclizations.

It was clear from this literature review that although the related 5-exo-dig and 5-exo-trig cyclizations had been reported earlier, formation of 2.68, 2.69, and 2.70 were the first reported 6-exo-trig examples of this type of intramolecular reaction. Furthermore, although the migration of the phenyl ring has also been observed by Bachi in the formation of thionolactones, formation of the N-glycoside 2.70 was unprecedented and we believe constitutes a fundamentally new way of making glycosides. In addition, N-glycoside 2.70 is a rare example of both a N-hexopyranoside and a branched chain N-glycoside. Most importantly, an acyclic carbohydrate derived precursor had been used to prepare a glycoside by a fundamentally new type of glycoside formation.
Based upon Bachi's results and his reported mechanism for thionolactone formation, we believe our results can be rationalized by considering the mechanism proposed below (Scheme 2.17). Attack of the thiocarbonyl of O-phenyl thiocarbonate 2.65 by tributyltin radical gives Barton intermediate 2.88. In the presence of an activated olefin, radical intermediate 2.88 can be trapped in a 6-exo-trig manner to yield intermediate 2.89 faster than C-O bond homolysis can take place to give deoxygenated 2.93. The presence of the phenyl moiety in 2.89 allows for transfer of the aromatic system as depicted for 2.89→2.90→2.68. It is also highly probable that the phenoxy group is on the same side (β) as the 2-C-sidechain since a trans-disposition of these groups might prevent the phenyl transfer. In the absence of the phenyl moiety and at elevated temperatures or in the presence of sufficiently high concentrations of tributyltin hydride, phenyl transfer can be suppressed in 2.89 and thionolactone formation favored to give 2.92. Forcing conditions can lead to complete desulfurization to give 2.69. We found that this cyclization is best accomplished by reverse addition of the thionocarbonate to excess tributyltin hydride. Our results involving O-phenyl thiocarbonates are in accordance with the results obtained by Bachi.
Scheme 2.17 Modification of Bachi's mechanism to rationalize our experimental results.

However, a significant difference was observed between our results and those of Bachi's involving the use of thiocarbamates. Scheme 2.18, essentially the mechanism originally proposed by Bachi for the thiocarbonates, rationalizes our result satisfactorily. Attack of tributyltin radical on thiocarbamate 2.67 gives the anticipated Barton intermediate 2.94 which undergoes trapping to give radical intermediate 2.95. Hydrogen transfer then occurs in the presence of tributyltin hydride to give intermediate 2.96. At elevated temperatures and at low tributyltin hydride concentrations, thiolactone formation is favored to give 2.97 as was reported by Bachi. However, under the conditions which we employed involving the presence of excess tributyltin hydride, the relatively weak C-S bond in 2.96 undergoes cleavage to give the N-glycoside 2.70. We were able to isolate 2.70 since we employed reverse
addition of the thiocarbamate 2.68 to an excess of tributyltin hydride in order to ensure efficient trapping of 2.94. This reverse addition of substrate suppressed formation of thiolactone 2.97.

Scheme 2.18 Modification of thioimidazole transfer and other related reactions.

This last result involving formation of N-glycoside 2.70 along with the more thorough understanding of the mechanism immediately pointed to a new and exciting direction for our research. We realized that transfer of the phenyl group was unique to O-phenyl thiocarbonates and postulated that thiocarbonates in general should give O-glycosides in the presence of excess tributyltin hydride by a mechanism analogous to that proposed for the formation of N-glycoside above.

Since there are few examples of N-pyranosides, a potentially more biologically important class of N-pyranosides bearing nucleoside bases such as purines and pyrimidines would be accessible by simple
modification of the starting thiocarbamate. *Cyclization and subsequent desulfurization illustrate that intramolecular trapping of specifically designed thiocarbonates and thiocarbamates might be used as a general method to O- and N-glycosylations* (Scheme 2.19).

![Scheme 2.19 Proposed routes to disaccharides and hexopyranosyl nucleosides](image)

Before turning our attention to a general route to mixed thiocarbonate and thiocarbamates, we wished to establish if the 6-exo cyclization observed with 2.68 would take place on substrates lacking either a dioxolane function, an activated radical acceptor, or both. We prepared a number of representative substrates (2.100-2.104) below and exposed them to the conditions described in entry 3, Table 2.3 and Table 2.6 below. In each case examined, decomposition products were obtained.
Scheme 2.20 Other substrates examined. Reagents and Conditions: (a) Dibal-H, CH₂Cl₂, -78 °C; 90%. (b) Ph₃PCH₃Br', n-BuLi, THF, -20→25 °C; 75%. (c) 3.5 equiv. PhOC(S)Cl, 4.0 equiv. DMAP, CH₂Cl₂, 0→25 °C; 97%. (d) 2 equiv. Im⁻C=S, THF, reflux; 73%. (e) 2 equiv. Ph₃P=CHCO₂Bu', DME, 25 °C, 18 h; 81%. (f) 3.5 equiv. PhOC(S)Cl, 1:1 pyr/CH₂Cl₂, 0→25 °C, 12 h; 74%. (g) 2 equiv. Im⁻C=S, THF, reflux; 84%. (h) 2 equiv. Ph₃PCH₃Br', THF, n-BuLi, -20→25 °C; 91%. (i) 3.5 equiv. PhOC(S)Cl, 1:1 pyr/CH₂Cl₂, 0→25 °C, 12 h; 65%.

Table 2.6 Conditions investigated to determine the generality of the novel 6-exo cyclization.
2.6 Chapter Summary

Our initial goal was to develop a radical based methodology into cyclobutanoids for application to carbocycles of medicinal interest. The Cp₂TiCl mediated cyclization of epoxide 2.48 lead to a novel 3-deoxy-3-C-α-D-erythrofuranoside 2.57 via a methylcyclobutyl radical rearrangement. Attempts to facilitate cyclobutane formation by applying thiocarboxylic acid derivatives 2.65-2.67 under Barton-McCombie conditions provided glycosides 2.68-2.70 by a novel 6-endo-trig cyclization of the so called Barton intermediate 2.88. Furthermore, we recognized that this mode of cyclization of thiocarbonates and thiocarbamates might provide a new and general method of O- and N-glycoside synthesis.
CHAPTER 3

TRIBUTYL Tin MEDIATED HEPT-6-ENYL RADICAL CYCLIZATIONS: SYNTHESIS OF THIONOCARBONATES AND THIOCARBAMATES

3.1 Introduction

3.1.1 Examples of Important Pyanosyl Nucleosides and Their Synthesis

The overwhelming majority of complex nucleosides are built around a furanosyl aglycon. There are several examples, however, of complex nucleosides incorporating a pyranosyl aglycon including hikizimycin (3.1), miharamycin, and amipurimycin. Much simpler hexopyranosyl nucleosides such as 1-(2-deoxy-β-D-erythro-hexopyranosyl)thymine are potent mammalian uridine phosphorylase inhibitors.

![Figure 3.1 Examples of pyranosyl nucleosides of biological interest.](image)

Figure 3.1 Examples of pyranosyl nucleosides of biological interest.
Others such as 2-amino-9-(2-deoxy-β-D-ribo-hexopyranosyl)purin-6-one (3.2) have recently been used as biological probes of enzymes involved in nucleic acid metabolism\textsuperscript{163} while pentopyranine A (3.3) and pentopyranine B (3.4) have been shown to inhibit RNA synthesis.\textsuperscript{164}

The last decade has also seen an increase in the synthesis of complex nucleoside antibiotics.\textsuperscript{161} This class of natural products has undoubtedly attracted the attention of synthetic chemists because of their structural and biological relevance. These antibiotics often incorporate one or more heterocyclic bases, mono-, di- or oligosaccharide, peptide, and or lipid functionalities. Knapp has noted that interest in these complex nucleoside antibiotics has paralleled improvements in methods of \textit{N}-glycosylation, for the simple reason that "unless one starts with a commercially available nucleoside, \textit{N}-glycosylation is the \textit{sine qua non} of nucleoside synthesis".\textsuperscript{161,165}

Historically, the first \textit{N}-glycosylations involved the condensation of chloromercury derivatives of purine with ribofuranosyl halides (Koenigs-Knorr method) or the fusion of peracetylated sugars with purines in the presence of \textit{p}-toluenesulfonic acid (Helferich method).\textsuperscript{166} The Hilbert-Johnson method used throughout the 1960-1970's relied upon the condensation of an \textit{O}-silylated pyrimidine or purine acceptor with a glycosyl halide donor.\textsuperscript{166} In 1981, Vorbrüggen reported a modification of the Hilbert-Johnson method where silylated pyrimidines or acylated purines were condensed with glycosyl acetates in the presence of promoters such as silver perchlorate or trimethylsilyl triflate.\textsuperscript{167} Despite this continuing evolution in \textit{N}-glycosylations, these methods are all variations of the same theme: condensation of an activated purine or pyrimidine acceptor with a glycosyl donor. This \textit{N}-glycosylation methodology has two principle limitations; that a glycosyl donor with the desired configuration be accessible and that formation of an \textit{N}-glycoside linkage \textit{requires a pre-existing anomeric center}.

3.1.2 \textbf{Current Methods of \textit{O}-Glycoside Synthesis}

Recent advances in the understanding of the role that glycoconjugates play in a variety of important human biological functions have led to an explosion in the methodology of oligosaccharide
Fundamental to oligosaccharide synthesis is the high stereocontrol required at the anomeric center during formation of the glycoside bond. Although generalizations are always difficult, especially in as large and diverse an area as oligosaccharide synthesis, the overwhelming majority of synthetically useful O-glycosylation reactions remain limited to nucleophilic substitution of activated leaving groups from anomeric centers (glycosyl donors) by sugar nucleophiles (glycosyl acceptors). The glycosyl donors available include glycosyl halides, thioglycosides, glycosyl acetates, glycosyl imidates, glycosyl sulfoxides, and 4-pentenyl glycosides, just to name a few. The exact glycosyl donor and promoter pair chosen will depend largely on the nature of the linkage required between the donor and acceptor (i.e., 1,2-cis-α, 1,2-cis-β, 1,2-trans-α, or 1,2-trans-β). Since both N- and O-glycosylations rely on glycosyl donors, they both share the same limitations as described previously.

3.2 Thiocarbamates and Thionocarbonates as Precursors for N- and O-Glycosides

As discussed in the previous chapter, the 6-exo-trig radical cyclizations of O-phenyl thionocarbonates and 1H-imidazole thiocarbamates provided monosaccharides incorporating both the phenyl and imidazole functions of the original thionocarbonate and thiocarbamate. We realized that if we could construct mixed thionocarbonates and thiocarbamates (Scheme 2.19), then we could exploit this new reaction as a general route to nucleosides and disaccharides. Based upon the classical route to 1H-imidazole thiocarbamates discussed in Chapter 2 involving 1,1'-thiocarbonyldiimidazole, we considered preparing the analogous purine and/or pyrimidine thiocarbamates from the corresponding 1,1'-thiocarbonyldipurine derivative 3.5 shown in Figure 3.2. Likewise, disaccharide syntheses via the 6-exo-trig cyclizations would require a general route to mixed thionocarbonates such as 3.6 shown below.
3.2.1 Preparation of 1,1'-Thiocarbonyldiazoles

Commercially available 1,1'-thiocarbonyldiimidazole is prepared according to the method reported by Staab or one of its variations. Thioacetylation of imidazole with thiophosgene gives the aminothiocarbamoyl chloride which then undergoes further reaction with excess imidazole to give the desired 1,1'-thiocarbonyldiimidazole (3.8) in high yield. Modifications on this method have included thioacetylation of 1-trimethylsilylimidazoles which benefits from lower stoichiometry of imidazole and ease of purification.

\[
\begin{align*}
\text{Scheme 3.1 Preparation of 1,1'-thiocarbonyldiimidazole. Reagents and conditions:} & \quad (a) 0.25 \text{ equiv. } \text{Cl}_2\text{C}=\text{S}, \text{PhH, } 25^\circ\text{C, 1 h; 92%}. \\
& \quad (b) \text{HMDS, reflux, 10 h; 85%}. \\
& \quad (c) 0.5 \text{ equiv. } \text{Cl}_2\text{C}=\text{S}, \\
& \quad \text{CCl}_4, 25^\circ\text{C, 8 h; 99%}. \\
\end{align*}
\]

All of the symmetrical thioureas known in the literature are from the azole family (Table 3.1) and no examples of 1,1'-thiocarbonyldipurines or dipyrimidines have been reported. Of those thioureas
reported, several incorporating benzimidazole (3.10), benzotriazole (3.11), and indazole (3.13) are less moisture sensitive and as expected have lower reactivity as compared to 1,1'-thiocarbonyldiimidazole.\textsuperscript{172}

One thiourea of particular interest is the 1,1'-thiocarbonyldi(1,2,4-triazole) (3.38) which is more reactive than 3.8. For example, 1,1'-thiocarbonyldi(1,2,4-triazole) reacts with two equivalents of phenol at 25 °C to give diphenylthionocarbonate whereas 1,1'-thiocarbonyldiimidazole requires 6 h at 90 °C.\textsuperscript{172}

\[
\begin{align*}
\text{X} & = \text{Azole} \\
3.7 & \quad \text{imidazole (Im)}^{170} \\
3.9 & \quad 3,5\text{-dimethylpyrazole (DmP)}^{173} \\
3.10 & \quad \text{benzimidazole (BzIm)}^{174} \\
3.11 & \quad \text{benzotriazole (BzTr)}^{175} \\
3.12 & \quad \text{pyrazole (Py)}^{172} \\
3.13 & \quad \text{indazole (In)}^{172} \\
3.14 & \quad 1,2,4\text{-triazole (TrA)}^{172}
\end{align*}
\]

Table 3.1 Azole based thioureas.

3.2.2 Acylation of Purines

Our initial plan was to expose a readily available nucleoside base, such as adenine (3.15) or 6-chloropurine (3.16) to the same conditions used to prepare 1,1'-thiocarbonyldiimidazole (Figure 3.3). With adenine readily available, the issue of protection of the 6-amine function was investigated as well as the regioselectivity of acylation ($N^7$ vs $N^9$). The 6-amine function of adenine was protected as its benzamide. This was easily accomplished by fusion of adenine with benzoic anhydride to give the $N^6$-benzoyladenine in 75% yield as described by van Boom (Figure 3.4).\textsuperscript{176}
The regioselectivity of acylation was found to be a moot point since a review of the heterocyclic literature revealed that, in general, purines are alkylated under basic conditions almost exclusively at the $N^\circ$ position with small amounts of $N^1$ alkylation occurring under neutral conditions. Likewise, acylation of adenine under basic conditions proceeds almost exclusively to give the corresponding $N^\circ$-carbamates. The few examples of $N^\circ$-carbamates which exist involve acylation of purine with chloroformates. No examples of the corresponding $N^\circ$-thiocarbamates were found.

Several examples of mixed ureas containing purine were found resulting from condensation of purine with isocyanates, while only three examples of mixed thioureas containing purines were found resulting from the condensation of purine with methyl-, butyl-, or phenyl isothiocyanates.
Scheme 3.2 Regioselective acylation of adenine. Reagents and conditions: (a) 4.8 N NaOH, CICO₂Et, 0 °C, 1 h; 72%. (b) methyl isocyanate, DMSO, 25 °C, 6 h; 69%. (c) methyl isothiocyanate, DMSO, 90 °C, 5 h; 40%.

3.2.3 Attempted Preparation of 1,1'-Thiocarboxylidipurine Using Thiophosgene

Characterization data obtained from several reported thioureas indicated the desired 1,1'-thiocarboxylidipurines to have a characteristic C=S signal at ca. δ₁₀ = 170 ppm and an absorbance in the infrared ca. ν(C=S) = 1305 cm⁻¹. To corroborate this, 1,1'-thiocarbonyldiimidazole was prepared by the method of Staab and characterized by ¹H-, ¹³C-NMR, and FT-IR for comparison. We found that the reported value for ν(C-S) to be of medium intensity and indistinguishable from other signals and, therefore, of little diagnostic value. The thiophosgene used was obtained commercially, handled using standard syringe techniques, and carefully stored under nitrogen at 0 °C with protection from moisture. Because of the reagent’s toxicity, no attempt was made initially to purify the reagent by distillation prior to its use. 6-Chloropurine and N⁶-benzoyladenine were exposed to conditions used to prepare 1,1'-thiocarboxylidimidazole as described in Table 3.2.
Table 3.2 Initial attempts to prepare 1,1'-thiocarbonyldipurines with thiophosgene.

Exposure of four equivalents of \(N^6\)-benzoyladenine to one equivalent of thiophosgene (entry 1, Table 3.2) in benzene at 25 °C for 1 h gave a fine white powder which was shown to be recovered starting material (90%) along with a 10 mg of a pale yellow solid whose \(^1H\)-NMR showed a downfield shift of adenine's H-8 and H-2 signals. The reaction was then repeated twice more in benzene and tetrahydrofuran and warmed to reflux for 5 h. After cooling, vacuum filtration of the reaction mixture provided in each case essentially quantitative recovery of \(N^6\)-benzoyladenine.

The next attempted thioacylation was performed on \(N^6\)-benzoyl-\(N^9\)-sodium adenide.\(^{177}\) In the early 1980's, Rasmussen had used lithium, sodium, and potassium \(N^6\)-acyladenides to study their ambident nucleophilicity in the presence of alkylating reagents. The \(N^6\)-benzoyl-\(N^9\)-sodium adenide was prepared by deprotonation of \(N^6\)-benzoyladenine with NaH in acetonitrile at 25 °C for 12 h. The solvents were removed and the \(N^6\)-benzoyl-\(N^9\)-sodium adenide was dissolved in dry DMF. The clear yellow solution was cooled to 0 °C and 0.25 equivalents of thiophosgene added to give a dull red solution. The cooling bath was removed and the reaction stirred at 25 °C for 18 h. Vacuum filtration gave a dark red
gum and a clear filtrate which was concentrated to give recovered starting material by $^1$H-NMR (DMSO-$d_6$).

Additional attempts were made to prepare the desired 1,1'-thiocarbonyldipurine involving thiophosgene met with similar results (Table 3.2). It became clear that an alternate route to the desired 1,1'-thiocarbonyldipurines would have to be found.

3.2.4 Attempted Preparation of Purine Thiocarbamates via Nucleophilic Acyl Substitution

Hirai reported the nucleophilic acyl substitution of imidazole from O-benzyl 1H-imidazole thiocarbamate (3.21) by benzylmethylamine to give O-benzyl benzylmethyl thiocarbamate (3.22) as depicted below. However, when attempts to displace the imidazole from O-m-cresol 1H-imidazole thiocarbamate (3.21), a mixed thiourea 3.23 resulted. Hirai noted that these results could be rationalized by simple $pK_a$ considerations.

\[
\begin{align*}
\text{Im}_2C=S & \quad \xrightarrow{\text{ROH}} \quad \text{Im} \quad \xrightarrow{\text{MeNH_Bn}} \quad \text{BnMeN} \quad \text{OBn} \quad \text{R = Bn} \\
3.21 & \quad \text{R = m-cresol} \\
3.22 & \quad 3.23
\end{align*}
\]

Scheme 3.3 Selective Acyl Substitution of Thiocarbamates.

Nucleophilic attack on the thiocarbamate by a suitable nucleophile will displace the stronger acid preferentially. In the first case, imidazole ($pK_a = 14.4$) is the stronger acid and is displaced preferentially over benzyl alcohol ($pK_a = 16.0$). Similarly, m-cresol is the stronger acid ($pK_a = 10.0$) and is displaced preferentially over imidazole.

These results lead us to the realization that the 1,1'-thiocarbonyldipurines need not be the only intermediates for the preparation of 9H-purine thiocarbamates. What was needed was any mixed thiourea.
or thiocarbamate which had a leaving group (LG) with a lower $pK_a$ than $N^6$-benzoyladenine ($pK_a$ ca. 9-10) as depicted below.

In light of the information obtained from our initial literature review concerning the alkylation and acylation of adenine (Scheme 3.2), we first attempted to prepare a simple mixed thiourea of adenine.185

Scheme 3.4 Modified Route to 9H-purine Thiocarbamates.

4-Nitrophenyl isothiocyanate was accessible in one step from commercially available 4-nitroaniline and thiophosgene. Subsequent condensation of 4-nitrophenyl isothiocyanate and $N^6$-benzoyladenine should then give the target 4-nitroaniline 9H-(N$^6$-benzoylpurine) thiocarbamate. The necessary 4-nitrophenyl isothiocyanate was easily prepared from 4-nitroaniline and thiophosgene in acetone in 92% yield.174 Several attempts (entries 1-3, Table 3.2) were made to condense the 4-nitrophenyl isothiocyanate with $N^6$-benzoyladenine in polar solvents under basic and forcing conditions.181 Each failed to give anything other than starting materials by TLC, $^1$H- and $^{13}$C-NMR analysis.
Another route we investigated involved the generation of an intermediate thiuram sulfide 3.28 which has been reported to be a valuable intermediate for the synthesis of mixed thioureas such as 3.29. Initial experiments under these conditions resulted in recovery of unreacted starting materials (entries 4-6, Table 3.3).

**Table 3.3** Attempts to prepare mixed thioureas.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NHBz</td>
<td>4-nitrophenyl isothiocyanate, DMSO, 80 °C, 5 h</td>
<td>No Reaction</td>
</tr>
<tr>
<td>2</td>
<td>NHBz</td>
<td>NaH, 4-nitrophenyl isothiocyanate, DMF, 120 °C, 5 hr</td>
<td>No Reaction</td>
</tr>
<tr>
<td>3</td>
<td>NHBz</td>
<td>1. K, THF, 25 °C, 25 h</td>
<td>No Reaction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. 4-nitrophenyl isothiocyanate, reflux</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>NHBz</td>
<td>DMSO, NaOH(aq.), CS₂, I₂</td>
<td>No Reaction</td>
</tr>
<tr>
<td>5</td>
<td>NHBz</td>
<td>Acetone, NaOH(aq.), CS₂, I₂</td>
<td>No Reaction</td>
</tr>
<tr>
<td>6</td>
<td>NHBz</td>
<td>Et₂O, NaOH(aq.), CS₂, I₂</td>
<td>No Reaction</td>
</tr>
</tbody>
</table>

Scheme 3.5 Reported preparation of mixed thioureas via thiuram sulfides.

R₁R₂NH = morpholinyl, piperidinyl, pyrrolyl, pyrrolidinyl
R₃NH₂ = Me, Et, i-Pr, Cy, Ph, o-tolyl, Bn
3.2.5 A General Route to Thiocarbamates: Thioacylation with Chlorothioformates Followed by Nucleophilic Acyl Substitution

As per a suggestion by Professor Peter Jacobi (Dartmouth College), we reacted commercially available O-phenyl chlorothioformate with 6-chloropurine under standard acylation conditions and found to our surprise that we could isolate in low yield O-phenyl 9H-(6-chloropurine) thiocarbamate (3.30). Thiocarbamate 3.30 was easily recognized on $^1H$-NMR by the presence of both the phenyl signals from the chlorothioformate and the prominent singlets due to purine's H-2 and H-8 at $\delta_H = 9.05$ and $\delta_H = 8.94$, each 0.5 ppm deshielded from the original 6-chloropurine. Compound 3.30 also exhibited a very strong, sharp absorbance at $\nu = 1215$ cm$^{-1}$ in the IR which has tentatively been assigned the C=S stretching mode. $^{13}C$-NMR analysis provided a singlet at $\delta_C = 182.1$ which we have assigned as the thiocarbamate C=S resonance. Final support for thiocarbamate 3.30 came from satisfactory carbon, hydrogen, nitrogen, and sulfur analysis for $C_{12}H_{17}N_4OSCl$.

Based upon the acidity of phenol ($pK_a \sim 9.00$) one would predict that nucleophilic acyl substitution of a substrate such as thiocarbamate 3.30 by an alcohol might displace the heterocycle ($9.0 < pK_a < 10.0$) preferentially over the phenol. In fact, we found that to be the case. When O-phenyl 9H-(6-chloropurine) thiocarbamate (3.30) was exposed to a simple alcohol under basic conditions, we isolated the known O-benzyl O-phenyl thiocarbonate (3.31) in 53% yield which exhibited a characteristic singlet in the $^{13}C$-NMR at $\delta_C = 195.2$ assigned as the thiocarbonate C=S resonance.

![Scheme 3.6 Thioacylation of 6-chloropurine. Reagents and conditions: (a) O-phenyl chlorothioformate, pyridine, 0→25 °C, 12 h; 20%. (b) BnOH, NaH, MeCN, 25 °C, 0.5 h; 53%](image)

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The preparation of O-phenyl 9H-(6-chloropurine) thiocarbamate (3.30) was a major breakthrough since it opened the door to other 9H-purine thiocarbamates. Modification of phenol to reduce its pKa and to improve its leaving group ability lead us to attempt the thioacylation of 6-chloropurine with commercially available O-pentafluorophenyl chlorothioformate. This gave the desired O-pentafluoro-phenyl 9H-(6-chloropurine) thiocarbamate (3.32) in 23% yield. The thiocarbamate 3.32 exhibited a sharp infrared absorbance at ν = 1215 cm⁻¹, deshielded H-2 and H-8 signals (δH = 9.00, δH = 8.96), and a resonance at δC = 178.2 (s, C=S). Subsequent nucleophilic acyl substitution of the pentafluorophenol by benzyl alcohol under neutral conditions lead to the desired O-benzyl 9H-(6-chloropurine) thiocarbamate (3.33) in 55% yield. Thiocarbamate 3.33 exhibited infrared absorbance at ν = 1215 cm⁻¹ and a resonance at δC = 182.9 (s, C=S).

These last two experiments demonstrated that heterocycles could be thioacylated with commercially available chlorothioformates. The pentafluorophenols could in turn be selectively replaced by an alcohol under neutral conditions to give the target O-sugar 9H-purine thiocarbamates as initially proposed (Scheme 2.19). The advantages of this method over our initial plans involving the use of thiophosgene to prepare 1,1' thiocarbonyldiazoles are obvious; this new route avoids working with the noxious thiophosgene, but more importantly, avoids the inherent weakness of the
1,1'-thiocarbonyldipurine route which wastes one equivalent of heterocycle in the process. Furthermore, the chlorothioformates are commercially available and/or easily prepared$^{186}$ and the new route is as concise as the route initially proposed.

Exposure of (Z)-tert-butyl 7-O-tert-butylidemethylsilyl-2,3-dideoxy-4,5-O-isopropylidene-D-ribo-hept-2-enoate (2.52) to 0.73 equivalents of O-pentafluorophenyl 9H-(6-chloropurine) thiocarbamate (3.32) gave the unexpected lactone 3.34 along with unreacted starting materials. The tentative assignment of lactone 3.34 was based upon the observation that the isolated material contained the acetonide and TBDMS signals in the $^1$H-NMR but lacked the tert-butyl function from the original ester. The olefin signal was intact, though deshielded considerable from that of the starting material. The presence of a lactone is strongly suggested by the absence of a hydroxyl function and the presence of a strong absorbance at $\nu = 1759 \text{ cm}^{-1}$.

![Scheme 3.8 Attempted thioacyl substitution under neutral conditions. Reagents and conditions: (a) DME, reflux, 48 h; 40%.

These two absorbances differ from the acyclic precursor ($\nu = 1714 \text{ cm}^{-1}$) and are consistent with unsaturated lactones. Oddly, a medium absorbance ($\nu = 1216 \text{ cm}^{-1}$) was also present. Further support for the lactone comes from the presence of a DEPT singlet at $\delta = 172.9$. If nucleophilic acyl substitution did not proceed under neutral conditions, then another option was to attempt the substitution under basic conditions with the concomitant risk of competitive C-glycoside formation.

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Reactions with 6-methoxypurine (3.35) showed the yields of thioacylation to improve with electron-rich heterocycles, providing $O$-pentafluorophenyl 9H-(6-methoxypurine) thiocarbamate (3.36) in 71% yield. Formation of 3.36 was supported by an IR absorbance at $\nu = 1216 \text{ cm}^{-1}$ along with a singlet (DEPT) at $\delta_C = 178.9$ and satisfactory carbon, hydrogen, nitrogen, and sulfur analysis.

![Scheme 3.9 Thioacylation of 6-methoxypurine. Reagents and conditions: (a) $O$-pentafluorophenyl chlorothioformate, $\text{CH}_2\text{Cl}_2$, pyridine, cat. DMAP, 0-25 °C, 12 h; 71%.

Attempts to substitute the pentafluorophenol moiety of $O$-pentafluorophenyl 9H-(6-methoxypurine) thiocarbamate (3.36) with (Z)-tert-butyl 7-O-tert-butyldimethylsilyl-2,3-dideoxy-4,5-O-isopropylidene-D-ribo-hept-2-enoate (2.48) under neutral conditions resulted in recovery of the desired (E)- and (Z)-tert-butyl 7-O-tert-butyldimethylsilyl-2,3-dideoxy-4,5-O-isopropylidene-D-ribo-hept-2-enoate 9H-(6-methoxy-purinyl) thiocarbamate (3.37) in 14% yield along with unreacted starting materials. The structural assignment of thiocarbamate 3.37 was based in part upon $^1$H-NMR hydrogen count of 42 hydrogen as well as the characteristic thiocarbamate signal ($\delta_C = 181.0$).

The same substitution reaction was attempted under basic conditions (Scheme 3.10), and only after warming to 50 °C for 45 minutes was any visible progress in the reaction detected by TLC. Final recovery of the desired $O$-sugar 9H-(6-methoxypurine) thiocarbamate (3.37) occurred in only 16% yield along with unreacted starting materials.
These preliminary results towards the preparation of (Z)-tert-butyl 7-O-tert-butyltrimethylsilyl-
2,3-dideoxy-4,5-O-isopropylidene-D-ribo-hept-2-enoate 9H-(6-methoxypurine) thiocarbamate (3.37),
although low in yield, demonstrate the potential this protocol has for preparing the desired O-sugar
9H-purine thiocarbamates and point to further efforts needed to optimize the reaction conditions.

3.2.6 A New Reaction of Triazole Thiocarbamate: The Newman-Kwart Rearrangement in
Aliphatic Systems

Concurrent with our work described above, we decided to prepare some of the symmetrical
thioureas described in Table 3.1 so that we could investigate the \(\text{6-exo-trig}\) radical cyclization of other
1H-azole thiocarbamates. We also prepared 1,1'-thiocarbonyldi(1,2,4-triazole) (3.38) as we wished to
exploit its reported ease of substitution. We also elected to prepare the 1,1'-thiocarbonyldibenzimidazole
(3.39) for its close structural similarity to the purines. Based upon the \(pK_a\) of 1,2,4-triazole (10.0), we felt
that this reagent might be an easily handled, thiophosgene equivalent. Each of the reagents 3.38 and 3.39
were prepared according to the method described by Harpp\textsuperscript{172} in 73% and 45% overall yield respectively
and exhibited characteristic signals in the IR (\(v = 1376 \text{ cm}^{-1}\)) and \(\delta_C = 168.4\) and \(\delta_C = 172.0\).
Scheme 3.11 Preparation of 1,1'-thiocarbonyldi(1,2,4-triazole) and 1,1'-thiocarbonyldi-benzimidazole. Reagents and conditions: (a) HMDS, ammonium sulfate, reflux, 10 h; 94%. (b) Cl₂C=S, PhH, 60 °C, 0.5 h; 48%. (c) HMDS, ammonium sulfate, reflux, 10 h; 73%. (d) Cl₂C=S, PhH, 60 °C, 0.5 h; quantitative.

We next attempted the preparation of O-cholesterol thiocarbamates using 3.38 and 3.39 to test each reagent's activity. In accord with Harpp's report, we found that 1,1'-thiocarbonyldibenzimidazole was unreactive under neutral and forcing conditions and that 1,1'-thiocarbonyldi(1,2,4-triazole) gave the desired O-cholesteryl 1H-(1,2,4-triazole) thiocarbamate (3.41) in 58% yield.

Scheme 3.12 Reactivity tests of 1,1'-thiocarbonyldiazoles. Reagents and conditions: (a) 1,1'-thiocarbonyldi(1,2,4-triazole), THF, reflux, 2 h; 58%. (b) 1,1'-thiocarbonyldibenzo[diazole, 1,2-dichloroethane, reflux, 18 h; no reaction.
The thiocarbamate 3.41 assignment was based in part on the presence of an infrared absorbance at $\nu = 1250 \text{ cm}^{-1}$, a singlet at $\delta_C = 181.5$, and satisfactory elemental analysis. We also observed a significant downfield shift of H-3$\alpha$ (1.9 ppm) upon thioacylation.

To test whether the 1,1'-thiocarbonyldi(1,2,4-triazole) could function as a thiophosgene equivalent, we attempted to substitute the 1,2,4-triazole of thiocarbamate 3.41 with benzyl alcohol under both neutral and basic conditions. Substitution under basic conditions yielded the desired O-benzyl O-cholesteryl thiocarbonate (3.43) in 50% yield ($\nu = 1215 \text{ cm}^{-1}$, a singlet at $\delta_C = 194.6$, and satisfactory elemental analysis). Attempts to displace 1,2,4-triazole in 3.41 under neutral conditions yielded a compound which by TLC and $^1H$-NMR was at first considered to be unreacted starting material.

![Scheme 3.13](image)

**Scheme 3.13** Attempts to substitute 1,2,4-triazole under neutral and basic conditions. Reagents and conditions: (a) BnOH, NaH, MeCN, 25°C, 2 h; 50%. (b) BnOH, 1,2-dichloroethane, reflux, 18 h; 35%.

Upon careful inspection, however, the isolated product's 1,2,4-triazole proton resonances were slightly shielded relative to those of authentic starting thiocarbamate. The infrared spectrum of 3.44 contained $\nu = 1215 \text{ cm}^{-1}$, but the $^{13}$C-NMR signal of the starting thiocarbamate of 3.41 ($\delta_C = 183.0$) had shifted upfield to $\delta_C = 167.7$. The C-3 doublet had shifted upfield from $\delta_C = 85.1$ to $\delta_C = 45.2$ and H-3 was also shielded from $\delta_H = 5.40$ to $\delta_H = 3.50$ ppm. High resolution mass spectral analysis indicated a base signal of C$_{27}$H$_{44}$ [M-thiocarbonyl 1H-(1,2,4-triazole)]$^+$. 

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An earlier literature search had revealed a thermal rearrangement of diaryl thiocarbonates which lead us to suspect some form of thermal thiocarbamate rearrangement was taking place. In 1930, Schönberg first discovered that thermal rearrangement of di-\(O\)-aryl thiocarbonates (3.45) gave the corresponding \(S\)-aryl \(O\)-aryl thiolcarbonates (3.46).\(^{187}\) This reaction has since been exploited to covert phenols to thiophenols.

![Figure 3.5 Thermal rearrangement of di-\(O\)-aryl thiocarbonates: the Schönberg Rearrangement.](image)

The currently accepted mechanism\(^ {188}\) is thought to proceed by intramolecular nucleophilic addition by sulfur at the ipso-position in 3.45 with subsequent elimination of oxygen to give the observed \(S\)-aryl thiolcarbonate 3.46. To support this mechanism is the observed rate acceleration by thiocarbonates bearing electron-withdrawing groups on the aromatic ring.

![Figure 3.6 Proposed mechanism of the Schönberg and related rearrangements.](image)
The Schönberg Rearrangement is similar to several other named reactions including the thermal rearrangements of o-hydroxydiphenyl sulfones 3.48 (Smiles Rearrangement) and arylimino ethers 3.50 (Chapman Rearrangement).

In 1966, Newman reported that the pyrolysis of O-aryl dimethylthiocarbamates 3.52 gave S-aryl dimethylthiocarbamates 3.53 in high yield. Almost simultaneously, Kwart reported the vapor phase rearrangement of O-aryl diethylthiocarbamates at 400 °C to give the corresponding S-aryl diethylthiocarbamates. This so called Newman-Kwart Rearrangement was also used for the preparation of thiophenols, and is a better alternative to the Schönberg Rearrangement for the conversion of phenol to thiophenol since it precludes the loss of one of the aromatic units.
A literature search gave several recent applications of the Newman-Kwart Rearrangement to O-aryl dialkylthiocarbamates but failed to provide a single example of the thermal rearrangement of an O-alkyl dialkylthiocarbamate (vide supra, Scheme 3.13). Attempts to substitute the 1,2,4-triazole heterocycle in O-cholesteryl 1H-(1,2,4-triazole) thiocarbamate (3.41) with a benzyl alcohol (Scheme 3.13) under neutral conditions gave S-cholesteryl 1H-(1,2,4-triazole) thiolcarbonate (3.44), and to the best of our knowledge, constituted the first such example of an O-alkyl Newman-Kwart Rearrangement. This is also the first example of a Newman-Kwart Rearrangement involving a heterocyclic thiocarbamate.

Support for our structural assignment in 3.44 comes from several representative S-alkyl thiocarbamates. For example, S-ethyl dipropyl, S-ethyl dibutyl, and S-propyl dipropylthiocarbamates have reported \([\text{N-C(=O)-S}]\) resonances of \(\delta_C = 167.6, 168.5,\) and \(167.8\) respectively. Thus, the thiocarbonyl resonance of \(\delta_C = 167.5\) of the S-cholesteryl 1H-(1,2,4-triazole) thiocarbamate (3.44) was consistent with the proposed structure.

The stereochemical assignment in 3.44 was challenging since the H-3 signal was a multiplet obscured by the H-6 signal thereby denying us important vicinal coupling data in the \(^1H\)-NMR. Furthermore, there were few examples of cholest-5-en-3α-ol and cholest-5-en-3α-thiol derivatives to help with the correlation of structure. Therefore, the tentative stereochemical assignment in 3.44 is based on \(^{13}C\)-NMR chemical shift analysis.

It has long been recognized that within a family of compounds, a given substituent produces similar \(^{13}C\) shielding effects at or near the site of substitution and this principle is the basis of Schoolery's Rules and the additivity of substituent effects. This trend has also been used to assist in the \(^{13}C\) assignment of steroids and related compounds. Furthermore, it was also known that among cycloalkanes, axial substituents on ring carbons experience a larger shielding effect than do equatorial substituents.
Since $^{13}$C-NMR data was not available for several key steroids, we needed to determine what affect substitution of an oxygen for sulfur would have on the $^{13}$C chemical shift at the C-3 position of a cholest-5-en-3-ol.

<table>
<thead>
<tr>
<th>Entry</th>
<th>C Substrate</th>
<th>$\delta_{C}$</th>
<th>Comparison</th>
<th>$\delta_{C}$</th>
<th>$\Delta\delta_{C}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 Cyclohexanol</td>
<td>69.5</td>
<td>Cyclohexanethiol</td>
<td>38.5</td>
<td>31.0</td>
</tr>
<tr>
<td>2</td>
<td>3 Cholest-5-en-3β-ol</td>
<td>71.6</td>
<td>Thiocholest-5-en-3β-ol</td>
<td>42.3</td>
<td>29.3</td>
</tr>
<tr>
<td>3</td>
<td>C-OH</td>
<td>-</td>
<td>C-SH</td>
<td>-</td>
<td>30.0</td>
</tr>
<tr>
<td>4</td>
<td>3 5β-Cholestan-3β-ol</td>
<td>72.2</td>
<td>5β-Cholestan-3α-ol</td>
<td>67.1</td>
<td>5.1</td>
</tr>
<tr>
<td>5</td>
<td>3 5α-Cholestan-3β-ol</td>
<td>71.4</td>
<td>5α-Cholestan-3α-ol</td>
<td>66.5</td>
<td>4.9</td>
</tr>
<tr>
<td>6</td>
<td>equitorial substituent</td>
<td>-</td>
<td>axial substituent</td>
<td>-</td>
<td>5.0</td>
</tr>
<tr>
<td>7</td>
<td>3 Cholest-5-en-3β-ol</td>
<td>71.6</td>
<td>Cholest-5-en-3α-ol</td>
<td>66.6</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>3 Thiocarbamate 3.41A</td>
<td>85.1</td>
<td>Thiocarbamate 3.41B</td>
<td>80.1</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>3 Thiocarbamate 3.41A</td>
<td>85.1</td>
<td>Thiocarbamate 3.44A</td>
<td>55.1</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>3 Thiocarbamate 3.41B</td>
<td>80.1</td>
<td>Thiocarbamate 3.44B</td>
<td>50.1</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>3 3.44A calcd.</td>
<td>55.1</td>
<td>3.44 minor product obsd</td>
<td>47.7</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>3 3.44B calcd.</td>
<td>50.1</td>
<td>3.44 major product obsd</td>
<td>45.2</td>
<td>-</td>
</tr>
</tbody>
</table>

Note: italics indicate approximate values

Table 3.4 $^{13}$C-NMR shift correlation to assign the stereochemistry of 3.44

For this data, we observed the chemical shift difference ($\Delta\delta$) for two related compounds for which data was available, cyclohexanol and cholesterol (entries 1 and 2, Table 3.3), and determined that a change in substituents from oxygen to sulfur would lead to an upfield shift of approximately 30 ppm (entry 3). The difference in chemical shift between equitorial and axial substituents at C-3 was next determined from related steroids (entries 4 and 5) and found to be on the order of 5.0 ppm (entry 6). We could then derive an approximate C-3 chemical shift for cholest-5-en-3α-ol (entry 7). Since we knew that the C-3 substituent in thiocarbamate 3.41 was β- (3.41B, entry 8) and the difference between axial and equitorial substituents, we could derive a value for the C-3 epimer of 3.41 (3.41A, entry 8). Assuming a change from an O-alkyl thiocarbamate 3.41 to an S-alkyl thiocarbamate 3.44 involved a chemical shift approximately equal to 30 ppm (entry 3), we could then estimate C-3 chemical shifts of both axial and equitorial S-alkyl thiocarbamates 3.44A and 3.44B (entries 9 and 10).
Analysis of the crude Newman-Kwart reaction products by $^{13}$C-NMR (DEPT) showed what appeared to be a mixture of two compounds. Two singlets at $\delta_C = 168.6$ and $\delta_C = 167.4$ were observed. With the aid of the reported carbon assignments for cholesterol, we were able to identify doublets resulting from C-8, C-9, C-14, C-17, C-20, and C-25. The remaining doublets at $\delta_C = 45.1$ (major) and $\delta_C = 47.7$ (minor) were assigned to C-3. Following purification, the major compound isolated (35%) exhibited carbon signals at $\delta_C = 167.5$ and $\delta_C = 45.2$, infrared absorbance at $\nu = 1215$ cm$^{-1}$. The minor isomer (17%) exhibited $\delta_C = 168.6$, $\delta_C = 47.7$. Based upon this data and its agreement with our predicted values (Table 3.3), we have tentatively assigned the stereochemistry of the major isomer as the axial S'-cholesteryl thiocarbamate 3.44A and the minor isomer as the equitorial S'-cholesteryl thiocarbamate 3.44B. We plan to confirm this assignment in the future with chemical and additional spectroscopic methods.

The most likely rationalization of these results is the intermolecular $S_n2$ displacement of the C-3 oxygen in the O-cholesteryl thiocarbamate by sulfur to give the S-cholesteryl thiolcarbamate with inversion of stereochemistry. In 1966, Kinoshita found that O-alkyl thiocarbamates rearrange smoothly to S-alkyl thiolcarbamates when heated in the presence of catalytic amounts of Lewis acid such as boron trifluoride etherate or p-toluenesulfonic acid. Unlike the thermal rearrangement of O-aryl thiocarbamates which proceed via an intramolecular process, later experiments by Kinoshita indicate that the rearrangement of O-alkyl thiocarbamates proceeds by way of an $S_n2$ type intermolecular S-alkylation process. However, products resulting from an $S_n1$ type mechanism have been isolated when conditions were favorable such as with secondary O-alkyl thiocarbamates in polar solvents, or when approach of the nucleophile was sterically blocked.

The relatively low temperature at which the reaction takes place compared to the original rearrangement make this an attractive alternate for application to more sensitive compounds. This fact may be rationalized in part by the electron-rich nature of the 1,2,4-triazole being a much better electron-donor compared with simple dialkyamines and thus increasing the nucleophilicity of sulfur.
3.2.7 Synthesis of Heterocyclic Thiocarbamate Precursors

Scheme 3.14 Synthesis of 1H-benzimidazole, 1H-imidazole and 1H-(1,2,4-triazole) thiocarbamates. Reagents and conditions: (a) TrCl, DMAP, CH₂Cl₂; 59%. (b) TBDMSCI, imidazole, DMF, 10–25 °C, 12 h; 72%. (c) DME, KH, 1,1'-thiocarbonyldi(1,2,4-triazole), 30–25 °C; 20%. (d) DME, KH, 1,1'-thiocarbonyldibenzimidazole, 30–25 °C; 60%. (e) DME, 1,1'-thiocarbonyldi(1,2,4-triazole), reflux, 2 h; 20%. (f) DME, 1,1'-thiocarbonyldimidazole, reflux, 2 h; 60%. (g) DME, 1,1'-thiocarbonyldi(1,2,4-triazole), reflux, 2 h; 39%. (h) DME, KH, 1,1'-thiocarbonyldibenzimidazole, 30–25 °C; 80%. (i) DME, KH, 6-methoxypurine, 30–25 °C; 9%.

With the availability of the 1,1'-thiocarbonyldiazole reagents 3.38 and 3.39, a series of thiocarbamates were prepared from available sugar-derived substrates as summarized in the Scheme 3.14. Because of the reduced reactivity of 1,1'-thiocarbonyldibenzimidazole, preparation of the 1H-benzimidazolethiocarbamate (3.57) and the (Z)-tert-butyl 7-O-tert-butyldimethylsilyl-2,3-dideoxy-4,5-O-isopropylidene-D-ribo-hept-2-enate 1H-benzimidazole thiocarbamate (3.61) required basic conditions. These gave consistently better yields than the corresponding 1H-(1,2,4-triazole) thiocarbamates 3.56,
3.58, and 3.60. The triazole 3.60 was converted to the 9H-(6-methoxypurine) thiocarbamate 3.37 by displacement of the 1,2,4-triazole with 6-methoxypurine under basic conditions as described by Hirai. 183

3.3 Synthetic Route to Mixed Thionocarbonates

Our initial plans to prepare the mixed thionocarbonates centered upon the simple assumption that we could prepare the thionocarbonate in a stepwise manner using thiophosgene by way of an intermediate O-alkyl chlorothioformate (3.62) as shown below.

![Scheme 3.15 Proposed route to thionocarbonates involving thiophosgene.](image)

A literature review provided numerous examples of O-aryl chlorothioformates yet few examples of simple O-alkyl chlorothioformate 3.62 could be found. Attempts to isolate and characterize these O-alkyl chlorothioformates lead to diminished yields and were subsequently abandoned. The O-alkyl chlorothioformate were generated and used in situ.

3.3.1 Attempts to Prepare Mixed Thionocarbonates Using Thiophosgene

Our initial attempts to prepare and isolate an O-aryl chlorothioformates followed the procedure reported for O-(1,2:3,4-di-O-isopropylidene-α-D-glucoside) chlorothioformate (3.64). The addition of a solution of the potassium alkoxide of diacetone-D-glucose was added to a solution of thiophosgene at -65 °C, and the resulting solution was stirred at -65 °C for an additional 30 minutes. A quick aqueous work-up (H₂O, brine, anhydrous MgSO₄) yielded a yellow syrup which upon characterization yielded strong IR absorbance at ν = 3438 (br), ν = 1260 and ν = 1215 cm⁻¹. 13C-NMR signals at δC = 193 and at δC = 184 supported the chlorothioformate structure 3.64 since they were approximately the same as the C=S signal reported for O-phenyl chlorothioformate of δC = 182.9.
Scheme 3.16 An attempt to prepare a mixed thiocarbonate of diacetone glucose. Reagents and conditions: (a) THF, KH, 25→65 °C. (b) Cl\(_2\)C=S, 65→25 °C. (c) CH\(_2\)Cl\(_2\), cat. DMAP, methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside.

On standing, a precipitate began to appear. The crude chlorothioformate 3.64 was exposed to acylating conditions (CH\(_2\)Cl\(_2\), 1.0 equivalent DMAP, 0-25 °C, methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside, 12 h) which gave only unreacted starting diacetone glucose and starting glucoside by TLC.

Under carefully controlled conditions within a glove box, several attempts were made to prepare the chlorothioformate 3.64 and O-methyl thionocarbonate of diacetone glucose (DME, KH, distilled thiophosgene, 30 °C; methanol) without success. Under slightly different conditions as indicated in Scheme 3.17 below.

Scheme 3.17 Attempts to prepare a thiocarbamate of diacetone glucose. Reagents and conditions: (a) CH\(_2\)Cl\(_2\), pyridine, cat. DMAP, Cl\(_2\)C=S, 25 °C. (b) diisopropyl amine, CH\(_2\)Cl\(_2\), pyridine, 25 °C.
Diacetone glucose was exposed to ten equivalents of thiophosgene, and following removal of all volatiles, exposed to diisopropyl amine to give the desired $O$-($1,2:4,5$-$O$-isopropylidene-$\alpha$-$D$-glucofuranosyl) diisopropylthiocarbamate (3.66) in 20% yield along with the previously reported di-$O$-($1,2:4,5$-$O$-isopropylidene-$\alpha$-$D$-glucofuranosyl) thionocarbonate (3.67) in 14% yield$^{206}$ Assignment of thiocarbamate 3.66 was based in part upon the presence of a singlet at $\delta_C = 187.3$ and an infrared absorbance at $\nu = 1229$ cm$^{-1}$ and satisfactory carbon, hydrogen, nitrogen, and sulfur analysis. Isolation of the previously reported bis-thionocarbonate 3.67 was confirmed by the presence of a singlet at $\delta_C = 187.3$ and carbon, hydrogen and sulfur elemental analysis. One possible rationalization for these results is that even in the presence of excess thiophosgene, the thionocarbonate 3.67 was formed preferentially, and that the observed diisopropylthiocarbamate 3.66 could have resulted from amine substitution of the thionocarbamate 3.66 as opposed to reaction with the chlorothioformate 3.64.

Faced with these practical difficulties involving $O$-alkyl chlorothioformates and thiophosgene, and encouraged by what we had learned previously working toward sugar thiocarbamates, we decided to take advantage of carefully selected, easily prepared $O$-aryl chlorothioformates as a means of preparing the desired mixed thionocarbonates.

### 3.3.2 Mixed and Cyclic Thionocarbonates via Thiocarbamates

Since $O$-aryl chlorothioformates are easily prepared, isolable, and often commercially available$^{201}$ we decided to prepare $O$-(2,4-dinitrophenyl) chlorothioformate (3.68) as we expected substitution of the 2,4-dinitrophenol ($pK_a = 3.98$) by sugar hydroxyl groups would take place under mild conditions to give the mixed thionocarbonates 3.69 as depicted in Scheme 3.18.

$O$-(2,4-Dinitrophenyl) chlorothioformate (3.68) was conveniently prepared and isolated under aqueous conditions$^{186}$ to give a pale solid in 50% yield. However, an attempt to prepare the 3-$O$-cholesteryl $O$-(2,4-dinitrophenyl) thionocarbonate under standard conditions gave the nucleophilic aromatic substitution product $O$-cholesteryl $O$-(2,4-dinitrophenyl) ether (3.71), rather than the expected
mixed thionocarbonate (Scheme 3.19). Support for structure 3.71 comes from the absence of a signal \( \delta_C = 180-190 \), absence of an infrared signal \( v = 1215 \text{ cm}^{-1} \) and elemental analysis satisfying \( C_{33}H_{48}N_2O_2 \).

![Scheme 3.18](image)

**Scheme 3.18** Route to mixed thionocarbonates via O-aryl thiocarbonates.

![Scheme 3.19](image)

**Scheme 3.19** O-Aryl thiocarbonates yield nucleophilic aromatic substitution products. Reagents and conditions: (a) acetone, \( \text{Cl}_2\text{C}=\text{S}, \text{Na}_2\text{CO}_3 \text{(aq)}, 0^\circ\text{C} \); 50%. (b) cholesterol, pyr., 0 °C.

While attempting to prepare O-cholesteryl 9H-(benzimidazole)thiocarbamate (3.42) from cholesterol and 1,1'-thiocarboxyldibenzimidazole under basic conditions, the remaining potassium hydride was quenched with a small amount of methanol (Scheme 3.20). Upon purification it was found that thiocarbamate 3.42 in 17% yield along with 33% of a compound identified as the O-methyl O-cholesteryl thionocarbonate (3.72) was formed. Data supporting the assignment of thiocarbamate 3.42 include infrared absorbance at \( v = 1215 \text{ cm}^{-1} \), singlet at \( \delta_C = 184.8 \), and satisfactory elemental analysis.
Likewise, thiocarbonate 3.72 exhibited $\nu = 1215$ cm$^{-1}$, a singlet at $\delta_C = 195.8$, and satisfactory elemental analysis.

\begin{figure}
\centering
\includegraphics[width=0.8\textwidth]{fig3.20.png}
\caption{Scheme 3.20 Reagents and conditions: (a) DME, NaH, 1,1'-thiocarbonyldibenzimidazole, 25 °C. (b) MeOH.}
\end{figure}

In addition to finding the conditions needed to facilitate 1H-benzimidazole thiocarbamate formation, it became obvious that 1H-azole thiocarbamates in general could be used as intermediates to mixed thionocarbonates. No further $O$-aryl chlorothioformates were necessary since we realized any 1,1'-thiocarbonyldiazole could now be employed as a thiophosgene equivalent.

With the route to mixed thionocarbonates now clear, several representative, mixed thionocarbonates were prepared bearing primary 3.73, secondary 3.75, and glycosyl 3.74 groups (Scheme 3.21). The structural assignment of mixed thionocarbonate 3.75 was straightforward with the $^1$H-NMR exhibiting the correct hydrogen count (56 hydrogens) and exhibiting a singlet $\delta_C = 193.6$ (s, C=S). Likewise, mixed thionocarbonate 3.74 exhibited 64 hydrogens in the $^1$H-NMR and a singlet $\delta_C = 192.6$ (s, C=S). Substitution of the 1,2,4-triazole in 3.60 as indicated by the NMR experiment in Scheme 3.21 (acetonitrile-$d_3$, 80 °C), could not be accomplished under neutral conditions but required basic conditions at low temperature.
Scheme 3.21 Route to mixed thionocarbonates. Reagents and conditions: (a) DME, KH, MeOH, 30→25 °C; 61%. (b) DME, KH, 5-O-tert-butyldimethylsilyl-2,3-O-isopropylidene-β-D-ribofuranose, 30→25 °C; 76%. (c) DME, KH, diacetone-D-glucose, 30→25 °C; 52%. (d) acetonitrile-d₅, diacetone-D-glucose, 80 °C, 18 h.

Figure 3.9 Thionocarbonates from thiocarbamates under Beau’s conditions. Reagents and conditions: (a) pentafluorophenol, PhH, reflux; no reaction.

Beau has reported that under neutral conditions substitution of imidazole from an O-alkyl 1H-imidazole thiocarbamate by pentafluorophenol takes place in refluxing benzene to give the
corresponding O-alkyl O-pentafluorophenyl thiocarbonate (3.97). In an attempt to reproduce this result as described in Figure 3.9, nothing other than starting materials were recovered as determined by TLC.

3.4 Tributytin Mediated Cyclizations of Thiocarbamates, Cyclic and Mixed Thionocarbonates

3.4.1 Preparation of Cyclic Thiocarbonates

The use of 1,1'-thiocarbonyldiimazole to prepare thiocarbonates is not without precedent. It has been known for some time that vicinal diols give cyclic thiocarbonates with 1,1'-thiocarbonyldiimidazole. Treatment of these cyclic thiocarbonates with phosphites leads to olefins (Corey-Winter Reaction).208

![Scheme 3.22 Preparation of cyclic thiocarbonates. Reagents and conditions: (a) DME, 1,1'-thiocarbonyldiimidazole, reflux, 2 h; 65%. (b) DME, 1,1'-thiocarbonyldiimidazole, reflux, 2 h: 94%. (c) 1.0 M TBAF in THF, 0 °C; 47%.](image)

This reaction is a powerful means of preparing olefins with well defined stereochemistry when used in conjunction with methods of preparing vicinal diols stereoselectively.209 These cyclic thiocarbonates have also been used as a means of regioselective radical generation from vicinal diols.210
This led us to consider preparing and cyclizing several cyclic thionocarbonates of our precursors. The preparation of two cyclic thionocarbonates is shown in Scheme 3.22. The formation of cyclic thionocarbonate 3.77 was supported by IR ($\nu = 1215$ cm$^{-1}$), $\delta_C = 191.6$, and elemental analysis data. Likewise, formation of cyclic thionocarbonate 3.77 was supported by infrared ($\nu = 1215$ cm$^{-1}$), $\delta_C = 191.8$, and elemental analysis data.

Having prepared several cyclic and mixed thionocarbonates as well as thiocarbamates containing known azoles and a novel purine thiocarbamate, we next exposed these substrates to conditions essentially identical to those reported for the preparation of 2.70 as shown in Scheme 2.18.

3.4.2 Cyclization of Cyclic Thionocarbonates

Cyclization of 2,3-O-isopropylidene-4,5-thiocarbo-D-ribofuranose, O-methyl oxime (3.76) gave a white waxy solid which has been identified as 2-amino-2,5-anhydro-3,4-O-isopropylidene-D-allonothioic acid, $\epsilon$-lactone (3.78) in 60% yield. Immediately evident from the $^1$H- and $^{13}$C-NMR spectra of this new compound was the absence of the methoxy function. The presence of a broad multiplet at $\delta_H = 2.49$ which integrated to two protons suggested the presence of an $-\text{NH}_2$ function. Strong, sharp absorbances in the infrared region (KBr) at $\nu = 3418$ and 3335 cm$^{-1}$ correlate with the asymmetric and symmetric N-H stretching modes characteristic of primary amines. In chloroform, a strong absorbance at $\nu = 1214$ cm$^{-1}$ was observed. This signal has been a common feature of the thiocarbonates and thiocarbamates we have prepared and is most likely the C=S stretch. A new signal at $\delta_C = 216.0$ suggested the presence of a thioester. The presence of the amine function was further supported when an analytically pure sample of 3.78 was acetylated to give 3.79. In addition to the expected acetyl signal, a new signal emerged in the $^1$H-NMR $\delta_H = 7.52$ (m, 1 H) which was compatible with an amide N-H function. The structural assignment for 3.79 was deduced from $^1$H-NMR, $^{13}$C-NMR, IR data, with the presence of both nitrogen and sulfur later confirmed by elemental analysis.
We rationalized loss of the methoxy group as resulting from thermal elimination of methanol under the reaction conditions. Working through a mechanism analogous to that proposed earlier in Scheme 2.17 and Scheme 2.18, we envisioned that the Barton intermediate 3.80 was trapped by the oxime ether to give 3.81 with subsequent elimination of methanol to give the proposed orthoester intermediate 3.82. The dioxabicyclo-[3.2.1]-octane skeleton presumably undergoes hydrolysis via 3.83 followed by aminal formation upon work-up to give the D-"allo-e-"lactone 3.78.

Under similar conditions, the corresponding (Z)-tert-butyl 2,3-dideoxy-4,5-O-isopropylidene-6,7-O-thiocarbo-D-"ribo-hept-2-enote (3.77) gave 2-deoxy-2-(2-"tert-butoxy-2-oxoethyl)-3,4-O-isopropylidene-D-allonothioic acid, \( \delta \)-lactone (3.84). This structural assignment was based in part upon a characteristic signal at \( \delta_C = 218.5 \) indicating the presence of a thioester as well as the presence of a free hydroxyl
function observed in the compound's infrared spectrum. Furthermore, loss of unsaturation was evident from the presence of a well resolved ABX spin system assigned as the exocyclic 2-C-methylene unit. The stereochemistry at the C-2 position has been tentatively assigned the *allo*-3.84 configuration based upon the vicinal coupling constant of $J_{1,2} = 3.6$ Hz and the similarity to data provided by allopypuranitol 2.69, and D-allopyranosyl 1H-imidazole 2.70 ($J_{1,2} = 3.2$ Hz) (*vide infra*).

An attempt to simplify purification by acetylating the free hydroxyl at $\delta_H = 2.15$ (t, 1 H) lead to isolation of acetyl 6-O-acetyl-1,5-anhydro-2-C-(2-tert-butoxy-2-oxoethyl)-3,4-O-isopropylidene-2-deoxy-1-thio-D-ribo-hex-1-enitol 3.85. This structure was assigned based upon the loss of the thioester signal ($\delta_C = 218.5$) and the emergence of a new, acyclic thioester signal at $\delta_C = 191.9$ and acetal signal at $\delta_C = 169.9$. The 2-C-side chain ABX spin system in 3.84 coalesced to $\delta_H = 3.20$ (m, 2H) and two new singlets emerged at $\delta_C = 146.3$ and $\delta_C = 116.9$ consistent with the unsaturation. The presence of sulfur in 3.85 was later confirmed by elemental analysis.

![Scheme 3.24 Preparation of 2-deoxy-1-thio-D-ribo-hex-1-enitol 3.85. Reagents and conditions: (a) 2.2 equiv. tributyltin hydride, 0.05 M toluene, 90 °C, reverse addition of 3.77 with 0.2 equiv. AIBN in toluene; 50%. (b) Ac$_2$O, CH$_2$Cl$_2$, pyridine, 0-25 °C, 12 h; 64%.

In light of Wilcox’s results (Scheme 1.1 and Figure 1.3), it appears reasonable for cyclization of 3.77 to occur via Barton intermediate 3.86 via the lower energy of two possible transition states (Scheme 3.25). Radical addition to the *re* face of the olefin requires the ester to adopt a pseudo-equatorial
conformation with significant torsional strain as illustrated in 3.86b. On the other hand, radical addition onto the \textit{si} face of the double bond as shown in 3.86a avoids the torsional strain and provides a lower energy pathway for cyclization to intermediate 3.87. Cyclization via the lower energy transition state 3.86a, and in the absence of an epimerization pathway, should ultimately yield \textit{alto}-3.84. However, the \textit{alto}-3.84 assignment was difficult to defend given a $J_{2,3}$ coupling constant of only 3.6 Hz. Equally difficult was the notion of cyclization occurring via the higher energy transition state 3.86b. Therefore, given that the coupling data is in support an \textit{allo}-3.84 assignment, and since every compound isolated thus far resulting from 6-exo-trig radical cyclization of thiocarbonates and thiocarbamates has been recovered as a single diastereomer, the most likely pathway involves radical cyclization via 3.86a and some form of epimerization pathway under the reaction conditions to give the observed results.
In either event, opening of the orthoester 3.87 occurs to yield the lower energy 6-membered thionolactone *altro*-3.84 over the 7-membered thionolactone (not shown). The thionolactone can then be acetylated to give the observed 2-deoxy-1-thio-D-ribo-hex-1-enitol 3.85.

### 3.4.3 Cyclization of Mixed Thionocarbonates

In an attempt to prepare a disaccharide by this new route, we exposed the mixed thionocarbonates 3.73 and 3.74 to the radical reaction conditions. In each case, following addition of the substrate, TLC analysis showed complete consumption of the starting materials. Each reaction was then cooled, concentrated, and purified by flash chromatography. Isolated material from each reaction was analyzed by $^1$H-NMR and exhibited signals from the acetonide, *tert*-butyl ester and silyl protecting group along with unresolved signals between $\delta_H = 3.50 - 4.75$ which we attributed to unidentified decomposition products.

![Decomposition Products](image)

<table>
<thead>
<tr>
<th>X</th>
<th>Reverse Add. of Substrate</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.73</td>
<td>0.05 M tol w/0.2 equiv. AIBN</td>
<td>2.5 equiv. TBTH, 0.05 M tol, 110 °C</td>
</tr>
<tr>
<td>3.74</td>
<td>0.05 M PhH w/0.2 equiv. AIBN</td>
<td>2.5 equiv. TBTH, 0.05 M PhH, 80 °C</td>
</tr>
</tbody>
</table>

*Table 3.5 Cyclization of thionocarbonates.*

### 3.4.4 Cyclization of Heterocyclic Thiocarbamates

*(Z)*-*tert*-butyl 2,3-dideoxy-7-0-*tert*-butylidemethylsilyl-4,5-0-isopropylidene-D-ribo-hept-2-enoate 1H-benzimidazole thiocarbamate (3.61) was next cyclized under standard conditions and two compounds

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were isolated. The first was identified as the 1,2-dideoxy-2-(2-tert-butoxy-2-oxoethyl)-6-O-tert-butyldimethylsilyl-3,4-O-isopropylidene-β-D-allopyranosyl 1H-benzimidazole (3.90) resulting from a mechanism proposed earlier for the corresponding D-allopyranosyl 1H-imidazole 2.70, Scheme 2.18. Also isolated was 1,5-anhydro-2-dideoxy-2-(2-tert-butoxy-2-oxoethyl)-6-O-tert-butyldimethylsilyl-3,4-O-isopropylidene-D-ribo-hex-1-enopyranosyl 1H-benzimidazole (3.91).

Figure 3.10 Preparation of β-D-allopyranosyl 1H-benzimidazole 3.90. Reagents and conditions: (a) 1.6 equiv. tributyltin hydride, 0.05 M toluene, 90 °C, reverse addition of 3.62 with 0.2 equiv. AIBN in toluene; 3.90 4%, 3.91 6%.

Scheme 3.26 Proposed Pathway to β-D-allopyranosyl 1H-benzimidazole 3.90 and D-ribo-hex-1-enopyranosyl 1H-benzimidazole 3.91.
The tentative *allo*-3.90 assignment was based upon the $J_{2,3}$ coupling constant of 3.5 Hz, and its similarity to data provided by D-allonothioic acid, 8-lactone 3.84, allopurinol 2.69, and D-allopyranosyl 1H-imidazole 2.70. The structural assignment for 3.91 follows from the simplification of the 2-C side chain ABX spin system in 3.90 to an AB quartet in 3.91, and a loss of the anomeric signal. The assignment for both 3.90 and 3.91 where further supported by HRMS data. Further attempts to cyclize the 1H-(1,2,4-triazole) thiocarbamates lead to unidentifiable decomposition products (Table 3.6.)

Throughout our study involving the cyclization of thionocarbonates and thiocarbamates, we have added our substrates to excess tributyltin hydride to favor N- and O-glycoside formation via C-S bond cleavage and suppress thionolactone formation as was shown in Scheme 2.17 and Scheme 2.18. It is very likely that thionolactone formation is favored not only by low concentrations of tributyltin hydride, but also by elevated temperatures as are other reaction pathways which may lead to unwanted decomposition or epimerization of products.

![Diagram of decomposition products](image)

<table>
<thead>
<tr>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>Reverse Addn of Substrate</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>BzIm</td>
<td>Tr</td>
<td>NOMe</td>
<td>0.05 M tol, 0.2 eq. AIBN</td>
<td>2.1 eq. TBTH, 0.05 M tol, 90 °C</td>
</tr>
<tr>
<td>TrA</td>
<td>TBDMS</td>
<td>NOMe</td>
<td>0.05 M tol, 0.2 eq. AIBN</td>
<td>2.1 eq. TBTH, 0.05 M tol, 90 °C</td>
</tr>
<tr>
<td>TrA</td>
<td>TBDMS</td>
<td>CHCO$_2$Bu$'$</td>
<td>0.05 M tol, 0.2 eq. AIBN</td>
<td>1.6 eq. TBTH, 0.05 M tol, 90 °C</td>
</tr>
</tbody>
</table>

*Table 3.6* Cyclization of heterocyclic thiocarbamates.

However, the reaction conditions we have chosen to generate the necessary tributyltin radicals rely upon the thermal decomposition of AIBN to initiate and sustain the free radical chain reaction. We chose a reaction temperature of ca. 90 °C because it appeared to offer a balance between the mildest conditions necessary and the need to ensure a uniform decomposition of AIBN and reliable chain
propagation. Unfortunately, these conditions are not compatible with minimizing thionolactone formation and we have long suspected that this may be in part responsible for the low yields of the desired N- and O-glycosides. Even though we were able to show the viability of the heterocyclic transfer, the reaction has not yet been optimized. This avenue will be further pursued in future work.

3.5 Search for Milder Cyclization Conditions

There have been two principal alternatives to thermal initiation of tributyltin radical chain reactions at temperatures significantly below 80 °C and these include the use of tributyltin hydride/triethylborane/air\(^{212}\) and photoinitiated decomposition of AIBN.\(^{213}\)

The first conditions explored were those reported by Oshima\(^{214}\) whereby a solution of 0.1 equivalents of triethylborane (1.0 M in hexanes) was added to a benzene solution containing 1.0 equivalent of substrate and 1.2 equivalents of triphenyltin hydride or tributyltin hydride at 25 °C. The progress of the reaction was monitored by TLC and no visible progress in the reaction was detected at 25 °C until air was bubbled through the reaction. After 3 h, unreacted starting material was recovered along with unidentified decomposition products.

![Figure 3.11 Attempt to cyclize onto oxime 3.57. Reagents and conditions: (a) 2.1 equiv. tributyltin hydride, 0.05 M toluene, 0-25 °C, 0.2 equiv. triethylborane (1.0 M in hexanes), air.](image)

Other reports have appeared claiming photoinitiation of tributyltin hydride in the presence of AIBN, which unfortunately often omit the specific light source and temperature at which the reaction
 occurred. Several experiments were conducted attempting to photoinitiate the decomposition of AIBN using high intensity, 500 watt incandescent and halogen lamps. Each experiment began at 0 °C with direct and prolonged exposure to the light source. The temperature was allowed to rise slowly with constant monitoring of the reaction by TLC to detect the first sign of photoinitiation.

In all cases, no sign of photoinitiation was observed until the reaction temperature met or exceeded 45-50 °C and ultimately yielded consumption of the substrate resulting in multiple, unidentified products. Similar results were obtained when the reaction was repeated using a Rayonet ultraviolet light source (λ = 350 nm). There was no indication by TLC of the reaction progressing until the reaction temperature exceeded 45-50 °C with complete consumption of starting materials and numerous unidentified sideproducts.

\[
\begin{align*}
\text{TBDMSO} & \quad \overset{\text{TBDMSO}}{\text{O}} \quad \overset{\text{X}}{\text{CO}_2\text{Bu}'} \\
\text{3.37 } X = 9\text{H-(6-methoxypurine)} & \quad \text{Cyclization Products (See Table 3.7)}
\end{align*}
\]

\[
\begin{align*}
\text{TBDMSO} & \quad \overset{\text{Im}}{\text{O}} \quad \overset{\text{NOMe}}{\text{O}} \\
\text{3.59} & \quad x
\end{align*}
\]

\[
\begin{array}{|c|c|c|c|c|c|c|c|}
\hline
\text{Substrate} & \text{Substrate Conc.} & \text{Solvent} & \text{Equiv. TBTH} & \text{Equiv. AIBN} & \text{Temp. °C} & \text{Light Source} & \text{Results} \\
\hline
3.37 & 0.015M & toluene & 2.5 & 0.2 & 0-50 & 500 W incandescent & Decomp. \\
3.59 & 0.016M & toluene & 2.5 & 0.2 & 0-50 & 500 W incandescent & Decomp. \\
3.74 & 0.015M & benzene & 2.5 & 0.2 & 0-35 & 500 W Halogen & Figure 3.12 \\
2.60 & 0.015M & toluene & 2.5 & 0.2 & 0-35 & 500 W incandescent & Decomp. \\
2.60 & 0.015M & toluene & 2.5 & 0.2 & 0 & 500 W incandescent & No Reaction \\
2.60 & 0.015M & toluene & 2.5 & 0.2 & 0-50 & UV (350 nm) & Decomp. \\
\hline
\end{array}
\]

Table 3.7 Attempts to photoinitiate 6-exo-trig cyclizations.

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The one exception was the reaction of thionocarbonate 3.75 which gave aliphatic thioester 3.94 along with a trace of what has tentatively been assigned as 2-deoxy-2-(2-tert-butoxy-2-oxoethyl)-6-O-tert-butylidimethylsilyl-3,4-O-isopropylidene-D-altronothioic acid, α-lactone (3.95).

Structural assignment of thioester 3.94 was based in part upon the observed loss of unsaturation, the presence of the characteristic thioester signal in the $^{13}$C-NMR and the presence of a distinct hydroxyl function in the infrared spectrum. Tentative assignment of thionolactone 3.95 is based upon $^1$H-NMR and $^{13}$C-NMR data ($\delta_c = 218.6$ (thioester)) of recovered material.

![Diagram](image)

**Figure 3.12** Undesired acyclic thioester formation. Reagents and conditions: (a) 3.74 0.015 M in benzene, 2.5 equiv. tributyltin hydride, 0.2 equiv. AIBN $\rightarrow$50 °C, 500 W Halogen.

Both thioesters 3.94 and 3.95 were easily rationalized as the result of competing pathways as described in Scheme 2.17 and Scheme 2.18 for the decomposition of reaction intermediate 3.96. At low concentrations of tributyltin hydride, thionolactone formation has traditionally been observed. However, in the case of 3.94, pyran opening is competitive with loss of sugar residue to give the aliphatic thioester.
Figure 3.13. Pathway to thioesters 3.94 and 3.95.

Other reports had been found describing the homolysis of tributyltin and triphenyltin hydride at 0 °C under sonication. After ensuring that our sonication bath had sufficient output, these conditions were also examined with no reaction observed at temperatures below 50 °C.

Figure 3.14. Radical initiation under sonication conditions. Reagents and conditions: (a) 2.67, 0.024 M in toluene, 2.1 equiv. tributyltin hydride, 0.2 equiv. AIBN, 0 - 50 °C, sonication.

3.6 Summary

Our investigation into a new O- and N-glycoside forming reaction based upon the 6-exo-trig cyclization of thionocarbonates 2.68 and thiocarbamates 2.70 began with the development of a general route to sugar thiocarbamates by thioacylation of heterocycles such as purine with activated O-phenyl chlorothioformates. The activated phenols could then be selectively substituted by carbohydrate
derivatives to give the target thiocarbamates. We found that the corresponding mixed sugar thionocarbonates were available via a similar procedure involving the selective substitution of phenol from $O$-phenyl thionocarbonates, or by the selective substitution of imidazole or 1,2,4-triazole from sugar thiocarbamates. During our studies, we also found a novel variation of the Newman-Kwart Rearrangement of $O$-aryl dialkylthiocarbamates, and observed several interesting cyclizations of cyclic thiocarbonates. Although the initial conditions we investigated to cyclize the sugar thionocarbonates and sugar thiocarbamates yielded few positive results, ongoing work will concentrate on developing cyclization conditions to improved the yields of both $O$- and $N$-glycoside products.

Having succeeded in the preparation of complex mixed thionocarbonates and thiocarbamates, one obvious line of future research is to attempt the new glycoside forming reaction in the context of furanosides. The kinetic advantage of the 5-membered ring formation can be expected to lead to a more efficient cyclization reaction. This line of research is currently being pursued in our laboratory.
LIST OF REFERENCES


15. For recent reviews of cyclohexanes and cyclopentanes derived from carbohydrates, see: (a) RajanBabu, T. V. Preparative Carbohydrate Chemistry; Hansessian, S., Ed.; Marcel Dekker: New York, 1997; Chapter 25, pp 545-568. (b) Ferrier, R. J.; Middleton, S. Chem. Rev. 1993, 93, 2779-2831.


38. Several non-radical approaches to the preparation of carbocycles from carbohydrates have been reported. See ref. (2) in: Wilcox, C. S.; Thomasco, L. M. *J. Org. Chem.* 1985, 50, 546-547


55. See reference 24(c).


123


66. See reference 58(a).

67. See reference 58(b).


See reference 84(a).


Dane, E.; Dockner, T. Angew. Chem. 1964, 76, 342.


See reference 82(a).


94. The conditions reported for the closure of azidohydrins covered a variety of solvents (CH₂Cl₂, THF, toluene, DMF). We observed later in the project the dramatic change in yields in the Mitsunobu reaction as a function of solvent.

95. Reactions were run using isolated (Cp₂TiCl₂) in a glovebox with freshly distilled and degassed solvent kept over molecular sieves and stored in the glovebox.


98. Akitt, J. W. Multinuclear NMR; Mason, J., Ed.: Prenum; New York, 1987; Chapter 9, p 278.


107. It must be noted that the \((\text{Cp}_2\text{TiCl}_2)\) used was the same material which was earlier shown by \(^{27}\text{Al}-\text{NMR}\) to contain residual \(\text{AlCl}_3\).


112. See reference 111(a).


114. See reference 113(a).


122. See reference 121(a).


132. Examples of C-glycosides from Wittig olefination of furanoses, see: (a) See references 129(a) and 130(c). (b) Moffatt, J. G.; Ohnui, H.; Jones, G. H.; Maddox, M. L.; Christensen, A. T.; Byram, S. *K. J. Am. Chem. Soc.* 1975, 97, 4602-4613. (c) See reference 129(c). (d) See reference 4, pp 120-122.


140. See reference 136(a).


145. The olefin geometry is clearly indicated by the proton chemical shifts and coupling constants. For example, coupling constant for the (E)-isomer is ca. $J = 15.6$ Hz; the (Z)-isomer is ca. $J = 11.6$ Hz.

146. See reference 4, pp 389-399.


129

153. See reference 152, p 209.

154. See reference 151(b).

155. $^{13}$C-NMR obtained in 0.1N HCl, see reference 151(b), p 270-271.


169. See reference 168(b).


180. See reference 178(b).

181. See reference 178(f).


131


199. See reference 151(b); p 136 and 210


206. See Reference 205(b)


214. See reference 212(c).


217. $^{13}$C-NMR spectra were calibrated relative to the deuterated solvent used. The most common solvent used, chloroform-d, was assigned $\delta_C = 77.23$.


231. Low yields following chromatography are to be expected. Products are too labile on silica gel.
233. See reference 222, pp 466-467.
234. See reference 222, p 786.
244. See reference 222, p 660.

249. Kovac, P.; Sklenar, V.; Glaudemans, C. P. *Carbohydr. Res.* 1988, 175, 201-213. NBS was dried overnight under high vacuum before use to remove trace HBr from decomposition of NBS.


262. See reference 122, p 422.

263. See reference 130(d).


282. See reference 176.

APPENDIX A

EXPERIMENTAL

General

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Proton nuclear magnetic resonance spectra were recorded on Bruker AM-200, 250, 300, 400, and 500 MHz Fourier transform spectrometers and are reported in parts per million on the δ scale from an internal tetramethylsilane (TMS) standard. Spectral data are reported as follows: chemical shift (multiplicity [s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet], coupling constants, integration, assignment). Carbon magnetic resonance spectra were recorded on Bruker 50, 62.5, 75, 100 and 125 MHz fourier transform spectrometers and are reported in parts per million on the δ scale. Spectral data are reported as follows: chemical shift (multiplicity, assignment). Spectral assignments were based upon one or more of the following: proton-proton decoupling experiments, HOMOCORR, HETCORR, DEPT, APT, NOESY, and correlation with known compounds. Infrared spectra were obtained on Perkin-Elmer 283b or 1600 Infrared Spectrometers and are reported in reciprocal centimeters (cm⁻¹) and the relative intensity reported as follows: br = broad, s = strong, m = medium, w = weak. High resolution mass spectra were performed by The Ohio State University's Shared Analytical Instrumentation Laboratory (SAIL) and were recorded on Kratos MS-30 or Kratos VG 70-250S mass spectrometers at an ionization energy of 70 eV. New compounds submitted for elemental analysis were purified by chromatography and dried for 12-18 h in a drying pistol (P₂O₅, 60 °C). Elemental analysis was performed by Atlantic.
Microlabs of Norcross, GA. Optical rotations were obtained on a Perkin-Elmer 241 MC Polarimeter with a sodium lamp at 589 nm and 1 mm slit width. Concentrations are reported in g/dL.

Solvents and reagents were purified prior to use:221,222 tetrahydrofuran and dimethoxyethane (distillation from Na/benzophenone), diethyl ether (distillation from Na/benzophenone), dimethylformamide (vacuum distillation from CaH₂ and stored over 4 Å molecular sieves), dimethyl sulfoxide (distillation from CaH₂ and stored over 4 Å molecular sieves), toluene (distillation from CaH₂), benzene (distillation from Na/benzophenone), dichloromethane (distillation from CaH₂), pyridine (distillation from KOH and stored over 4 Å molecular sieves). All reactions were carried out in oven or flame-dried glassware under an atmosphere of nitrogen using standard inert atmosphere techniques.223 Reactions were monitored by thin layer chromatography (TLC) using EM Science precoated 60 F₂₅₄ plates and visualized224,225 with polyphosphomolybdic acid (PMA), KMnO₄, or concentrated sulfuric acid. Flash column chromatography226 was performed over EM Laboratories silica gel (70-230 mesh). Preparative TLC was performed on Merck 2 mm preparative TLC plates. Unless otherwise indicated, reactions involving the use of air sensitive Ti(III) were performed in a Vacuum/Atmospheres DRI-LAB glove box equipped with a HE-493 DRI-TRAIN purifier. Likewise, (Cp₂TiCl)₂ was prepared and isolated under an inert atmosphere in a glove box⁶¹ or by standard Schlenk procedure⁶⁴.

For uniformity and to the greatest extent possible, the title of each experimental section contains the Chemical Abstract Service (CAS) nomenclature for the prepared compound. For simplicity however, the text may contain nomenclature which conforms to more generally accepted usage.

Chapter 1 Experimentals

Preparation of 1,2:5,6-bis-O-(1-methyldene)-α-D-glucofuranoside, S-methyl carbonodithioate (1.82a)(Scheme 1.17).227 A 25 mL round-bottom flask equipped with stir bar, rubber septum, and nitrogen inlet was charged with a 0.25 M solution of diacetone-D-glucose (206 mg, 0.76 mmol) in tetrahydrofuran (3.0 mL) containing 5 mol% imidazole (30 mg). To this was added 1.5 equivalents of NaH (60% in mineral oil, 45 mg, 1.14 mmol) in small portions over several minutes. The evolution of
hydrogen was observed and the reaction was stirred at 25 °C for 0.5 h to yield a yellow solution. Three equivalents of CS₂ (140 μL, 2.30 mmol) were added dropwise via syringe and the resulting orange solution stirred for an additional 0.5 h followed by addition of 1.2 equivalents of MeI (100 μL, 0.90 mmol). The reaction was stirred at 25 °C for an additional 2 h until consumption of starting material was indicated by TLC. The reaction was then quenched with saturated ammonium chloride (1 mL) and then extracted with diethyl ether (3 x 25 mL) and the combined organic phase washed with H₂O (20 mL), saturated brine (15 mL) and then dried over anhydrous MgSO₄. Vacuum filtration followed by concentration in vacuo yielded 311 mg of a yellow oil. Flash chromatography (silica gel, 20:1 hexanes/ethyl acetate) yielded 162 mg (61%) of the previously reported 1,2:5,6-di-O-isopropylidene-3-O-(S-methyl dithiocarbonate)-α-D-glucosyluronide (1.82a) as a light orange oil. Characterization by NMR matched data previously reported.227

\[ R_f = 0.55 \text{ (20:1 petroleum ether/ethyl acetate); IR (Neat), 2986s, 2935s, 2895m, 1716w, 1454m, 1423m, 1372s, 1197s, 1083s, 1023s, 913m, 877m, 846s, 731m cm}^{-1}; \text{ }^1H-NMR (250 MHz, CDCl}_3) 5.92 (m, 2 H), 4.67 (d, J = 3.8 Hz, 1 H), 4.33-4.28 (m, 2 H), 4.10-4.05 (m, 2 H), 2.59 (s, 3 H, SMe), 1.53 (s, 3 H, CH₃), 1.41 (s, 3 H, CH₃), 1.33 (s, 3 H, CH₃), 1.32 (s, 3 H, CH₃).\\]

**Attempted Reduction of 1,2:5,6-bis-O-(1-methylidene)-α-D-glucosyluronide, S-methyl carbonodithioate (1.82a) with Cp₂TiCl (in situ) (Scheme 1.20).** A 50 mL, three-necked, round-bottom flask equipped with a magnetic stir bar, addition funnel, and nitrogen inlet was charged with a 0.01 M solution of 1,2:5,6-di-O-isopropylidene-3-O-(S-methyl dithiocarbonate)-α-D-glucosyluronide (1.82a, 50 mg, 0.14 mmol) in tetrahydrofuran (14.0 mL) containing 4.4 equivalents of γ-terpinene (100 μL, 0.62 mmol). A separate 25 mL flask equipped with magnetic stir bar, rubber septum, and nitrogen inlet was charged with titanocene dichloride (54 mg, 0.21 mmol) in tetrahydrofuran (1.0 mL) and 6.0 equivalents of
activated zinc$^8$ (82 mg, 1.26 mmol) and stirred for 2 h to yield a green colored solution characteristic of 
Cp$_2$TiCl (1.55) formation. $^6$ The solution was transferred via canula to the addition funnel and diluted 
with additional tetrahydrofuran (2 mL). The green Cp$_2$TiCl solution was added dropwise to the xanthate 
slowly over 20 minutes with the green color of the titanium (III) yielding a yellow solution on addition to 
the xanthate 1.82a. Following addition of Cp$_2$TiCl, the reaction was stirred for an additional 0.5 h. The 
reaction was quenched with saturated KH$_2$PO$_4$ (20 mL) and extracted with diethyl ether (3 x 30 mL). The 
combined organic phase was washed with water (25 mL), saturated brine (25 mL) and then dried over 
anhydrous MgSO$_4$. Vacuum filtration and concentration in vacuo yielded a yellow oil which was shown 
by TLC and $^1$H-NMR analysis to be recovered starting material as the sole product.

**Preparation of (oxiranylmethyl)-2-propenyl-propanedioic acid, diethyl ester (1.63).** $^{56,228}$ A 250 mL 
round-bottom flask equipped with a magnetic stir bar and nitrogen inlet was charged with a 0.33 M 
solution of diethyl diallyl malonate (4.80 g, 20.0 mmol) in dichloromethane (60 mL) followed by 1.0 
equivalent of MCPBA$^{229}$ (3.452 g, 20.0 mmol) added in small portions over 0.5 h. The reaction was 
allowed to stir at 25 °C for 12 h. The reaction mixture was then diluted with diethyl ether (200 mL) and 
washed with saturated aqueous sodium bicarbonate (50 mL), 5% aqueous sodium bisulfite (50 mL), 
saturated aqueous sodium bicarbonate (50 mL), water (50 mL), saturated brine (25 mL) and then dried 
over anhydrous MgSO$_4$. Vacuum filtration and concentration in vacuo yielded the crude monoepoxide as 
a colorless oil which was purified by flash chromatography (silica gel, 5:1 hexanes/ethyl acetate) to give 
1.277 g (26.5%) of recovered starting diene ($R_f$ = 0.72) and 2.197 g (42.8%) of the previously reported 
(oxiranylmethyl)-2-propenyl-propanedioic acid, diethyl ester (1.63) as a colorless liquid.

$$
\text{O} \\
\text{BO}_2\text{C} \quad \text{CO}_2\text{B}
$$

$R_f$ = 0.40 (5:1 hexanes/ethyl acetate); IR (neat) 3078w, 2982m, 2936w, 1732s, 1641w, 1466w, 1444m, 
1389w, 1367m, 1320m, 1288m, 1256m, 1218s, 1198s, 1151m, 1096m, 1032m, 927m, 856m cm$^{-1}$; $^1$H-NMR
\[(200 \text{ MHz, CDCl}_3) \delta 5.66 (m, 1 H, H-6), 5.18 (m, 1 H, H-7a), 5.14 (s, 1 H, H-7b), 4.20 (q, J = 7.1 Hz, 1 H, OCH$_2$CH$_3$), 4.19 (q, J = 7.1 Hz, 1 H, OCH$_2$CH$_3$), 4.18 (q, J = 7.1 Hz, 2 H, OCH$_2$CH$_3$), 2.96 (m, 1 H, H-2), 2.75 (m, 1 H, H-5a), 2.73 (s, 1 H, H-5b), 2.71 (m, 1 H, H-1), 2.44 (dd, J = 5.1 Hz, J = 2.6 Hz, 1 H, H-1), 2.17 (dd, J$_{gem} = 14.6$ Hz, J$_{3a,2} = 4.8$ Hz, 1 H, H-3a), 1.99 (dd, J$_{gem} = 14.6$ Hz, J$_{3b,2} = 6.8$ Hz, 1 H, H-3b), 1.26 (t, J = 7.1 Hz, 3 H, CH$_3$), 1.25 (t, J = 7.1 Hz, 3 H, CH$_3$); ^{13}$C-NMR (75 MHz, CDCl$_3$) δ 170.77 (s, CO$_2$Et), 171.70 (s, CO$_2$Et), 132.2 (d, C$_6$), 119.5 (t, C$_7$), 61.57 (t, OCH$_2$CH$_3$), 61.48 (t, OCH$_2$CH$_3$), 56.3 (s, C$_4$), 48.5 (d, C$_2$), 46.8 (t, C$_3$), 37.9 (t, C$_3$), 36.0 (t, C$_3$), 14.1 (q, OCH$_2$CH$_3$).

**Attempted Reductive Cyclization of 4-pentenyl oxirane (1.63) with Cp$_2$TiCl (1.55) (Scheme 1.21).** A 50 mL, three-necked, round-bottom flask equipped with a magnetic stir bar, addition funnel, and nitrogen inlet was charged with a 0.044 M solution of 4-pentenyl oxirane (1.63, 58 mg, 0.22 mmol) in tetrahydrofuran (5.0 mL). A 25 mL, round-bottom flask equipped with magnetic stir bar, septum, and nitrogen inlet was charged with titanocene dichloride (128 mg, 0.51 mmol) in tetrahydrofuran (6.0 mL) and 6.0 equivalents of activated zinc$^{80}$ (82 mg, 1.26 mmol) and stirred for 3 h to yield a green color characteristic of the titanium(III) species.$^{60}$ The Cp$_2$TiCl generated in situ was transferred via canula to the addition funnel. The 0.085 M Cp$_2$TiCl solution was added dropwise to the monoepoxide slowly over 1 h with the green color of the titanium (III) yielding a yellow solution on addition to the epoxide 1.63. Following addition, the reaction was stirred for an additional 1 h. Analysis by TLC (4:1 hexanes/ethyl acetate) indicated no further monoepoxide remained. The reaction was quenched with 10% H$_2$SO$_4$ (10 mL) and extracted with diethyl ether (3 x 25 mL). The combined organic phase was washed with water (25 mL), saturated brine (25 mL) and then dried over anhydrous MgSO$_4$. Vacuum filtration and concentration in vacuo yielded a yellow oil which by $^1$H-NMR analysis lacked the desired doublet ca $\delta_H = 0.9$ ppm characteristic of the cyclized product's exocyclic methyl.$^{66}$ Gas chromatographic and mass spectrometric analysis indicated the product was the 1,6-heptadiene 1.90 resulting from deoxygenation of the starting epoxide.
Preparation of Chloro bis(\(\eta^5\)-2,4-cyclopentadien-1-yl)-titanium (1.54) (Eqn. 3, Scheme 1.10). A 250 mL round-bottom flask equipped with a side-arm stopcock, magnetic stir bar, and water condenser was charged with 2.0 equivalents of sublimed cyclopentadienyllithium\(^{230}\) (1.934 g, 7.17 mmol) and the reaction vessel purged with nitrogen. In a nitrogen filled glove bag, a 100 mL round-bottom flask equipped with a rubber septum was charged with titanium(III) chloride (552 mg, 3.58 mmol). The titanium (III) chloride was taken out of the glove bag and dissolved in tetrahydrofuran (8.5 mL). The purple titanium (III) chloride solution was then transferred to the reaction flask dropwise via syringe to yield a pale yellow mixture. The reaction mixture was heated to reflux for 1 h to give a dark green solution. The reaction was cooled to 25 °C and the reaction mixture was filtered (Schlenk technique)\(^{223}\) and the solids washed with tetrahydrofuran (2 x 8 mL). The combined filtrates were concentrated in vacuo to yield 420 mg (60%) of the \((\text{Cp}_2\text{TiCl})_2\) (1.54) as a dark green solid. The isolated green solid was stored under nitrogen in a glove box refrigerator at -33 °C.

\((\text{Cp}_2\text{TiCl})_2\)

Preparation of 2-methylcyclopentanemethanol (1.88) with isolated \((\text{Cp}_2\text{TiCl})_2\) (1.54) (Scheme 1.21).\(^{66}\) In a glove box, a 25 mL round-bottom flask equipped with a stir bar and addition funnel was charged with a 0.04 M solution of 4-pentenyl oxirane (1.63, 20 mg, 0.18 mmol) in tetrahydrofuran (2.75 mL). The addition funnel was charged with a 0.08 M solution of the green \((\text{Cp}_2\text{TiCl})_2\)\(^{64}\) (1.54, 96 mg, 0.225 mmol) in tetrahydrofuran (5.6 mL). The contents of the addition funnel were added to the epoxy-olefin over the course of about 20 minutes to give a bright yellow-orange solution. The reaction was stirred for an additional 20 minutes, removed from the glove box, and diluted with ethyl acetate (10 mL). The reaction was then washed with 10% H\(_2\)SO\(_4\) (3 mL), water (2 mL), saturated brine (2 mL) and then dried over anhydrous MgSO\(_4\). Vacuum filtration and concentration in vacuo yielded 17 mg of a bright red film. Proton NMR analysis of the crude reaction mixture showed the absence of the signals characteristic of the olefin \(\delta_H = 6.0-4.7\) and epoxide \(\delta_H = 3.0-2.2\) functions, and the presence of two doublets resulting from the 5-\(\text{exo}\)- and 5-\(\text{endo}\)-methyl signals at \(\delta_H = 0.96-0.84\).\(^{66}\)
Preparation of Chloro bis($\eta^5$-2,4-cyclopentadien-1-yl)-titanium (1.54) (Eq. 2, Scheme 1.10). In a glove box, a 250 mL round-bottom flask with magnetic stir bar was charged with a 0.65 M solution of titanocene dichloride (26.78 g, 107 mmol) in tetrahydrofuran (175 mL) along with 4.6 equivalents of aluminum foil (Aldrich gold label, 10.00 g, 0.375 mol) and the reaction stirred for 18 h. The solids were removed via filtration and the filtrate concentrated under reduced pressure to yield a dark green solid. The solid was broken up and washed with diethyl ether (3 x 50 mL) and dried in vacuo to yield 19.9 g (93%) of the desired (Cp$_2$TiCl)$_2$ (1.54) as a dark green solid which was stored in a glove box at -33 °C. The activity of the reagent was checked as described above. This material maintained its activity even after storage at -33 °C for 27 months.

(Cp$_2$TiCl)$_2$

Preparation of phenylmethyl-\textit{N}-[1-methyl-3-(methoxycarbonyl)propene]-\textit{L}-threonine (1.92) (Scheme 1.22). A 100 mL, round-bottom flask equipped with stir bar, rubber septum, and nitrogen inlet was charged with 0.50 M solution of KOH (1.036 g, 18.47 mmol) in absolute methanol (35 mL). To this was added L-threonine (2.008 g, 16.79 mmol) followed 15 minutes later by dropwise addition of methyl acetoacetate (1.90 mL, 17.63 mmol). The reaction was stirred at 25 °C for an additional 5 h. Removal of solvent under reduced pressure yielded a white solid which was dissolved in dichloromethane (56 mL) and stirred vigorously for 1 h. The resulting mixture was vacuum filtered and the collected solid dried under high vacuum to yield 2.00 g (94%) of the previously reported potassium \textit{N}-[1-methyl-3-(methoxycarbonyl)propene]-\textit{L}-threonine (1.91, Dane's salt) as a fine white powder and used in the next step without further purification. A 0.75 M solution of Dane's salt (1.91, 1.00 g, 3.91 mmol) in DMF (5.0 mL) was stirred at 25 °C until homogenous. To this was added 1.07 equivalents of benzyl bromide (500 µL, 4.20 mmol) in one portion and the resulting solution allowed to stir at 25 °C for 24 h.
The reaction was diluted with ethyl acetate (30 mL), washed with saturated sodium bicarbonate (30 mL), water (30 mL), saturated brine (30 mL) and then dried over anhydrous MgSO₄. Vacuum filtration and concentration in vacuo yielded 4.97 g (96%) of the previously reported benzyl-N-[1-Methyl-3-(methoxycarbonyl)propenyl]-L-threonine (1.92) as an orange-yellow oil. An analytical sample was flash chromatographed (silica gel, 20:1 petroleum ether/diethyl ether, 5% Et₃NH) and characterized.

\[ R_f = 0.40 \text{(20:1 petroleum ether/diethyl ether, 5\% Et₃NH)}; \]^H-NMR (250 MHz, CDCl₃) δ 7.34 (s, 5 H, Ar-H), 5.19 (m, 2 H, OCH₂Ph), 4.67 (s, 1 H), 4.58 (s, 1 H), 4.25 (dd, J₁,₂ = 6.4 Hz, J₁,₃ = 3.9 Hz, 1 H, H-3), 4.00 (dd, J = 9.9 Hz, J = 3.9 Hz, 1 H, H-2), 3.62 (s, 3 H, CO₂CH₃), 2.85 (s, 1 H), 1.85 (s, 3 H, CH₃-vinyl), 1.24 (d, J₄ = 6.4 Hz, 3 H, H-4); \[^{13}\text{C-NMR (62.9 MHz, CDCl₃) δ} 170.8 \text{(s, CO₂), 170.5 \text{(s, CO₂), 160.4 \text{(s, C-1')}, 135.2 \text{(s, Ar), 128.8 \text{(d, Ar), 128.64 \text{(d, Ar), 128.62 \text{(d, Ar), 128.3 \text{(d, Ar), 127.7 \text{(d, Ar), 85.3 \text{(d, C-2')}, 68.4 \text{(d, C-4), 67.4 (t, benzyl), 61.7 (d, C-3), 50.1 (q, OCH₃), 19.5 (q, C-4).}})


Preparation of N-(triphenylmethyl)-L-threonine, phenylmethyl ester (1.94) (Scheme 1.22).^232

A 100 mL round-bottom flask equipped with stir bar, rubber septum, and nitrogen inlet was charged with 0.50 M solution of phenylmethyl-N-[1-methyl-2-(methoxycarbonyl)vinyl]-L-threonine (1.92, 880 mg, 2.86 mmol) in distilled dioxane (6.0 mL) containing 1.2 equivalents of p-toluenesulfonic acid monohydrate (652 mg, 3.43 mmol) and the reaction stirred at 25 °C for 12 h. The reaction was diluted with diethyl ether (50 mL) and washed with water (25 mL). The aqueous phase was neutralized to pH 10 with K₂CO₃ and back extracted with ethyl acetate (25 mL) and the combined organic phase washed with saturated brine (20 mL) and dried over anhydrous MgSO₄. Vacuum filtration and concentration in vacuo yielded 450 mg of a clear oil which was taken up in CHCl₃ (5 mL) and the solution cooled to 0 °C. To this was
added triethylamine (300 μL) and trityl chloride (600 mg, 2.15 mmol) and the reaction allowed to
warm slowly to 25 °C and stirred an additional 24 h. The reaction was then diluted with dichloromethane
(10 mL) and washed with 10% citric acid (5 mL), water (5 mL), saturated brine (5 mL) and then dried
over anhydrous MgSO₄. Vacuum filtration and concentration in vacuo yielded a clear oil. Flash
chromatography (silica gel, 5:1 hexanes/ethyl acetate) yielded 960 mg (74%) of the previously reported
benzyl N-trityl-L-threonine (1.94) as a colorless oil.

\[
\begin{align*}
\text{Rf} & = 0.30 \ (5:1 \ \text{hexanes/ethyl acetate}; \ \text{^1}H-\text{NMR} \ (300 \ \text{MHz, CDCl}_3) \ \delta \ 7.55-7.40 \ (m, \ 5 \ H, \ Ar), \ 7.35-7.10 \ (m, \ 15 \ H, \ trityl), \ 4.50 \ (m, \ 2 \ H, \ benzyl), \ 3.85-3.70 \ (m, \ 1 \ H), \ 3.60-3.40 \ (m, \ 2 \ H), \ 3.00-2.80 \ (s, \ 1H, \ OH). \ 1.15 \ (d, \ 3 \ H, \ H-4).
\end{align*}
\]

Preparation of N-[(1,1-dimethylethoxy)carbonyl]-L-threonine, phenylmethyl ester (1.97)

(Scheme 1.22). A 50 mL, round-bottom flask equipped with a magnetic stir bar and nitrogen
inlet was charged with a 0.5 M solution of L-threonine (580 mg, 4.87 mmol) in 1.0 M NaOH (10 mL) and
cooled to 0 °C. To this solution was added 1.2 equivalents of di-tert-butyl dicarbonate (1.275 g, 5.84
mmol) in dioxane (5.0 mL) dropwise over 0.5 h. The cooling bath was removed and the reaction allowed
to warm to 25 °C and stirred an additional 12 h. The reaction was then acidified to pH = 3 with 1.0 M
KH₂SO₄ and the combined phases extracted with ethyl acetate (3 x 25 mL). The combined organic phase
was then washed with water, saturated brine and then dried with anhydrous MgSO₄. Vacuum filtration
and concentration in vacuo yielded 846 mg (79%) of the intermediate N-Boc-threonine which was used in
the next step without further purification. To a 0.7 M solution of the N-Boc-threonine (460 mg, 2.09
mmol) in dimethylformamide (3.00 mL) was added 1.03 equivalents each of K₂CO₃ (300 mg, 2.17 mmol)
and benzyl bromide (260 μL, 2.19 mmol). The reaction was stirred at 25 °C for 24 h. The reaction was
then partitioned between ethyl acetate and saturated bicarbonate. The organic phase was washed with
water, saturated brine and then dried over anhydrous MgSO₄. Vacuum filtration and concentration in

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vacuo gave a clear oil. Flash chromatography (silica gel, 20:1 petroleum ether/ethyl acetate) yielded 910 mg (60%) of the previously reported benzyl 3-((tert-butylcarbonyl)-L-threonine (1.97) as a colorless oil. Characterization of 1.97 matched previously reported data.236

\[ R_f = 0.20 \text{ (20:1 petroleum ether/ethyl acetate)} \]

\[ ^1H-NMR \text{ (200 MHz, CDCl}_3 \text{) } \delta 7.35 \text{ (s, 5 H, Ar), 5.40 \text{ (m, 1 H), 5.19 \text{ (m, 2 H, benzyl), 4.30 \text{ (m, 2 H), 2.40 \text{ (m, 1 H), 1.43 \text{ (s, 9 H, t-Bu), 1.23 \text{ (d, J = 6.4 Hz, 3 H, H-4).}}} \]

Preparation of (2S-trans)-3-Methyl-1-(triphenylmethyl)-2-aziridinecarboxylic acid, phenylmethyl ester (1.94) (Scheme 1.22).87 A 100 mL, 3-necked, round-bottom flask equipped with a magnetic stir bar, addition funnel, and nitrogen inlet was charged with a 0.04 M solution of benzyl 3-trityl-threonine (1.93, 4.51 g, 10.0 mmol) in toluene (250 mL) containing 3.0 equivalents of triethylamine (4.20 mL, 30.0 mmol) and the reaction vessel cooled to -50 °C (cyclohexanone/liq. N₂). The addition funnel was charged with 1.5 equivalents of a solution of sulfuryl chloride (1.0 M in dichloromethane) in toluene (0.11 M, 136 mL) and the contents of the addition funnel added to the reaction over the course of 15 minutes. The reaction was stirred at -50 °C for an additional 1 h when the cooling bath was removed and the reaction stirred at 25 °C for an additional 2 h. The reaction was then diluted with ethyl acetate (100 mL) and washed with water, 10% brine solution (2 x 50 mL), and then dried over anhydrous MgSO₄. Vacuum filtration and concentration in vacuo gave a dark orange oil. Flash chromatography (silica gel, 25:1 hexanes/ethyl acetate) yielded 2.140 g (49%) of the previously reported (2S-trans)-benzyl 3-methyl-1-trityl-2-aziridinecarboxylate (1.94) as a white solid along with 2.013 g (45%) of recovered starting material. Characterization of aziridine 1.94 matched data previously reported.87
$R_f = 0.30$ (25:1 hexanes/ethyl acetate); $\text{Mp} = 101.0-102.0^\circ\text{C}$ (Lit. $\text{Mp} 99-101^\circ\text{C}$.\textsuperscript{87}) $^1\text{H}-\text{NMR}$ (300 MHz, CDCl$_3$) $\delta$ 7.53-7.19 (m, 20 H, Ar), 5.27 (d, $J_{\text{gem}} = 12.3$ Hz, 1H, benzyl), 5.13 (d, $J_{\text{gem}} = 12.3$ Hz, 1 H, benzyl), 1.93 (d, $J_{2,3} = 6.5$ Hz, 1 H, H-2), 1.63 (dd, $J_{3,2} = 6.5$ Hz, $J_{3,4} = 5.5$ Hz, 1 H, H-3), 1.35 (d, $J_{4,3} = 5.5$ Hz, 3 H, CH$_3$); $^{13}\text{C}-\text{NMR}$ (62.9 MHz, CDCl$_3$) $\delta$ 170.4 (CO$_2$), 144.1 (Ar), 136.2 (Ar), 129.6 (Ar), 128.7(Ar), 128.5 (Ar), 128.4 (Ar), 128.1 (Ar), 127.8 (Ar), 127.0 (Ar), 75.2 (CPh$_3$), 66.7 (OCH$_2$Ph), 36.3 (C-2), 35.2 (C-3), 13.5 (CH$_3$). HRMS (EI) calcd for C$_{30}$H$_{26}$NO$_2$: 432.196279. Obsd: 432.198150.

Preparation of (2S-trans)-3-methyl-2-aziridinecarboxylic acid, phenylmethyl ester (1.95)

(Scheme 1.22).\textsuperscript{87,232,237} A 25 mL, round-bottom flask equipped with a magnetic stir bar, septum, and nitrogen inlet was charged with a 0.14 M solution of benzyl 3-methyl-1-trityl-2-aziridinecarboxylate (1.94, 425 mg, 0.98 mmol) in absolute methanol (7.0 mL) and cooled to 0°C. Ninety five equivalents of formic acid (4.0 mL, 93.0 mmol) was added dropwise to the reaction over several minutes. After several minutes at 0°C, a white solid was observed. The reaction was stirred for an additional 1 h at 0°C when the cooling bath was removed and the reaction stirred at 25°C for 1 h. The reaction was filtered to yield 177 mg of a white solid. The recovered solid was flash chromatographed (silica gel, dichloromethane/2% Et$_2$NH) to give 69 mg (38%) of previously reported (2S-trans)-benzyl 3-methyl-2-aziridinecarboxylate (1.95). Characterization matched data previously reported.\textsuperscript{87}

$^1\text{H}-\text{NMR}$ (200 MHz, CDCl$_3$) $\delta$ 7.38-7.35 (m, 5 H, Ar), 5.20 (s, 2 H, OCH$_2$Ph), 2.66 (m, 1 H), 2.34 (m, 1H), 1.28 (d, $J_{4,3} = 5.6$ Hz, 3 H, CH$_3$), 1.2-1.0 (m, 1H).

Preparation of (2S-trans)-1-acetyl-3-methyl-2-aziridinecarboxylic acid, phenylmethyl ester (1.96)

(Scheme 1.22).\textsuperscript{232,237} A 25 mL round-bottom flask equipped with a magnetic stir bar, rubber septum, and nitrogen inlet was charged with a 0.6 M solution of benzyl 3-methyl-1-trityl-2-aziridinecarboxylate (1.94, 150 mg, 0.35 mmol) in 1:1 CHCl$_3$/MeOH (1.0 mL) and cooled to 0°C. Twenty three equivalents of trifluoroacetic acid (0.60 mL, 7.9 mmol) was added dropwise to the reaction over several minutes. After
20 minutes, no further starting material was detected by TLC. The solvents were removed under reduced pressure to yield a yellow oil and the residual trifluoroacetic acid removed by azeotropic distillation with toluene. The resulting crude product was partitioned between diethyl ether and saturated bicarbonate and the organic phase was separated and dried over anhydrous MgSO$_4$. Vacuum filtration and concentration in vacuo yielded a clear oil which was dissolved in CHCl$_3$ (1.0 mL) containing triethylamine (100 µL, 0.70 mmol) and cooled to 0 °C. Addition of 1 equivalent of acetic anhydride (35 µL, 0.35 mmol) was followed by stirring at 0 °C for 3 h. The cooling bath was then removed and the reaction allowed to slowly come to 25 °C and stir an additional 14 h. The reaction was diluted with additional CHCl$_3$ (10 mL), washed with 10% citric acid (10 mL), water (10 mL), saturated brine (10 mL) and then dried with anhydrous MgSO$_4$. Vacuum filtration and concentration in vacuo yielded 143 mg of a clear oil. Flash chromatography (silica gel, 3:1 hexanes/ethyl acetate) yielded 33 mg (40%) of the previously reported (2S-trans)-benzyl 1-acetyl-3-methyl-2-aziridinecarboxylate (1.96) as a clear oil.

\[
\text{\begin{align*}
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{OO}_2\text{CH}_2\text{Ph}
\end{array}
\end{align*}
\]

$^1$H-NMR (300 MHz, CDCl$_3$) δ 7.38-7.35 (m, 5 H, Ar), 5.22 (s, 2 H, OCH$_2$Ph), 3.22 (d, J$_{2,3}$ = 6.4 Hz, 1 H, H-2), 2.78 (dd, J$_{3,2}$ = 6.4 Hz, J$_{3,4}$ = 5.6 Hz, 1 H, H-3), 2.15 (s, 3 H, acetyl), 1.35 (d, J$_{4,3}$ = 5.5 Hz, 3 H, CH$_3$); $^{13}$C-NMR (75.5 MHz, CDCl$_3$) δ 181.8 (acetyl), 167.8 (ester), 135.5 (Ar), 128.9 (Ar), 128.8 (Ar), 128.8 (Ar), 128.7 (Ar), 128.5 (Ar), 67.5 (OCH$_2$Ph), 39.2 (C-3), 38.3 (C-2), 23.5 (acetyl), 13.0 (Me).

Attempted reduction of (2S-trans)-3-methyl-1-(triphenylmethyl)-2-aziridinecarboxylic acid (1.94), phenylmethyl ester with isolated (Cp$_2$TiCl)$_2$ (1.54) (Scheme 1.24). In a glove box, a 10 mL, round-bottom flask equipped with a magnetic stir bar and addition funnel was charged with a 0.04 M solution of (2S-trans)-benzyl 3-methyl-1-trityl-2-aziridinecarboxylate (1.94, 25 mg, 57.7 µmol) in tetrahydrofuran (1.5 mL). The addition funnel was then charged with a 0.04 M solution of (Cp$_2$TiCl)$_2$ (1.54, 31 mg, 72.5 µmol) in tetrahydrofuran (3.0 mL). The green titanium(III) reagent was added dropwise over 0.5 h to give a yellow solution and was allowed to stir for an additional 1 h. The reaction was taken out of the
glove box and quenched with saturated KH₂PO₄ (3 mL) and extracted with diethyl ether (3 x 5 mL). The combined organic phase was washed with water (5 mL), saturated brine (5 mL) and then dried over anhydrous MgSO₄. Vacuum filtration and concentration in vacuo yielded a red residue which was chromatographed on a preparative scale (silica gel, dichloromethane/2% Et₂NH) to yield 6 mg (24%) of unreacted starting material.

Attempted reduction of (2S-trans)-1-acetyl-3-methyl-2-aziridinecarboxylic acid (1.96), phenylmethyl ester with isolated (Cp₂TiCl)₂ (1.54) (Scheme 1.26). In a glove box, a 10 mL round-bottom flask equipped with a magnetic stir bar and addition funnel was charged with a 0.04 M solution of (2S-trans)-benzyl 3-methyl-1-acetyl-2-aziridinecarboxylate (1.96, 30 mg, 0.128 mmol) in tetrahydrofuran (3.2 mL) in the presence of excess γ-terpinene (3 drops). The addition funnel was then charged with a 0.08 M solution of (Cp₂TiCl)₂ (62 mg, 0.135 mmol) in tetrahydrofuran (3.3 mL). The green titanium(III) reagent was added dropwise over 0.5 h to give a yellow solution and following addition was allowed to stir for an additional 1 h. The reaction was taken out of the glove box and TLC analysis showed starting material remained in addition to several more polar compounds. The reaction was quenched with saturated KH₂PO₄ (3 mL) and extracted with diethyl ether (3 x 5 mL). The combined organic phase was washed with water (5 mL), saturated brine (5 mL) and then dried over anhydrous MgSO₄. Vacuum filtration and concentration in vacuo yielded 34 mg of a bright red residue which was flash chromatographed (silica gel, 3:1 hexanes/ethyl acetate) to yield 2 compounds A & B. Based upon ¹H-NMR analysis, compound A was a small amount of unidentified side product with the balance of the material identified as starting material.

Preparation of α-(azidomethyl)-benzenemethanol (1.102) (Scheme 1.23). A 250 mL, round-bottom flask equipped with a magnetic stir bar, condenser, and nitrogen inlet was charged with a 0.64 M solution of styrene oxide (9.50 mL, 83.2 mmol) in dioxane (130 mL). To this solution was added 1.25 equivalents of sodium azide (6.80 g, 104.6 mmol) in water (17.5 mL) and the reaction mixture refluxed for 24 h yielding a yellow solution. The reaction was cooled, the phases separated and the organic phase
washed with water, saturated brine and then dried over anhydrous MgSO₄. Vacuum filtration and distillation (107-112 °C/1 mm Hg) yielded 4.250 g (31%) of previously reported α-(azidomethyl)-benzenemethanol (1.102) as a colorless oil.

\[
\begin{align*}
R_f &= 0.50 \text{(4:1 hexanes/ethyl acetate)}; 
\text{IR (neat) } 3374\text{br}, 3085\text{m}, 3063\text{m}, 3031\text{m}, 2927\text{m}, 2878\text{m}, 2492\text{w}. \\
2101\text{s(N₃)}, 1955\text{w}, 1882\text{w}, 1811\text{w}, 1757\text{w}, 1652\text{w}, 1602\text{m}, 1585\text{w}, 1493\text{s}, 1453\text{s}, 1391\text{m}, 1343\text{s}, 1310\text{s}, \\
1252\text{s(N₃)}, 1181\text{m}, 1069\text{s}, 1040\text{s}, 914\text{m}, 871\text{m}, 758\text{s}, 700\text{s} \text{ cm}^{-1}; \\
{^1}\text{H-NMR (300 MHz, CDCI₃/D₂O) } \delta 7.37-7.30 \text{ (m, 5 H, Ar), 4.62 (dd, } J = 9.1 \text{ Hz, } J = 6.9 \text{ Hz, 1 H, benzyl), 3.68 (d, } J = 6.9 \text{ Hz, 1 H, CH₂N₃). 3.66} \\
\text{(d, } J = 9.1 \text{ Hz, 1 H, CH₂N₃), 2.70-2.50} \text{ (br, 1H, D₂O exch., OH).}
\end{align*}
\]

Preparation of N-(phenylmethylene)-benzimidine (1.100) (Scheme 1.23). A 25 mL, round-bottom flask was charged with 1.0 equivalent of benzaldehyde (1.050 g, 9.89 mmol) and aniline (920 mg, 9.89 mmol). The flask was swirled for several minutes until the contents homogenous and then the flask was set aside for 15 minutes. The reaction was then diluted with 95% ethanol (1.6 mL) and cooled to 0 °C for 0.5 h. The solids were recovered by vacuum filtration, rinsed with additional solvent, azeotroped with toluene, and dried under vacuum to give 1.23 g (62%) of the previously reported N-benzyl-benzimidine (1.100) as a white solid. Characterization matched data previously reported.  

\[
\text{PhCH=NPh}
\]

\[
{^1}\text{H-NMR (300 MHz, CDCI₃) } \delta 8.42 \text{ (s, 1 H), 7.93-7.85 (m, 2 H, Ar), 7.50-7.32 (m, 5 H, Ar), 7.25-7.15} \text{ (m, 3 H, Ar).}
\]

Preparation of 1,2-diphenylaziridine (1.101) (Scheme 1.23). A 50 mL, round-bottom flask equipped with a magnetic stir bar, rubber septum, and nitrogen inlet was charged with 1.2 M solution of NaN₃ (380 mg, 9.53 mmol) in dimethyl sulfoxide (8.0 mL) and warmed to 55 °C for 20 minutes and then cooled to 25 °C. The reaction was then diluted with tetrahydrofuran (8 mL) and cooled to 0 °C followed by addition of 0.85 equivalents of trimethylsulfonium iodide (1.647 g, 8.07 mmol) in small
portions over several minutes. After 15 minutes, 0.77 equivalents of \( N \)-(phenylmethylene)-benzenimine (1.100, 1.23 g, 7.33 mmol) was added and the reaction was stirred at 0 °C for an additional 0.5 h, then warmed to 25 °C and stirred an additional 0.5 h. The reaction was diluted with 1:1 pentane/diethyl ether (50 mL) and washed with water (180 mL), saturated brine (15 mL) and then dried over anhydrous MgSO\(_4\). Vacuum filtration and concentration in vacuo yielded 1.063 g (55%) of the previously reported 1,2-diphenylaziridine (1.103). The material was used in subsequent steps without the need for further purification.

\[
\begin{align*}
\text{Ph} & \quad N \\
\quad & \quad \text{Ph}
\end{align*}
\]

\(^1\)H-NMR (300 MHz, CDCl\(_3\)) \& 7.45-6.90 (m, 10 H, Ar), 3.08 (dd, \( J = 6.4 \) Hz, \( J = 3.3 \) Hz, 1 H), 2.44 (dd, \( J = 6.4 \) Hz, \( J = 1.2 \) Hz, 1 H), 2.38 (dd, \( J = 3.3 \) Hz, \( J = 1.2 \) Hz, 1 H).

Attempted addition of ethyl acrylate to \( N \)-phenyl-2-phenylazlridine (1.101) in the presence of \( (\text{Cp}_2\text{TiCl})_2 \) (1.54) (Scheme 1.24). \(^6\) In a glove box, a 100 mL, round-bottom flask equipped with a magnetic stir bar, rubber septum, addition funnel, and nitrogen inlet was charged with a 0.01 M solution of \( N \)-phenyl-2-phenylaziridine (1.101, 57 mg, 0.29 mmol) in tetrahydrofuran (30.0 mL) containing 15 equivalents of freshly distilled ethyl acrylate (462 mg, 4.6 mmol). The addition funnel was charged with a 0.022 M solution of \( (\text{Cp}_2\text{TiCl})_2 \) (284 mg, 0.66 mmol) in tetrahydrofuran (30 mL) and added to the aziridine solution dropwise slowly over the course of 0.5 h. On addition, the green Ti(III) reagent gave way to a light brown color. The reaction was removed from the glove box and diluted with diethyl ether (150 mL) and washed with 10% KH\(_2\)PO\(_4\) (25 mL), water (25 mL), saturated brine (25 mL) and then dried over anhydrous MgSO\(_4\). Vacuum filtration and concentration in vacuo yielded a brown viscous oil. Flash chromatography (silica gel, 10:1 hexanes/ethyl acetate w/2% Et\(_2\)NH) yielded four unidentified compounds.

Preparation of methyl 4,6-O-(phenylmethylene)-\( \alpha \)-D-glucopyranoside. \(^2\) A 500 mL round-bottom flask equipped with a magnetic stir bar was charged with a 0.15 M solution of methyl \( \alpha \)-D-
glucopyranoside (2.90 g, 15.0 mmol) in acetonitrile (100 mL) containing 5 mol% $p$-toluenesulfonic acid monohydrate (150 mg). To this solution was added 4 equivalents of benzaldehyde dimethyl acetal (9.0 mL, 60.0 mmol) and the cloudy reaction mixture stirred at 25 °C under nitrogen for 24 h. Triethylamine (2.0 ml) was then added to the clear reaction solution and the solvent removed under reduced pressure to yield a crude white solid. This solid was taken up in chloroform (50 mL) and washed with water (10 mL), saturated aqueous brine (10 mL) and then dried over anhydrous MgSO$_4$. Vacuum filtration and concentration in vacuo yielded a white solid which was recrystallized from water and dried under vacuum in the presence of P$_2$O$_5$ to yield 3.167 g (75%) of the previously preported methyl 4,6-O-benzylidene-D-glucopyranoside.$^{243,244}$

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

$^\circ$H-NMR (300 MHz, DMSO-$d_6$) $\delta$ 7.46-7.43 (m, 2 H, Ar), 7.39-7.35 (m, 3 H, Ar), 5.56 (s, 1 H, benzylidene), 5.17 (d, $J = 5.0$ Hz, 1 H, $D_2O$ exch., OH), 4.99 (d, $J = 6.6$ Hz, 1 H, $D_2O$ exch., OH), 4.63 (d, $J_{1,2} = 3.7$ Hz, 1 H), 4.16 (dd, $J = 9.7$ Hz, $J = 4.5$ Hz, 1 H), 3.72-3.66 (m, 1H), 3.62-3.54 (m, 2 H), 3.40-3.33 (m, 1 H), 3.31 (s, 3 H, OCH$_3$); $^{13}$C-NMR (75 MHz, DMSO-$d_6$) $\delta$ 137.2 (i-Ar), 129.4 (p-Ar), 128.5 (o-Ar), 126.5 (m-Ar), 102.1 (C-7), 100.0 (C-1α), 81.1 (C-4), 73.1 (C-2), 72.0 (C-3), 69.1 (C-6), 62.6 (C-5), 55.7 (OCH$_3$).

**Preparation of methyl 2,3-bis-O-(phenylmethyl)-4,6-O-(phenylmethylene)-α-D-glucopyranoside (Scheme 1.27).**$^{242}$ A 500 mL, 3-neck, round-bottom flask equipped with a large magnetic stir bar, water condenser, addition funnel, and nitrogen inlet was charged with 2.0 equivalents of potassium hydride (35% in mineral oil, 7.305 g, 63.76 mmol) and washed three times with petroleum ether.$^{245}$ The last traces of ether were removed under high vacuum and the flask charged with dimethoxymethane (160 mL). Under a stream of nitrogen, methyl 4,6-O-benzylidene-α-D-glucopyranoside (4.50 g, 15.94 mmol) was
added in small portions over 15 minutes. Following addition of the pyranoside, the reaction mixture was stirred vigorously for and additional 0.5 h until the evolution of hydrogen ceased. The addition funnel was then charged with 2.0 equivalents of distilled benzyl bromide (10.55 mL, 63.76 mmol) and the contents added slowly to the stirred alkoxide solution over 0.5 h. Following addition, the reaction was allowed to stir at 25° C under nitrogen for 24 h to yield a homogenous white suspension. Residual KH was quenched by slow addition of methanol (10 mL) and after stirring for 15 minutes the reaction was concentrated under reduced pressure to give a white solid. The crude product was taken up in chloroform (100 mL) and washed with water (3 x 20 mL), saturated brine (10 mL) and then dried over anhydrous MgSO4. Vacuum filtration and concentration in vacuo yielded a crude white solid which when recrystallized from diethyl ether provided 5.772 g (78%) of the previously reported methyl 2,3-di-O-benzyl-4,6-O-benzylidene-α-D-glucopyranoside.

![Chemical structure](image)

Mp = 95-97 °C [Lit. Mp = 96-98 °C];246 IR (KBr) 3087w, 3062w, 3026m, 3006w, 2978w, 2920m, 2874m, 2820m, 2343w, 1963w, 1901w, 1874 w, 1814w, 1602w, 1583w, 1558w, 1496s, 1452s, 1383s, 1365s, 1336m, 1308m, 1282m, 1251m, 1237m, 1216m, 1187s, 1139s, 1094s, 1051s, 1020s, 988s, 967s, 933s, 915s cm⁻¹;¹H-NMR (300 MHz, CDCl₃) δ 7.50-7.30 (m, 15 H, Ar), 5.54 (s, 1 H, benzylidene), 4.86 (ABq, v₁ = 4.88, v₂ = 4.84, J = 11.3 Hz, 2 H, benzyl). 4.77 (ABq, v₁ = 4.84, v₂ = 4.69, J = 12.1 Hz, 2 H, benzyl), 4.57 (d, J₁,₂ = 4.6 Hz, 1 H, H-1), 4.26 (dd, J = 9.9 Hz, J = 4.6 Hz, 1 H), 4.04 (app. t, J₁,₂ = J₁,₃ = 9.3 Hz, 1 H, H-3), 3.81 (dd, J = 9.8 Hz, J = 4.5 Hz, 1 H), 3.70 (t, J = 10.1 Hz, 1 H), 3.61 (d, J = 9.3 Hz, 1 H), 3.55 (dd, J = 9.3 Hz, J = 3.7 Hz, 1 H), 3.39 (s, 3 H, OCH₃);¹³C-NMR (75 MHz, CDCl₃) δ 138.9 (i-Ar), 138.4 (i-Ar), 137.6 (i-Ar), 129.1 (Ar), 128.6 (Ar), 128.3(Ar), 128.2(Ar), 128.1(Ar), 127.0(Ar), 126.2 (Ar), 101.4 (C-7), 99.4 (C-1α), 82.3 (C-4), 79.4 (benzyl), 78.8 (benzyl), 75.5 (C-2), 74.0 (C-3), 69.3 (C-6), 62.5 (C-5), 55.5 (OCH₃).
Preparation of methyl 2,3,4-tris-O-(phenylmethyl)-α-D-glucopyranoside (Scheme 1.27). A 250 mL round-bottom flask equipped with an addition funnel, water condenser, nitrogen inlet, and magnetic stir bar was charged with a 0.04 M solution of methyl 2,3-di-O-benzyl-4,6-O-benzylidene-α-D-glucopyranoside (1.071 g, 2.31 mmol) in 5:3 dichloromethane/diethyl ether (160 mL) containing 4.3 equivalents of LAH (377 mg, 9.93 mmol). The addition funnel was charged with a solution containing 3.6 equivalents of AlCl₃ (1.127 g, 8.45 mmol) in diethyl ether (30 mL). Following slow addition of the aluminum chloride/ether solution the reaction vessel was warmed to 40 °C for 2 h. The reaction was cooled to 25 °C and excess LAH was carefully quenched with ethyl acetate (10 mL). The contents of the reaction flask was transferred to a separatory funnel and washed with water (3 x 20 mL), saturated brine (20 mL) and then dried over anhydrous MgSO₄. Vacuum filtration and concentration in vacuo yielded 1.051 g of a cloudy oil which was flash chromatographed (silica gel, 3:1 hexanes/ethyl acetate) to yield 1.043 g (97 %) of the previously reported methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside.

Mp = 53-54 °C [Lit. Mp = 66.5-67.0 °C]; IR (KBr); 3477s, 3066w, 3028m, 3001w, 2963m, 2902m, 2871m, 1952w, 1873w, 1813w, 1748w, 1605w, 1497m, 1453s, 1398m, 1384s, 1364m, 1307w, 1290w, 1227m, 1193m, 1160s, 1128s, 1084s, 1025s, 913m, 836w, 745s, 732s, 696s cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 7.38-7.28 (m, 15 H, Ar), 4.91 (ABq, v₁ = 4.98, v₂ = 4.83, J₆₋₅ = 10.8 Hz, 2 H, benzyl), 4.75 (ABq, v₁ = 4.82, v₂ = 4.69, J₆₋₅ = 11.7 Hz, 2 H, benzyl), 4.72 (ABq, v₁ = 4.79, v₂ = 4.65, J₆₋₅ = 12.1 Hz, 2 H, benzyl), 4.56 (d, J₁₋₂ = 3.5 Hz, 1 H, H-1), 4.00 (app. t, J₂₋₃ = J₃₋₄ = 9.2 Hz, 1 H, H-3), 3.80-3.61 (m, 3 H, H-5 and H-6), 3.54-3.47 (m, 3 H, benzyl), 2.89 (dd, J₁₋₂ = 3.2 Hz, J₀₋₁ₛ = 7.2 Hz, J₀₋₁ₛ = 5.4 Hz, 1H, D₂O exch., OH); ¹³C-NMR (75 MHz, CDCl₃) δ 138.9 (i-Ar), 138.3 (i-Ar), 128.7 (Ar), 128.6(Ar), 128.3(Ar), 128.2(Ar), 128.1(Ar), 128.0(Ar), 127.8(Ar), 98.4 (C-1α), 82.1 (C-3), 80.2 (C-2), 76.4 (C-4), 75.9 (benzyl), 75.2 (benzyl), 73.6 (benzyl), 70.8 (C-5), 62.1 (C-6), 55.4 (OCH₃).
Preparation of methyl 6-bromo-6-deoxy-2,3,4-tris-0-(phenylmethyl)-α-D-glucopyranoside (1.107)
(Scheme 1.27)\(^{128}\) A 250 mL, round-bottom flask equipped with a magnetic stir bar, a water condenser, and nitrogen inlet was charged with a 0.1 M solution of methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside (2.822 g, 6.07 mmol) in dichloromethane (60 mL) containing 2.0 equivalents of N-bromosuccinimide\(^{250}\) (2.160 g, 12.14 mmol). The reaction vessel was cooled to 0 °C followed by addition of 2.0 equivalents of triphenylphosphine (3.184 g, 12.14 mmol) in small portions over 0.5 h at such a rate as to maintain the reaction temperature below 5 °C. Following addition of the triphenylphosphine, barium carbonate (400 mg, 2.02 mmol) was added and the reaction mixture warmed to reflux for 20 minutes. The reaction was then cooled to 25 °C, vacuum filtered, and concentrated in vacuo to yield a crude golden oil. The crude product was taken up in diethyl ether (90 mL) and the organic phase washed with water (15 mL), saturated brine (15 mL) and then dried over anhydrous MgSO\(_4\). Vacuum filtration and concentration in vacuo yielded a crude white solid which when flash chromatographed (silica gel, 10:1 hexanes/ethyl acetate) provided 2.662 g (83%) of the previously reported methyl 2,3,4-tri-O-benzyl-6-bromo-6-deoxy-α-D-glucopyranoside (1.107) as a clear oil which solidified on standing.

\[
\text{R}_{f} = 0.50 \text{ (10:1 hexanes/ethyl acetate)}; \text{Mp} = 57.0-58.0 ^\circ\text{C} \left[\text{Lit. mp} = 62 ^\circ\text{C}\right];^{247,251} \text{IR (neat)} 3062w, 3030m, 3004w, 2911m, 2848m, 2825w, 2359w, 1950w, 1875w, 1810w, 1733w, 1604w, 1585w, 1496m, 1453f, 1327m, 1319m, 1267m, 1238m, 1196m, 1155s, 1138s, 1090s, 1070s, 1051s, 1028s, 995s, 910m, 818w, 737s, 697s, 602m \text{ cm}^{-1}; ^{1}\text{H-NMR (300 MHz, CDCl}_3\right)^{251} \delta 7.43-7.30 \text{ (m, 15 H, Ar)}, 4.96 \text{ (ABq, } \nu_1 = 5.05, \nu_2 = 4.87, J = 10.9 \text{ Hz, 2 H, benzyl)}, 4.85 \text{ (ABq, } \nu_1 = 4.98, \nu_2 = 4.72, J = 11.0 \text{ Hz, 2 H, benzyl)}, 4.77 \text{ (ABq, } \nu_1 = 4.84, \nu_2 = 4.71, J = 11.9 \text{ Hz, 2 H, benzyl)}, 4.68 \text{ (d, } J_{1,2} = 3.5 \text{ Hz, 1 H, H-1)}, 4.07 \text{ (app. t, } J = 9.0 \text{ Hz, } J = 9.4 \text{ Hz, 1 H, H-3)}, 3.85 \text{ (ddd, } J = 9.5 \text{ Hz, } J = 5.1 \text{ Hz, } J = 2.4 \text{ Hz, 1 H)}, 3.70-3.52 \text{ (m, 4 H)}, 4.44 \text{ (s, 3 H, OCH}_3\right); ^{13}\text{C-NMR (62.8 MHz, CDCl}_3\right)^{247} \delta 138.7 \text{ (s, i-Ar)}, 138.1 \text{ (s, i-Ar)}, 138.1 \text{ (s, i-Ar)}, 157
Preparation of 5,6-dideoxy-2,3,4-tris-O-(phenylmethyl)-D-ribo-hex-5-enose (1.108) (Scheme 1.27). A 50 mL round-bottom flask equipped with a magnetic stir bar and a water condenser with nitrogen inlet was charged with a 0.05 M solution of methyl 2,3,4-tri-O-benzyl-6-bromo-6-deoxy-α-D-glucopyranoside (1.107, 160 mg, 0.303 mmol) in absolute ethanol (6.0 mL) containing 11 equivalents of freshly prepared Zn/Cu couple (425 mg, 3.30 mmol). The reaction vessel was brought to reflux for 1 h after which no starting material was detected by TLC ($R_f = 0.40$, 85:10:5 hexanes/CH$_2$Cl$_2$/MeOH). The reaction was cooled to 25 °C, filtered over Celite, and the solvent removed under reduced pressure. The resulting crude oil was dissolved in dichloromethane (10 mL) and washed with 5% aqueous HCl (5 mL) and the aqueous phase back extracted with additional dichloromethane (3 x 5 mL). The combined organic phase was then washed with saturated brine (10 mL) and dried over anhydrous MgSO$_4$. Vacuum filtration and concentration in vacuo yielded 118 mg of a cloudy, pungent oil. Preparative thin layer chromatography (silica gel, 85:10:5 hexanes/CH$_2$Cl$_2$/MeOH) provided 55 mg (43%) of the previously reported 5,6-dideoxy-2,3,4-tri-O-benzyl-D-ribo-hex-5-enose (1.108) as a clear oil.

$R_f = 0.22$, (85:10:5 hexanes/CH$_2$Cl$_2$/MeOH); IR (thin film) 3064$m$, 3029$y$, 2867$r$, 1951$w$, 1877$w$, 1810$w$, 1730$s$, 1640$w$, 1605$w$, 1586$w$, 1496$s$, 1454$s$, 1350$m$, 1305$m$, 1216$s$, 1071$s$, 1027$s$, 994$m$, 934$m$, 912$m$, 842$w$ cm$^{-1}$; $^1$H-NMR (300 MHz, CDC$_3$) δ 9.64 (d, $J = 0.8$ Hz, 1 H, H-1), 7.39-7.20 (m, 15 H, Ar), 5.88-5.76 (m, 1 H, H-5), 5.29 (s, 1 H, H-6a), 5.24 (dd, $J_{6a,5} = 6.1$ Hz, $J_{6a,4} = 0.9$ Hz, 1 H, H-6b), 4.73-4.34 (m, 6H, benzyl), 4.14 (ddd, $J_{4,5} = 6.9$ Hz, $J_{4,3} = 4.7$ Hz, $J_{4,6b} = 0.9$ Hz, 1 H, H-4), 3.88 (dd, $J_{3,2} = 4.5$ Hz, $J_{3,1} = 0.9$ Hz, 1 H, H-2), 3.79 (app. t, $J_{3,2} = 4.5$ Hz, $J_{3,4} = 4.7$ Hz, 1 H, H-3); $^{13}$C-NMR (50 MHz, CDCl$_3$) δ 201.5 (C-1), 137.6 (i-Ar), 137.1 (i-Ar), 134.7 (i-Ar), 128.4 (Ar), 128.3 (Ar), 128.2 (Ar), 128.1 (Ar), 128.0 (Ar), 127.7 (d, Ar), 128.2 (d, Ar), 128.1 (d, Ar), 128.0 (d, Ar), 98.2 (d, C-1α), 81.8 (d, C-3), 79.7 (d, C-4), 75.8 (t, benzyl), 75.5 (t, benzyl), 73.5 (t, benzyl), 69.5 (d, C-5), 55.4 (q, OCH$_3$), 33.7 (t, C-6).
127.8 (Ar), 127.5 (Ar), 119.3 (Ar), 82.2 (C-3), 81.6 (C-2), 79.8 (C-4), 74.4 (benzyl), 73.1 (benzyl), 70.8 (benzyl).

Reaction of (Cp₂TiCl)₂ (1.54) with 5,6-dideoxy-2,3,4-tri-O-(phenylmethyl)-D-ribo-hex-5-eneose (1.108) (Scheme 1.29). In a glove box, a 50 mL round-bottom flask equipped with a magnetic stir bar and addition funnel was charged with a 0.04 M solution of 5,6-dideoxy-2,3,4-tri-O-benzyl-D-ribo-hex-5-eneose (1.108, 55 mg, 0.13 mmol) in tetrahydrofuran (3.25 mL). The dropping funnel was then charged with a 0.04 M solution of (Cp₂TiCl)₂ (1.54, 70 mg, 0.165 mmol) in tetrahydrofuran (4.0 mL) and the dark green titanium reagent added slowly to the rapidly stirred substrate over 10 minutes. The dark green color of the titanium(III) solution was discharged upon addition to the clear substrate solution. After addition of contents of the addition funnel, a dark brown solution resulted. The reaction was stirred for an additional 0.5 h at 25 °C. At this time the dark brown reaction mixture was quenched with 1.0 equivalent (with respect to titanium) of HCl (1.0 M in diethyl ether) and the resulting mixture stirred for 0.5 h at which time a bright red suspension resulted. The volume of solvent was then reduced to about 5 mL and the solution filtered over Celite and rinsed with ethyl acetate. Filtration was repeated as necessary to remove the solid titanocene dichloride. The combined organic phase was concentrated under reduced pressure and the resulting crude product was flash chromatographed (silica gel, 15:1 hexanes/ethyl acetate) to yield 34 mg of recovered starting material in addition to 17 mg of unidentified products.

Preparation of 2-Propenyl 2-Deoxy-4,6-O-(phenylmethylene)-α-D-arabino-hexopyranoside (Scheme 1.28). 58,100,102 500 mL, 3-neck, round-bottom flask equipped with a large magnetic stir bar, water condenser, and nitrogen inlet was charged with 3 Å molecular sieves, flame dried and cooled under a stream of nitrogen. The reaction flask was then charged with a 0.62 M solution of 2-deoxy-D-glucose (15.216 g, 92.7 mmol) in allyl alcohol (150 mL) along with Amberlite IR-120 strongly acidic ion-exchange resin (3.750 g) and the reaction warmed to 40 °C with rapid stirring for 24 h to yield a light yellow solution. The reaction was then vacuum filtered and the allyl alcohol was removed under reduced pressure to yield a yellow syrup which solidified on standing. Recrystallization from ethyl acetate yielded
11.59 g (61%) of the previously reported allyl 2-deoxy-\(\alpha\)-D-glucopyranoside as an off-white solid whose 
\(^1\)H-NMR matched that reported previously.\(^{100}\)

\[
\begin{align*}
\text{HO} & \quad \text{O} & \quad \text{O} & \quad \text{CH} \\
\text{HO-} & \quad \text{H} & \quad \text{CH} & \quad \text{OH}
\end{align*}
\]

\(\text{\(^1\)H-NMR (CDCl}_3\)} \delta 5.89 (m, 1 H), 5.28 (dd, \(J = 7.1\) Hz, \(J = 1.5\) Hz, 1 H), 5.19 (dd, \(J = 10.1\) Hz, \(J = 1.2\) Hz, 1 H), 4.94 (d, \(J = 2.9\) Hz, 1 H), 4.11 (m, 2 H), 3.71-4.02 (m, 3 H), 3.45-3.61 (m, 2 H), 3.06 (s, 1 H), 2.09 (m, 3 H), 1.69 (m, 1 H).

A 100 mL, 3-neck, round-bottom flask equipped with a magnetic stir bar, water condenser, septum, and nitrogen inlet was charged with a 0.24 M solution of allyl 2-deoxy-\(\alpha\)-D-glucopyranoside (5.530 g, 27.1 mmol) in pyridine (50 mL) containing 1.2 equivalents of benzal bromide\(^{253}\) (5.3 mL, 32.5 mmol). The clear reaction solution was warmed to reflux for 1 h to yield a deep purple solution. The reaction was cooled to 25 °C, diluted with CHCl\(_3\) (125 mL), and washed with water (2 x100 mL), saturated brine (50 mL) and then dried over anhydrous MgSO\(_4\) with a small amount of decolorizing charcoal. Vacuum filtration and concentration in vacuo yielded 6.542 g of a red solid. Flash chromatography (silica gel, 5:1 hexanes/ethyl acetate) to yielded 5.191 g (65%) of the previously reported allyl 4,6-\(\beta\)-benzylidene-\(\alpha\)-D-glucoside which was characterized as its acetate.\(^{254}\)

\[
\begin{align*}
\text{Ph} & \quad \text{O} & \quad \text{O} & \quad \text{CH=CH}_2 \\
\text{OAc} & \quad \text{O} & \quad \text{H}
\end{align*}
\]

\(R_t = 0.25\) (5:1 hexanes/ethyl acetate); IR (CHCl\(_3\)) 3066\(m\), 3035\(m\), 2970\(m\), 2932\(m\), 2864\(m\), 1739\(s\), 1646\(w\), 1497\(w\), 1455\(m\), 1414\(m\), 1370\(s\), 1309\(m\), 1239\(s\), 1204\(s\), 1174\(m\), 1122\(s\), 1097\(s\), 1032\(s\), 923\(m\), 891\(m\), 854\(m\), 752\(m\), 699\(s\), 673\(w\), 653\(m\), 603\(w\) cm\(^{-1}\); \(\text{\(^1\)H-NMR (300 MHz, CDCl}_3\)} \delta 7.48-7.44 (m, 2 H, Ar), 7.39-7.32 (m, 3 H, Ar), 5.91 (ddddd, \(J_{\text{MAN}} = 17.2\) Hz, \(J_{\text{CA}} = 11.2\) Hz, \(J = 6.1\) Hz, \(J = 5.1\) Hz, 1 H, -OCH\(_2\)CH=CH\(_2\)), 5.55 (s, 1 H, benzylidene), 5.39 (ddddd, \(J_{3,2} = 15.0\) Hz, \(J_{3,4} = 9.5\) Hz, \(J_{3,2} = 5.4\) Hz, 1H, H-3), 5.30 (ddddd, \(J_{\text{MAN}} =

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17.2 Hz, J_{gem} = J_{allylic} = 1.6 Hz, 1H, -OCH_{2}CH=CH_{2}), 5.20 (dddd, \textit{J}_{\text{gem}} = 10.4 Hz, J_{gem} = 1.6 Hz, J_{allylic} = 1.3 Hz, 1H, -OCH_{2}CH=CH_{2}), 4.95 (dd, J_{1,2} = 3.2 Hz, J_{1,2} = 1.1 Hz, 1H, H-1\alpha), 4.25 (dd, J_{gem} = 10.2 Hz, J_{6,5} = 4.8 Hz, 1H, H-6eq), 4.16 (dddd, J_{gem} = 12.9 Hz, J = 5.1 Hz, J_{allylic} = 1.3 Hz, J_{allylic} = 1.6 Hz, 1H, -OCH_{2}CH=CH_{2}), 3.99-3.90 (m, 2H, H-5 and H-8), 3.75 (app. t, J_{gem} = J_{6,5} = 10.2 Hz, 1H, H-6ax), 3.66 (t, J_{4,3} = J_{4,5} = 9.5, H-4), 2.37 (ddd, J_{gem} = 13.0 Hz, J_{2,3} = 5.4 Hz, J_{2,1} = 1.1 Hz, H-2eq), 2.04 (s, 3H, acetyl), 1.79 (ddd, J_{2,3} = 15.0 Hz, J_{gem} = 13.0 Hz, J_{2,1} = 3.2 Hz, 1H, H-2ax); $^{13}$C-NMR (75.5 MHz, CDCl$_3$) δ 170.2 (s, acetyl), 137.5 (s, Ar), 134.0 (d, vinyl), 129.2 (d, Ar), 128.4 (d, Ar), 126.4 (d, Ar), 117.6 (t, vinyl), 101.9 (d, benzylidene), 96.9 (d, C-1\alpha), 80.7 (d, C-4), 69.2 (t, C-2), 68.28 (t, C-6), 68.20 (d, C-3), 63.3 (d, C-5), 35.8 (t, allyl), 21.3 (q, acetyl).

**Preparation of 2-propenyl 2-deoxy-3-O-(phenylmethyl)-4,6-O-(phenylmethylene)-\alpha-D-arabinofuranoside (Scheme 1.28).** A 250 mL, 3-neck, round-bottom flask equipped with a magnetic stir bar, water condenser, addition funnel, and nitrogen inlet was charged with 1.2 equivalents of KH (35% mineral oil, 3.90 g, 32.7 mmol) and washed three times with petroleum ether and residual ether removed under vacuum. The flask was then charged with tetrahydrofuran (40 mL) and the reaction cooled to 0 °C. The addition funnel was charged with ally 4,6-O-benzylidene-\alpha-D-glucopyranoside (8.00 g, 27.3 mmol) in tetrahydrofuran (50 mL) and added slowly to the reaction solution to give a light yellow solution. When addition of the pyranoside was complete, the addition funnel was rinsed with additional tetrahydrofuran (3 mL) and the reaction warmed to 25 °C and stirred for 0.5 h. The reaction was cooled to 0 °C and 1.5 equivalents of benzyl bromide (4.90 mL, 41.0 mmol) added dropwise via syringe to yield a dark brown solution. On complete addition of the benzyl bromide, the reaction was allowed to warm slowly to 25 °C and stirred for an additional 12 h. The reaction was then diluted with diethyl ether (150 mL) and washed with water (3 x 50 mL), saturated brine (25 mL) and then dried with anhydrous MgSO$_4$. Vacuum filtration and concentration in vacuo yielded a dark brown syrup which was flash chromatographed (silica gel, 20:1 petroleum ether/ethyl acetate) to give 7.602 g (73%) of the previously reported allyl 3-O-benzyl-4,6-O-benzylidene-D-glucopyranoside as an orange oil which
solidified on standing ($\alpha/\beta = 1:1$). NMR analysis of the protected glucoside matched that reported previously.256

Preparation of 2-deoxy-3-O-(phenylmethyl)-4,6-O-(phenylmethylene)-\(\alpha\)-D-arabinono-hexopyranose (1.109) (Scheme 1.28). 58,100,104 250 mL, three-necked, round-bottom flask equipped with a large magnetic stir bar, hydrogen filled balloon, nitrogen inlet, and exit bubbler was charged with a 0.1 M solution of allyl 3-O-benzyl-4,6-O-benzylidene-D-glucopyranoside (3.661 g, 9.51 mmol) in tetrahydrofuran (100 mL) along with 1 mol% Ir[(COD)(PPhMe)\(_2\)]\(^{1}\)PF\(_6\) (61 mg). The flask was evacuated and flushed with hydrogen (3 times) and the reaction stirred under an atmosphere of hydrogen for 5 minutes. The hydrogen was then purged with a steady flow of nitrogen. The reaction was stirred for an additional 5 h and the solvents removed under reduced pressure to give a yellow oil. The crude enol ether was dissolved in 10:1 acetone/H\(_2\)O (50 mL) followed by addition of a solution of 1.0 equivalent of HgO (2.07 g, 9.55 mmol) and 1.0 equivalent of HgCl\(_2\) (2.59 g, 9.53 mmol) in 10:1 acetone/H\(_2\)O (10 mL). The reaction was stirred at 25 °C for 5 h and the solids removed by filtration through Celite. Concentration in vacuo yielded a white solid which was flash chromatographed (silica gel, 4:1 hexanes/ethyl acetate) to yield 2.012 g (61%) of the previously reported free glucopyranose 1.109 as a white crystalline solid ($\alpha/\beta = 1.2:1$). The compound was characterized as its acetate and matched data which has been reported previously.100

\[
\begin{align*}
\text{Ph} & \quad \text{OAc} \\
\text{Ph} & \quad \text{OCH}_2\text{Ph}
\end{align*}
\]

\(^1\)H-NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.52-7.26 (m, 10 H, Ar), 6.20 (dd, J = 3.7 Hz, J = 1.1 Hz, 0.54 H, H-1), 5.78 (dd, J = 10.1 Hz, J = 2.5 Hz, 0.46 H, H-1), 5.62 (s, 0.53 H, benzylidene), 5.59 (s, 0.47 H, benzylidene), 4.85 (dd, J = 11.9 Hz, J = 10.8 Hz, 1 H), 4.70 (d, J = 12.0 Hz, 1 H), 4.36-4.24 (m, 1 H),
4.07-3.44 (m, 4 H), 2.36-2.22 (m, 1 H), 2.10 (s, 1.32 H, acetyl), 2.09 (s, 1.67 H, acetyl), 1.98-1.76 (m, 1 H).

Preparation of ethyl 2,3,4-trideoxy-5-O-(phenylmethyl)-6,8-O-(phenylmethylene)-D-arabino-oct-2-enoate (Scheme 1.28).

A 250 mL round-bottom flask equipped with a magnetic stir bar, condenser and nitrogen inlet hydrogen was charged with a 0.24 M solution of 3-O-benzyl-4,6-O-benzylidene-2-deoxy-α-D-glucopyranose (1.109 g, 3.60 mmol) in dimethoxyethane (15 mL) along with 2.0 equivalents of (carbethoxymethylene)triphenylphosphorane (2.54 g, 7.30 mmol) and 5 mol% benzoic acid (20 mg). The reaction was heated to reflux for 16 h. The reaction was then cooled to 25 °C, diluted with 1:1 diethyl ether/pentane (100 mL) and filtered over Celite. The filtrate was then concentrated to give a yellow oil which solidified on standing. Flash chromatography (silica gel, 3:1 hexanes/ethyl acetate) yielded 1.050 g (70%) of the previously reported ethyl 2,3,4-trideoxy-5-O-benzyl-6,8-O-benzylidene-D-arabino-oct-2-enoate as a yellow oil (E/Z = 3). The compound matched data which has been previously reported.

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\text{R_f = 0.35 (3:1 hexanes/ethyl acetate); (E)-isomer: IR (CHCl_3) 3501 (br), 3018 (s), 2981 (m), 2931 (m), 2905 (m), 2864 (m), 1955 (w), 1885 (w), 1813 (w), 1711 (s), 1655 (m), 1518 (w), 1496 (w), 1454 (m), 1394 (m), 1369 (m), 1272 (m), 1215 (s), 1178 (m), 1077 (s), 1043 (s), 1028 (s), 984 (m), 927 (m), 851 (w), 757 (s), 688 (s), 688 cm^{-1}; }^1\text{H-NMR (300 MHz, CDCl}_3\text{) }\delta 7.48-7.32 (m, 10 H, Ar), 6.99 (s, 1 H, benzyl), 4.65 (ABq, \text{J} = 11.6 Hz, 2 H, benzyl), 4.27 (dd, \text{J} = 10.8 Hz, 2 H, benzyl), 4.19 (q, \text{J} = 7.1 Hz, 2 H, OCH}_2\text{CH}_3\text{), 4.00 (m, 1 H, H-8), 3.92 (dd, \text{J} = 7.7 Hz, 2 H, benzyl), 3.75 (dd, \text{J} = 5.3 Hz, 2 H, benzyl), 3.70 (s, 1 H, benzyl), 3.65 (m, 1 H, H-5), 3.57 (dd, \text{J} = 10.8 Hz, 2 H, benzyl), 2.71 (ddd, \text{J} = 7.4 Hz, 2 H, benzyl), 2.50 (s, 1 H, OH), 1.29
(t, J = 7.1 Hz, 3 H, OCH₂CH₃). $^{13}$C-NMR (75.5 MHz, CDCl₃) δ 166.4 (s, C-1), 145.1 (d, C-3), 137.6 (s), 137.4 (s), 129.2 (d), 128.9 (d), 128.6 (d), 128.4 (d), 126.3 (d), 124.1 (d), 101.6 (d), 100.2, 80.0 (d), 77.6 (d), 73.0 (t), 70.9 (t), 62.2 (d), 60.5 (t), 45.3 (s), 32.9 (t), 14.4 (q). Anal. cald for C₂₄H₂₈O₆: C, 69.89; H, 6.84. Obsd: C, 69.73; H, 6.97. HRMS (EI) calcd for C₂₄H₂₈O₆: 412.188588. Obsd: 412.187210.

Preparation of ethyl 2,3,4-trideoxy-7-oxo-5-O-(phenylmethyl)-6,8-O-(phenylmethylene)-D-arabino-oct-2-enoate (1.110) (Scheme 1.28). A 25 mL, round-bottom flask equipped with a magnetic stir bar, septum, and nitrogen inlet was charged with a 1.5 equivalents of N-chlorosuccinimide (146 mg, 1.10 mmol) in toluene (3.6 mL) and cooled to 0 °C. Next was added, via syringe, 1.25 equivalents of dimethylsulfide (66 µL, 0.90 mmol), and the reaction stirred for 15 minutes and then cooled to -25 °C (xylene/liq. N₂). To this solution was added 1.0 equivalent of ethyl 2,3,4-trideoxy-5-O-benzyl-6,8-O-benzylidene-D-arabino-oct-2-enoate (300 mg, 0.73 mmol) in toluene (0.7 mL) and the reaction stirred at -20 °C for 2 h. The reaction was quenched with 1.9 equivalents of triethylamine (100 µL, 1.38 mmol) at -20 °C and after 5 minutes the cooling bath removed and the reaction stirred for an additional 5 minutes. The reaction was then diluted with diethyl ether (50 mL) and washed with 1% HCl (aq) (25 mL), water (25 mL), saturated brine (20 mL) and then dried over anhydrous MgSO₄. Vacuum filtration and concentration in vacuo provided 300 mg of a cloudy oil. Flash chromatography (silica gel, 4:1 hexanes/ethyl acetate) yielded 141 mg (47%) of the desired ethyl 2,3,4-trideoxy-5-O-benzyl-6,8-O-benzylidene-7-oxo-D-arabino-oct-2-enoate (1.110) as a clear oil.

$$R_f = 0.25 \text{ (3:1 hexanes/ethyl acetate)}; {^1}H-NMR (300 MHz, CDCl₃) \delta 7.49-7.28 \text{ (m, 10 H, Ar). 6.85 (ddd, J₃.₂ = 15.6 Hz, J₃.₄ = 8.1 Hz, J₃.₄ = 7.7 Hz, 1 H, H-3), 5.84 (s, 1 H, benzylidene), 5.84 (ddd, J₂.₃ = 15.6 Hz, J₂.₄ = 1.2 Hz, J₂.₄ = 1.2 Hz, 1 H, H-2), 4.14-4.07 (m, 3 H), 4.54-4.31 (m, 5 H), 2.65-2.56 (m, 2 H), 1.21 (t, J = 7.1 Hz, 3 H, OCH₂CH₃);} {^{13}}C-NMR (75.5, CDCl₃) \delta 205.3 (C-7), 166.3 (C-3), 143.8 (C-2), 137.8 (Ar), 164
Cyclization of ethyl 2,3,4-trideoxy-7-oxo-5-O-(phenylmethyl)-6,8-O-(phenylmethylen)-D-arabino-oct-2-enoate (1.110) with (Cp₂TiCl)₂ (1.54): Preparation of lactone 1.113 (Scheme 1.30). In a glove box, a 25 mL, round-bottom flask equipped with a magnetic stir bar and addition funnel was charged with a 0.08 M solution of ethyl 2,3,4-trideoxy-5-O-benzyl-6,8-O-benzylidene-7-oxo-D-arabino-oct-2-enoate (1.110, 100 mg, 0.24 mmol) in tetrahydrofuran (3.0 mL). The addition funnel was charged with a 1.25 equivalents of (Cp₂TiCl)₂ (1.54, 128 mg, 0.3 mmol) in tetrahydrofuran (15.0 mL) and the green titanium(III) reagent added dropwise to the ketone solution over the course of 0.5 h. Upon addition, the green of the titanium(III) reagent yielded a pale yellow color. Following complete addition of the titanium(III) reagent, the solution was stirred at 25 °C for 3 h eventually yielding a dark green solution. The reaction vessel was removed from the glove box, diluted with diethyl ether (100 mL) and washed with 10% Na₂HPO₄ (10 mL), water (3 x 20 mL), saturated brine (10 mL) and then dried over anhydrous MgSO₄. Vacuum filtration and concentration in vacuo yielded 153 mg of a bright red oil. Flash chromatography (silica gel, 3:1 hexane/ethyl acetate) yielded 71 mg of a white solid which by 'H- and ¹³C-NMR was tentatively identified as lactone 1.113 and starting ketone 1.110 in a ratio of 4:1 respectively. The recovered products were re-exposed to identical reaction conditions for 24 h and following work-up no further starting ketone detected. Re-purification of the combined products yielded 32 mg (35%) of the lactone 1.113.
benzyl), 4.48 (dd, J = 11.5 Hz, J = 7.0 Hz, 1 H), 4.20-4.05 (m, 2 H), 3.95 (dd, J = 13.2 Hz, 8.8 Hz, 1 H), 3.86 (app t, J = 12.8 Hz, 1 H), 3.12 (dd, J = 18.5 Hz, J = 7.9 Hz, 1 H), 2.78 (dd, J = 18.5 Hz, J = 7.0 Hz, 1 H); $^{13}$C-NMR (75.5 MHz, CDCl$_3$) δ 137.9 (s), 136.8 (s), 129.5 (d), 128.7 (d), 128.5 (d), 128.2 (d), 127.9 (d), 126.2 (d), 101.7 (d), 81.1 (d), 73.3 (d), 72.5 (t), 68.5 (t), 67.9 (d), 36.2 (t). HRMS(ESI) calcd for C$_{32}$H$_{52}$O$_5$: 366.14724. Obsd: 366.147369.

Preparation of 1,1-dimethyl-2,3,4-trideoxy-5-O-(phenylmethyl)-6,8-O-(phenylmethylene)-D-arabino-oct-2-enol (Scheme 1.28). A 25 mL round-bottom flask equipped with a magnetic stir bar and nitrogen inlet was charged with 3.0 equivalents of (carbtert-butoxy)methylenetriphenylphosphonium bromide$^{137,139}$ (1.70 g, 3.72 mmol) in 1:1 CHCl$_3$/H$_2$O (14 mL) containing 1.30 equivalents of KOH (196 mg, 4.90 mmol) and the reaction stirred vigorously for 0.5 h. The reaction was diluted with CHCl$_3$ (20 mL) and the aqueous phase separated. The organic phase was washed with water (10 mL), saturated brine (10 mL) and then dried over anhydrous MgSO$_4$. Vacuum filtration and concentration in vacuo yielded the intermediate phosphorane as a white foam. The phosphorane was taken up in dimethoxyethane (10.0 mL) and 1.0 equivalent of 3-O-benzyl-4,6-O-benzylidene-2-deoxy-D-glucopyranose (424 mg, 1.23 mmol) was added in one portion and the reaction stirred at 25 °C for 36 h. Consumption of the starting material was monitored by TLC ($R_f = 0.44$, 3:1 hexanes/ethyl acetate). The reaction was then concentrated and the resulting syrup flash chromatographed (silica gel, 4:1 hexanes/ethyl acetate) yielded 478 mg (88%) of the desired tert-butyl 5-O-benzyl-6,8-O-benzylidene-2,3,4-trideoxy-D-arabino-oct-2-enate as a clear oil ($E/Z = 2.3$).

$R_f = 0.50$ (3:1 hexane/ethyl acetate); IR (CHCl$_3$) 3472 br, 2974 m, 2930 m, 2865 m, 1954 w, 1883 w, 1813 w, 1711 s, 1652 m, 1496 w, 1454 m, 1393 m, 1367 m, 1319 m, 1254 m, 1220 m, 1154 s, 1090 s, 1028 s, 983 m, 916 w, 849 w, 754 s, 698 w cm$^{-1}$; mixture of isomers $^1$H-NMR δ 7.48-7.28 (m, 10 H, Ar), 6.89 (ddd, $J_{3,2} = 15.2$ Hz,
J_{3,4} = 7.8 \text{ Hz}, J_{2,4} = 7.4 \text{ Hz}, 1 \text{ H, H-3\text{-major}}, \quad 6.18 \text{ (ddd, } J_{3,4} = 11.5 \text{ Hz}, J_{3,4} = 7.5 \text{ Hz}, J_{3,4} = 7.4 \text{ Hz, 1 H, H-3\text{-minor}}), \quad 5.86 \text{ (dt, } J_{2,3} = 15.2 \text{ Hz, } J_{2,4} = 1.3 \text{ Hz, 1 H, H-2\text{-major}}), \quad 5.77 \text{ (dt, } J_{2,3} = 11.6 \text{ Hz, } J_{2,4} = 1.6 \text{ Hz, 1 H, H-2\text{-minor}}), \quad 5.44 \text{ (s, 1 H, benzylidene)}, \quad 4.67 \text{ (ABq, } v_1 = 4.56, v_2 = 4.78, J = 11.6 \text{ Hz, 2 H, benzyl\text{-major}}), \quad 4.63 \text{ (ABq, } v_1 = 4.52, v_2 = 4.74, J = 11.6 \text{ Hz, 2 H, benzyl\text{-minor}}), \quad 4.28 \text{ (dd, } J = 10.7 \text{ Hz, } J = 5.3 \text{ Hz, 1 H}), \quad 4.06-3.95 \text{ (m, 1 H)}, \quad 3.92-3.87 \text{ (m, 1 H)}, \quad 3.74 \text{ (dd, } J = 9.2 \text{ Hz, } J = 3.6 \text{ Hz, 1 H}), \quad 3.57 \text{ (app. t, } J = 10.6 \text{ Hz, } J = 10.2 \text{ Hz, 1 H)}, \quad 3.29-3.00 \text{ (m, 1 H)}, \quad 2.75 - 2.62 \text{ (m, 2 H)}, \quad 2.56 \text{ (d, } J = 2.83 \text{ Hz, 1 H, OH}), \quad 1.62 \text{ (s, 3 H, t-Bu\text{-major}}), \quad 1.47 \text{ (s, 3 H, t-Bu\text{-minor}}); \quad ^{13}\text{C-NMR } \delta 165.9 \text{ (s, C-1\text{-minor}}), \quad 165.8 \text{ (s, C-1\text{-major}}), \quad 144.3 \text{ (d, C-2\text{-minor}}), \quad 143.8 \text{ (d, C-2\text{-major}}), \quad 137.9 \text{ (s, Ar\text{-minor}}), \quad 137.8 \text{ (s, Ar\text{-minor}}), \quad 137.6 \text{ (s, Ar\text{-major}}), \quad 137.5 \text{ (s, Ar\text{-major}}), \quad 129.1 \text{ (d, Ar)}, \quad 128.8 \text{ (d, Ar)}, \quad 128.5 \text{ (d, Ar)}, \quad 128.4 \text{ (d, Ar)}, \quad 126.4 \text{ (d, Ar)}, \quad 126.3 \text{ (d, Ar)}, \quad 125.8 \text{ (d, Ar)}, \quad 123.4 \text{ (d, Ar)}, \quad 101.6 \text{ (d), 80.8 (d), 80.5 (s), 80.4 (s), 80.1 (d), 78.1 (d)}, \quad 77.5 \text{ (d), 72.9 (t, C-6), 72.5, 70.9 (t, C-6), 62.2 \text{ (d\text{-minor}}), \quad 62.1 \text{ (d\text{-major}}), \quad 32.7 \text{ (t, C-2\text{-major}}), \quad 29.4 \text{ (t, C-2\text{-minor}}), \quad 28.3 \text{ (q, C(CH3))}. \quad \text{Anal. calcd for } C_{26}H_{32}O_6: \quad \text{C, 70.89; H, 7.32. Obsd: C, 70.08; H, 7.29.}

**Preparation of 1,1-dimethylethyl 2,3,4-trideoxy-7-oxo-5-O-(phenylmethyl)-6,8-O-(phenylmethylene)-D-arabino-oct-2-enoate (1.111) (Scheme 1.28).** A 25 mL, 3-neck, round-bottom flask equipped with magnetic stir bar, septum, addition funnel, and nitrogen inlet was charged with a 5 equivalents of dimethyl sulfoxide (113 µL, 1.59 mmol) in dichloromethane (0.5 M, 3.20 mL) and cooled to -78 °C. Next, 4.0 equivalents of distilled TFAA (180 µL, 1.27 mmol) was then slowly added via syringe and the reaction stirred at -78 °C for 0.5 h. The addition funnel was charged with a 0.1 M solution of tert-butyl 2,3,4-trideoxy-5-O-benzyl-6,8-O-benzylidene-D-arabino-oct-2-enoate (140 mg, 0.318 mmol) in dichloromethane (3.0 mL) and added to the reaction mixture slowly over several minutes. The addition funnel was rinsed with additional dichloromethane (0.5 mL) and the reaction stirred at -78 °C for 1.5 h until no further starting material remained by TLC (R_f = 0.45, 4:1 hexanes/ethyl acetate). Four equivalents of triethylamine (177µL, 1.27 mmol) was then slowly added via syringe at -78 °C and 15 minutes later the cooling bath removed and the reaction allow to warm slowly to 25 °C. The reaction was diluted with dichloromethane and washed with saturated bicarbonate, water, saturated brine and then
dried over anhydrous MgSO₄. Vacuum filtration and concentration in vacuo yielded a cloudy oil. Flash chromatography (silica gel, 8:1 hexanes/ethyl acetate) yielded 86 mg (62%) of the desired tert-butyl 2,3,4-trIDEOxy-5-O-benzyl-6,8-O-benzylidene-7-oxo-D-arabino-oct-2-enoate (1.111) as a colorless oil (E/Z = 8)

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R_f = 0.42 \ (8:1 \ \text{hexane/ethyl acetate}); \ \text{mixture of isomers: IR} \ (\text{CHCl}_3) \ 3064w, 3030w, 2979m, 2930w, 2868w, 1957w, 1889w, 1810w, 1736s, 1710s, 1653w, 1575w, 1496w, 1454s, 1420w, 1392s, 1375s, 1344s, 1295s, 1256s, 1218s, 1099s, 1027s, 983s, 916w, 850w, 755s, 698s cm\textsuperscript{-1}; \ ^1\text{H}-\text{NMR} \ (300 \text{ MHz, CDCl}_3) \ \delta 7.49-7.28 \ (m, 10 \ H, \text{Ar}), 6.81 \ (\text{ddd}, J_{3,2} = 15.3 \ Hz, J_{3,4} = 8.0 \ Hz, J_{3,4} = 7.3 \ Hz, 0.89 \ H, \text{H-3}), 6.22 \ (\text{ddd}, J_{3,4} = 11.5 \ Hz, J_{3,4} = 7.6 \ Hz, J_{3,4} = 7.5 \ Hz, 0.11 \ H, \text{H-3}), 5.91 \ (s, 1 \ H, \text{benzylidene}), 5.84 \ (\text{dt}, J_{2,3} = 15.6 \ Hz, J_{2,4} = 1.2 \ Hz, 0.89 \ H, \text{H-2}), 5.77 \ (\text{dt}, J_{2,3} = 11.6 \ Hz, J_{2,4} = 1.5 \ Hz, 0.11 \ H, \text{H-2}), 4.56 \ (\text{ABq}, v_1 = 4.51, v_2 = 4.61, J = 11.6 \ Hz, 2 \ H, \text{benzyl}), 4.46 \ (\text{ABq}, v_1 = 4.38, v_2 = 4.54, J = 16.9 \ Hz, 2 \ H, \text{H-8}), 4.50 \ (m, 1 \ H, \text{H-6}), 4.16 \ (\text{ddd}, J = 7.8 \ Hz, J = 6.2 \ Hz, J = 2.7 \ Hz, 1 \ H, \text{H-5}), 3.15 \ (\text{app. tt}, J = 7.2 \ Hz, J = 1.7 \ Hz, 0.22 \ H, \text{H-4}), 2.75-2.56 \ (m, 1.78 \ H, \text{H-4}), 1.47 \ (s, 2.67 \ H, \ t-\text{Bu}_\text{major}), 1.46 \ (s, 0.33 \ H, \ t-\text{Bu}_\text{minor}); \ (E)-isomer: ^1\text{C}-\text{NMR} \ \delta 205.4 \ (s, \text{C-7}), 165.6 \ (s, \text{C-1}), 142.5 \ (d, \text{C-3}), 137.9 \ (s, \text{Ar}), 137.1 \ (s, \text{Ar}), 129.4 \ (d), 128.5 \ (d), 128.49 \ (d), 128.45 \ (d), 128.0 \ (d), 127.9 \ (d), 126.47 \ (d), 126.45 \ (d), 99.2 \ (d), 83.6 \ (d), 80.5 \ (s, \text{CMe}_3), 77.3 \ (d), 73.1 (t), 72.9 (t), 33.12 \ (t, \text{C-4}), 28.39 \ (q, \text{CMe}_3), 28.34 \ (q, \text{CMe}_3). \ \text{Ketone} \ 1.111 \ did \ not \ provide \ satisfactory \ elemental \ analysis. \ \text{Cyclization \ of} \ 1,1-\text{dimethylethyl} \ 2,3,4-\text{trIDEOxy-7-oxo-5-O-(phenylmethyl)-6,8-O-(phenylmethylene)-D-arabino-oct-2-enoate} \ (1.111) \ with \ (\text{Cp}_2\text{TiCl})_2 \ (1.54): \ \text{Preparation \ of} \ [2\text{R}-(2\alpha,4\alpha\beta,5\alpha,7\beta\beta)]-\text{tetrahydro-5-[2(1,1-\text{dimethylethylmethanoloxy})]-2-phenyl-7-(phenylmethoxy)-cyclopenta-1,3-dioxin-4a(4H)-methanol} \ (1.114) \ (\text{Scheme} \ 1.30). \ \text{In \ a \ glove \ box,} \ a 25 \ \text{mL, \ round-bottom} \ \text{flask} \ \text{equipped with a magnetic stir bar} \ \text{was charged with} \ a \ 0.04 \ M \ \text{solution \ of} \ \text{tert-butyl} \ 5-O-benzyl-6,8-O-benzylidene-2,3,4-
trideoxy-7-oxo-D-arabino-oct-2-enoate (1.111, 70 mg, 0.159 mmol) in tetrahydrofuran (4.0 mL). The addition funnel was charged with a 3.09 equivalents of (Cp₂TiCl)₂ (1.54, 105 mg, 0.246 mmol) in tetrahydrofuran (5.5 mL) and the green titanium(III) reagent added dropwise to the ketone solution over the course of 0.5 h. Upon addition, the characteristic green of the titanium(III) reagent gave way to a pale yellow color. Following complete addition of the titanium(III) reagent, the solution was stirred at 25 °C for 3 h eventually yielding a dark green solution. The reaction was then removed from the glove box and diluted with 1:1 diethyl ether/ethyl acetate (10 mL) and washed with saturated KH₂PO₄ (5 mL), water (5 mL), saturated brine (5 mL) and then dried over anhydrous MgSO₄. Vacuum filtration and concentration in vacuo yielded a red residue which was flash chromatographed (silica gel, 5:1 hexane/ethyl acetate) to give 33 mg (47%) of [2R-(2α,4αβ,5α,7β,7αβ)]-tetrahydro-5-[2(1,1-dimethylethylethanolyl)]-2-phenyl-7-(phenylmethoxy)-cyclopenta-1,3-dioxin-4a(4H)-methanol (1.114) as a yellow oil. Attempts to acetylate the tertiary alcohol under standard conditions (Ac₂O, pyr, DMAP, 0 °C) gave only unreacted starting material. Absolute stereochemistry was assigned in part by NOE difference experiments.

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\text{IR (CHCl}_3) \text{ 3483br, 3089w, 3065w, 3031m, 3008m, 2977s, 2930s, 2868m, 2358w, 1954w, 1878m, 1725s, 1651w, 1607w, 1587w, 1496m, 1454s, 1392s, 1367s, 1314s, 1255s, 1216s, 1151s, 1090s, 1028s, 1003s, 983s, 915m, 848m, 754s, 698s, 666m cm}^{-1}; \text{ }^{1} \text{H-NMR (300 MHz, CDCl}_3) \delta 7.45-7.28 (m, 10 H, Ar), 5.52 (s, 1 H, H-2), 4.60 (ABq, v₁ = 4.62, v₂ = 4.58, J = 11.7 Hz, 2 H, H-4), 4.16 (s, 1 H, H-7a), 4.07 (m, 2 H, benzyl), 4.04 (d, J₇,₆a = 4.9 Hz, 1 H, H-7), 3.28 (br s, 1 H, OH), 2.80 (dd, J₇,₆ = 14.7 Hz, J₈,₅ = 8.8 Hz, 1 H, H-8), 2.80-2.70 (m, 1 H, H-5), 2.51 (dd, J₇,₆ = 14.9 Hz, J₈,₅ = 8.6 Hz, 1 H, H-8), 2.47 (dd, J₇,₆ = 14.7 Hz, J₉,₅ = 8.4 Hz, 1 H, H-6β), 1.89 (ddd, J₇,₆ = 14.7 Hz, J₆,₈ = 8.1 Hz, 1 H, H-8), 1.45 (s, 9 H, t-Bu); \text{ }^{13} \text{C-NMR (125 MHz, CDCl}_3) \delta 172.84 (s, CO₂), 137.8 (s, Ar), 137.7 (s, Ar), 129.3 (d, Ar), 128.7 (d, Ar), 128.6 (d, Ar), 128.5 (d, Ar), 128.1 (d, Ar), 127.9 (d, Ar), 126.4 (d, Ar), 126.2 (d, Ar),
100.3 (d), 86.6 (d), 82.9 (d), 80.6 (d), 74.6 (s), 71.5 (d), 69.8 (d), 44.9 (d), 38.7 (t), 37.7 (t), 28.3 (q, CMe3). HRMS (EI) calcd for C22H24O6 (M-C4H9)+: 384.1572887. Obsd: 384.1556091.

Preparation of 2-deoxy-3-O-(phenylmethyl)-4,6-O-(phenylmethylene)-D-arabinohexopyranose, O-benzylxime (Scheme 1.28). A 50 mL, round-bottom flask equipped with a magnetic stir bar, condenser, and nitrogen inlet was charged with a 0.15 M solution of 2-deoxy-3-O-benzyl-4,6-O-benzylidene-D-glucopyranose (1.109, 1.12 g, 3.27 mmol) in 12:1 methanol/pyridine (22.0 mL) containing 1.2 equivalents of benzyl hydroxyl amine hydrochloride (650 mg, 4.00 mmol) and heated at reflux for 8 h. The reaction was then concentrated under reduced pressure and the pyridine removed by repeated azeotropic distillation with toluene. The remaining colorless oil was flash chromatographed (silica gel, 5:1 hexanes/ethyl acetate) to yield 1.114 g (76%) of desired O-benzylxime (E/Z = 1.4). The clear oil was characterized as its acetate.

$$R_f = 0.25 \text{ (5:1 hexanes/ethyl acetate)}; \text{ IR (thin film) } 3452 \text{ br}, 3032 \text{ m}, 2926 \text{ m}, 2860 \text{ m}, 1956 \text{ w}, 1812 \text{ w}, 1720 \text{ w}, 1631 \text{ w}, 1605 \text{ w}, 1586 \text{ w}, 1496 \text{ m}, 1454 \text{ m}, 1397 \text{ m}, 1362 \text{ m}, 1313 \text{ m}, 1266 \text{ m}, 1212 \text{ m}, 1090 \text{ s}, 1027 \text{ s}, 918 \text{ m}, 735 \text{ s}, 698 \text{ s cm}^{-1}; \text{ mixture of isomers } ^1H-NMR (300 MHz, CDCl}_3) \delta 7.53 (t, J_{1,2} = 6.1, 0.58 H, H-1), 7.47-7.25 (m, 15 H, Ar), 6.88 (t, J_{1,2} = 5.5 Hz, 0.42 Hz, H-1), 5.48 and 5.43 (s, 1 H, benzylidene), 5.09 (d, J_{gem} = 18.5 Hz, 2 H, benzyl), 5.18-5.08 (m, 1 H), 4.61 (dd, J = 11.8 Hz, J = 1.6 Hz, 1 H), 4.48-4.43 (m, 2 H), 3.88-3.82 (m, 1 H), 3.80 (dd, J = 9.6 Hz, J = 1.9 Hz, 1 H), 3.51 (ddd, J = 10.4 Hz, J = 10.4 Hz, J = 6.2 Hz, 1 H), 2.92-2.65 (m, 1 H), 2.70-2.65 (m, 1 H), 1.87 and 1.84 (s, 3 H, acetyl); $^{13}$C-NMR (75.5, CDCl}_3) \delta 169.6 (s), 148.6 (d), 148.4 (d), 138.0 (s), 137.7 (s), 132.4 (s), 129.1 (d), 128.6 (d), 8.5 (d), 128.4 (d), 128.3 (d), 128.2 (d), 128.06 (d), 128.03 (d), 126.4 (d), 126.3 (d), 101.7 (d), 101.6 (d), 100.2 (d), 80.0 (d), 79.4 (d), 76.1 (t), 75.8 (t), 73.5 (d), 72.5 (d), 71.9 (t), 71.8 (t), 68.0 (t), 63.16 (d), 63.12 (d), 30.0
Preparation of 2-deoxy-5-oxo-3-O-(phenylmethyl)-4,6-O-(phenylmethylene)-D-arabino-hexopyranose, O-benzyloxime (1.112) (Scheme 1.28).\(^{257}\) A 25 mL, round-bottom flask equipped with a magnetic stir bar, septum, and nitrogen inlet was charged with a 5.0 equivalents of dimethyl sulfoxide (20 μL, 0.28 mmol) in dichloromethane (250 μL) and cooled to -78 °C. Dropwise addition of 4.0 equivalents of distilled TFAA (30 μL, 0.22 mmol) and 10 minutes later addition of 1.0 equivalents of 3-O-benzyl-4,6-O-benzylidene-2-deoxy-5-oxo-D-glucopyranose, O-benzyloxime (25 mg, 0.055 mmol) in dichloromethane (250 μL). The reaction was stirred at -78 °C for 1 h followed by addition of 4.0 equivalents of diisopropylamine (0.40 mL, 0.25 mmol). The cooling bath was removed and the reaction allowed to warm slowly to 25 °C. The reaction was diluted with dichloromethane (5 mL) and washed with saturated bicarbonate (3 mL). The aqueous phase was back extracted with additional dichloromethane (3 mL) and the combined organic phase washed with water (2 x 5 mL), saturated brine (5 mL) and then dried over anhydrous MgSO₄. Vacuum filtration and concentration in vacuo yielded 25 mg of a yellow oil. Flash chromatography (silica gel, 2:1 hexanes/ethyl acetate) yielded 20 mg (80%) of desired ketone 1.112 as a mixture of isomers (E/Z = 1.4).

\[
\begin{array}{c}
\text{Rf} = 0.15 \ (2:1 \ \text{hexanes/ethyl acetate}) ; \ \text{IR (CHCl}_3) \ 3417 \text{br}, 3031 \text{w}, 2923 \text{m}, 2871 \text{m}, 2667 \text{s}, 1736 \text{s}, 1688 \text{s}, 1496 \text{m}, 1454 \text{m}, 1454 \text{s}, 1396 \text{m}, 1363 \text{m}, 1260 \text{m}, 1201 \text{s}, 1097 \text{s}, 1027 \text{s}, 918 \text{m}, 799 \text{m}, 750 \text{s}, 698 \text{s} \ \text{cm}^{-1} ; \\
mixture \ of \ isomers: \ ^1\text{H-NMR (300 MHz, CDCl}_3) \ \delta \ 7.54-7.46 \ (t, J_{1,2} = 6.1, 0.59 \ \text{H, H-1}), \ 7.54-7.24 \ (m, 15 \ \text{H, Ar}), \ 6.85 \ (t, J_{1,2} = 5.5 \ \text{Hz, 0.41 \ H, H-1}), \ 5.79 \ (s, 1 \ \text{H, benzylidene}), \ 5.07 \ (d, J_{\text{gem}} = 16.3 \ \text{Hz, 2 \ H, benzyl}), \ 4.54 \ (d, J = 15.7 \ \text{Hz, J = 11.5 \ Hz, 2 \ H}), \ 4.45-4.31 \ (m, 4 \ \text{H}), \ 2.87-2.80 \ (m, 1 \ \text{H, H-2}), \ 2.71-2.62
\end{array}
\]
Attempted cyclization of 2-deoxy-5-oxo-3-O-(phenylmethyl)-4,6-O-(phenylmethylene)-D-arabino-hexopyranose, O-benzyl oxime (1.112) with (Cp₂TiCl)₂ (1.54) (Scheme 1.31). In a glove box, a 25 mL round-bottom flask equipped with a magnetic stir bar was charged with a 0.06 M solution of 3-O-benzyl-4,6-O-benzylidene-2-deoxy-5-oxo-D-glucopyranose, O-benzyl oxime (1.112, 12 mg, 0.027 mmol) in tetrahydrofuran (450 µL). The addition funnel was charged with a 2.44 equivalents of (Cp₂TiCl)₂ (1.54, 14 mg, 0.033 mmol) in tetrahydrofuran (560 µL) and the green titanium(II) reagent added dropwise to the oxime solution over the course of 10 minutes. The characteristic green color of the titanium(III) reagent gave way to a pale yellow color. Following complete addition of the titanium(III) reagent, the solution was stirred at 25 °C for 0.5 h eventually yielding a dark green solution. The reaction was quenched by addition of 1.0 equivalent (w/respect to titanium) of HCl (1.0 M in diethyl ether, 67 µL, 0.067 mmol) to give after several minutes a bright red solution. The reaction was then removed from the glove box and carefully concentrated. The crude products were then dissolved in pyridine (250 µL) and acetylated in the presence of catalytic 4-dimethylaminopyridine (10 mg) and acetic anhydride (100 µL). After 12 h, the reaction was diluted with CHCl₃ (5 mL), washed with 5% HCl (1 mL), water (1 mL), saturated brine (1 mL) and the organic phase dried over anhydrous MgSO₄. Vacuum filtration and concentration in vacuo yielded a red residue which was chromatographed by preparative TLC gave 3 mg of benzyl acetate as determined by ¹H-NMR along with 10 mg of unidentified (3) side products.

Chapter 2 Experimental

Preparation of 2,3-O-(1-methylethylidene)-D-ribonic acid-γ-lactone (Scheme 2.6). A 250 mL round-bottom flask equipped with a magnetic stir bar was charged with a 0.3 M solution of D-ribo-γ-lactone (2.50 g, 16.88 mmol) in dry acetone (60 mL) containing 14 mol% I₂ (600 mg, 2.36 mmol) and anhydrous MgSO₄ (1.25 g). The reaction mixture was stirred under nitrogen at 25 °C for 12 h until no further starting material was detected by TLC (Rf = 0.10, 6:1 chloroform/methanol). The reaction was
diluted with chloroform (150 mL) and the solids removed by vacuum filtration. The filtrate was washed
with 0.2 M sodium thiosulfate (2 x 75 mL). The combined aqueous phase was back extracted with
additional chloroform (50 mL) and the combined organic phase washed with saturated brine (15 mL) and
then dried over anhydrous MgSO₄. Vacuum filtration and concentration in vacuo yielded a crude white
solid which was recrystallized from acetone/hexane to give 2.831 g (89%) of the previously reported 2,3-
O-isopropylidene-D-ribonic acid-γ-lactone as white needles.

\[
\begin{align*}
R_f &= 0.56 \text{ (6:1 chloroform/methanol); } \\
\text{Mp} &= 135.0-136.0 \degree C \text{ [Lit. mp 134-136 \degree C]}; \quad \text{IR (KBr) } 3462 \text{br.} \\
2990 \text{s}, 2934 \text{s}, 2896 \text{w}, 2839 \text{w}, 2740 \text{w}, 2688 \text{w}, 2558 \text{w}, 2360 \text{s}, 1765 \text{w}, 1467 \text{w}, 1388 \text{w}, 1280 \text{w}, 1224 \text{s}, 1151 \text{s}, \\
1075 \text{w}, 1009 \text{m}, 973 \text{m}, 925 \text{m}, 891 \text{m}, 856 \text{m}, 809 \text{m}, 773 \text{m cm}^{-1}; \quad \text{H-NMR (250 MHz, CDCl₃)}^{259} \delta 4.83 \text{ (d,} \\
J_{2,3} &= 5.6 \text{ Hz, } 1 \text{ H, H-2), 4.77 \text{ (d,} J_{3,2} = 5.6 \text{ Hz, } 1 \text{ H, H-3), 4.62 \text{ (app. t,} J_{4,5} = 1.9 \text{ Hz,} J_{4,5'} = 2.2 \text{ Hz, } 1 \text{ H, H-} \\
4), 3.98 \text{ (ddd,} J_{\text{gem}} = 12.2 \text{ Hz,} J_{5a,OH} = 5.4 \text{ Hz,} J_{5a,4} = 2.2 \text{ Hz, } 1 \text{ H, H-5a), 3.80 \text{ (ddd,} J_{\text{gem}} = 12.2 \text{ Hz,} J_{5b,OH} = \\
5.6 \text{ Hz,} J_{5b,4} = 1.9 \text{ Hz, } 1 \text{ H, H-5b), 2.28 \text{ (app. t,} J_{\text{OH,5a}} = 5.4 \text{ Hz,} J_{\text{OH,5b}} = 5.6 \text{ Hz, D}_{2}O \text{ exch., } 1 \text{ H, OH), 1.47} \\
s, 3 \text{ H, CH}_3), 1.38 \text{ (s, } 3 \text{ H, CH}_3); \quad \text{C-NMR (75 MHz, CDCl₃)}^{260} \delta 175.1 \text{ (C-1), 113.3 \text{ (CMe}_2), 82.9 \text{ (C-} \\
f-2), 79.5 \text{ (C-3), 75.9 \text{ (C-4), 62.2 \text{ (C-5), 26.9 \text{ (CH}_3), 25.7 \text{ (CH}_3).} \\

\text{Preparation of } 5\text{-Bromo-5-deoxy-2,3-O-(1-methylethylidene)-D-ribose acid γ-lactone (Scheme} \\
2.6)^{128,261} \quad \text{A 100 mL round-bottom flask equipped with a magnetic stir bar, water condenser, and} \\
nitrogen inlet was charged with a 0.1 M solution of 2,3-O-isopropylidene-D-ribo-γ-lactone (1.00 g, 5.31} \\
mmol) in dichloromethane (40 mL) containing 2.0 equivalents of \text{N-bromosuccinimde}^{250,262} \text{ (1.89 g,} \\
10.62 \text{ mmol). The reaction vessel was cooled to 0 \degree C followed by addition of 2.0 equivalents of} \\
\text{triphenylphosphine (2.70 g, 10.62 mmol) in small portions over 0.5 h maintaining the reaction vessel} \\
temperature below 5 \degree C. Following addition of the triphenylphosphine, barium carbonate (400 mg, 2.02} \\
173
mmol) was added and the reaction mixture warmed to reflux for 20 minutes. The reaction was then
cooled to 25 °C, the solids removed by vacuum filtration and the filtrate concentrated under reduce
pressure to yield an red oil. The crude product was taken up in diethyl ether (60 mL) and the organic
phase washed with water (10 mL), saturated brine (5 mL) and then dried over anhydrous MgSO₄.
Vacuum filtration and concentration in vacuo yielded a crude white solid which was flash
chromatographed (silica gel, 7:3 hexanes/ethyl acetate) to yield 1.006 g (75%) of the previously reported
5-bromo-5-deoxy-2,3-O-isopropylidene-D-ribonolactone as a colorless oil which solidified on
standing.

\[ R_f = 0.28 \text{ (10:1 hexanes/ethyl acetate); } \text{Mp} = 87.5-89.5 \degree \text{C; [Lit. mp} = 88.5-89.5 \degree \text{C.]} \]
\[ \text{IR (KBr)} 3542m, 3047m, 2968m, 2938m, 2527w, 2348w, 2293w, 2207w, 2121w, 1778s, 1654w, 1460m,
1430m, 1386s, 1351s, 1281s, 1249s, 1216s, 1180s, 1072s, 1024s, 979s, 945s, 881s, 855s, 817s, 755m,
703m, 607m, 545m, 515m \text{ cm}^{-1}; \text{^1H-NMR (300 MHz, CDCl}_3 \rangle \delta 4.88 \text{ (d, } J_{2,3} = 5.9 \text{ Hz, } 1 \text{ H, H-2)}, 4.81 \text{ (t,}
J_{4,5} = 3.5 \text{ Hz, } 1 \text{ H, H-4)}, 4.65 \text{ (d, } J_{3,2} = 5.9 \text{ Hz, } 1 \text{ H, H-3)}, 3.62 - 3.60 \text{ (m, } 2 \text{ H, H-5)}, 1.42 \text{ (s, }
3 \text{ H, CH}_3), 1.32 \text{ (s, } 3 \text{ H, CH}_3); \text{^{13}C-NMR (75 MHz, CDCl}_3 \rangle \delta 173.3 \text{ (s, C}_1), 113.7 \text{ (s, CMe}_2), 80.6 \text{ (d, C}_4), 79.0 \text{ (d,}
C_2), 75.2 \text{ (d, C}_3), 33.0 \text{ (t, C}_5), 26.5 \text{ (q, CH}_3), 25.3 \text{ (q, CH}_3).

\textbf{Preparation of 5-bromo-5-deoxy-2,3-O-(1-methylethylidene)-\beta-D-ribofuranose (Scheme 2.6).} A 100
mL three-necked round-bottomed flask equipped with a magnetic stir bar, addition funnel, thermocouple
lead, and nitrogen inlet was charged with a 0.25 M solution of 5-bromo-5-deoxy-2,3-O-isopropylidene-D-
ribono-\gamma-lactone (2.00 g, 7.96 mmol) in diethyl ether (32.0 mL). The addition funnel was then charged
with 1.5 equivalents of Dibal-H (1.5 M in toluene, 8.0 mL, 12.0 mmol). The flask was cooled to -78° C
(dry ice/acetone) followed by dropwise addition of the hydride solution over 0.5 h maintaining the
temperature at or below -73° C. Following complete addition of the metal hydride reagent, the reaction was stirred at -78° C for an additional 1.5 h. Excess metal hydride reagent was quenched by slow, dropwise addition of absolute methanol (2 mL) and after 5 minutes the cooling bath was removed and the reaction allowed to come to 25 °C. The contents of the reaction vessel were then transferred to a separatory funnel and the reaction washed with saturated aqueous potassium tartrate (25 mL). The organic phase was washed with water (10 mL) and the combined aqueous phase was back extracted with diethyl ether (30 mL). The combined organic phase was then washed with saturated brine (10 mL) and dried over anhydrous MgSO₄. Vacuum filtration and concentration in vacuo yielded 1.927 g (95.6%) of the previously reported 5-bromo-5-deoxy-2,3-O-isopropylidene-β-D-ribofuranose (β/α = 18) as a colorless syrup which solidified on standing. This material was used in the next step without further purification.

\[
R_f = 0.56, \ (3:1 \text{ hexanes/ethyl acetate}); \ \text{Mp} \ 79.0-80.0 \ ^\circ C; \ \text{IR} \ (\text{thin film}) \ 3425\text{br}, 2985s, 2942s, 2359m, 1631w, 1439m, 1376s, 1328m, 1272s, 1243s, 1210s, 1160s, 1070s, 1027s, 969s, 929m, 867s, 820m \text{ cm}^{-1}.
\]

\[\text{H-NMR (300 MHz, CDCl}_3] \delta 5.48 (d, J_{1,OH} = 3.1 \text{ Hz, } 1 \text{ H, H-1β}), 4.79 (dd, J_{2,3} = 5.9 \text{ Hz, } J_{2,4} = 0.9 \text{ Hz, } 1 \text{ H, H-3}), 4.39 (ddd, J_{4,5a} = 9.1 \text{ Hz, } J_{4,5b} = 6.1 \text{ Hz, } J_{4,2} = 0.9 \text{ Hz, } 1 \text{ H, H-4}), 3.59 (d, J_{5a,1} = 3.1 \text{ Hz, } D_2O \text{ exch., } 1 \text{ H, OH}), 3.45 (d, J_{5a,4} = 9.1 \text{ Hz, } 1 \text{ H, H-5a}), 3.42 (d, J_{5b,4} = 6.1 \text{ Hz, } 1 \text{ H, H-5b}), 1.47 (s, 3 \text{ H, CH}_3), 1.31 (s, 3 \text{ H, CH}_3); ^{13}\text{C-NMR (75 MHz, CDCl}_3] \delta 113.0 (\text{CMe}_2), 103.3 (\text{C-1β}), 97.4 (\text{C-1α minor}), 86.9 (\text{C-2}), 85.9 (\text{C-3}), 83.1 (\text{C-4}), 33.4 (\text{C-5}), 26.6 (\text{CH}_3), 25.1 (\text{CH}_3).
\]

Preparation of (2E)- and (2Z)-ethyl 7-bromo-2,3,7-trideoxy-4,5-O-(1-methylethylidene)-D-ribo-hept-2-enoate (2.33) (Scheme 2.6).²⁶³ A 100 mL round-bottom flask equipped with a magnetic stir bar and nitrogen inlet was charged with a 0.15 M solution of 5-bromo-5-deoxy-2,3-O-isopropylidene-β-D-ribofuranose (300 mg, 1.20 mmol) in dimethoxyethane (8.0 mL) followed by 2.0 equivalents of
(carbethoxymethylene)-triphenylphosphorane (836 mg, 2.40 mmol). The heterogeneous mixture was stirred vigorously at 25 °C for 36 h until homogeneous and no further starting material remained by TLC ($R_f = 0.75, 3:1$ hexanes/ethyl acetate). The solvent was then removed under reduced pressure and the resulting crude oil (Z/E = 2.76) was flash chromatographed (silica gel, 6:1 hexanes/ethyl acetate) to give 300 mg of the previously reported (Z)-ethyl 7-bromo-2,3,7-trideoxy-4,5-O-isopropylidene-D-ribo-hept-2-enoate (2.33) and 295 mg of a 1:1 mixture of (E/Z) isomers both as colorless oils and in a combined yield of 76%.

(Z)-isomer: $R_f = 0.59, (6:1$ hexanes/ethyl acetate); IR (thin film) 3450 br, 2986 s, 2937 m, 2904 m, 1715 s, 1649 m, 1418 s, 1382 s, 1373 s, 1299 m, 1220 s, 1197 s, 1162 s, 1056 s, 1028 s, 966 w, 871 s, 829 m cm$^{-1}$; $^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 6.23 (dd, $J_{3,2} = 11.6$ Hz, $J_{3,4} = 8.3$ Hz, 1 H, H-3), 5.99 (dd, $J_{2,3} = 11.6$ Hz, $J_{2,4} = 1.3$ Hz, 1 H, H-2), 5.57 (ddd, $J_{4,3} = 8.3$ Hz, $J_{4,5} = 6.3$ Hz, $J_{4,2} = 1.3$ Hz, 1 H, H-4), 4.27 (dd, $J_{5,6} = 8.2$ Hz, $J_{5,4} = 6.3$ Hz, 1 H, H-5), 4.17 (d, $J = 7.1$ Hz, 2 H, OCH$_2$CH$_3$), 3.73-3.67 (m, 1 H, H-6), 3.64 (dd, $J_{gem} = 10.5$ Hz, $J_{7a,6} = 2.4$ Hz, 1 H, H-7), 3.52 (dd, $J_{gem} = 10.5$, $J_{7b,6} = 6.4$ Hz, 1 H, H-7b), 3.22 (d, $J_{OH,g} = 3.8$ Hz, 1 H, D$_2$O exch., OH), 1.47 (s, 3 H, CH$_3$), 1.38 (s, 3 H, CH$_3$), 1.28 (t, $J = 7.1$ Hz, 3 H, OCH$_2$CH$_3$); $^{13}$C-NMR (75.0 MHz, CDCl$_3$) $\delta$ 167.1 (s, C-1), 145.5 (d, C-3), 122.8 (d, C-2), 109.8 (s, CMe$_2$), 79.9 (d), 74.7 (d), 69.7 (d), 61.3 (t, OCH$_2$CH$_3$), 37.5 (t, C-7), 28.0 (q, CH$_3$), 25.1 (q, CH$_3$), 14.3 (q, OCH$_2$CH$_3$).

(E)-isomer: $R_f = 0.47, (6:1$ hexanes/ethyl acetate); IR (thin film) 3466 br, 2986 s, 2936 m, 1720 s, 1659 m, 1455 w, 1372 s, 1309 s, 1261 s, 1216 s, 1163 s, 1059 s, 981 m, 883 m, 866 m, 798 w cm$^{-1}$; $^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ ...
\( ^{1}H\ NMR (62.8\ MHz,\ \text{CDCl}_3) \delta 7.05\ (dd, J_{3,2} = 15.6\ Hz,\ J_{3,4} = 4.8\ Hz,\ 1\ H,\ H-3),\ 6.14\ (dd, J_{2,3} = 15.6\ Hz,\ J_{2,4} = 1.7\ Hz,\ 1\ H,\ H-2).\)

4.86 (ddd, \( J_{5,6} = 6.6\ Hz,\ J_{4,5} = 4.8\ Hz,\ J_{4,2} = 1.7\ Hz,\ 1\ H,\ H-5),\ 3.67-3.60\ (m, 1\ H,\ H-6),\ 3.71\ (dd, J_{gem} = 10.1\ Hz,\ J_{a,b} = 2.3\ Hz,\ 1\ H,\ H-7a),\ 3.52\ (dd, J_{gem} = 10.1\ Hz,\ J_{b,6} = 6.7\ Hz,\ 1\ H,\ H-7b),\ 2.54\ (s, 1\ H,\ D_2O\ exch.,\ OH),\ 1.48\ (s, 3\ H,\ CH_3),\ 1.37\ (s, 3\ H,\ CH_3),\ 1.28\ (t, J = 7.1\ Hz,\ 3\ H,\ OCH_2CH_3);\ ^{13}C\ NMR (62.8\ MHz,\ \text{CDCl}_3) \delta 166.4\ (C-1),\ 143.1\ (C-3),\ 122.7\ (C-2),\ 109.9\ (CMe_2),\ 78.9,\ 76.7,\ 69.4,\ 60.7\ (OCH_2CH_3),\ 39.0\ (C-7),\ 27.8\ (CH_3),\ 25.4\ (CH_3),\ 14.4\ (OCH_2CH_3).

Preparation of 5-\( O-\)[(1,1-dimethylethyl)dimethylsilyl]-2,3-\( O-\)(1-methylethylidene)-\( \beta\)-D-ribofuranose (Scheme 2.7)\(^\text{264}\) A 250 mL. three-neck, round-bottom flask equipped with an addition funnel, thermocouple lead, and nitrogen inlet was charged with 5-\( O\)-tert-butyldimethylsilyl-2,3-\( O\)-isopropylidene-\( \beta\)-D-ribo-\( \gamma\)-lactone (2.36, 10.0 g, 33.0 mmol) and diethyl ether (130 mL). The addition funnel was then charged with 1.5 equivalents Dibal-H (1.5 M in toluene, 33.0 mL, 49.50 mmol). The flask was cooled to -78 °C (CO\(_2\)/acetone) followed by dropwise addition of the hydride solution over 0.5 h maintaining the temperature between -66 °C and -71 °C. Following addition of the metal hydride reagent, the reaction was stirred at or below -72 °C for an additional 1.5 h. Excess hydride was quenched by slow, dropwise addition of absolute methanol (5 mL) after which the cooling bath was removed and the reaction allowed to warm to 25 °C. The reaction was then quenched with saturated aqueous potassium tartrate (50 mL) and stirred at 25 °C overnight. The contents of the reaction vessel were transferred to a separatory funnel and partitioned and the organic phase washed with water (10 mL). The combined aqueous phase was then back extracted with diethyl ether (30 mL) and the combined organic phase washed with saturated aqueous brine (10 mL) and then dried over anhydrous MgSO\(_4\). Vacuum filtration and concentration in vacuo yielded 9.53 g (95.3%) of the previously reported 5-\( O\)-tert-butyldimethylsilyl-2,3-\( O\)-isopropylidene-\( \beta\)-D-ribofuranose as a colorless syrup which solidified on standing. This material was used in the next step without further purification.
Bu'Me₂SiO

\[ R_f = 0.53 \ (7:3 \text{ hexanes/ethyl acetate}); \text{Mp} 52.0-53.0^\circ \text{C} \text{ [Lit. 52-54}^\circ \text{C]} \text{, IR (thin film) 3418}br, 2944s, 2853m, 1793s, 1472m, 1378m, 1257s, 1211m, 1159m, 1081s, 1004m, 958m, 940m, 837m, 780m\text{ cm}^{-1}; \text{ }^1\text{H}-\text{NMR (200 MHz. CDCl}_3)^{265} \delta 5.28 \ (d, J_{1,OH} = 11.9 \text{ Hz}, 1 \text{ H, H-1}), 4.78 \ (d, J_{OH,1} = 11.9 \text{ Hz}, 1 \text{ H, OH}), 4.69 \ (d, J_{2,2} = 5.9 \text{ Hz}, 1 \text{ H, H-3}), 4.50 \ (d, J_{2,3} = 5.9 \text{ Hz}, 1 \text{ H, H-2}), 4.36 \ (m, 1 \text{ H, H-4}), 3.76 \ (m, 1 \text{ H, 2 H, H-5}), 1.48 \ (s, 3 \text{ H, CH}_3), 1.32 \ (s, 3 \text{ H, CH}_3), 0.93 \ (s, 9 \text{ H, CMe}_3), 0.14 \ (s, 6 \text{ H, SiMe}_3); ^{13}\text{C-NMR (62.8 MHz. CDCl}_3)^{265} \delta 112.3 \ (s, \text{ CMe}_2), 103.7 \ (d, C-1\beta), 87.8 \ (d, C-2), 87.2 \ (d, C-4), 81.9 \ (d, C-3), 65.0 \ (t, C-5), 26.7 \ (q, \text{ CMe}_2), 25.9 \ (q, \text{ CMe}_2), 25.1 \ (q, \text{ CMe}_2), 18.4 \ (s, \text{ SiCMe}_3), -5.43 \ (q, \text{ SiMe}), -5.48 \ (q, \text{ SiMe}).

Isomerization of (2Z)-ethyl 7-bromo-2,3,7-trideoxy-4,5-\text{O}-(1\text{-methylethylidene})\text{-D-ribo-hept-2-enoate (}2.33\text{) with silver(I) oxide (Scheme 2.6).}^{266,267} \text{ A 10 mL round-bottom flask equipped with a magnetic stir bar and nitrogen inlet was charged with a 0.05 M solution of (Z)-ethyl 7-bromo-2,3,7-trideoxy-4,5-\text{O}-isopropylidene-\text{D-ribo-hept-2-enoate (}2.33\text{, 80 mg, 0.247 mmol) in acetonitrile (5.0 mL) and cooled to 0}^\circ \text{C. To this solution was added 1.1 equivalents of Ag}_2\text{O (63 mg, 0.272 mmol) in small portions over 10 minutes. The reaction was stirred at 0}^\circ \text{C for 45 minutes and then the cooling bath removed and the reaction warmed to 25}^\circ \text{C. After 1.5 h, the starting material had been consumed as indicated by TLC (}R_f = 0.42, 4:1 \text{ hexanes/ethyl acetate). The reaction was filtered over a pad of Celite and the Celite rinsed with ethyl acetate (5 mL) and the combined organic phase concentrated in vacuo to yield a yellow oil. Flash chromatography (silica gel, 5:1 \text{ hexanes/ethyl acetate) yielded 50 mg (62.5\%)}\text{ of a colorless oil which was identical to (E)-ethyl 7-bromo-2,3,7-trideoxy-4,5-\text{O-isopropylidene-\text{D-ribo-hept-2-enoate (}2.33\text{) isolated previously.}}\]
Preparation of (2Z)- and (2E)-ethyl 2,3-dideoxy-7-O-[(1,1-dimethylethyl)dimethylsilyl]-4,5-O-(1-methylethylidene)-D-ribo-hept-2-enoate (2.37) (Scheme 2.7).

A 250 mL round-bottom flask equipped with a magnetic stir bar and nitrogen inlet was charged with a 0.15 M solution of 5-O-tert-butylidimethylsilyl-2,3-O-isopropylidene-β-D-ribofuranose (6.19 g, 20.3 mmol) in dimethoxyethane (135 mL). To this solution was added 2.0 equivalents of (carbethoxymethylene)triphenylphosphorane (14.165 g, 40.66 mmol) and the heterogeneous mixture stirred rapidly under nitrogen at 25 °C for 72 h until homogenous and no further starting material remained by TLC analysis ($R_f = 0.60$, 3:1 hexanes/ethyl acetate). The solvent was then removed under reduced pressure and the resulting crude oil flash chromatographed (silica gel, 10:1 hexanes/ethyl acetate) to give 7.536 g (98%) of desired ethyl 7-O-tert-butyldimethylsilyl-2,3-dideoxy-4,5-O-isopropylidene-D-ribo-hept-2-enoate (2.37) as a colorless oil (Z/E = 2.3).

(Z)-isomer: IR (thin film): 3484m, 2987s, 2953s, 2857s, 1721s, 1651m, 1471s, 1417s, 1391s, 1299m, 1253s, 1220s, 1190s, 1057s cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 6.29 (dd, $J_{3,2} = 11.6$ Hz, $J_{3,4} = 8.6$ Hz, 1 H, H-3), 5.97 (dd, $J_{2,3} = 11.6$ Hz, $J_{2,4} = 1.3$ Hz, 1 H, H-2), 5.76 (ddd, $J_{4,3} = 8.6$ Hz, $J_{4,5} = 6.3$ Hz, $J_{4,2} = 1.3$ Hz, 1 H, H-4), 4.26 (dd, $J_{5,6} = 8.3$ Hz, $J_{5,4} = 6.3$ Hz, 1 H, H-5), 4.19 (q, $J = 7.1$ Hz, 1 H, OCH₂CH₃), 3.79 (dd, $J = 7.0$ Hz, $J = 3.0$ Hz, 1 H, H-7), 3.73-3.64 (m, 1 H, H-7), 3.64-3.59 (m, 1 H, H-6), 2.68 (d, $J = 4.5$ Hz, 1 H, D₂O exch., OH), 1.47 (s, 3 H, CH₃), 1.36 (s, 3 H, CH₃), 1.29 (t, $J = 7.1$ Hz, 3 H, CH₃).
OCH$_2$CH$_3$), 0.90 (s, 6 H, CMe$_2$), 0.07 (s, 6 H, SiMe$_2$); $^{13}$C-NMR (75.0 MHz, CDCl$_3$) $\delta$ 166.3 (s, C-1), 144.7 (d, C-3), 122.3 (d, C-4), 109.3 (s, CMe$_2$), 78.2 (d), 74.0 (d), 70.1 (d), 64.5 (t, C-7), 60.7 (t, OCH$_2$CH$_3$), 28.2 (q, CMe$_2$), 26.1 (q, CMe$_2$), 25.6 (q, CMe$_2$), 18.5 (s, SiCMe$_2$), 14.3 (q, OCH$_2$CH$_3$), -5.14 (q, SiMe$_2$), -5.19 (q, SiMe$_2$). Further proof of structure provided by elemental analysis was obtained on advanced intermediates (vide infra).

![Structural Diagram]

(E)-isomer: IR (thin film); 3431 br, 2983 s, 2952 s, 2991 s, 2936 s, 2886 s, 2858 s, 1721 s, 1658 m, 1598 s, 1373 s, 1304 m, 1251 s, 1213 s, 1162 s, 1072 m, 1004 m, 939 m, 870 s, 838 s, 779 s cm$^{-1}$; $^1$H-NMR (300 MHz) 7.11 (dd, J$_{3,2}$ = 15.6 Hz, J$_{3,\alpha}$ = 4.9 Hz, 1 H, H-3), 6.13 (dd, J$_{2,3}$ = 15.6 Hz, J$_{2,\alpha}$ = 1.7 Hz, 1 H, H-2), 4.86 (ddd, J$_{4,3}$ = 6.8 Hz, J$_{4,5}$ = 5.5 Hz, J$_{4,\alpha}$ = 1.7 Hz, 1 H, H-4), 4.57 (ddd, J$_{6,5}$ = 6.5 Hz, J$_{6,\beta}$ = 4.9 Hz, J$_{6,\gamma}$ = 2.4 Hz, 1 H, H-6), 4.47 (ddd, J$_{5,6}$ = J$_{5,\gamma}$ = 6.5 Hz, 1 H, H-5), 4.20 (q, J = 7.1 Hz, 2 H, OCH$_2$CH$_3$), 3.96 (dd, J$_{\text{gem}}$ = 12.0 Hz, J$_{7,\alpha}$ = 2.4 Hz, 1 H, H-7), 3.86 (dd, J$_{\text{gem}}$ = 12.0 Hz, J$_{7,\beta}$ = 4.9 Hz, 1 H, H-7), 1.49 (s, 3 H, CH$_3$), 1.37 (s, 3 H, CH$_3$), 1.29 (t, J = 7.1 Hz, 3 H, OCH$_2$CH$_3$) 0.89 (s, 9 H, SiCMe$_3$), 0.07 (s, 6 H, SiMe$_2$); $^{13}$C-NMR (75 MHz) 166.5 (s, C-1), 144.1 (d, C-3), 122.5 (d, C-2), 103.7 (s, CMe$_2$), 87.8 (d), 82.0 (d), 69.8 (d), 64.5 (t, C-7), 60.6 (t, OEt), 27.8 (q, CMe$_2$), 26.0 (q, CMe$_2$), 25.5 (q, CMe$_2$), 18.5 (s, SiCMe$_3$), 14.4 (q, OEt), -5.1 (q, SiMe), -5.2 (q, SiMe). Further proof of structure provided by elemental analyses was obtained on advanced intermediates (vide infra).

Preparation of (2Z)- and (2E)-ethyl 2,3-dideoxy-7-O-[(1,1-dimethylethyl)dimethylsilyl]-6-O-(methanesulfonyl)-4,5-O-(1-methylethylidene)-D-ribo-hept-2-enoate (2.38) (Scheme 2.7). A 25 mL round-bottom flask equipped with a magnetic stir bar and nitrogen inlet was charged with a 0.05 M solution of (Z)-ethyl 7-O-tert-butyldimethylsilyl-2,3-dideoxy-4,5-O-isopropylidene-D-ribo-hept-2-enoate (2.37, 1.00 g, 2.67 mmol) in pyridine (5.0 mL) and the solution cooled to 0 °C. To this solution was
added 1.2 equivalents of methanesulfonyl chloride (255 μL, 3.30 mmol) and the reaction stirred at 0 °C for 5 h. The cooling bath was removed and the reaction allowed to warm to 25 °C and the reaction quenched with saturated aqueous ammonium chloride (20 mL). The contents of the reaction vessel were transferred to a separatory funnel and extracted with dichloromethane (20 mL) and the organic layer washed with water (2 x 5 mL), saturated brine (5 mL) and then dried over anhydrous MgSO₄. The organic layer was then vacuum filtered and concentrated in vacuo to give a crude yellow oil which was flash chromatographed (silica gel, 7:1 hexanes/ethyl acetate) to give 889 mg (73%) of (Z)-ethyl 2,3-dideoxy-7-O-tert-butyldimethylsilyl-6-O-mesyl-4,5-O-isopropylidene-D-ribo-hept-2-enoate (2.38) and 40 mg (4%) of (E)-ethyl 2,3-dideoxy-7-O-tert-butyldimethylsilyl-6-O-mesyl-4,5-O-isopropylidene-D-ribo-hept-2-enoate (2.37).

(Z)-isomer: \( R_f = 0.47 \), (7:1 hexanes/ethyl acetate); IR (thin film): 2984\( m \), 2953\( m \), 2885\( s \), 2857\( m \), 1718\( s \), 1647\( w \), 1472\( m \), 1416\( m \), 1362\( s \), 1255\( s \), 1225\( s \), 1195\( s \), 1177\( s \), 1111\( s \), 1059\( s \), 1030\( s \), 969\( m \), 922\( s \), 836\( s \), 780\( s \) cm\(^{-1}\); \(^1\)H-NMR (300 MHz, CDCl\(_3\)) \( \delta 6.28 \) (dd, \( J_{1,2} = 11.6 \) Hz, \( J_{3,4} = 7.2 \) Hz, 1 H, H-3), 5.99 (dd, \( J_{2,3} = 11.6 \) Hz, \( J_{5,4} = 1.7 \) Hz, 1 H, H-2), 5.71 (ddd, \( J_{4,5} = 7.2 \) Hz, \( J_{4,2} = 1.7 \) Hz, 1 H, H-4), 4.65 (dd, \( J_{5,4} = 7.2 \) Hz, \( J_{5,6} = 4.5 \) Hz, 1 H, H-5), 4.57 (ddd, \( J_{6,7a} = 6.4 \) Hz, \( J_{6,5} = 4.5 \) Hz, \( J_{6,7b} = 3.0 \) Hz, 1 H, H-6), 4.22-4.12 (m, 2 H, OCH\(_2\)CH\(_3\)), 3.83 (dd, \( J_{7a,6} = 12.0 \) Hz, \( J_{7b,6} = 6.4 \) Hz, 1 H, H-7a), 3.77 (dd, \( J_{7a,8} = 12.0 \) Hz, \( J_{7b,6} = 3.0 \) Hz, 1 H, H-7b), 3.02 (s, 3 H, SO\(_2\)CH\(_3\)), 1.45 (s, 3 H, CH\(_3\)), 1.34 (s, 3 H, CH\(_3\)), 1.27 (t, \( J = 7.1 \) Hz, 3 H, OCH\(_2\)CH\(_3\)), 0.87 (s, 9 H, CMe\(_3\)), 0.05 (s, 3 H, SiMe), 0.04, (s, 3 H, SiMe); \(^{13}\)C-NMR (75 MHz, CDCl\(_3\)) \( \delta 165.5 \) (C-1), 143.9 (C-2), 123.2 (C-3), 109.3 (CMe\(_2\)), 82.6, 76.8, 74.2, 62.6 (C-7), 60.8 (OCH\(_2\)CH\(_3\)), 39.1 (SO\(_2\)CH\(_3\)), 27.0 (CMe\(_2\)), 25.9 (CMe\(_3\)), 24.6 (CMe\(_2\)), 18.5 (SiCMe\(_3\)), 14.3 (OCH\(_2\)CH\(_3\)), -5.2 (SiMe), -5.3
(SiMe$_3$). HRMS (El) cald for C$_{18}$H$_{33}$O$_8$SiS (m-CH$_3$)$^+$: 437.166543. Obsd: 437.166540. Anal. cald for C$_{19}$H$_{36}$O$_8$SiS: C, 50.42; H, 8.02; S, 7.08. Obsd: C, 50.46; H, 8.05; S, 7.01.

(E)-isomer: $R_f = 0.45$. (7:1 hexanes/ethyl acetate); IR (thin film): 2985$m$, 2953$m$, 2933$s$, 2885$m$, 2857$m$, 1721$i$, 1660$w$, 1464$m$, 1364$s$, 1306$m$, 1257$s$, 1217$m$, 1178$s$, 1112$m$, 1071$m$, 1036$m$, 969$m$, 923$s$, 836$s$, 780$m$ cm$^{-1}$; $^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 6.97 (dd, $J_{J_2,2} = 15.6$ Hz, $J_{J_3,a} = 5.2$ Hz, 1 H, H-3), 6.17 (dd, $J_{J_3,3} = 15.6$ Hz, $J_{J_4,4} = 1.7$ Hz, 1 H, H-2), 4.86 (ddd, $J_{J_a,5} = 6.5$ Hz, $J_{J_b,3} = 5.2$ Hz, $J_{J_c,2} = 1.7$ Hz, 1 H, H-4), 4.57 (ddd, $J_{J_e,6} = 6.5$ Hz, $J_{J_f,7a} = 4.9$ Hz, $J_{J_g,7b} = 2.4$ Hz, 1 H, H-6), 4.47 (dd, $J_{J_e,5} = J_{J_f,6} = 6.5$ Hz, 1 H, H-3), 4.20 (q, $J = 7.1$ Hz, 2 H, OCH$_2$CH$_3$), 3.96 (dd, $J_{J_{7a,6}} = 12.0$ Hz, $J_{J_{6b,6}} = 2.4$ Hz, 1 H, H-7b), 3.86 (dd, $J_{J_{6b,6}} = 12.0$ Hz, $J_{7a,6} = 4.9$ Hz, 1 H, H-7a), 3.06 (s, 3 H, SO$_2$CH$_3$), 1.49 (s, 3 H, CH$_3$), 1.37 (s, 3 H, CH$_3$), 1.29 (t, $J = 7.1$ Hz, 3 H, OCH$_2$CH$_3$), 0.89 (s, 9 H, CMe$_3$), 0.07 (s, 6H, SiMe); $^{13}$C-NMR (62.8 MHz, CDCl$_3$) $\delta$ 165.9 (C-1), 141.4 (C-2), 123.8 (C-3), 110.6 (CMe$_2$), 80.9, 76.2, 76.1, 62.3 (C-7), 60.8 (OCH$_2$CH$_3$), 39.2 (SO$_2$CH$_3$), 27.4 (CMe$_2$), 26.0 (CMe$_2$), 25.2 (CMe$_2$), 18.5 (SiCMe$_3$), 14.4 (OCH$_2$CH$_3$), -5.30 (SiMe), -5.35 (SiMe). HRMS (El) for C$_{18}$H$_{33}$O$_8$SiS (m-CH$_3$)$^+$: 437.166543. Obsd: 437.166473

Preparation of (2Z)-ethyl 2,3-dideoxy-7-O-[(1,1-dimethylethyl)dimethylsilyl]-4,5-O-(1-methylthylethylidene)-6-oxo-D-ribo-hept-2-enoate (2.41) (Scheme 2.7). A 50 mL, 3-neck, round-bottom flask equipped with a magnetic stir bar, addition funnel, nitrogen inlet, and rubber septa was flame dried and cooled under nitrogen. The dropping funnel was charged with a 0.25 M solution of (Z)-ethyl 7-O-tert-butyldimethylsilyl-2,3-dideoxy-4,5-O-isopropylidene-D-ribo-hept-2-enoate (2.37, 444 mg, 1.18 mmol) in dichloromethane (4.75 mL) and the reaction flask charged with dichloromethane (5.0 mL) followed by 4.0 equivalents of dimethyl sulfoxide (336 µL, 4.74 mmol). The reaction vessel was then
cooled to -78 °C (CO₂/acetone) and 5.0 equivalents of distilled TFAA (837 μL, 5.93 mmol) was added slowly to the reaction flask and the contents stirred for 10 minutes. The contents of the dropping funnel were next added dropwise over several minutes maintaining the reaction temperature below -70 °C. The reaction was stirred at -78 °C for 2 h followed by slow addition of 4.0 equivalents of triethylamine (660 μL, 4.74 mmol). The reaction was allowed to stir for an additional 5 minutes at -78 °C before removing the cooling bath and allowing the vessel and its contents to warm to 25 °C. The contents of the flask were transferred to a separatory funnel and diluted with additional dichloromethane (15 mL) and washed with aqueous saturated bicarbonate (15 mL). The aqueous phase was back extracted with additional dichloromethane and the combined organic phase dried over anhydrous MgSO₄. Vacuum filtration and concentration in vacuo yielded 500 mg of a crude yellow oil. The crude oil was flash chromatographed (silica gel, 10:1 hexanes/ethyl acetate) to yield 212 mg (48%) of (Z)-ethyl 7-O-tert-butyldimethylsilyl-2,3-dideoxy-4,5-O-isopropylidene-6-oxo-D-ribo-hept-2-enoate (2.41).

![Structure](image)

\[ R_f = 0.41 \quad (10:1 \text{ hexanes/ethyl acetate}); \quad \text{IR (thin film) 2984m, 2930m, 2857m, 1740m, 1720s, 1651w, 1472m, 1415m, 1375m, 1254m, 1217s, 1193s, 1130m, 1059s, 837s, 779m cm}^{-1}; \quad \text{¹H-NMR (250 MHz, CDCl₃) δ 6.08 (dd, J_2,3 = 11.0 Hz, J_3,4 = 7.8 Hz, 1 H, H-3), 5.89 (app. d, J = 1.5 Hz, 1 H, H-5), 5.87-5.83 (m, 1 H, H-2), 4.94 (app. d, J_4,5 = 7.8 Hz, 1 H, H-4), 4.36 (ABq, v₁ = 4.46, v₂ = 4.25, J_{gem} = 19.0, 2 H, H-7), 4.19 (q, J = 7.2 Hz, 2 H, OCH₂CH₃), 1.60 (s, 3 H, CH₃), 1.47 (s, 3 H, CH₃), 1.30 (t, J = 7.2 Hz, 3 H, OCH₂CH₃) 0.91 (s, 9 H, CMe₃), 0.06 (s, 6 H, SiMe₂); \quad \text{¹³C-NMR (62.8MHz, CDCl₃) δ 205.6 (s, C-6), 165.4 (s, C-1), 143.1 (d, C-3), 123.2 (d, C-2), 110.9 (s, CMe₂), 80.8 (d), 74.9 (d), 68.7 (t, C-7), 60.7 (t, OCH₂CH₃), 26.9 (q, CMe₂), 25.9 (q, CMe₃), 24.9 (q, CMe₂), 18.6 (s, SiCMe₃), 14.2 (q, OCH₂CH₃), -5.1} \]
(q, SiMe), -5.2 (q, SiMe). HRMS (El) cald for C_{18}H_{32}O_7Si: 373.204642. Obsd: 373.2067566. Anal. calcd for C_{18}H_{32}O_7Si: C, 58.03; H, 8.66. Obsd: C, 58.09; H, 8.66.

Reaction of (Cp_2TiCl)_2 (1.54) with (2Z)-ethyl 2,3-dideoxy-7-O-[(1,1-dimethylethyl)dimethylsilyl]-4,5-O-(1-methylethylidene)-6-oxo-D-ribo-hept-2-enoate (2.41) (Scheme 2.7). In a glove box, a 50 mL round-bottom flask equipped with a magnetic stir bar and dropping funnel was charged with a 0.04 M solution of (Z)-ethyl 7-O-tert-butyldimethylsilyl-2,3-dideoxy-4,5-O-isopropylidene-6-oxo-D-ribo-hept-2-enoate (2.41, 117 mg, 0.314 mmol) in tetrahydrofuran (7.5 mL). The dropping funnel was then charged with a 0.04 M solution of (Cp_2TiCl)_2 (1.54, 2.50 equivalents, 170 mg, 0.40 mmol) in tetrahydrofuran (10.0 mL) and the dark green titanium reagent added slowly to the rapidly stirred substrate over 10 minutes. Upon addition of the dark green titanium solution the clear substrate solution turned a light green which upon addition of the contents of the addition funnel remained light green. Following complete addition of the titanium reagent, the reaction was stirred for an additional 1.5 h at 25 °C. At this time the light green reaction mixture was quenched with 1.0 equivalent (with respect to titanium) of HCl (1.0 M in diethyl ether) and resulting mixture allowed stirred for 0.5 h at which time a bright red suspension resulted. The volume of solvent was then reduced to about 5 mL and the solution filtered over a pad of Celite and the pad rinsed with additional ethyl acetate, and repeated as necessary, to remove the solid titanocene dichloride. The combined organic phase was concentrated under reduced pressure and the resulting yellow crude product was analyzed by ^1^H-NMR spectroscopy and was found to be identical to the starting ketone.

Deprotection of (2Z)-ethyl 2,3-dideoxy-6-O-(methanesulfonyl)-7-O-[(1,1-dimethylethyl)dimethylsilyl]-4,5-O-(1-methylethylidene)-D-ribo-hept-2-enoate (2.38); Isolation of (2Z)-ethyl 2,3-dideoxy-6-O-(methanesulfonyl)-4,5-O-(1-methylethylidene)-D-ribo-hept-2-enoate (2.40) (Scheme 2.7). A 25 mL polypropylene vial equipped with a magnetic stir bar and nitrogen inlet was charged with a 0.05 M solution of (Z)-ethyl 7-O-tert-butyldimethylsilyl-2,3-dideoxy-4,5-O-isopropylidene-6-O-mesyl-D-ribo-hept-2-enoate (2.38, 39 mg, 0.086 mmol) in acetonitrile (2.0 mL) and the solution cooled to
0 °C. To this solution was added via propylene pipette aqueous hydrofluoric acid (48%, 3 drops) and the reaction stirred vigorously at 0 °C until the disappearance of starting material by TLC ($R_f = 0.90, 6:1$ hexanes/ethyl acetate) was complete after 0.5 h. The contents of the flask was quenched at 0 °C with saturated aqueous sodium bicarbonate (2 mL) and the mixture transferred to a separatory funnel and extracted with diethyl ether (2 x 10 mL). The combined organic phases were washed with saturated brine (5 mL) and dried over anhydrous MgSO$_4$. Vacuum filtration and concentration in vacuo yielded 20 mg (68%) of (Z)-ethyl 2,3-dideoxy-4,5-O-isopropylidene-6-O-mesyl-D-ribo-hept-2-enoate (2.40) as the sole product.

![Chemical structure](image)

$R_f = 0.90, \ (6:1 \ \text{hexanes/ethyl acetate}); ^1$H-NMR (300 MHz, CDCl$_3$) δ 6.34 (dd, $J_{3,2} = 11.5$ Hz, $J_{3,4} = 6.9$ Hz, 1 H, H-3), 6.04 (dd, $J_{2,3} = 11.5$ Hz, $J_{2,4} = 1.7$ Hz, 1 H, H-2), 5.68 (ddd, $J_{4,5} = 7.3$ Hz, $J_{4,3} = 6.9$ Hz, $J_{4,2} = 1.7$ Hz, 1 H, H-4), 4.67-4.63 (m, 1 H, H-6), 4.23-4.16 (m, 2 H, OCH$_2$CH$_3$), 3.88-3.82 (m, 2 H, H-7), 3.08 (s, 3 H, SO$_2$CH$_3$), 2.30 (s, D$_2$O exch., 1H, OH), 1.42 (s, 3 H, CH$_3$), 1.38 (s, 3 H, CH$_3$), 1.28 (t, $J = 7.2$ Hz, 3 H, OCH$_2$CH$_3$); $^{13}$C-NMR (75 MHz, CDCl$_3$) 172.9 (C-1), 144.4 (C-3), 123.2 (C-2), 109.7 (CMe$_2$), 85.7, 81.7, 74.6, 62.3 (C-7), 61.1 (OCH$_2$CH$_3$), 38.9 (SO$_2$CH$_3$), 26.9 (CMe$_2$), 24.9 (CMe$_2$), 14.3 (OCH$_2$CH$_3$).

**Preparation of (2Z)-ethyl 2,3-dideoxy-4,5-O-(1-methylethylidene)-D-ribo-hept-2-enoate (2.42)** (Scheme 2.7). A 60 mL polypropylene vessel with nitrogen inlet and magnetic stir bar was charged with a 0.05 M solution of (Z)-ethyl 7-O-tert-butylimethylsilyl-2,3-dideoxy-4,5-O-isopropylidene-D-ribo-hept-2-enoate (2.37, 500 mg, 1.33 mmol) in acetonitrile (27 mL) and cooled to 0 °C. Aqueous hydrofluoric acid (48%, 8 drops) was added slowly via polypropylene pipette to the vigorously stirred
solution. The consumption of the starting material was monitored by TLC ($R_f = 0.92$, 20:1 chloroform/methanol) and after 0.5 h the reaction was quenched at 0 °C with saturated aqueous sodium bicarbonate (5 mL). The contents of the vessel were transferred to a separatory funnel and separated. The aqueous layer was then extracted with chloroform (2 x 60 mL) and the combined aqueous layers washed with water (10 mL) and saturated aqueous brine (10 mL) and then dried over anhydrous MgSO$_4$. Vacuum filtration and concentration in vacuo yielded 332 mg of a clear oil which was flash chromatographed (silica gel, 20:1 chloroform/methanol) to provide 203 mg (59%) of the previously reported (Z)-ethyl 2,3-dideoxy-4,5-O-isopropyldiene-D-ribo-hept-2-enoate (2.42) as a colorless oil.

\[ R_f = 0.34 \text{ (10:1 chloroform/methanol); IR (CHCl}_3) 3427m(br), 2987m, 2936m, 1715s, 1649w, 1418m, 1372m, 1325w, 1302w, 1219s, 1194s, 1163s, 1057s, 1026s, 1026s, 869m, 829w cm}^{-1}; \text{^1H-NMR (300 MHz, CDCl}_3) \delta 6.28 (dd, J_{3,2} = 11.6 Hz, J_{3,4} = 8.4 Hz, 1 H, H-3), 6.03 (dd, J_{2,3} = 11.6 Hz, J_{2,4} = 1.3 Hz, 1 H, H-2), 5.45 (ddd, J_{4,3} = 8.4 Hz, J_{4,5} = 6.3 Hz, J_{4,2} = 1.3 Hz, 1 H, H-4), 4.33 (ddd, J_{5,6} = 8.1 Hz, J_{5,4} = 6.3 Hz, 1 H, H-5), 4.21 (q, J = 7.1 Hz, 2 H, OCHOCH}_3), 3.79-3.63 (m, 3 H, H-6, H-7), 3.48 (d, J_{OCH}_2 = 3.1 Hz, 1 H, D$_2$O exch., OH), 2.50 (app. t, J$_{OH,a} = 5.7$ Hz, J$_{OH,b} = 6.2$ Hz, 1 H, D$_2$O exch., OH), 1.50 (s, 3 H, CH$_3$), 1.38 (s, 3 H, CH$_3$), 1.31 (t, J = 7.1 Hz, 3 H, OCH$_2$CH$_3$); \text{^13C-NMR (75 MHz, CDCl}_3) \delta 167.4 \text{ (s, C-1), 146.2 (d, C-3), 122.4 (d, C-2), 109.8 (s, CMe}_2), 79.4 (d), 74.9 (d), 70.3 (d), 64.3 (t, C-7), 61.4 (t, OCH$_2$CH$_3$), 28.0 (q, CMe}_2), 25.5 (q, CMe}_2), 14.2 (q, OCH$_2$CH$_3$).}

\text{Preparation of 2,3-O-(1-methylethylidene)-D-ribofuranose, diacetate.}^{269} \text{ A 100 mL round-bottom flask equipped with a magnetic stir bar and nitrogen inlet was charged with a 0.5 M solution of D-ribofuranose (2.0 g, 13.32 mmol) in dimethylformamide (25 mL) to which was added 1 mol%}
p-toluenesulfonic acid monohydrate (30 mg, 0.15 mmol) and 3.05 equivalents of acetone dimethyl acetal (5.0 mL, 40.66 mmol). The reaction was stirred vigorously at 25 °C under nitrogen for 3 h. Amberlite IR-120 basic ion-exchange resin (100 mg) was added and the mixture stirred for an additional 20 minutes. The resulting clear solution was filtered and the resin washed with additional solvent (10 mL) and the solvents removed at 60 °C under high vacuum. Flash chromatography of the resulting syrup (silica gel, 500 mL each of chloroform; 50:1 chloroform/methanol; and 25:1 chloroform/methanol) yielded 1.62 g (73%) of the previously reported 2,3-O-isopropylidene-β-D-ribofuranose along with 230 mg (9%) of 2,3-O-isopropylidene-α-D-ribofuranose both as clear syrups. Both anomers were characterized by their diacetate.

β-anomer: \( R_f = 0.20 \) (4:1 hexanes/ethyl acetate); IR (neat) 2989 w, 2942 w, 1746 m, 1457 w, 1437 w, 1374 m, 1236 s, 1161 m, 1117 m, 1074 m, 1040 m, 1007 m, 967 m, 867 w, 764 w, 646 w, 603 w cm⁻¹; \(^1\)H-NMR (300 MHz, CDCl₃) \( \delta \) 6.11 (s, 1 H, H-1β), 4.63 (s, 2 H, H-2 and H-3), 4.36 (app t, \( J_{4,5a} = 7.0 \) Hz, \( J_{4,5b} = 6.4 \) Hz, 1 H, H-4), 4.07 (dd, \( J_{gem} = 11.4 \) Hz, \( J_{5b,4} = 6.4 \) Hz, 1 H, H-5b), 4.00 (dd, \( J_{gem} = 11.4 \) Hz, \( J_{5a,4} = 7.0 \) Hz, 1 H, H-5a), 1.99 (s, 3 H, Ac), 1.96 (s, 3 H, Ac), 1.40 (s, 3 H, CH₃), 1.24 (s, 3 H, CH₃); \(^13\)C-NMR (50 MHz, CDCl₃) \( \delta \) 170.6 (s, Ac), 169.4 (s, Ac), 113.3 (s, CMesy), 102.2 (d, C-1β), 85.4 (d, C-2), 85.2 (d, C-3), 81.6 (d, C-4), 64.2 (t, C-5), 26.5 (q, CMesy), 25.2 (q, CMesy), 21.3 (q, Ac), 20.9 (q, Ac).

\[ \text{AcO} \]

\[ \text{OAc} \]

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α-anomer: $R_F = 0.10$ (4:1 hexanes/ethyl acetate); IR (neat) 2990w, 2942w, 1747s, 1457w, 1435w, 1374s, 1235s, 1218s, 1160m, 1128m, 1051m, 1011m, 991m, 958m, 894w, 863w, 798w cm$^{-1}$; $^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 6.06 (d, $J_{1,2} = 7.0$ Hz, 1 H, H-1α), 5.03 (dd, $J_{2,1} = 7.0$ Hz, $J_{2,3} = 2.9$ Hz, 1 H, H-2), 4.56 (dd, $J_{3,4} = 7.5$ Hz, $J_{3,2} = 2.9$ Hz, 1 H, H-3), 4.32 (ddd, $J_{4,5a} = 7.5$ Hz, $J_{4,5b} = 2.0$ Hz, 1 H, H-4; $J_{5a,5b} = 1.5$ Hz, 1 H, H-5), 3.80 (ddd, $J_{gem} = 13.1$ Hz, $J_{5a,5b} = 2.0$ Hz, 1 H, H-5a), 3.67 (dd, $J_{gem} = 13.1$ Hz, $J_{5b,4} = 1.4$ Hz, 1 H, H-5b), 2.10 (s, 3 H, Ac), 1.99 (s, 3 H, Ac), 1.48 (s, 3 H, CH$_3$), 1.28 (s, 3 H, CH$_3$); $^{13}$C-NMR (50 MHz, CDCl$_3$) $\delta$ 170.2 (s, Ac), 170.0 (s, Ac), 110.8 (s, CMe$_2$), 91.5 (d, C-1α), 73.6 (d, C-2), 71.7 (d, C-3), 69.0 (d, C-4), 64.0 (t, C-5), 26.2 (q, CMe$_2$), 25.1 (q, CMe$_2$), 21.2 (q, Ac), 21.0 (q, Ac).

Preparation of (2Z)-1,1-dimethylethyl 2,3-dideoxy-4,5-(1-methylthymidene)-D-ribo-hept-2-enoate (2.43) (Scheme 2.8). A 500 mL round-bottom flask was charged with a 0.15 M solution of tert-butyl bromoacetate (28.5g, 146 mmol) in benzene (100 mL). To this was added 1.0 equivalent of triphenylphosphine (38.29g, 146 mmol) in benzene (100 mL). The reaction was stirred vigorously under nitrogen for 18 h. The solids were then removed by vacuum filtration and rinsed with additional solvent and then dried under high vacuum to give 65.0 g of (carbtert-butoxymethylene)-triphenylphosphonium bromide in quantitative yield, mp = 180.0-181.0 °C (Lit. mp = 177.0 °C). A 500 ml separatory funnel was next charged with (carbtert-butoxymethylene)triphenylphosphonium bromide (15.3 g, 33.6 mmol) in chloroform (80mL) followed by two drops of phenolphthalein solution. A 2.0 M solution of aqueous sodium hydroxide solution (80 mL) was added to the separatory funnel and the contents gently shaken until the aqueous phase remained light pink. The organic layer was then separated and washed with saturated brine (10 mL) and dried over anhydrous MgSO$_4$. Vacuum filtration and concentration in vacuo yielded the crude (carbtert-butoxymethylene)-triphenylphosphorane as a yellow syrup which was used in the next step without further purification. The crude phosphorane was dissolved in dimethoxyethane (60 mL) followed by addition of a solution of 2,3-O-isopropylidene-β-D-ribofuranose (3.20 g, 16.8 mmol) in dimethoxyethane (60 mL). The reaction mixture was stirred at 25 °C for 12 h. The disappearance of starting material was monitored by TLC ($R_F = 0.23$; 1:1 hexanes/ethyl acetate). Concentration in vacuo
and flash chromatography (silica gel; 1:1 hexanes/ethyl acetate) yielded 2.905 g (60%) of tert-butyl 2,3-dideoxy-4,5-O-isopropylidene-D-ribo-hept-2-enoate (2.43) as a waxy solid. The less polar (Z)-2.43 was isolated but the more polar (E)-2.43 always contained inseparable (Z)-isomer. Elemental analysis was obtained on (Z) tert-butyl 6,7-di-O-(acetyl)-2,3-dideoxy-4,5-O-isopropylidene-D-ribo-hept-2-enoate, the diacetate of 2.43.

(Z)-isomer: $R_f = 0.34$ (10:1 chloroform/methanol); Mp 71.0-73.0 °C, $[\alpha]^{19.5}_{D} = +90.4^o$ (c 1.18, CHCl$_3$); IR (CHCl$_3$) 4213w, 3682w, 3415w(br), 3018s, 298m, 2936m, 2400w, 1684m, 1521w, 1477w, 1455w, 1413m, 1370m, 1331w, 1214s, 1157m, 1106w, 1059m, 929w cm$^{-1}$; $^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 6.15 (dd, $J_{3,2} = 11.6$ Hz, $J_{3,4} = 8.4$ Hz, 1 H, H-3), 5.95 (dd, $J_{2,3} = 11.6$ Hz, $J_{2,4} = 1.3$ Hz, 1 H, H-2), 5.45 (ddd, $J_{4,3} = 8.4$ Hz, $J_{4,5} = 6.3$ Hz, $J_{4,2} = 1.3$ Hz, 1 H, H-4), 4.30 (dd, $J_{5,6} = 8.4$ Hz, $J_{5,4} = 6.3$ Hz, 1 H, H-5), 3.72-3.62 (m, 3 H, D$_2$O exch., H-6 and H-7, OH), 2.23 (m, 1 H, D$_2$O exch., OH), 1.53 (s, 3 H, CH$_3$), 1.50 (s, 9 H, t-Bu), 1.41 (s, 3 H, CH$_3$); $^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ 167.0 (s, C-1), 144.8 (d, C-3), 124.0 (d, C-2), 109.6 (s, CMe$_2$), 82.4 (s, CMe$_3$), 79.2 (d), 74.8 (d), 69.8 (d), 63.9 (t, C-7), 27.89 (q, CMe$_2$), 27.84 (q, CMe$_2$), 25.4 (q, CMe$_2$). HRMS (El) calcd for C$_{14}$H$_{25}$O$_6$ (M$^+$): 289.165113. Obsd: 289.166320.

(Z)-isomer: $[\alpha]^{19.5}_{D} = +155.3^o$ (c 1.835, CHCl$_3$); IR (thin film) 2900m, 2937w, 1747s, 1713s, 1649w, 1480w, 1455w, 1414m, 1370w, 1328w, 1336s, 1220s, 1157s, 1061m, 954w, 874w, 858w, 828w cm$^{-1}$;
\[ {^1}H\text{-NMR} (200 \text{ MHz, CDCl}_3) \delta 6.13 \text{ (dd, } J_{3,4} = 11.6 \text{ Hz, } J_{5,6} = 7.4 \text{ Hz, } 1 \text{ H, H-3)}, 5.82 \text{ (dd, } J_{2,3} = 11.6 \text{ Hz, } J_{2,4} = 1.5 \text{ Hz, } 1 \text{ H, H-2)}, 5.69 \text{ (ddd, } J_{4,3} = 7.4 \text{ Hz, } J_{4,5} = 6.2 \text{ Hz, } J_{4,2} = 1.5 \text{ Hz, } 1 \text{ H, H-4}), 4.97 \text{ (ddd, } J_{6,5} = 7.4 \text{ Hz, } J_{6,7} = 6.2 \text{ Hz, } J_{6,3} = 2.4 \text{ Hz, } 1 \text{ H, H-6}), 4.50 \text{ (dd, } J_{5,6} = 7.4 \text{ Hz, } J_{5,4} = 6.2 \text{ Hz, } 1 \text{ H, H-5}). 4.43 \text{ (dd, } J_{gem} = 12.2 \text{ Hz, } J_{7a,6} = 2.4 \text{ Hz, } 1 \text{ H, H-7a}), 4.03 \text{ (dd, } J_{gem} = 12.2 \text{ Hz, } J_{7b,6} = 6.2 \text{ Hz, } 1 \text{ H, H-7b). 2.00 \text{ (s, } 3 \text{ H, CH}_3CO), 1.93 \text{ (s, } 3 \text{ H, CH}_3CO), 1.46 \text{ (s, } 3 \text{ H, CH}_3), 1.45 \text{ (s, } 9 \text{ H, } \text{t-Bu}), 1.34 \text{ (s, } 3 \text{ H, CH}_3); {^{13}}C\text{-NMR} (75 \text{ MHz, CDCl}_3) \delta 170.8 \text{ (s, } CH_3CO), 169.9 \text{ (s, } CH_3CO), 164.8 \text{ (s, } C-1), 142.6 \text{ (d, } C-3), 124.4 \text{ (d, } C-2), 109.65 \text{ (s, } CMe_2), 82.2 \text{ (s, } CMe_3), 75.9 \text{ (d), } 74.2 \text{ (d), } 69.6 \text{ (d), } 63.3 \text{ (t, } C-7), 28.2 \text{ (q, } CMe_3), 27.6 \text{ (q, } CMe_2), 25.2 \text{ (q, } CMe_2), 21.1 \text{ (q, } CH_3CO), 20.9 \text{ (q, } CH_3CO). \text{ Anal. calcd for C}_{18}H_{29}O_6(diacetate): C, 58.04; H, 7.58. Obsd: C, 58.00; H, 7.54.

Wittig olefination of 4,5-O-(1-methylethylidene)-β-D-ribofuranose: Preparation of Ethyl (2,3-dideoxy-4,5-O-(1-methylethylidene)-D-ribofuranosyl)acetate. A 50 mL round-bottom flask equipped with a magnetic stir bar and nitrogen inlet was charged with a 0.15 M solution of 2,3-dideoxy-4,5-O-isopropylidene-β-D-ribofuranose (1.50 g, 7.88 mmol) in dimethoxyethane (52 mL) followed by 2.0 equivalents of (carbethoxymethylene)triphenylphosphorane (5.480 g, 15.76 mmol) in dimethoxyethane (52 mL) followed by 2.0 equivalents of (carbethoxymethylene)triphenylphosphorane (5.480 g, 15.76 mmol). The reaction was stirred at 25 °C under nitrogen for 24 h. The solvent was removed under vacuum and the crude syrup flash chromatographed (silica gel, 20:1 chloroform/methanol) to provide a mixture of the previously reported ethyl (2,3-dideoxy-4,5-O-isopropylidene-D-ribofuranosyl)acetate as the sole product. An}

IR (CHCl\textsubscript{3}) 3470(br), 2984m, 2936m, 1734s, 1456w, 1372m, 1346w, 1257m, 1181m, 1158m, 1077s, 967w, 921w cm \textsuperscript{-1}; \textsuperscript{1}H-NMR (300 MHz, CDCl\textsubscript{3}) \delta 4.73 (ddd, J = 5.8 Hz, J = 4.5 Hz, J = 0.8 Hz, 1 H), 4.54 (ddd, J = 5.7 Hz, J = 4.9 Hz, J = 0.8 Hz, 1 H), 4.26 (ddd, J\textsubscript{gem} = 11.4 Hz, J = 4.8 Hz, 1 H), 4.16 (q, J = 7.1 Hz, 2 H, OCH\textsubscript{2}CH\textsubscript{3}), 4.08 (dd, J = 6.5 Hz, J = 2.9 Hz, 1 H), 3.80 (d, J = 12.1 Hz, 1 H), 3.67-3.63 (m, 1 H), 2.78
preparation of (2Z)-1,1-dimethylethyl 2,3-dideoxy-7-O-(4-methylbenzenesulfonyl)-4,5-0-(1-methylethylidene)-D-ribo-hept-2-enoate (2.47) (Scheme 2.8).

A 250 mL round-bottom flask equipped with a rubber septa and nitrogen inlet was charged with a 0.15 M solution of (2T)-rerr-butyl 2,3-dideoxy-4,5-0-isopropylidene-D-ribo-hept-2-enoate (2.43, 648 mg, 2.24 mmol) in 1:1 dichloromethane/pyridine (15.0 mL). The solution was cooled to 0 °C and 0.1 equivalents of 4-dimethylaminopyridine (30 mg, 0.22 mmol) followed 5 minutes later by addition of 1.0 equivalent of toluenesulfonyl chloride (427 mg, 2.24 mmol). The reaction was stirred under nitrogen at 0 °C for 3 h. The cooling bath was removed and reaction stirred at 25 °C for 12 h. The pyridine was removed by repeated co-distillation with 4:1 chloroform/ethanol and the crude product dissolved in chloroform (25 mL) and washed with water (10 mL), saturated brine (10 mL) and then dried over anhydrous MgSO₄. Vacuum filtration and concentration in vacuo yielded an oil which was flash chromatographed (silica gel, 4:1 hexane/ethyl acetate) to yield 400 mg (40%) of (Z)-terr-butyl 2,3-dideoxy-4,5-O-isopropylidene-7-O-tosyl-D-ribo-hept-2-enoate (2.47) as a colorless syrup.

Rf = 0.10 (4:1 hexanes/ethyl acetate); [α]¹⁹⁺ = + 96.3 (c 1.80, CHCl₃); IR (thin film) 3424w(br), 3035w, 2984w, 2936w, 2362w, 2343w, 1965w, 1919w, 1818w, 1711s, 1684m, 1598m, 1479w, 1455w, 1413m, 1369s, 1307w, 1239s, 1215s, 1189s, 1177s, 1159s, 1119m, 1096m, 1060s, 1020w, 981m cm⁻¹; ¹H-NMR
(300 MHz, CDCl₃) δ 7.81 (d, J = 8.3, 2 H, Ar-H), 7.30 (d, J = 8.3, 2 H, Ar-H), 6.09 (dd, J₃,₂ = 11.6 Hz, J₃,₄ = 8.1 Hz), 5.92 (dd, J₂,₃ = 11.6 Hz, J₂,₄ = 1.0 Hz), 5.47 (dd, J₄,₃ = 8.1 Hz, J₄,₅ = 6.3 Hz), 4.28 (dd, J₇₆ = 10.2 Hz, J₇₉ = 2.4 Hz, 1 H, H-7a), 4.23 (dd, J₅,₆ = 8.5 Hz, J₅,₄ = 6.3 Hz), 4.01 (dd, J₁,₂ = 10.2 Hz, J₁,₃ = 6.3 Hz, 1 H, H-7b), 3.72 (dd, J₁,₂ = 8.5 Hz, J₁,₃ = 6.3 Hz, J₁,₄ = 2.8 Hz, 1 H, OH), 2.44 (s, 3. Ar-CH₃), 1.46 (s, 9 H, t-Bu), 1.43 (s, 3 H, CH₃), 1.32 (s, 3 H, CH₃), 13C-NMR (75 MHz, CDCl₃) δ 166.8 (s, C-1), 144.9 (s), 144.1 (d), 133.1 (s), 129.9 (d), 128.2 (d), 124.7 (d), 109.5 (s, CMe₂), 82.5 (s, CMe₃), 78.3 (d), 74.8 (d), 71.9 (t), 68.7 (d), 28.1 (q, CMe₃), 27.9 (q ), 25.5 (q), 21.6 (q). Anal. calcd for C₂₁H₂₃O₈S: C, 57.00; H, 6.83. Obsd: C, 56.42; H, 6.66. HRMS (EI) calcd for C₂₁H₂₃O₈S: 443.173965. Obsd: 443.169021.

Preparation of (2Z)-1,1-dimethylethyl 6,7-anhydro-2,3-di-deoxy-4,5-O-(1-methylthylidene)-D-ribo-hept-2-enoate (2.48) under Williamson conditions (Scheme 2.8). A 50 mL round-bottom flask equipped with a magnetic stir bar, rubber septum, and nitrogen inlet was charged with a 0.02 M solution of (Z)-tert-butyl 2,3-dideoxy-4,5-O-isopropylidene-7-O-tosyl-D-ribo-hept-2-enoate (2.47, 125 mg, 0.33 mmol) in chloroform (15.0 mL). Next was added dropwise a 1.65 M solution of sodium methoxide in methanol (0.5 mL) which gave after 5 minutes a cloudy solution. The consumption of starting material was monitored by TLC (starting material Rₜ = 0.16, 4:1 hexanes/ethyl acetate). The reaction was stopped after 0.5 h and the reaction transferred to a separatory funnel. The organic phase was washed with water (10 mL) and then dried over anhydrous MgSO₄. Vacuum filtration and concentration in vacuo yielded a colorless oil. Flash chromatography (silica gel, 4:1 hexanes/ethyl acetate) gave 58 mg (24%) of desired (Z)-1,1-dimethylethyl 6,7-anhydro-2,3-dideoxy-4,5-O-isopropylidene-D-ribo-hept-2-enoate (2.48). Undesired side products resulting from competing 5-exo-trig closure included 103 mg (26%) of tert-butyl (2,3-O-isopropylidene-5-O-tosyl-D-ribofuranosyl)acetate and 44 mg (12%) of methyl (2,3-O-isopropylidene-5-O-tosyl-D-ribofuranosyl)acetate.
$R_f = 0.41$ (2:1 hexanes/ethyl acetate); $[\alpha]^{19.0}_D = +185.6 \degree$ (c 2.68, CHCl$_3$); IR (CHCl$_3$) 2983m, 2937m, 1809s, 1768s, 1722s, 1641w, 1466m, 1410m, 1370s, 1332m, 1253s, 1214s, 1161s, 1089s, 1052s, 1004m, 959w, 883m, 859m, 834m, 768m, 720w cm$^{-1}$; $^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 6.22 (dd, $J_{3,2} = 11.6$ Hz, $J_{3,4} = 7.1$ Hz, 1 H, H-3), 5.91 (dd, $J_{2,3} = 11.6$ Hz, $J_{2,4} = 1.7$ Hz, 1 H, H-2), 5.72 (ddd, $J_{4,2} = 1.7$ Hz, $J_{4,3} = 7.1$ Hz, 1 H, H-4), 4.16 (app. t, $J_{5,4} = 6.2$ Hz, $J_{5,6} = 5.7$ Hz, 1 H, H-5), 2.85 (ddd, $J_{6,7a} = 2.5$ Hz, $J_{6,7b} = 3.9$ Hz, $J_{6,5} = 5.7$ Hz, 1 H, H-6), 2.70 (dd, $J_{7b,6} = 3.9$ Hz, $J_{gem} = 5.2$ Hz, 1 H, H-7b), 2.64 (dd, $J_{7a,5} = 2.5$ Hz, $J_{gem} = 5.2$ Hz, 1 H, H-7a), 1.48 (s, 3 H, CH$_3$), 1.45 (s, 9 H, t-Bu), 1.35 (s, 3 H, CH$_3$); $^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ 165.0 (s, C-1), 143.1 (d, C-3), 124.5 (d, C-2), 109.4 (s, CMe$_2$), 81.0 (s, CMe$_3$), 77.8 (d, C-4), 74.9 (d, C-5), 50.1 (d, C-6), 44.7 (t, C-7), 28.2 (q, CMe$_2$), 27.6 (q, CMe$_3$), 25.0 (q, CMe$_2$). HRMS (El) calcd for C$_{14}$H$_{22}$O$_5$: 270.146724. Obsd: 270.145660.

Preparation of (2Z)-1,1-dimethylethyl 6,7-anhydro-2,3-di-deoxy-4,5-O-(1-methylethylidene)-D-ribo-hept-2-enoate (2.48) under Mitsunobu conditions (Scheme 2.8). A 250 mL, round-bottom flask was charged with (Z)-tert-butyl 2,3-dideoxy-4,5-O-isopropylidene-D-ribo-hept-2-enoate (2.43, 1.90 g, 6.59 mmol) and azeotroped with toluene (2 x 50 mL). The diol 2.43 was then dissolved in toluene (35 mL) and 2.0 equivalents of triphenylphosphine (3.45 g, 13.18 mmol) was added and the mixture stirred until homogenous and then the solvent once again removed. Fresh toluene was added (20 mL) and the flask equipped with a magnetic stir bar, Claisen adapter, and water condenser and the reaction mixture cooled to 0 °C. Two equivalents of diethyl azidodicarboxylate (2.29g, 13.18 mmol) was then added dropwise over several minutes and the reaction stirred at 0 °C for 0.5 h then slowly warmed to reflux for 1.5 h. The disappearance of starting material was monitored by TLC ($R_f = 0.41$; 2:1 hexanes/ethyl acetate). The reaction was then cooled to 25 °C and the solvents removed in vacuo. Purification by flash chromatography (silica gel, 4:1 hexanes/ethyl acetate) yielded 425 mg (24%) (Z)-of tert-butyl 6,7-
anhydro-2,3-dideoxy-4,5-0-isopropylidene-D-ribo-hept-2-enoate (2.48) as a colorless oil identical to that reported previously (Z/E > 20).

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

**Preparation of 2,3-O-(1-methylethylidene)-D-ribose, O-methyloxime (2.49) (Scheme 2.9).** A 500 mL round-bottom flask equipped with a magnetic stir bar, water condenser, and nitrogen inlet was charged with a 0.15 M solution of 2,3-O-isopropylidene-D-ribofuranose (3.22 g, 16.92 mmol) in 12:1 methanol/pyridine (112 mL) followed by 1.5 equivalents of methoxylamine hydrochloride (2.12 g, 25.39 mmol). The reaction was warmed to reflux under nitrogen for 8 h at which time additional starting material remained by TLC ($R_f = 0.31$, 10:1 chloroform/methanol). An additional 0.35 equivalents of methoxylamine hydrochloride (500 mg, 5.98 mmol) were added and the reflux resumed another 4 h to at which time no further starting material was detected. The solvent was removed under reduced pressure to give a colorless syrup. The crude product was flash chromatographed (silica gel, 20:1 chloroform/methanol) to provide 2.10 g (67%) of the previously reported 2,3-O-isopropylidene-D-ribose.

**O-methyloxime (2.49) as a white solid ($E/Z = 5$)**

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

Mixture of isomers: $R_f = 0.31$, (10:1 chloroform/methanol); Mp = 87.5-89.0 °C; IR (KBr) 3348 br, 3236 br, 2998 s, 2942 s, 2863 s, 2818 s, 2637 w, 2569 w, 2445 w, 1898 w, 1734 w, 1630 m, 1597 m, 1384 s, 1336 m, 1312 m, 1270 m, 1249 m, 1215 m, 1165 m, 1049 s, 969 m, 928 m, 870 s cm$^{-1}$; $^1$H-NMR (300 MHz, CDCl$_3$) δ 7.45 (d, $J_{1,2} = 7.0$ Hz, 0.83 H, (E)-H-1), 6.87 (d, $J_{1,2} = 5.7$ Hz, 0.16 H, (Z)-H-1), 5.26 (dd, $J = 6.3$ Hz, $J = 5.9$ Hz, 0.17 H), 4.78 (app. t, $J = 6.6$ Hz, $J = 6.4$ Hz, 0.89 H), 4.30 (dd, $J = 7.8$ Hz, $J = 6.5$ Hz, 0.18 H), 4.21 (dd, $J = 8.4$ Hz, $J = 6.3$ Hz, 0.87 H), 3.94 (s, 0.46 H, OCH$_3$), 3.88 (s, 2.54 H, OCH$_3$), 3.82-
3.74 (m, 3 H), 3.00 (s, 0.17 H, D$_2$O exch., OH), 2.83 (s, 0.85 H, D$_2$O exch., OH), 2.10 (s, 1 H, D$_2$O exch., OH), 1.47 (s, 3 H, CH$_3$), 1.37 (s, 3 H, CH$_3$); (E)-isomer $^{13}$C-NMR (50 MHz, CDCl$_3$) δ 148.5 (d, C-1), 110.4 (s, CMe$_2$), 77.8 (d, C-4), 75.2 (d, C-3), 69.9 (d, C-2), 64.3 (t, C-5), 62.2 (q, OCH$_3$), 27.9 (q, CMe$_2$). 25.6 (q, CMe$_2$); (Z)-isomer $^{13}$C-NMR (50 MHz, CDCl$_3$) δ 150.7 (d, C-1), 110.0 (s, CMe$_2$), 78.6 (d, C-4), 71.6 (d, C-3), 70.8 (d, C-2), 64.0 (t, C-5), 62.6 (q, OCH$_3$), 27.5 (q, CMe$_2$), 25.2 (q, CMe$_2$). HRMS (El) for C$_9$H$_{17}$O$_3$N: 219.110672. Obsd: 219.1117859. Anal calcd for the diacetate C$_{13}$H$_{21}$O$_5$N: C, 51.46; H, 6.98. Obsd: C, 51.54; H, 6.99.

Preparation of 5-O-(4-methylbenzenesulfonyloxy)-2,3-O-(1-methylethylidene)-D-ribofuranose, O-methyloxime (2.50) (Scheme 2.9). A 250 mL round-bottom flask equipped with a rubber septum and nitrogen inlet was charged with a 0.15 M solution of 2,3-O-isopropylidene-D-ribofuranose, O-methyloxime (2.49, 980 mg, 4.47 mmol) in 1:1 dichloromethane/pyridine (30 mL). The solution was cooled to 0 °C and 0.1 equivalents of 4-dimethylaminopyridine (60 mg, 0.44 mmol) followed 5 minutes later by addition of 1.0 equivalent of tosyl chloride (852 mg, 4.47 mmol). The reaction was stirred under nitrogen at 0 °C for 3 h and the cooling bath removed and reaction stirred at 25 °C for 12 h. The consumption of starting material was monitored by TLC ($R_f = 0.30$, 4:1 hexanes/ethanol). The pyridine was removed by repeated co-distillation with 4:1 chloroform/ethanol. The residue was then dissolved in chloroform (50 mL) and washed with water (15 mL), saturated brine (15 mL) and then dried over anhydrous MgSO$_4$. Vacuum filtration and concentration in vacuo yielded a colorless oil which was flash chromatographed (4:1 hexane/ethyl acetate) to yield 1.019 g (61%) of desired 2,3-O-isopropylidene-5-O-tosyl-D-ribofuranose, O-methyloxime (2.50) as a colorless syrup ($E/Z = 24$).

$R_f = 0.30$ (4:1 hexanes/ethyl acetate); IR (thin film) 3502w(br), 2988m, 2939m, 2902m, 2802w, 1925w, 1818w, 1736w, 1627w, 1598m, 1494w, 1454m, 1363s, 1308m, 1247m, 1220s, 1177s, 1096s, 1066s, 1043s,
981s, 908s, 885s, 863s, 815s, 789s cm⁻¹, ¹H-NMR (300 MHz, CDCl₃) δ 7.78 (d, J = 8.3 Hz, 2 H, Ar-H), 7.35 (d, J₁,₂ = 7.0 Hz, 1 H, H-1), 7.32 (d, J = 8.3 Hz, 2 H, Ar-H), 4.72 (dd, J₂,₁ = 7.0 Hz, J₂,₃ = 6.3, 1 H, H-2), 4.27 (dd, J₃,₄ = 10.4 Hz, J₅,₆ = 2.4 Hz, 1 H, H-5), 4.08-4.02 (m, 2 H, H-4, H-5), 3.87-3.83 (m, 1 H, H-3), 3.81 (s, 3 H, OMe), 3.03 (s, 1 H, OH), 2.42 (s, 3 H, Ar-CH₃), 1.38 (s, 3 H, CH₃), 1.29 (s, 3 H, CH₃); ¹³C-NMR (75 MHz, CDCl₃) δ 147.1 (d, C-1), 145.2 (s, Ar-Me), 132.7 (s, Ar-SO₂), 129.9 (d, Ar-H), 128.1 (d, Ar-H), 110.3 (s, CMe₂), 76.9 (d), 75.0 (d), 71.9 (t, C-5), 68.0 (d), 62.0 (q, OMe), 27.7 (q, CMe₂), 25.3 (q, CMe₂), 21.6 (q, Ar-CH₃). HRMS (EI) calcd for C₁₅H₂₂O₅N₅S: 358.096049. Obsd: 358.093841.

Preparation of 4,5-anhydro-2,3-O-(1-methylethylidene)-D-ribofuranose, O-methyloxime (2.51) under Mitsunobu conditions (Scheme 2.9). A 250 mL round-bottom flask equipped with a magnetic stir bar, water condenser, rubber septum, and nitrogen inlet was charged with a 0.15 M solution of 2,3-O-isopropylidene-D-ribofuranose, O-methyloxime (2.49, 580 mg, 2.64 mmol) in benzene (17.0 mL). The solution was warmed until the solution was homogenous after which 2.0 equivalents of triphenylphosphine (1.387 g, 5.29 mmol) were added followed by 2.1 equivalents of diethyl azidodicarboxylate (1.00 g, 5.74 mmol). The reaction mixture was brought to reflux and the consumption of starting material monitored by TLC (Rf = 0.35, 10:1 chloroform/methanol). The reaction was stopped after 14 h, cooled to 25 °C and concentrated to yield an orange syrup which was subsequently flash chromatographed (silica gel, 5:1 hexanes/ethyl acetate, 500 mL; 3:1, 500 mL) to give 160 mg (30.0%) of 4,5-anhydro-2,3-O-isopropylidene-D-ribofuranose, O-methyloxime (2.51) as a colorless oil (Z/E = 4).

Mixture of isomers; Rf = 0.47 (4:1 hexanes/ethyl acetate); IR (CHCl₃) 2992s, 2939m, 2902m, 2821w, 2361w, 2253w, 1735m, 1628w, 1463m, 1383s, 1247s (oxirane), 1218s, 1160m, 1077m, 1047s (oxirane), 909s, 865s (oxirane); ¹H-NMR (300 MHz, CDCl₃) δ 7.44 (d, J₁,₂ = 7.8 Hz, 0.78 H, (E)-H-1), 6.87 (d, J₁,₂ = 4.9 Hz, 0.22 H, (Z)-H-1), 5.26 (dd, J₂,₁ = 4.9 Hz, J₂,₃ = 6.8 Hz, 0.20 H, H-2), 4.80 (dd, J₂,₁ = 7.8 Hz, J₂,₃ = 6.8 Hz, 0.20 H, H-2).
6.5 Hz, 0.80 H, H-2), 4.20 (dd, J_{3,4} = 5.3 Hz, J_{3,2} = 6.8 Hz, 0.20 H, H-3), 3.96 (dd, J_{3,4} = 6.4 Hz, J_{3,2} = 6.5 Hz, 0.80 H, H-3), 3.90 (s, 0.6 H, OMe), 3.88 (s, 2.4 H, OCH₃), 2.99 (ddd, J_{4,3} = 6.4 Hz, J_{4,5_{anti}} = 3.9 Hz, J_{4,5_{syn}} = 2.5 Hz, 0.8 H, H-4), 2.92 (ddd, J_{4,3} = 5.3 Hz, J_{4,5_{anti}} = 3.9 Hz, J_{4,5_{syn}} = 2.7 Hz, 0.2 H, H-4), 2.85 (dd, J_{gen} = 5.0 Hz, J_{5,4} = 3.9 Hz, 1 H, H-5_{syn}), 2.77 (dd, J_{gen} = 5.0 Hz, J_{5,4} = 2.5 Hz, 1 H, H-5_{anti}), 1.52 (s, 2.4 H, CH₃), 1.48 (s, 0.6 H, CH₃), 1.38 (s, 3 H, CH₃), 1.34 (s, 0.6 H, CH₃); (Z)-isomer, $^{13}$C-NMR (75.0 MHz, CDCl₃) δ 145.8 (d, C-1), 110.6 (s, CMe₂), 78.2 (d, C₂), 75.4 (d, C₃), 62.2 (q, OCH₃), 49.5 (d, C₄), 45.8 (t, C₅), 27.7 (q, CMe₂), 25.7 (q, CMe₂); (E)-isomer, $^{13}$C-NMR (75.0 MHz, CDCl₃) δ 148.4 (s, C-1), 110.6 (s, CMe₂), 78.2 (d, C-2), 72.2 (d, C-3), 62.5 (q, OCH₃), 50.1 (d, C-4), 44.4 (t, C-5), 27.3 (q, CMe₂), 24.9 (q, CMe₂). Anal. calcd for C₂₅H₂₅O₄N: C, 53.72; H, 7.51. Obsd: C 53.56; H: 7.47.

Preparation of (2Z)-1,1-dimethylethyl 2,3-dideoxy-7-O-[(1,1-dimethylethyl)dimethylsilyl]-4,5-O-(1-methylethylidene)-D-ribo-hept-2-enoate (2.52) (Scheme 2.10). $^{137}$ A 500 mL separatory funnel was charged with 1.6 equivalents of (carb/err-butoxy)methylene)triphenylphosphonium bromide $^{139}$ (30.0 g, 65.77 mmol) in chloroform (200 mL) followed by several drops of phenolphthalein solution. A 2.5 M solution of aqueous sodium hydroxide solution (200 mL) was added to the separatory funnel and gently shaken until the aqueous phase remained light pink. The organic layer was then separated and washed with saturated brine (30 mL) and dried over anhydrous MgSO₄. Vacuum filtration and concentration in vacuo yielded the crude (carb/err-butoxy)methylene)triphenylphosphorane as a yellow oil which was used in the next step without further purification. The crude phosphorane was dissolved in dimethoxyethane (100 mL) followed by addition of a solution of 5-O-tert-butylidimethylsilyl-2,3-O-isopropylidene-β-D-ribofuranose (12.5 g, 41.06 mmol) in dimethoxyethane (200 mL). This solution stirred rapidly under nitrogen at 25 °C for 24 h until homogenous. The solvent was then removed under reduced pressure and the resulting crude oil was flash chromatographed (silica gel, 93:7 hexanes/acetone) to give 10.41g (63%) of desired tert-butyl 2,3-dideoxy-7-O-tert-butylidimethylsilyl-4,5-O-isopropylidene-D-ribo-hept-2-enoate (2.52) as a colorless syrup (Z/E= 6.7), along with 3.25 g (26%) unreacted starting material. The minor
(E)-2.52 could not be isolated from the major (Z)-2.52 and, therefore, only (Z)-2.52 was fully characterized.

![Chemical structure](image)

(Z)-isomer ($R_f = 0.30$, 10:1 hexanes/ethyl acetate); $[\alpha]_{D}^{19.0} = +72.6^\circ$ ($c$ 1.39, CHCl$_3$); IR (thin film) 3471m, 2980s, 2955s, 2932s, 2884s, 2857s, 2835w, 1714s, 16931m, 1644m, 1471m, 1462m, 1414m, 1391m, 1381m, 1369s, 1330m, 1299w, 1254s, 1158s, 1057s, 984w, 939w, 920w cm$^{-1}$; $^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 6.18 (dd, $J_3,2 = 11.6$ Hz, $J_3,4 = 8.6$ Hz, 1 H, H-3), 4.26 (dd, $J_5,6 = 8.4$ Hz, $J_5,4 = 6.3$ Hz, 1 H, H-5), 3.78 (dd, $J_6,5 = 8.4$ Hz, $J_6,7 = 5.4$ Hz, 1 H, H-6), 2.9 (br s, 1H, D$_2$O exch., OH), 1.47 (s, 9 H, t-Bu), 1.47 (s, 3 H, CH$_3$), 1.36 (s, 3 H, CH$_3$), 0.90 (s, 9 H, SiBu$'$), 0.07 (s, 6H, SiMe$_2$); $^{13}$C-NMR (75.0 MHz, CDCl$_3$) $\delta$ 165.9 (s, C-1), 143.5 (d, C-3), 124.3 (d, C-2), 109.2 (s, CMe$_2$), 81.4 (s, OCMMe), 78.2 (d, C-5), 74.1 (d, C-4), 70.3 (d, C-6), 64.8 (t, C-7), 28.3 (q, CMe$_2$), 28.2 (q, t-Bu), 25.6 (q, CMe$_2$), 18.6 (s, SiCMe$_3$), -5.12 (q, SiMe$_2$), -5.16 (q, SiMe$_2$). Anal. calcd. for C$_{31}$H$_{57}$O$_6$Si: C, 59.67; H, 9.52. Obsd: C, 59.76; H, 9.69.

Preparation of 1,1-dimethylethyl [4-O-(4-methylbenzenesulfonyl)-2,3-O-(1-methylethylidene)-D-ribopyranosyl] acetate (2.54) (Scheme 2.10). A 50 mL, round-bottom flask equipped with stir bar and nitrogen inlet was charged with a 0.09 M solution of (Z)-tert-butyl 2,3-dideoxy-7-O-tert-butyldimethylsilyl-4,5-O-isopropyldiene-6-O-tosyl-D-ribo-hept-2-enoate (2.53, 100 mg, 0.18 mmol) in dimethoxyethane (2.0 mL) and cooled to 0 °C. To this was added 1 equivalent of tetrabutylammonium fluoride (1.0 M in tetrahydrofuran, 180 µL, 0.18 mmol) and the reaction stirred at 0 °C for 0.5 h until no further starting material was detected by TLC ($R_f = 0.30$, 5:1 hexanes/acetone). The reaction was then diluted with diethyl ether (5 mL) and washed with water (1 mL), saturated brine (1 mL) and then dried.
over anhydrous MgSO$_4$. Vacuum filtration and concentration in vacuo yielded 78 mg of a cloudy syrup with was then flash chromatographed (silica gel, 5:1 hexanes/acetone) to give 48 mg (60%) of undesired tert-butyl (2,3-O-isopropylidene-4-O-tosyl-D-ribopyranosyl)acetate (2.54) as a colorless syrup.

\[ R_f = 0.15, \ (5:1 \ \text{hexanes/acetone}); \ \{\alpha\}^{19.0}_{D} = +14.8^\circ \ (c \ 0.92, \ CHCl_3); \ \text{IR} \ (\text{thin film}); \ 3530 \ \text{w(br)}, \ 2966s, \ 2931s, \ 2296w, \ 1924w, \ 1731s, \ 1595m, \ 1495m, \ 1454m, \ 1372s, \ 1290m, \ 1249s, \ 1219s, \ 1190s, \ 1170s, \ 1150s, \ 1096s, \ 1067s, \ 1049s, \ 1031s, \ 990s \ \text{cm}^{-1}; \ \text{H-NMR} \ (300 \ \text{MHz}, \ CDCl_3) \ \delta \ 7.82 \ (d, \ J = 8.3 \ Hz, \ 2 \ H, \ Ar-H), \ 7.34 \ (d, \ J = 8.3 \ Hz, \ 2 \ H, \ Ar-H), \ 4.69 \ (ddd, \ J = 10.5 \ Hz, \ J = 6.0 \ Hz, \ J = 3.8 \ Hz, \ 1 \ H), \ 4.32 \ (dd, \ J = 4.2 \ Hz, \ J = 4.0 \ Hz, \ 1 \ H), \ 3.80 \ (dd, \ J = 9.3 \ Hz, \ J = 4.5 \ Hz, \ 1 \ H), \ 3.74-3.55 \ (m, \ 3 \ H), \ 2.53 \ (dd, \ J_{gem} = 15.4 \ Hz, \ J = 3.2 \ Hz, \ 1 \ H, \ CH_2CO_2R), \ 2.44 \ (s, \ 3 \ H, \ Ar-CH_3), \ 2.24 \ (dd, \ J_{gem} = 15.4 \ Hz, \ J = 9.0 \ Hz, \ 1 \ H, \ CH_2CO_2R), \ 1.51 \ (s, \ 3 \ H, \ CH_3), \ 1.43 \ (s, \ 9 \ H, \ t-Bu), \ 1.26 \ (s, \ 3 \ H, \ CH_3); \ ^{13}C-NMR \ (75.0 \ \text{MHz}, \ CDCl_3) \ \delta \ 170.0 \ (s, \ C=O), \ 145.4 \ (s, \ Ar-SO_3), \ 133.8 \ (s, \ Ar-CH_3), \ 130.1 \ (d, \ Ar-H), \ 128.1 \ (d, \ Ar-H), \ 111.3 \ (s, \ CMe_2), \ 81.1 \ (s, \ OCMMe_2), \ 76.5 \ (d), \ 75.0 \ (d), \ 70.3 \ (d), \ 64.0 \ (t, \ C-5), \ 39.1 \ (t, \ CH_2CO_2R), \ 28.29 \ (q, \ OCMMe_2), \ 28.26 \ (q, \ CMe_2), \ 26.5 \ (q, \ CMe_2), \ 21.8 \ (q, \ Ar-CH_3). \ \text{Anal. calcd for C}_{31}H_{30}O_8S: \ C, \ 57.00; \ H, \ 6.83; \ S, \ 7.24. \ \text{Obsd:} \ C, \ 56.92; \ H, \ 6.90; \ S, \ 7.15.

Preparation of (E) 3-deoxy-3-C-[3-(1,1-dimethylethoxy)-3-oxopropenyl]-1,2-O-(1-methylethylidene)-\alpha-D-erythrosfuranoside (2.57) (Scheme 2.11). In a glove box, a 100 mL round-bottom flask equipped with a magnetic stir bar and dropping funnel was charged with a 0.04 M solution of (Z)-tert-butyl 6,7-anhydro-2,3-dideoxy-4,5-O-isopropylidene-D-ribo-hept-2-enoate (2.48, 127 mg, 0.47 mmol) in tetrahydrofuran (12.5 mL). The dropping funnel was then charged with 1.25 equivalents of (Cp$_2$TiCl)$_2$ (1.54, 255 mg, 0.60 mmol) in tetrahydrofuran (12.0 mL, 0.04 M). The green titanium(III) reagent was then added dropwise to the clear epoxide solution over 20 minutes to give a dull red solution. Following complete addition of the contents of the dropping funnel, the reaction was allowed to stir and additional
20 minutes at 25 °C. The reaction flask was then fitted with a rubber septa, removed from the glove box, fitted with a nitrogen inlet and slowly quenched with HCl (1.0 M in diethyl ether. 0.96 mL. 0.96 mmol) and the mixture allowed to stir for 0.5 h at 25 °C to yield a bright red solution. The solvent was removed and the resulting bright red residue flash chromatographed (silica gel, 5:1 hexanes/ethyl acetate) to give two unidentified compounds A (4 mg, \( R_f = 0.75 \)) and B (8 mg, \( R_f = 0.40 \)) (2.58), along with C (\( R_f = 0.25 \)) 17 mg (13%) of 3-deoxy-3-C-(3-tert-butoxy-3-oxopropenyl)-1,2-O-isopropylidene-\( \alpha \)-D-erythrofuranoside (2.57) as a clear oil.

\( R_f = 0.25 \) (5:1 hexanes/ethyl acetate); \([\alpha]^{19}_{D} = + 94.4^\circ \) (c 0.54, CHCl₃). IR (CHCl₃) 2979s. 2934m. 2876m. 1712s. 1655m. 1473w. 1456m. 1382m. 1369m. 1297m. 1249s. 1215s. 1160s. 1129s. 1101s. 1067m. 1016s. 984m. 870m. 756m cm⁻¹; \(^1\)H-NMR (300 MHz, CDCl₃) δ 6.85 (dd, \( J_{1',2'} = 15.8 \) Hz, \( J_{1',3} = 8.5 \) Hz, 1 H, H-1'), 5.88 (dd, \( J_{2',1} = 15.8 \) Hz, \( J_{2',3} = 1.0 \) Hz, 1 H, H-2'), 5.85 (d, \( J_{1,2} = 3.9 \) Hz, 1 H, H-1). 4.61 (app. t, \( J_{2,3} = 4.1 \) Hz, \( J_{2,1} = 3.9 \) Hz, 1 H, H-2). 3.93-3.81 (m, 2 H, H-4). 2.83 (ddddd, \( J_{3,4} = 10.6 \) Hz, \( J_{3,1} = 8.5 \) Hz, \( J_{3,4a} = 8.0 \) Hz, \( J_{3,2} = 4.1 \) Hz, \( J_{3,2'} = 1.0 \) Hz, 1 H, H-3). 1.52 (s, 3 H, CH₃). 1.48 (s, 9 H, t-Bu). 1.31 (s, 3 H, CH₃); \(^{13}\)C-NMR (75 MHz, CDCl₃) δ 165.4 (s, C=O), 140.4 (d, C-1'), 126.6 (d, C-2'), 112.4 (s, CMe₂), 106.5 (d, C-1). 82.0 (d, C-2). 80.8 (s, CMe₃). 69.4 (t, C-4). 47.3 (d, C-3). 28.3 (q, CMe₃). 26.7 (q, CMe₂). 26.4 (CMe₂). Anal. calcd for C₁₄H₂₂O₅: C. 62.19; H. 8.21. Obsd: C. 62.02; H. 8.24. HRMS (El) calcd for C₁₀H₁₉O₄(m-OC₄H₉)^+: 197.081384. Obsd: 197.0815887.
Compound B was tentatively assigned the above structure 2.58 based upon the loss of oxirane signals and
the presence of olefinic signals (5 H) in the \(^1\)H-NMR in addition to HRMS (EI) calcd for C\(_{10}\)H\(_{13}\)O\(_3\) (M-

Preparation of (2Z)-1,1-dimethyl-ethyl 2,3-dideoxy-6-O-(4-methylbenzenesulfonfyl)-7-O-[(1,1-
dimethyl ethyl)dimethylsilyl]- 4,5-O-(1-methylethylidene)-D-ribo-hept-2-enoate (2.53) (Scheme 2.10).

A 100 mL round-bottom flask equipped with a rubber septum, stir bar and nitrogen inlet was charged with
a 0.5 M solution of (Z)-tert-butyl 7-O-tert-butylidemethylsilyl-2,3-dideoxy-4,5-O-isopropylidene-D-ribo-
hept-2-enoate (2.52, 500 mg, 1.24 mmol) in dichloromethane (2.5 mL) followed by 2.0 equivalents of 4-
dimethylaminopyridine (305 mg, 2.5 mmol) and the solution cooled to 0 °C. After several minutes, 1.2
 equivalents of tosyl chloride (290 mg, 1.50 mmol) was added in one portion and the solution allowed to
warm slowly to 25 °C and stirred for 18 h. The solvent was removed under reduced pressure and the
residue flash chromatographed (silica gel, 10:1 hexanes/ethyl acetate) to give 761 mg (90 %) of (Z)-tert-
butyl 7-O-tert-butylidemethylsilyl-2,3-dideoxy-4,5-O-isopropylidene-6-O-tosyl-D-ribo-hept-2-enoate (2.53)
as a colorless oil along with 50 mg of recovered starting material.

(Z)-isomer: \(R_f = 0.30\), (10:1 hexanes/ethyl acetate); \([\alpha]^1\)D = + 71.8 ° (c 2.19, CHCl\(_3\)); IR (thin film)
2930s, 2884m, 2856s, 1918w, 1711s, 1646m, 1599m, 1496w, 1471m, 1411s, 1396s, 1306m, 1294m,
1238s, 1212s, 1177s, 1061s, 982m, 962s, 920s cm \(^{-1}\); \(^1\)H-NMR (300 MHz, CDCl\(_3\)) \(\delta 7.76 (d, J = 8.3 Hz, \text{2}
H, Ar-H), 7.26 (d, J = 8.3 Hz, \text{2 H, Ar-H}), 6.16 (dd, \text{J}_{3,2} = 11.6 Hz, \text{J}_{3,4} = 7.6 Hz, \text{1 H, H-3}), 5.84 (dd, \text{J}_{2,3} =
11.6 Hz, \text{J}_{2,4} = 1.6 Hz, \text{1 H, H-2}), 5.72 (ddd, \text{J}_{4,3} = 7.6 Hz, \text{J}_{4,5} = 7.2 Hz, \text{J}_{4,2} = 1.6 Hz, \text{1 H, H-4}), 4.69 (dd,
\text{J}_{5,4} = 7.2 Hz, \text{J}_{5,6} = 4.3 Hz, \text{1 H, H-5}), 4.59 (ddd, \text{J}_{6,7} = 5.4 Hz, \text{J}_{6,5} = 4.3 Hz, \text{J}_{6,7} = 3.0 Hz, \text{1 H, H-6}), 3.75
(ddd, \text{J}_{\text{gem}} = 11.9 Hz, \text{J}_{\text{gem}} = 5.4 Hz, \text{1 H, H-7a}), 3.63 (dd, \text{J}_{\text{gem}} = 11.9 Hz, \text{J}_{\text{gem}} = 3.0 Hz, \text{1 H, H-7b}), 2.40 (s,
3 H, Ar-CH\(_3\)), 1.49 (s, 9 H, t-Bu), 1.40 (s, 3 H, CH\(_3\)), 1.32 (s, 3 H, CH\(_3\)), 0.80 (s, 9 H, SiBu\(_3\)), -0.05 (s, 3
H, SiMe2), -0.06 (s, 3 H, SiMe2); \(^{13}\text{C-NMR}\) (75.0 MHz, CDCl\(_3\)) \(\delta\) 164.8 (s, C-1), 144.3 (s, Ar-SO\(_2\)), 142.7 (d, C-3), 135.3 (s, Ar-CH\(_3\)), 129.7 (d, Ar-H), 127.9 (d, Ar-H), 124.4 (d, C-2), 109.1 (s, CMe\(_2\)), 82.2 (d, C-6), 81.3 (s, OCM\(_2\)), 76.8 (d), 73.8 (d), 70.3 (d), 61.8 (t, C-7), 28.3 (q, OCM\(_2\)), 27.0 (q, CMe\(_2\)), 26.1 (q, SiCMe\(_3\)), 24.8 (q, CMe\(_2\)), 21.7 (q, Ar-CH\(_2\)), 18.4 (s, SiCMe\(_3\)), -5.3 (q, SiMe\(_2\)), -5.4 (q, SiMe\(_2\)). Anal. calcd for C\(_{27}\)H\(_{44}\)O\(_9\)SSi: C, 58.25; H, 7.97. Obsd: C, 58.28; H, 7.84

O-6-[(2Z)-2,3-dideoxy-7-O-[(1,1-dimethyl)dimethylsilyl]-4,5-O-(1-methylthiylidene)-D-ribo-hept-2-enoic acid, ethyl ester] O-phenyl carbonothioate (2.65) (Scheme 2.13). \(^{54,106}\) A 100 mL, 3-neck, round-bottom flask equipped with a magnetic stir bar was charged with a 0.13 M solution of a (Z)-ethyl 7-O-tert-butyldimethylsilyl-2,3-dideoxy-4,5-O-isopropylidene-D-ribo-hept-2-enoate (2.37, 1.015 g, 2.70 mmol) in 1:1 dichloromethane/pyridine (20 mL). Four equivalents of phenyl chlorothioformate (1.50 mL, 10.84 mmol) was added dropwise to yield a yellow solution which gave a deep red color after 0.5 h. The reaction was allowed to stir for 12 h at 25 °C until no further starting material remained by TLC (\(R_f = 0.30; 10:1\) hexanes/ethyl acetate). The reaction mixture was transferred to a separatory funnel and diluted with dichloromethane (100 mL), then washed with 5% aqueous HCl (30 mL), water (40 mL), saturated brine (40 mL) and then dried over anhydrous MgSO\(_4\). Vacuum filtration and concentration in vacuo yielded a orange syrup which was flash chromatographed (silica gel, 20:1 hexanes/diethyl ether) to give 887mg (64%) of the desired (Z)-phenyl thionocarbonate 2.65 as a golden syrup.

\[
\text{Me}_2\text{Br'SiO} \quad \text{OPh} \quad \text{CO}_2\text{Et}
\]

\(R_f = 0.15\) (20:1 hexanes/diethyl ether); \([\alpha]^{18}_D = +145.0^\circ\) (c 1.54, CHCl\(_3\)); IR (CHCl\(_3\)) 3019\(m\), 2990\(m\), 2930\(m\), 2884\(w\), 2856\(m\), 2400\(w\), 1715\(m\), 1648\(w\), 1591\(w\), 1490\(m\), 1471\(w\), 1417\(w\), 1383\(m\), 1287\(m\), 1256\(m\), 1215\(s\), 1162\(m\), 1115\(m\), 1057\(m\), 1026\(m\), 1004\(w\), 938\(w\), 869\(w\), 835\(m\) \(^1\)\(\text{H-NMR}\) (300 MHz, CDCl\(_3\)) \(\delta\) 7.42-7.36 (m, 2 H, Ar-H), 7.30-7.24 (m, 1 H, Ar-H), 7.07-7.03 (m, 2 H, Ar-H), 6.31 (dd, \(J_{3,2} = 11.6\) Hz, 202
$J_{3,4} = 7.7$ Hz, 1 H, H-3), 5.99 (dd, $J_{2,3} = 11.6$ Hz, $J_{2,4} = 1.6$ Hz, 1 H, H-2), 5.85 (ddd, $J_{4,3} = 7.7$ Hz, $J_{4,5} = 6.5$ Hz, $J_{4,2} = 1.6$ Hz, 1 H, H-4), 5.30 (ddd, $J_{6,5} = 7.8$ Hz, $J_{6,7a} = 4.6$ Hz, $J_{6,7b} = 2.6$ Hz, 1 H, H-6), 4.80 (dd, $J_{5,6} = 7.8$ Hz, $J_{5,4} = 6.5$ Hz, 1 H, H-5), 4.18 (q, $J = 7.1$ Hz, 2 H, OCH$_2$CH$_3$), 4.03 (dd, $J_{1a,7b} = 11.9$ Hz, $J_{7a,6} = 2.6$ Hz, 1 H, H-7b), 1.51 (s, 3 H, CH$_3$), 1.40 (s, 3 H, CH$_3$), 1.25 (t, $J = 7.1$ Hz, 3 H, OCH$_2$CH$_3$), 0.91 (s, 9 H, t-Bu), 0.09 (s, 6H, SiMe$_3$); $^{13}$C-NMR (75 MHz, CDCl$_3$) δ 194.4 (s, C=S), 165.4 (s, C=O), 153.5 (s, i-Ar), 144.1 (d, C-3), 129.6 (d, C-2), 126.6 (d, m-Ar), 122.8 (d, p-Ar), 122.1 (d, o-Ar), 109.5 (d, CMe$_3$), 82.6 (d), 75.0 (d), 74.2 (d), 61.6 (t, C-7), 60.7 (t, OCH$_2$CH$_3$), 27.7 (q, CMe$_3$), 26.1 (q, CMe$_3$), 25.2 (q, CMe$_3$), 18.5 (s, CMe$_3$), 14.3 (q, OCH$_2$CH$_3$), -5.13 (q, SiMe$_3$), -5.17 (q, SiMe$_3$). Anal. calcd. For C$_{32}$H$_{47}$O$_2$SSi: C, 58.80; H, 7.51; Found: C, 58.94; H, 7.50.

HRMS (EI) calcd for C$_{32}$H$_{47}$O$_2$SSi (M+1)$^+$: 511.2185791. Obsd: 511.2159576.

O-6-[(2Z)-2,3-dideoxy-7-O-[(1,1-dimethylethyl)dimethylsilyl]-4,5-O-(1-methylethylidene)-D-ribo-hept-2-enoic acid, 1,1-dimethylethyl ester] O-phenyl carbonothioate (2.66) (Scheme 2.13). A 100 mL, 3-neck, round-bottom flask equipped with a magnetic stir bar was charged with a 0.10 M solution of (Z)-tert-butyl 7-O-tert-butylidemethylsilyl-2,3-dideoxy-4,5-O-isopropylidene-D-ribo-hept-2-enoate (2.52, 400 mg, 1.00 mmol) in dichloromethane (10 mL) containing 3.0 equivalents of 4-dimethylaminopyridine (366 mg, 3.00 mmol) and the solution cooled to 0 °C. To this was added 1.5 equivalents of phenyl chlorothioformate (210 µL, 1.5 mmol) dropwise to yield a yellow solution. The reaction was allowed to come to 25 °C and stirred for an additional 1 h. Two additional equivalents (70 µL, 0.5 mmol) of phenyl chlorothioformate were added after 12 h and 24 h respectively until only a small amount of starting material remained by TLC ($R_f = 0.23$; 5:1 hexanes/ethyl acetate). The reaction mixture was transferred to a separatory funnel and diluted with chloroform (100 mL), then washed with 5% aqueous HCl (50 mL), water (2 x 50 mL) and the aqueous phase back-extracted with additional chloroform. The combined organic phase was then washed with saturated brine (40 mL) and dried over anhydrous MgSO$_4$. Vacuum filtration and concentration in vacuo yielded a heterogeneous orange syrup which was flash chromatographed (silica gel, 10:1 hexanes/ethyl acetate) to give 508 mg (94%) of
(Z)-phenyl thiocarbonate 2.66 as a colorless oil which gave a waxy solid under high vacuum.

\[ R_f = 0.38 \text{ (10:1 hexanes/ethyl acetate); } [\alpha]^{17}_D = +82.13^\circ \text{ (c 2.84, CHCl}_3\text{)}; \text{ IR (CHCl}_3\text{) 3683w, 3615w, 3018s, 2956m, 2939m, 2884m, 2857m, 2400m, 2361w, 2338w, 1939w, 1888w, 1864w, 1784w, 1708m, 1648w, 1588m, 1490s, 1458m, 1414m, 1376m, 1278s, 1212s, 1174s, 1158s, 1056s, 1023m, 1003m, 930m, 904m, 877m, 835s cm}^{-1}; \]

\[ ^1\text{H-NMR (300 MHz, CDCl}_3\text{) } \delta 7.43-7.37 \text{ (m, 2 H, o-Ar-H), 7.30-7.24 \text{ (m, 1 H, p-Ar-H), 6.23 \text{ (dd, J} \text{3,2} = 11.6 \text{ Hz, J} \text{3,4} = 7.5 \text{ Hz, 1 H, H-3), 5.91 \text{ (dd, J} \text{2,3} = 11.6 \text{ Hz, J} \text{2,4} = 1.6 \text{ Hz, 1 H, H-2), 5.84 \text{ (ddd, J} \text{3,4} = 7.5 \text{ Hz, J} \text{4,5} = 6.5 \text{ Hz, J} \text{4,2} = 1.6 \text{ Hz, 1 H, H-4), 5.28 \text{ (ddd, J} \text{6,5} = 7.9 \text{ Hz, J} \text{6,7a} = 4.4 \text{ Hz, J} \text{6,7b} = 2.7 \text{ Hz, 1 H, H-5), 4.81 \text{ (dd, J} \text{5,6} = 7.9 \text{ Hz, J} \text{5,4} = 6.5 \text{ Hz, 1 H, H-5), 4.02 \text{ (dd, J} \text{7a,7b} = 11.8 \text{ Hz, J} \text{7a,6} = 2.7 \text{ Hz, 1 H, H-7a), 3.96 \text{ (dd, J} \text{7b,7a} = 11.8 \text{ Hz, J} \text{7b,6} = 4.4 \text{ Hz, 1 H, H-7b), 1.50 \text{ (s, 3 H, CH}_3\text{), 1.46 \text{ (s, 9 H, OBu'}, 1.40 \text{ (s, 3 H, CH}_3\text{), 0.91 \text{ (s, 9 H, SiBu'}, 0.09 \text{ (s, 6 H, SiMe}_3\text{); } ^{13}\text{C-NMR (75 MHz, CDCl}_3\text{) } \delta 194.5 \text{ (s, C=S), 165.8 \text{ (s, C=O), 153.6 \text{ (s, } \delta \text{-Ar), 142.8 \text{ (d, C}_3\text{), 129.6 \text{ (d, } \delta \text{-Ar), 126.6 \text{ (d, C-2), 124.6 \text{ (d, } \delta \text{-Ar), 122.2 \text{ (d, } \delta \text{-Ar), 109.3 \text{ (s, CMe}_2\text{), 82.6 \text{ (d), 81.2 \text{ (s, OCMe}_3\text{), 74.8 \text{ (d), 74.2 \text{ (d), 61.6 \text{ (t, C-7), 28.3 \text{ (q, OCMe}_3\text{), 27.7 \text{ (q, CMe}_2\text{), 26.0 \text{ (q, SiMe}_2\text{), 25.2 \text{ (q, CMe}_2\text{), 18.5 \text{ (s, SiMe}_2\text{), -5.0 \text{ (q, SiMe}_2\text{), -5.1 \text{ (q, SiMe}_2\text{); Analyst. calcld for C}_{27}\text{H}_{46}\text{O}_7\text{SSi: C, 60.20; H, 7.86; S, 5.94. Obsd: C, 59.97; H, 7.72; S, 6.22.}}\]

\[ O-6-\{(2Z)-2,3\text{-dideoxy-7-O-}\{(1,1\text{-dimethylethyl})\text{dimethylsilyl}\}-4,5\text{-O-}(1\text{-methylthiylidene})\text{-D-ribo-hept-2-enoic acid, 1,1\text{-dimethylethyl} 1H-imidazole-carbonothioic acid (2.67) (Scheme 2.13).}\]

A 50 mL, round-bottom flask equipped with septum, nitrogen inlet, a water condenser and magnetic stir bar was charged with a 0.13 M solution of (Z)-tert-butyl 7-O-tert-butyldimethylsilyl-2,3-dideoxy-4,5-O-isopropylidene-D-ribo-hept-2-enoate (2.52, 106 mg, 0.26 mmol) in dimethoxyethane (2.0 mL) containing 2.0 equivalents of 1,1-thiocarboxyliimidizole (3.8, 93 mg, 0.52 mmol) and the solution
heated to reflux for 2.5 h until no further starting material remained by TLC ($R_f = 0.30$; 5:1 hexanes/acetone). The reaction mixture was cooled to 25 °C and the solvent removed under vacuum. The residue flash chromatographed (silica gel, 5:1 hexanes/acetone) to give 120 mg (90%) of (Z)-thiocarbamate 2.67 as a yellow oil.

![Diagram of 1-α-1,2-dideoxy-2-[2-(1,1-dimethylethoxy)-2-oxoethyl]-6-O-[(1,1-dimethylethyl)dimethylsilyl]-3,4-O-(1-methylethyridene)-D-allopyranosyl 1H-imidazole](image)

$R_f = 0.23$ (5:1 hexanes/acetone); $[\alpha]^{	ext{D}}_{195} = +88.5^\circ$ (c 3.42, CHCl$_3$); IR (thin film) 3125w, 2980m, 2953m, 2938m, 2884m, 2857m, 1713s, 1658w, 1650m, 1531w, 1463m, 1413m, 1391s, 1371s, 1345m, 1327s, 1282s, 1245s, 1156s, 1109m, 1066s, 1022m, 986m, 957m, 876m, 833m cm$^{-1}$; $^1$H-NMR (250 MHz, CDCl$_3$) δ 8.25 (m, 1 H, Im-H), 7.53 (m, 1 H, Im-H), 6.98 (m, 1 H, Im-H), 6.13 (dd, $J_{3.2} = 11.6$ Hz, $J_{3.4} = 7.8$ Hz, 1 H, H$_3$), 5.75 (ddd, $J_{4.5} = 7.8$ Hz, $J_{4.3} = 6.4$ Hz, $J_{4.2} = 1.5$ Hz, 1 H, H$_4$), 5.68 (ddd, $J_{2.3} = 11.6$ Hz, $J_{2.4} = 1.6$ Hz, 1 H, H$_2$), 5.53 (ddd, $J_{6.5} = 8.1$ Hz, $J_{6.4} = 4.0$ Hz, $J_{6.3} = 2.8$ Hz, 1 H, H-6), 4.85 (dd, $J_{5.6} = 8.1$, $J_{5.4} = 6.3$, 1 H, H-5), 4.04-3.92 (m, 2 H, H-7) 1.50 (s, 3 H, CH$_3$), 1.40 (s, 9 H, OCMes$_3$), 1.40 (s, 3 H, CH$_3$), 0.83 (s, 9 H, SiCMes$_3$), -0.001 (s, 3 H, SiMe$_2$), -0.004 (s, 3 H, SiMe$_2$); $^{13}$C-NMR (75 MHz, CDCl$_3$) δ 183.3 (s, C=S), 164.8 (s, C=O), 142.3 (d, C$_3$), 137.2 (d, Im-H), 130.7 (d, Im-H), 124.6 (d, C-2), 118.0 (d, Im-H), 109.6 (d, CMe$_2$), 81.3 (d, C-6), 74.9 (d, C-5), 74.1 (d, C-4), 61.2 (t, C-7), 28.2 (q, OCMes$_3$), 27.9 (q, CMe$_2$), 25.9 (q, SiCMe$_3$), 25.4 (q, CMe$_2$), 18.3 (q, SiCMe$_3$), -5.3 (q, SiMe$_2$); Anal. calcd for C$_{24}$H$_{40}$O$_6$N$_2$SiS: C, 56.22; H, 7.87; S, 6.24; N, 5.47. Obsd: C, 56.42; H, 8.02; S, 6.07; N, 5.38.

**Preparation of 1-α-1,2-dideoxy-2-[2-(1,1-dimethylethoxy)-2-oxoethyl]-6-O-[(1,1-dimethylethyl)dimethylsilyl]-3,4-O-(1-methylethyridene)-D-allopyranosyl 1H-imidazole (2.70) (Figure 2.15).** A 50 mL round-bottom flask equipped with a Claisen head adapter, water-cooled condenser, magnetic stir bar, septa, and nitrogen inlet was charged with a 1.5 equivalents of tributyltin...
hydride\(^{150}\) (250 \(\mu\)L, 0.90 mmol) in toluene (12.0 mL) and the solution degassed and then warmed to 90 °C. To this was added a degassed solution of \((Z)\)-tert-butyl 7-\(O\)-tert-butylidemethylsilyl-2,3-dideoxy-4,5-\(O\)-isopropyldiene-\(D\)-ribo-hept-2-enoate thiocarbonylimidazole (2.67, 308 mg, 0.60 mmol) in toluene (5.0 mL) containing 0.2 equivalents of AIBN (20 mg, 0.12 mmol) and then added dropwise over the course of 3.5 h via syringe pump to give a colorless solution with the complete consumption of starting material by TLC \((R_f = 0.23, 5:1\) hexanes/ethyl acetate). The reaction was cooled to 25 °C, concentrated in vacuo, and the colorless oil flash chromatographed (silica gel, 12:1 hexanes/ethyl acetate) to yield 107 mg (37%) of 1-(6-\(O\)-tert-butyldimethylsilyl-2-[2-carboxyethyl]1,2-dideoxy-3,4-\(O\)-isopropyldiene-\(\beta\)-\(D\)-allopyranosyl)imidazole (2.70).

\[
\begin{align*}
\text{Bu'Me}_2\text{SiO} & \quad \text{N} \\
\text{O} & \quad \text{CO}_2\text{Bu'}
\end{align*}
\]

\(R_f = 0.30\) (4:1 hexanes/acetone); \([\alpha]^{18.0}_{D} = + 23.5 ^\circ\) \((c 3.16, \text{CHCl}_3)\); IR (CHCl\(_3\)) 3112w, 2979m, 2952m, 2930s, 2875m, 1729m, 1492m, 1472m, 1461m, 1381m, 1368m, 1335w, 1255s, 1219s, 1153s, 1163s, 1037m, 999m, 838s cm\(^{-1}\); \(^1\)H-NMR (300 MHz, CDCl\(_3\)) \(\delta 7.62\) (m, 1 H, Im-H), 7.08 (m, 1 H, Im-H), 6.96 (m, 1 H, Im-H), 5.89 (d, \(J_{1,2} = 3.2\) Hz, 1 H, H-1\(\alpha\)), 4.31-4.24 (m, 2 H, H-3 and H-4), 3.92 (dd, \(J_{6.5} = 11.5\) Hz, \(J_{6.5} = 2.1\) Hz, 1 H, H-6), 3.77 (dd, \(J_{2,1'} = 11.5\) Hz, \(J_{2,1'} = 4.4\) Hz, 1 H, H-6), 3.69 (ddd, \(J_{5,4} = 8.4\) Hz, \(J_{5,6} = 4.4\) Hz, \(J_{5,6} = 2.1\) Hz, 1 H, H-5), 2.88 (ddddd, \(J_{2,1'a} = 8.6\) Hz, \(J_{2,1'b} = 5.9\) Hz, \(J_{2,1} = 3.6\) Hz, \(J_{2,1} = 3.2\) Hz, 1 H, H-2), 2.25 (dd, \(J_{2,1'a} = 16.8\) Hz, \(J_{1'a,2} = 8.6\) Hz, 1 H, H-1\(a\)), 2.02 (dd, \(J_{2,1'b} = 16.8\) Hz, \(J_{1'b,2} = 5.9\) Hz, 1 H, H-1\(b\)), 1.52 (s, 3 H, CH\(_3\)), 1.40 (s, 9 H, OCMe\(_3\)), 1.37 (s, 3 H, CH\(_3\)), 0.91 (s, 9 H, SiCMe\(_3\)), 0.08 (s, 3 H, SiMe\(_2\)), 0.07 (s, 3 H, SiMe\(_2\)); \(^{13}\)C-NMR (75 MHz, CDCl\(_3\)) \(\delta 170.7\) (s, C=O), 135.2 (d, Im-H), 129.7 (d, Im-H), 116.4 (d, Im-H), 109.9 (s, CMe\(_2\)), 83.2 (d, C-1), 81.5 (s, CMe\(_3\)), 79.4 (d, C-5), 75.4 (d, C-3), 68.9 (d, C-4), 62.9 (t, C-6), 38.5 (d, C-2), 31.8 (t, C-1'), 28.1 (q, CMe\(_2\)), 26.0 (q, SiBu'), 18.5 (s, SiBu'), -5.0 (q, SiMe\(_2\)), -5.1 (q, SiMe\(_2\)). Anal. calcd. For C\(_{24}\)H\(_{32}\)O\(_4\)N\(_2\)Si: C, 59.72; H, 8.77; N, 5.80. Obsd: C, 59.51;
H, 8.61; N, 5.58; S, 0.0. On standing, a signal emerges at $\delta$ 5.68 ($d_1 = 8.54$ Hz, 1H, H-1β) with an equilibrium distribution of $\alpha/\beta = 72:28$.

2-deoxy-2-[2-(1,1-dimethylethoxy)-2-oxo-1-phenylethyl]-6-O-[(1,1-dimethylethyl)dimethylsilyl]-3,4-O-(1-methylethylidene)-D-altronic acid, δ-lactone (2.68b). A 100 mL round-bottom flask equipped with a Claisen head adapter, water condenser, magnetic stir bar, rubber septum, and nitrogen inlet was charged with 1.5 equivalents of tributyltin hydride (350 μL, 1.28 mmol) in toluene (17 mL) and the solution degassed and warmed to 90°C. To this was added a degassed solution of (Z)-tert-butyl 7-O-tert-butyl(dimethylsilyl)-2,3-dideoxy-4,5-O-isopropylidene-D-ribo-hept-2-enoate, 6-O-phenyl thionocarbonate (2.66, 462 mg, 0.857 mmol) in toluene (10 mL) containing 0.2 equivalents of AIBN (30 mg, 0.17 mmol) dropwise over the course of 3.5 h via syringe pump to give a colorless solution with the complete consumption of starting material by TLC ($R_f = 0.38$, 5:1 hexanes/ethyl acetate). The reaction was cooled to 25°C, concentrated in vacuo, and the crude syrup partitioned between hexanes and acetonitrile. The acetonitrile was then removed under vacuum and the colorless oil flash chromatographed (silica gel, 8:1 hexanes/ethyl acetate) to yield 40 mg (9%) of 2-deoxy-2-[2-(tert-butoxy)-2-oxo-1-phenylethyl]-6-O-tert-butyl(dimethylsilyl)-3,4-O-isopropylidene-D-altrono-δ-lactone (2.68b) along with 89 mg of recovered starting material.

$R_f = 0.30$ (8:1 hexanes/ethyl acetate); $[\alpha]^{20}_{D} = +47.20^\circ$ (c 0.66, CHCl₃) IR (CHCl₃); 2981m, 2953m, 2930m, 2889w, 2856m, 1748s, 1723s, 1603w, 1590w, 1490m, 1472m, 1455m, 1381m, 1254s, 1234s, 1215s, 1179s, 1154s, 1068s, 1004w, 978w, 960w, 945w, 923w, 891w, 836s, 815w, 777m, 755m cm⁻¹; $^1$H-NMR (250 MHz, CDCl₃) δ 7.33-7.29 (m, 5 H, Ar-H), 4.48 (app. t, $J_{3,4} = 6.7$ Hz, 1 H, H-3), 4.26 (d, $J_{1,2} = 5.2$ Hz, 1 H, H-1'), 4.20 (dd, $J_{4,5} = 9.6$ Hz, $J_{4,3} = 6.7$ Hz, 1 H, H-4), 4.04 (ddd, $J_{6,5} = 9.6$ Hz, $J_{6,4} = 6.7$ Hz, $J_{6,3} = 9.6$ Hz, 1 H, H-6), 4.41 (ddt, $J_{5,4} = 9.6$ Hz, 1 H, H-5), 4.39 (dd, $J_{5,4} = 9.6$ Hz, 1 H, H-5), 3.64 (s, 6 H, OCH₃), 3.31 (s, 1 H, OCH₃), 3.34 (s, 3 H, OCH₃), 3.13 (s, 3 H, OCH₃), 3.08 (m, 1 H, H-2'), 2.92 (s, 3 H, OCH₃), 2.88 (s, 3 H, OCH₃), 2.32 (s, 3 H, OCH₃), 2.16 (s, 3 H, OCH₃), 2.14 (m, 1 H, H-2'), 1.40 (s, 9 H, CD₃), 1.34 (s, 9 H, CD₃), 1.22 (s, 9 H, CD₃), 1.20 (s, 9 H, CD₃), 1.18 (d, $J_{6,5} = 6.7$ Hz, 1 H, H-6), 1.14 (d, $J_{6,5} = 6.7$ Hz, 1 H, H-6), 1.06 (d, $J_{6,5} = 6.7$ Hz, 1 H, H-6), 1.04 (d, $J_{6,5} = 6.7$ Hz, 1 H, H-6), 1.02 (d, $J_{6,5} = 6.7$ Hz, 1 H, H-6), 1.00 (s, 9 H, CD₃), 0.97 (s, 9 H, CD₃), 0.95 (s, 9 H, CD₃), 0.93 (s, 9 H, CD₃), 0.91 (s, 9 H, CD₃), 0.89 (s, 9 H, CD₃), 0.87 (s, 9 H, CD₃), 0.85 (s, 9 H, CD₃), 0.84 (s, 9 H, CD₃), 0.82 (s, 9 H, CD₃), 0.80 (s, 9 H, CD₃), 0.79 (s, 9 H, CD₃), 0.77 (s, 9 H, CD₃), 0.75 (s, 9 H, CD₃), 0.73 (s, 9 H, CD₃), 0.71 (s, 9 H, CD₃), 0.69 (s, 9 H, CD₃), 0.67 (s, 9 H, CD₃), 0.65 (s, 9 H, CD₃), 0.63 (s, 9 H, CD₃), 0.61 (s, 9 H, CD₃), 0.59 (s, 9 H, CD₃), 0.57 (s, 9 H, CD₃), 0.55 (s, 9 H, CD₃), 0.53 (s, 9 H, CD₃), 0.51 (s, 9 H, CD₃), 0.49 (s, 9 H, CD₃), 0.47 (s, 9 H, CD₃), 0.45 (s, 9 H, CD₃), 0.43 (s, 9 H, CD₃), 0.41 (s, 9 H, CD₃), 0.39 (s, 9 H, CD₃), 0.37 (s, 9 H, CD₃), 0.35 (s, 9 H, CD₃), 0.33 (s, 9 H, CD₃), 0.31 (s, 9 H, CD₃), 0.29 (s, 9 H, CD₃), 0.27 (s, 9 H, CD₃), 0.25 (s, 9 H, CD₃), 0.23 (s, 9 H, CD₃), 0.21 (s, 9 H, CD₃), 0.19 (s, 9 H, CD₃), 0.17 (s, 9 H, CD₃), 0.15 (s, 9 H, CD₃), 0.13 (s, 9 H, CD₃), 0.11 (s, 9 H, CD₃), 0.09 (s, 9 H, CD₃), 0.07 (s, 9 H, CD₃), 0.05 (s, 9 H, CD₃), 0.03 (s, 9 H, CD₃), 0.01 (s, 9 H, CD₃).
$J_{5,6a} = 4.7 \text{ Hz}$, $J_{5,6b} = 1.9 \text{ Hz}$, 1 H, H-5), 3.98 (dd, $J_{gem} = 11.8 \text{ Hz}$, $J_{6b,5} = 1.9 \text{ Hz}$, 1 H, H-6b), 3.83 ($J_{gem} = 11.8 \text{ Hz}$, $J_{6a,5} = 4.7 \text{ Hz}$, 1 H, H-6a), 3.19 (dd, $J_{2,3} = 6.7 \text{ Hz}$, $J_{2,1'} = 5.2 \text{ Hz}$, 1 H, H-2), 1.46 (s, 9 H, OMe). 1.33 (s, 3 H, CH$_3$), 1.16 (s, 3 H, CH$_3$), 0.89 (s, 9 H, SiMe$_3$), 0.08 (s, 6 H, SiMe$_2$); $^{13}$C-NMR (75 MHz, CDCl$_3$) δ 171.5 (s, ester), 170.5 (s, lactone), 135.9 (s, Ar), 129.7 (d, o-Ar), 128.5 (d, m-Ar), 127.5 (d, p-Ar), 110.6 (s, CMe$_2$), 81.8 (s, OMe), 78.4 (d, C-5), 72.5 (d, C-3), 70.9 (d, C-4), 62.1 (t, C-6), 50.6 (d, C-1'), 48.2 (d, C-2), 28.1 (q, OMe), 27.4 (q, CMe$_2$), 26.1 (q, SiMe$_3$), 24.9 (q, CMe$_3$), 18.6 (s, SiMe$_3$), -5.0 (q, SiMe$_2$). Anal. Calcd. For C$_{27}$H$_{42}$O$_6$Si: C, 64.00; H, 8.35; Found: C, 64.00; H, 8.25; S, 0.00.

Preparation of 2-deoxy-2-(2-ethoxy-2-oxo-1-phenylethyl)-6-O-[(1,1-dimethylsilyl)dimethylsilyl]-3,4-O-(1-methylethylidene)-D-altronic acid, δ-lactone (2.68a) (Scheme 2.14). A 250 mL round-bottom flask equipped with a Claisen head adapter, water-cooled condenser, magnetic stir bar and nitrogen inlet was charged with a 0.05 M solution of (Z)-tert-butyl 7-O-tert-butyl(dimethylsilyl)-2,3-dideoxy-4,5-O-isopropylidene-D-ribo-hept-2-enoate, O-phenyl thionocarbonate (2.65, 592 mg, 1.16 mmol) in toluene (23.0 mL). The flask was evacuated and filled with nitrogen (repeated 5 times) and immersed into an oil bath at 90 °C. A solution containing 1.74 equivalents of tributyltin hydride (506 mg, 1.74 mmol) and 0.2 equivalents of AIBN (38 mg, 0.23 mmol) in toluene (10 mL, 0.17 M) was added via syringe pump over 5 h (2.5 mL/hr). The reaction was then cooled and concentrated to give a light yellow colorless oil. The bulk tin residues were removed by dissolution in acetonitrile (30 mL) and washing with hexanes (2 x 20 mL). The acetonitrile was removed under reduced pressure to yield 470 mg of a yellow oil. Flash chromatography (silica gel, 10:1 hexanes/ethyl acetate) gave 170 mg (30.5 %) of D-altrono-δ-lactone 2.68a as colorless oil.
$R_f = 0.11$ (10:1 hexanes/diethyl ether); $[\alpha]^{19\circ}_D = + 59.3^\circ$ (c 1.43, CHCl$_3$); IR (thin film) 2985m, 2931s, 2857s, 1748s, 1731s, 1603w, 1585w, 1572m, 1454m, 1372s, 1253s, 1213s, 1177s, 1151s, 1069s, 978m, 938w, 892w, 835s, 814m, 777s, 707m cm$^{-1}$; $^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 7.34-7.29 (m, 5 H, Ar-H), 4.46 (dd, J$_{3,2} = 6.8$, J$_{3,4} = 6.9$ Hz, 1 H, H-3), 4.33 (d, J$\gamma$ = 5.4 Hz, 1 H, H-1'), 4.21 (dd, J$_{4,5} = 9.6$ Hz, J$_{4,3} = 6.9$ Hz, 1 H, H-4), 4.20 (q, J = 7.1 Hz, 2 H, OCH$_2$CH$_3$), 4.08 (ddd, J$_{5,4} = 9.6$ Hz, J$_{5,6a} = 4.8$ Hz, J$_{5,6b} = 2.0$ Hz, H, H-5), 3.98 (dd, J$_{gem} = 11.9$ Hz, J$_{6a,5} = 2.0$ Hz, 1 H, H-6b), 3.83 ( J$_{gem} = 11.9$ Hz, J$_{6a,5} = 4.8$ Hz, 1 H, H-6a), 3.27 (dd, J$_{2,3} = 6.8$ Hz, J$_{2,1} = 5.4$ Hz, 1 H, H-2), 1.35 (s, 3 H, CH$_3$), 1.18 (s, 3 H, CH$_3$), 1.25 (t, J = 7.1 Hz, 3 H, OCH$_2$CH$_3$), 0.90 (s, 9 H, Bu'), 0.08 (s, 3 H, SiMe$_2$), 0.07 (s, 3 H, SiMe$_2$); $^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ 172.4 (s, C=O), 170.4 (s, C=O), 135.3 (s, Ar), 129.8 (d, Ar), 128.6 (d, Ar), 127.7 (d, Ar), 110.8 (s, CMe$_2$), 78.5 (d, C-5), 72.5 (d, C-3), 70.9 (d, C-4), 62.1 (t, OCH$_2$CH$_3$), 61.4 (t, C-6), 49.9 (d, C-1'), 48.2 (d, C-2), 27.4 (q, CMe$_2$), 26.0 (q, CMe$_2$), 24.9 (q, CMe$_2$), 18.6 (s, CMe$_2$), 14.2 (q, OCH$_2$CH$_3$), -5.1 (q, SiMe$_3$); Anal. calcd for C$_{23}$H$_{34}$O$_7$Si: C, 62.73; H, 8.00. Obsd. C, 62.68; H, 7.96; S, 0.0. HRMS (EI) calcd for: C$_{23}$H$_{34}$O$_7$Si (M+1)$^+$: 479.2465073. Obsd: 479.2444763.

Preparation of 2-deoxy-2-(2-ethoxy-2-oxo-1-phenylethyl)-6-0-[(1,1-dimethylethyl)dimethylsilyl]-3,4-O-(1-methylidene)-D-altronic acid, 5-lactone (2.68) and 1,5-anhydro-2-deoxy-2-(2-ethoxy-2-oxoethyl)-6-0-[(1,1-dimethylethyl)dimethylsilyl]-3,4-O-(1-methylidene)-D-allopyranitol (2.69) (Table 2.3). A 100 mL round-bottom flask equipped with a Claisen head adapter, water condenser, magnetic stir bar and nitrogen inlet was charged with a 1.5 equivalents of tributyltin hydride$^{150}$ (640 $\mu$L, 0.69 mmol) in toluene (9.0 mL) and the yellow solution degassed and then warmed to 90 °C. A solution of (Z)-ethyl 7-O-tert-butyldimethylsilyl-2,3-dideoxy-4,5-O-isopropylidene-D-ribo-hept-2-enoate, 6-O-phenyl thionocarbonate (2.65, 234 mg, 0.45 mmol) in toluene (5.0 mL) containing 0.2 equivalents of AIBN (15 mg) was degassed and then added dropwise over the course of 2.5 h via syringe pump to give a colorless solution with the complete consumption of starting material by TLC ($R_f = 0.60$, 9:1 hexanes/ethyl acetate). The reaction was cooled to 25 °C, concentrated in vacuo, and the colorless oil flash chromatographed (silica gel, 12:1 hexanes/ethyl acetate) to yield 22 mg (10%) of 2-deoxy-2-C-(2-
carbethoxy-1-phenylethyl]-6-O-(tert-butyldimethylsilyl)-3,4-O-(isopropylidene)-D-altrono-δ-lactone (2.68a) isolated and characterized previously and 115 mg (65%) of 1,5-anhydro-2-deoxy-2-C-(2-ethoxy-2-oxo-ethyl)-6-O-tert-butyldimethylsilyl-3,4-O-isopropylidene-D-allopyranitol (2.69) and 32 mg of a mixture of both compounds.

Preparation of 2-deoxy-2-C-(2-ethoxy-2-oxo-1-phenylethyl]-6-O-[((1,1-dimethylethyl)dimethylsilyl]-3,4-O-(1-methylethylidene)-D-altronic acid, δ-lactone (2.68a) (Scheme 2.14). A 100 mL round-bottom flask equipped with a Claisen head adapter, water condenser, magnetic stir bar and nitrogen inlet was charged with a 0.05 M solution of (Z)-ethyl 7-O-tert-butyldimethylsilyl-2,3-dideoxy-4,5-O-isopropylidene-D-ribo-hept-2-enoate, 6-O-phenyl thionocarbonate (2.66, 323 mg, 0.63 mmol) in toluene (12.5 mL)
containing 1.2 equivalents of tributyltin hydride (2.54 μL, 0.94 mmol) and 0.2 equivalents of AIBN (21 mg, 0.12 mmol). The flask was evacuated and filled with nitrogen (repeated 5 times) and immersed into an oil bath at 75 °C. After 2 h, starting material remained by TLC ($R_f = 0.33, 10:1$ hexanes/ethyl acetate). Additional AIBN was added (20 mg) and the reaction heated for an additional 1 h. After the consumption of the starting material, the reaction was concentrated to give a colorless oil which was then dissolved in acetonitrile (15 mL) and washed with hexanes (2 x 10 mL). The acetonitrile was removed in vacuo to yield 125 mg of a yellow oil. The crude product was flash chromatographed (silica gel, 10:1 hexanes/diethyl ether) to give 75 mg (25%) of D-altrono-5-lactone (2.68a) as colorless oil and characterized previously (vide supra).

Preparation of (2Z)-1,1-dimethylethyl 6-O-acetyl-2,3,7-trideoxy-7-bromo-4,5-O-(1,1-methylethylidene)-D-ribo-hept-2-enoate (2.46), and (2Z)-1,1-dimethylethyl 7-O-acetyl-2,3-deoxy-4,5-O-(1,1-methylethylidene)-D-ribo-hept-2-enoate (2.45) (Scheme 2.8). A 100 mL round-bottom flask equipped with a magnetic stir bar and nitrogen inlet was charged with a 0.6 M solution of diol (2.43, 512 mg, 1.73 mmol) in dichloromethane (3.0 mL) followed by PPTS (4 mg, 10 mol%) and 1.2 equivalents of trimethylorthoacetate (260 μL, 2.0 mmol) and the reaction stirred at 25 °C for 0.5 h until no further starting material remained by TLC ($R_f = 0.10, 2:1$ hexanes/ethyl acetate). The solvent was then removed under reduced pressure to give a colorless oil which was dissolved in dichloromethane (3.0 mL). To this was added triethylamine (50 μL) followed by 1.2 equivalents of acetyl bromide (150 μL, 2.07 mmol) to give a light pink solution which was stirred at 25 °C for 0.5 h and the solvent again removed under reduced pressure. The residue was dissolved in methanol (5 mL) and Amberlite basic ion-exchange resin (10 mg) added and the reaction stirred for 20 minutes. The resin was then removed by filtration.
and solids rinsed with dichloromethane (5 mL). The organic phase was then washed with water and saturated brine and then dried over anhydrous MgSO₄. Vacuum filtration and concentration in vacuo yielded 550 mg of a pink oil. HPLC analysis indicates the presence of two compounds in relatively equal proportions (48:52). ¹H-NMR analysis of the crude indicated no epoxide present. The syrup was flash chromatographed (silica gel, 7:1 hexanes/ethyl acetate) to give 29 mg of what was tentatively identified as (Z)-tert-butyl 6-O-acetyl-2,3,7-trideoxy-7-bromo-4,5-O-isopropylidene-D-ribo-hept-2-enoate (2.46) and 135 mg of (Z)-tert-butyl 7-O-acetyl-2,3-deoxy-4,5-O-isopropylidene-D-ribo-hept-2-enoate (2.45).

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R_f = 0.50, \text{ (2:1 hexanes/ethyl acetate); } ^1H-NMR (200 MHz, CDCl}_3) \delta 6.11 (dd, J_{3,2} = 11.6 \text{ Hz}, J_{3,4} = 7.5 \text{ Hz}, 1 \text{ H, H-3}), 5.83 (dd, J_{2,3} = 11.6 \text{ Hz}, J_{2,4} = 1.5 \text{ Hz}, 1 \text{ H, H-2}), 5.81 (dd, J_{4,3} = 7.5 \text{ Hz}, J_{4,5} = 6.4 \text{ Hz}, J_{4,2} = 1.5 \text{ Hz}, 1 \text{ H, H-4}), 4.89 (ddd, J_{6,5} = 7.7 \text{ Hz}, J_{6,7} = 7.4 \text{ Hz}, J_{6,7} = 0.8 \text{ Hz}, 1 \text{ H, H-6}), 4.56 (dd, J_{5,6} = 7.7 \text{ Hz}, J_{5,4} = 6.4 \text{ Hz}, 1 \text{ H, H-5}), 3.60 (app. d, J = 0.8 \text{ Hz}, 2 \text{ H, H-7}), 1.99 (s, 3 \text{ H, Ac}), 1.46 (s, 3 \text{ H, CH}_3), 1.45 (s, 3 \text{ H, t-Bu}), 1.37 (s, 3 \text{ H, CH}_3); ^{13}C-NMR (50 MHz, CDCl}_3) \delta 169.9 (s, C=O), 164.7 (s, C=O), 142.3 (d, C-3), 124.6 (d, C-2), 109.5 (CMe₂), 81.4 (s, CMe₃), 80.9 (d), 74.1 (d), 69.9 (d), 33.0 (t, C-7), 28.2. (q, CMe₂), 27.7, (d, CMe₂), 25.4 (CH₃).

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R_f = 0.30, \text{ (2:1 hexanes/ethyl acetate); [\alpha]^{10.0}_D = + 147.7 ^\circ (c 1.04, \text{ CHCl}_3). IR (thin film) 3454br, 2982s, 2936m, 1742s, 1713s, 1646m, 1456w, 1413s, 1370s, 1240s, 1159s, 1057s, 871s cm⁻¹; } ^1H-NMR (200 MHz, CDCl}_3) \delta 6.15 (dd, J_{3,2} = 11.6 \text{ Hz}, J_{3,4} = 8.4 \text{ Hz}, 1 \text{ H, H-3}), 5.95 (dd, J_{2,3} = 11.6 \text{ Hz}, J_{2,4} = 1.0 \text{ Hz}, 1 \text{ H, H-2}), 5.48 (ddd, J = 7.4 \text{ Hz}, J = 7.0 \text{ Hz}, J = 1.3 \text{ Hz}, 1 \text{ H}), 4.36 (dd, J_{gem} = 11.5 \text{ Hz}, J = 1.3 \text{ Hz}, 1 \text{ H, H-7}), 4.27
(dd, J = 8.6 Hz, J = 6.2 Hz, 1 H), 4.08 (dd, Jgem = 11.5 Hz, J = 6.5 Hz, 1 H, H-7), 3.79-3.72 (m, 1 H), 3.67 (d, J = 2.3 Hz, 1 H, OH), 2.07 (s, 3 H, Ac), 1.48 (s, 3 H, CHj), 1.45 (s, 3 H, t-Bu), 1.35 (s, 3 H, CHj); \(^{13}\)C-NMR (50.0 MHz, CDCl\(_3\)) \(\delta\) 171.3 (s, C=O), 167.1 (s, C-1), 144.6 (d, C-3), 124.6 (d, C-2), 109.9 (s, CMe\(_2\)), 78.9 (d), 74.9 (d), 68.8 (d), 66.4 (t, C-7), 28.2 (q, CMe\(_2\)), 28.1 (q, CMe\(_2\)), 25.6 (q, CMe\(_2\)), 21 (q, CH\(_3\)C(O)).

Preparation of (2S)-1-(triphenylmethoxy)-hex-5-en-1,2-diol (2.101) (Scheme 2.20). A 250 mL round-bottom flask equipped with a thermocouple well was fitted with a thermocouple lead. Claisen adapter, addition funnel, magnetic stir bar, and flame dried and cooled under nitrogen. The round-bottom was charged with a 0.8 M solution of commercially available (5S)-dihydro-5-O-triphenylmethoxymethyl-2(3 H)-furanone (2.99, 2.50 g, 8.3 mmol) in dichloromethane (10 mL) and cooled to -78 °C. The addition funnel was next charged with 1.5 eq. of Dibal-H (1.5 M in toluene, 6.6 mL, 12.45 mmol) and added slowly, dropwise over 5 minutes. The dropping funnel was then rinsed with additional dichloromethane (5 mL) and added to the reaction mixture. The reaction was allowed to stir at -78 °C for 2 h when no further starting material was detected by TLC (Rf = 0.53, 3:1 hexanes/ethyl acetate). Excess hydride was quenched at -78 °C by slow addition of absolute methanol (5 mL). The cooling bath was removed after 5 minutes and the reaction vessel warmed to 25 °C. The contents of the round-bottom were transferred to a separatory funnel and diluted with diethyl ether (300 mL) and the organic phase washed with cold 0.4 M HCl (100 mL), saturated bicarbonate (100 mL), water (50 mL), saturated brine (50 mL) and then dried over anhydrous MgSO\(_4\). Vacuum filtration and concentration in vacuo yielded 2.25 g (74%) of the desired (5S)-tetrahydro-5-triphenylmethoxymethyl-2-furanol (2.100) as colorless syrup as determined by IR (CHCl\(_3\)) 3408\(br\) cm\(^{-1}\) and \(^{13}\)C-NMR (75 MHz, CDCl\(_3\)) \(\delta\) 98.9 (C-2). The lactol 2.100 was used in the next step without further purification.
A 100 ml, 3-neck, round-bottom flask equipped with two addition funnels, rubber septa, magnetic stir bar and nitrogen inlet was flame dried and cooled under a stream of nitrogen. The flask was charged with 2.0 equivalents of dried methyltriphenylphosphonium bromide (3.04 g, 8.50 mmol) in tetrahydrofuran (17 mL, 0.5 M) and cooled to ca. -20 °C (CO₂/ethylene glycol). One of the addition funnels were charged with 1.95 equivalents of n-BuLi\(^{279}\) (2.5M in hexanes, 3.30 mL, 8.24 mmol) and the other addition funnel was charged with (5S)-tetrahydro-5-triphenylmethoxymethyl-2-furanol (2.100, 1.54 g, 4.25 mmol) in tetrahydrofuran (8.5 mL, 0.5 M). Slow, dropwise addition of alkyl lithium to the phosphonium salt solution yielded a yellow, heterogeneous solution. The addition funnel was rinsed with additional solvent (3 mL) and the cooling bath removed. The yellow phosphorane solution was stirred at 25 °C for 45 minutes then cooled back down to -20 °C. The 2-furanol solution was then added slowly, dropwise and the addition funnel rinsed with additional solvent (3 mL). The cooling bath was removed and the reaction was allowed to warm slowly to 25 °C and left to stir for 18 h. An addition funnel was then replaced with an air condenser and the solution warmed to 50 °C for 15 minutes. The reaction was cooled to 25 °C and excess ylide quenched by slow addition of acetone (10 mL) and the reaction diluted with diethyl ether (150 mL) and the solids removed by vacuum filtration over a pad of Celite. The filtrate was concentrated, taken up in chloroform (50 mL) and washed with saturated bicarbonate (20 mL), water (10 mL), saturated brine (10 mL) then dried over anhydrous MgSO₄. Concentration in vacuo yielded a light yellow syrup which was flash chromatographed (silica gel, 12:1 hexanes/acetonitrile) to give 1.383 g (91%) of the previously reported (2S)-1-O-trityl-hex-5-en-2-ol (2.101) as a colorless oil.

\[
\begin{align*}
\text{Ph}_3\text{CO} & \quad \text{OH} \\
\end{align*}
\]

\(R_f = 0.30\) (10:1 hexanes/acetonitrile); IR (thin film); 3578\text{m}, 3455\text{br}, 3059\text{m}, 3032\text{m}, 2975\text{m}, 2925\text{m}, 2870\text{m}, 1959\text{w}, 1901\text{w}, 1819\text{w}, 1639\text{m}, 1596\text{m}, 1490\text{s}, 1448\text{s}, 1415\text{m}, 1318\text{m}, 1256\text{m}, 1218\text{s}, 1183\text{m}, 1153\text{m}, 1073\text{s}, 1032\text{s}, 1001\text{s}, 911\text{s} \text{cm}^{-1}; ^1\text{H-NMR} (250 \text{MHz, CDCl}_3) \delta 7.45-7.19 (m, 15 H, Ar-H), 5.76 (ddd, \(J_{5,5'}=16.9 \text{ Hz}, J_{5,6''}=10.2 \text{ Hz}, J_{5,4'}=J_{5,4''}=6.6 \text{ Hz}, 1 \text{ H, H-5}), 5.01-4.89 (m, 2 \text{ H, H-6}), 3.79 (dddd, J_{2,1}=7.4 \text{ Hz}, J_{2,1''}=3.4 \text{ Hz}, J_{2,0}=3.8 \text{ Hz}, J_{2,3}=J_{2,3''}=6.4 \text{ Hz}, 1 \text{ H, H-2}), 3.18 (dd, J_{gem}=9.3 \text{ Hz}, J_{1b,2}=

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3.4 Hz, 1 H, H-1b). 3.03 (dd, \( J_{\text{pp}} = 9.3 \) Hz, \( J_{1\alpha,2} = 7.4 \) Hz, 1 H, H-1a). 2.30 (d, \( J_{\text{OH,2}} = 3.8 \) Hz, 1 H, OH). 2.21-1.96 (m, 2 H, H-4). 1.66-1.44 (m, 2 H, H-3); \(^{13}\text{C}-\text{NMR (75 MHz, CDCl}_3\) \( \delta\) 144.0 (s, Ar). 138.4 (d, C-5). 128.8 (d, Ar). 128.0 (d, Ar). 127.2 (d, Ar). 114.9 (t, C-6). 86.8 (s, Ph$_3$CO). 70.5 (d, C-2). 67.8 (t, C-1). 32.6 (t, C-4). 29.9 (t, C-3).

**Preparation of 1,2-dideoxy-6-O-[(1,1-dimethylethyl)dimethylsilyl]-3,4-O-(1-methylethylidene)-D-ribo-hex-1-enitol (2.108)** (Scheme 2.20). A 100 ml, 3-neck, round-bottom flask equipped with two addition funnels, rubber septa, magnetic stir bar and nitrogen inlet was flame dried and cooled under a stream of nitrogen. The flask was charged with 2.0 equivalents of dried methyltriphenylphosphonium bromide (2.815 g, 7.87 mmol) in tetrahydrofuran (31.5 mL) and cooled to ca. -20° C (ethylene glycol/dry ice). One of the addition funnels were charged with 1.95 equivalents of \( n\)-BuLi (2.5M in hexanes, 3.05 mL, 7.63 mmol) and the other addition funnel was charged with 5-O-tert-butyldimethylsilyl-2,3-O-isopropylidene-D-ribofuranose (2.107, 1.20 g, 3.94 mmol) in tetrahydrofuran (16.0 mL). Slow, dropwise addition of the alkyl lithium to the phosphonium salt solution yielded a yellow heterogeneous solution. The addition funnel was rinsed with additional solvent (3 mL) and the cooling bath removed. The yellow phosphorane solution was stirred at 25 °C for 45 minutes then cooled back down to -20° C. The lactol solution was then added dropwise and the addition funnel rinsed with additional solvent (3 mL). The reaction was allowed to warm slowly to 25 °C and left to stir for 18 h. An addition funnel was replaced with a air condenser and the solution warmed to 50° C for 15 minutes. The reaction was cooled to 25 °C and excess phosphorane quenched with acetone (10 mL) and the reaction diluted with diethyl ether (150 mL) and the solids removed by vacuum filtration. The filtrate was concentrated, taken up in chloroform (50 mL) and washed with saturated bicarbonate (20 mL), water (10 mL), saturated brine and then dried over anhydrous MgSO$_4$. Concentration in vacuo yielded a light yellow syrup which was flash chromatographed (silica gel. 10:1 hexanes/acetone) to yield 304 mg (25 %) of the previously reported 6-\( O\)-tert-butyldimethylsilyl-1,2-dideoxy-3,4-O-(1-methylethylidene)-D-ribo-hex-1-enitol (2.108).
$R_f = 0.25$ (10:1 hexanes/acetone); IR (CHCl$_3$); 3496 br, 3011 m, 2981 m, 2955 s, 2991 s, 2884 m, 2858 m, 2359 w, 1724 s, 1471 m, 1463 m, 1411 w, 1384 s, 1370 s, 1315 m, 1257 s, 1216 s, 1151 s, 1062 s, 1005 m, 938 m, 879 m, 837 s cm$^{-1}$; $^1$H-NMR (250 MHz, CDCl$_3$) $\delta$ 6.03 (ddd, $J_{\text{trans}} = 17.1$, $J_{\text{gem}} = 10.4$, $J_{5,6} = 6.6$, 1 H, H5), 5.41 (ddd, $J_{\text{trans}} = 17.1$, $J_{\text{gem}} = 1.7$, $J_{6,4} = 1.4$, 1 H, H6), 5.27 (ddd, $J_{\text{trans}} = 17.1$, $J_{\text{gem}} = 1.7$, $J_{6,4} = 1.4$, 1 H, H6), 4.68 (dddd, $J_{4,5} = 6.4$, $J_{4,3} = 6.3$, $J_{4,6} = 1.4$, 1 H, H4), 4.05 (dd, $J = 8.8$, $J = 3.2$, 1 H, H3), 2.51 (d, $J_{\text{OH2}} = 5.1$, 1 H, OH), 1.46 (s, 3 H, CH$_3$), 1.35 (s, 3 H, CH$_3$), 0.91 (s, 9 H, t-Bu), (s, 6H, SiMe$_2$); $^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ 134.3 (s), 117.7 (t), 108.9 (s), 79.0 (d), 77.6 (d), 69.7 (d), 64.5 (t), 28.0 (q, CH$_3$), 26.0 (q, CH$_3$), 25.6 (q, CMe$_3$), 18.5 (s, SiCMe$_3$), -5.1 (q, SiCH$_3$), -5.2 (q, SiCH$_3$).

Preparation of $O$-$2$-[$(2S)$-$1$-$O$-(triphenylmethyl)-hex-5-enyl] $O$-phenyl carbonothioate (2.102) (Scheme 2.20).$^{54}$ A 100 ml round-bottom flask equipped with a magnetic stir bar, rubber septum, and nitrogen inlet was charged with a 0.50 M solution of (2S)-$1$-$O$-trityl-hex-5-en-2-ol (2.101, 500 mg, 1.39 mmol) in 1:1 dichloromethane/pyridine (2.80 mL) and the solution cooled to 0 °C. Three and one half equivalents of $O$-phenyl chlorothioformate (675 $\mu$L, 4.88 mmol) was then added dropwise and the clear solution gave a yellow heterogeneous solution with white suspension. The reaction was allowed to come slowly to 25 °C and stirred for 12 h until no further starting material remained by TLC ($R_f = 0.38$, 9:1 hexanes/ethyl acetate). The reaction was transferred to a separatory funnel, diluted with dichloromethane (50 mL) and washed with water (25 mL), saturated brine (10 mL) and then dried over anhydrous MgSO$_4$. Concentration in vacuo yielded a light orange syrup which was flash chromatographed (silica gel, 12:1 hexanes/ethyl acetate) to yield 323 mg (47%) of $O$-$2$-[$(2S)$-$1$-$O$-(triphenylmethyl)-hex-5-enyl] $O$-phenyl thiocarbonate (2.101) as a colorless oil.
\[
\begin{align*}
\text{PhjCO} & \quad \text{O} \\
\text{S} & \quad \text{O} \text{Ph}
\end{align*}
\]

\[R_f = 0.25 \text{ (10:1 hexanes/ethyl acetate); } [\alpha]^{19.0}_{D} = +30.65^\circ \text{ (c 1.11, CHCl}_3)\]. IR (CHCl\textsubscript{3}): 3049m, 3018s, 2930m, 2873w, 2400w, 1960w, 1868w, 1829w, 1640m, 1593s, 1490s, 1484m, 1364m, 1293s, 1215s, 1153m, 1079m, 1033m, 920m cm\textsuperscript{-1}; \textsuperscript{1}H-NMR (300 MHz, CDCl\textsubscript{3}) \delta 7.49-7.08 (m, 20 H, Ar-H), 5.77 (dddd, J = 16.8 Hz, J = 10.2 Hz, J = 6.5 Hz, J = 6.5 Hz, 1 H), 5.62 (m, 1 H), 5.01-4.93 (m, 2 H), 3.37 (dd, J = 10.2 Hz, J = 3.6 Hz, 1 H), 3.28 (dd, J = 10.2 Hz, J = 5.6 Hz, 1 H), 2.13-2.03 (m, 2 H), 2.06-1.79 (m, 2 H); \textsuperscript{13}C-NMR (75 MHz, CDCl\textsubscript{3}) \delta 195.1 (s, C=S), 153.6 (s, Ar-O), 143.9 (s, Ar-C), 137.5 (d, C-5), 129.7 (d, Ar-H), 129.6 (d, Ar-H), 128.8 (d, Ar-H), 128.5 (d, Ar-H), 128.0 (d, Ar-H), 127.2 (d, Ar-H), 126.6 (d, Ar-H), 122.2 (d), 115.6 (t, C-6), 86.8 (s, OCPh\textsubscript{3}), 83.9 (d, C-2), 64.2 (t, C-1), 30.0 (t, C-4), 29.5 (t, C-3). Anal. calcld for C\textsubscript{32}H\textsubscript{29}O\textsubscript{3}S: C, 77.70; H, 6.12; S, 6.47. Obsd: C, 77.89; H, 6.22; S, 6.28.

Preparation of O-2-[(2S)-1-O-(triphenylmethyl)-hex-5-enyl] 1H-imidazole-1-carbonothioic acid (2.103) (Scheme 2.20).\textsuperscript{44} A 100 mL round-bottom flask equipped with a Claisen adapter, water condenser, magnetic stir bar, rubber septum, and nitrogen inlet was charged with a 0.16 M solution of (2S)-1-O-trityl-hex-5-en-2-ol (2.101, 400 mg, 1.11 mmol) in tetrahydrofuran (7.0) containing 2.0 equivalents of commercially available 1,1-thiocarbonyldiimidazole (3.8, 400 mg, 2.23 mmol) and the clear solution warmed to reflux for 2 h until no further starting material remained by TLC (\(R_f = 0.30\), 8:1 hexanes/ethyl acetate). The reaction was concentrated under reduced pressure and the crude golden syrup flash chromatographed (silica gel, 6:1 hexanes/ethyl acetate) to yield 379 mg (73%) of O-2-[(2S)-1-O-(triphenylmethyl)-hex-5-enyl] 1H-imidazolethiocarbamate (2.103) as a colorless oil which solidified on standing.

\[\text{PhjCO} \quad \text{O} \\
\text{S} \quad \text{C} \text{Ph}
\]
\[ R_f = 0.20 \text{ (8:1 hexanes/ethyl acetate)}; \text{Mp} = 91.0-92.0 \degree \text{C.} \ \{\alpha\}_D^{20.0} = +15.85 \degree \ (c \ 2.81, \text{CHCl}_3) \].

IR (CHCl₃): 3060w, 3012w, 2979w, 2926w, 2872w, 2360w, 1961w, 1819w, 1641w, 1596w, 1530m, 1490m, 1464m, 1448m, 1385s, 1236s, 1284s, 1231s, 1216s, 1152m, 1097m, 1035m, 1001m, 966s cm⁻¹; ¹H-NMR (250 MHz, CDCl₃) \( \delta \): 8.33 (m, 1 H, ImH-2), 7.65 (m, 1 H, ImH-5), 7.42-7.21 (m, 15 H, Ar-H), 7.05 (dd, \( J = 1.5 \) Hz, \( J = 1.0 \) Hz, 1 H, ImH-4), 5.83-5.67 (m, 2 H, H-5 and H-2), 4.99 (dd, \( J = 6.2 \) Hz, \( J = 1.6 \) Hz, 1 H, H-6), 4.93 (m, 1 H, H-6), 3.45 (dd, \( J_{gem} = 10.7 \) Hz, \( J_{1a,2} = 3.4 \) Hz, 1 H, H-1a), 3.35 (dd, \( J_{gem} = 10.7 \) Hz, \( J_{1b,2} = 5.2 \) Hz, 1 H, H-1b), 2.10-1.90 (m, 4 H, H-3 and H-4); ¹³C-NMR (75 MHz, CDCl₃) \( \delta \): 183.9 (s, C=S), 143.6 (s, i-Ar), 137.1 (d, C-5), 137.1 (d, ImC-2), 130.9 (d, ImC-5), 128.7 (d, Ar-H), 128.1 (d, Ar-H), 127.4 (d, Ar-H), 118.1 (d, ImC-4), 115.9 (t, C-6), 86.9 (s, OCPPh₃), 83.0 (d, C-2), 63.8 (t, C-1), 29.8 (t, C-4), 29.5 (t, C-3). Anal. calcd for C₂₉H₂₉O₂S: C, 74.33; H, 6.03; N, 5.98; S, 6.83. Obsd: C, 74.09; H, 6.05; N, 6.00, S, 6.84.

**Preparation of O-5-(1,2-dideoxy-6-O-[(1,1-dimethylethyl)dimethylsilyl]-3,4-O-(1-methylethylidene)-D-ribo-hex-1-enitol) O-phenyl carbonothioic acid (2.109) (Scheme 2.20).** A 100 mL round-bottom flask equipped with a magnetic stir bar, rubber septum, and nitrogen inlet was charged with a 0.50 M solution of 6-O-tert-butyldimethylsilyl-1,2-dideoxy-3,4-O-isopropylidene-D-ribo-hex-1-enitol (2.108, 304 mg, 1.00 mmol) in 1:1 dichloromethane/pyridine (2 mL) and the solution cooled to 0 \degree \text{C}. Three and one half equivalents of O-phenyl chlorothioformate (485 \mu L, 3.50 mmol) was then added dropwise and the clear solution gave a yellow heterogeneous solution with white suspension. The reaction was allowed to come slowly to 25 \degree \text{C} and stirred for 18 h until no further starting material remained by TLC (\( R_f = 0.38, 3:1 \text{hexanes/ethyl acetate})\). The reaction dark red reaction mixture was transferred to a separatory funnel, diluted with dichloromethane (50 mL) and washed with cold 0.5 M HCl(aq) (2 x 25 mL) and water (25 mL), saturated brine (20 mL) and then dried over anhydrous MgSO₄. Concentration in vacuo yielded a green syrup which was flash chromatographed (silica gel, 6:1 hexanes/diethyl ether) to yield 270 mg (65%) of O-5-(1,2-dideoxy-6-O-[(1,1-dimethylethyl)dimethylsilyl]-3,4-O-(1-methylethylidene)-D-ribo-hex-1-enitol) O-phenyl thiocarbonate (2.109) as a colorless oil.
Preparation of 1,1-dimethylethyl 7-O-triphenylmethyln-6-hydroxy-hept-2-enoate (2.104) (Scheme 2.20) A 50 mL separatory funnel was charged with 2.2 equivalents of (carbtert-butoxymethylene)-triphenylphosphonium bromide\(^1\) (2.585 g, 5.67 mmol) in chloroform (7.5 mL) followed by several drops of phenolphthalein solution. A 2.0 N solution of aqueous sodium hydroxide solution (30 mL) was added to the separatory funnel and gently shaken until the aqueous phase remained light pink. The organic layer was then washed with saturated brine (10 mL) and dried over anhydrous MgSO\(_4\). Vacuum filtration and concentration in vacuo yielded the crude (carbtert-butoxy)methylene-triphenylphosphorane as a yellow oil which was used in the next step without further purification. The crude phosphorane was dissolved in dimethoxyethane (15.0 mL) followed by addition of a solution of (5S)-tetrahydro-5-.

\(R_f = 0.40\) (10:1 hexanes/diethyl ether); \([\alpha]^\circ_{D} = -4.99\) \(^{\circ}\) (c 2.48, CHCl\(_3\)); IR (CHCl\(_3\)); 3018m, 2955m, 2938m, 2856m, 2858m 2400w, 2252w, 1936w, 1866w, 1781m, 1591m, 1490m, 1471m, 1458m, 1392m, 1376m, 1344m, 1292s, 1254s, 1215s, 1160m, 1119m, 1057s, 1004m, 935m, 908s, 873m, 837m cm\(^{-1}\); \(^1\)H-NMR (250 MHz, CDCl\(_3\)) \(\delta\) 5.90 (ddd, \(J_{2,1\text{trans}} = 17.2\) Hz, \(J_{2,1\text{cis}} = 10.2\) Hz, \(J_{2,3} = 7.0\) Hz, 1 H, H-2), 5.44 (ddd, \(J_{1a,2\text{trans}} = 17.1\) Hz, \(J_{1\text{gen}} = 1.7\) Hz, \(J_{1a,3} = 1.3\) Hz, 1 H, H-1a), 5.29 (ddd, \(J_{1b,2\text{cis}} = 10.4\) Hz, \(J_{1\text{gen}} = 1.7\) Hz, \(J_{1b,3} = 1.3\) Hz, 1 H, H-1b), 5.22 (ddd, \(J_{5,4} = 8.4\) Hz, \(J_{5,6a} = 3.5\) Hz, \(J_{5,6b} = 2.3\) Hz, 1 H, H-5), 4.73 (ddddd, \(J_{3,2} = 7.0\) Hz, \(J_{3,4} = 6.3\) Hz, \(J_{3,1a} = J_{3,1b} = 1.2\) Hz, 1 H, H-3), 4.63 (dd, \(J_{4,5} = 8.4\) Hz, \(J_{4,3} = 6.3\) Hz, 1 H, H-4), 4.14 (ddd, \(J_{\text{gen}} = 11.9\) Hz, \(J_{6a,5} = 2.3\) Hz, 1 H, H-6a), 3.96 (ddd, \(J_{\text{gen}} = 11.9\) Hz, \(J_{6b,5} = 3.5\) Hz, 1 H, H-6b), 1.50 (s, 3 H, CH\(_3\)), 1.40 (s, 3 H, CH\(_3\)), 0.93 (s, 9 H, \(\iota\)-Bu), 0.10 (s, 3 H, SiMe), 0.09 (s, 3 H, SiMe); \(^1\)\(^3\)C-NMR (75 MHz, CDCl\(_3\)) \(\delta\) 194.0 (s, C=S), 153.4 (s, \(\iota\)-Ar), 133.0 (d, C-2), 129.6 (d, o-Ar-H), 126.6 (d, \(p\)-Ar-H), 122.0 (d, m-Ar-H), 118.4 (t, C-1), 109.1 (s, CMe\(_2\)), 82.2 (d), 78.5 (d), 74.9 (d), 60.9 (t, C-6), 27.8 (q, CMe\(_2\)), 26.0 (q, CMe\(_2\)), 25.4 (q, CMe\(_2\)), 18.5 (s, SiCMe\(_3\)), -5.1 (q, SiMe), -5.2 (q, SiMe).
triphenylmethoxymethyl-2-furanol (2.100, 980 mg, 2.70 mmol) in dimethoxyethane (18.0 mL). This solution stirred rapidly under nitrogen at 25 °C for 18 h until homogenous. The reaction was then diluted with diethyl ether (100 mL) and vacuum filtered through a pad of Celite. The filtrate was washed with saturated bicarbonate (30 mL), water (30 mL), saturated brine (20 mL) and then dried over anhydrous MgSO₄. Vacuum filtration and concentration in vacuo gave a colorless syrup which was flash chromatographed (silica gel, 10:1 hexanes/ethyl acetate) to give 1.079 g (81.5%) of the desired tert-butyl 7-O-triphenylmethyl-6-hydroxy-hept-2-enoate (2.104) as a colorless syrup.

\[
\text{Ph}_3\text{CO} \quad \text{OH} \quad \text{OH} \quad \text{CO}_2\text{Bu'}
\]

\[
R_f = 0.25 \quad (\text{8:1 hexanes/acetone}) \quad [\alpha]^{17.5}_{D} = -4.58 \quad (c 0.93, \text{CHCl}_3). \quad \text{IR (thin film): } 3474 \text{br}, 3086 \text{m}, 3058 \text{m}, 3008 \text{s}, 2977 \text{w}, 2930 \text{m}, 2871 \text{m}, 2403 \text{w}, 1959 \text{w}, 1897 \text{w}, 1819 \text{w}, 1711 \text{s}, 1651 \text{s}, 1596 \text{m}, 1490 \text{s}, 1448 \text{m}, 1315 \text{m}, 1316 \text{s}, 1255 \text{s}, 1218 \text{s}, 1152 \text{m}, 1074 \text{s}, 1032 \text{s}, 984 \text{cm}^{-1}; \quad \text{H-NMR (250 MHz, CDCl}_3) \delta 7.44-7.20 \text{ (m, 15 H, Ar-H)}, \delta 6.81 \text{ (ddd, } J_{3,2} = 15.6 \text{ Hz, } J_{3,4a} = J_{3,4b} = 6.9 \text{ Hz, 1 H, H-3)}, \delta 5.20 \text{ (ddd, } J_{2,3} = 15.6 \text{ Hz, } J_{2,4a} = J_{2,4b} = 1.5 \text{ Hz, 1 H, H-2)}, \delta 3.80-3.72 \text{ (m, 1 H, H-6)}, \delta 3.18 \text{ (dd, } J_{\text{gem}} = 9.4 \text{ Hz, } J_{3,6a} = 3.5 \text{ Hz, 1 H, H-7a)}, \delta 3.04 \text{ (dd, } J_{\text{gem}} = 9.4 \text{ Hz, } J_{7b,6} = 7.2 \text{ Hz, 1 H, H-7b)}, \delta 2.28 \text{ (d, } J_{\text{OH,6}} = 4.2 \text{ Hz, 1 H, OH)}, \delta 2.33-2.10 \text{ (m, 2 H, H-4)}, \delta 1.60-1.50 \text{ (m, 2 H, H-5)}, \delta 1.47 \text{ (s, 9 H, t-Bu)}; \quad \text{C-NMR (75 MHz, CDCl}_3) \delta 166.2 \text{ (s, C-1)}, 147.3 \text{ (d, C-3)}, 143.9 \text{ (s, Ar)}, 128.8 \text{ (d, } \pi-\text{Ar-H)}, 128.1 \text{ (d, } \pi-\text{Ar-H)}, 127.3 \text{ (d, } \pi-\text{Ar-H)}, 123.6 \text{ (d, C-2)}, 86.9 \text{ (s, Ph}_3\text{CO)}.

Preparation of O-6-(7-O-triphenylmethyl-hept-2-enoic acid, 1,1-dimethylethyl ester) O-phenyl carbonothioic acid (2.105)(Scheme 2.20).\textsuperscript{54} A 100 mL round-bottom flask equipped with a magnetic stir bar, rubber septum, and nitrogen inlet was charged with a 0.50 M solution of tert-butyl 7-O-triphenylmethyl-6-hydroxy-hept-2-enoate (2.104, 291 mg, 0.63 mmol) in 1:1 dichloromethane/pyridine (1.2 mL) and the solution cooled to 0 °C. Three equivalents of O-phenyl chlorothioformate (307 μL, 2.22 mmol) was then added dropwise and the clear solution gave a yellow heterogeneous solution with white suspension. The reaction was allowed to come slowly to 25 °C and stirred for 18 h until no further
starting material remained by TLC ($R_f = 0.30$, 8:1 hexanes/ethyl acetate). The reaction dark red reaction mixture was transferred to a separatory funnel, diluted with dichloromethane (10 mL) and washed with cold 0.5 M HCl (aq) (2 x 10 mL) and water (15 mL), saturated brine (15 mL) and then dried over anhydrous MgSO₄. Concentration in vacuo yielded a light red syrup which was flash chromatographed (silica gel, 15:1 hexanes/ethyl acetate) to yield 276 mg (74%) of O-6-(7-O-triphenylmethyl-hept-2-enoic acid, 1,1-dimethylethyl ester) O-phenyl thiocarbonate (2.105) as a colorless oil.

$$\begin{align*}
\text{Ph}_3\text{CO} & \quad \text{O} \\
\text{O} & \quad \text{Ph} \\
\text{O}_2\text{Bu}^+ 
\end{align*}$$

$R_f = 0.62$ (10:1 hexanes/ethyl acetate); $[\alpha]^{20}_D = +10.99^\circ$ (c 1.28, CHCl₃); IR (thin film) 3452br, 3034m, 2978m, 2929m, 2871w, 2922w, 1960w, 1816w, 1713s, 1651m, 1594m, 1490f, 1448m, 1391m, 1367s, 1292s, 1202s, 1153s, 1079m, 1034m, 985m cm⁻¹; ¹H-NMR (250 MHz, CDCl₃) δ 7.48-7.24 (m, 20 H, Ar-H), 6.81 (ddd, $J_{3,2} = 15.6$ Hz, $J_{1,4a} = J_{3,4b} = 6.7$ Hz, 1 H, H-3), 5.72 (ddd $J_{2,3} = 15.6$ Hz, $J_{2,4a} = J_{2,4b} = 1.5$ Hz, 1 H, H-2), 5.63-5.55 (m, 1 H, H-6), 3.36 (dd, $J_{\text{gem}} = 10.3$ Hz, $J_{7a,6} = 3.9$ Hz, 1 H, H-7a), 3.28 (dd, $J_{\text{gem}} = 10.3$ Hz, $J_{7b,6} = 5.4$ Hz, 1 H, H-7b), 2.26-2.18 (m, 2 H, H-4), 2.11-1.84 (m, 2 H, H-5), 1.47 (s, 9 H, t-Bu); ¹³C-NMR (75 MHz, CDCl₃) δ 195.0 (s, C=S), 166.0 (s, C-1), 153.6 (s, Ar-O), 146.2 (d, C-3), 143.8 (s, Ar-C), 129.7 (d, Ar-H), 128.8 (d, Ar-H), 128.1 (d, Ar-H), 127.3 (d, Ar-H), 126.7 (d, Ar-H), 124.0 (d, Ar-H), 122.2 (d, C-2), 86.9 (s, Ph₃CO), 83.5 (d, C-6), 80.4 (s, OCMMe₃), 64.0 (t, C-7), 29.3 (t, C-4), 28.3 (q, CMe₃), 27.8 (t, C-5). Thionocarbonate 2.105 did not provide satisfactory elemental analysis.

Preparation of O-6-(7-O-triphenylmethyl-hept-2-enoic acid, 1,1-dimethylethyl ester) 1H-imidazole-1-carbonothioic acid (2.106) (Scheme 2.20). A 100 mL, round-bottom flask equipped with a Claisen adapter, water-cooled condenser, magnetic stir bar, rubber septum, and nitrogen inlet was charged with a 0.15 M solution of tert-butyl 7-O-triphenylmethyl-6-hydroxy-hept-2-enoate (2.104, 528 mg, 1.15 mmol) in tetrahydrofuran (8.0 mL) containing 2.0 equivalents of commercially available 1,1-thiocarbonyldiimidazole (3.8, 410 mg, 2.23 mmol) and the clear solution warmed to reflux for 2 h until no further starting material remained by TLC ($R_f = 0.42$, 6:1 hexanes/ethyl acetate). The reaction was
concentrated under reduced pressure and the crude golden syrup flash chromatographed (silica gel, 8:1 hexanes/ethyl acetate) to yield 551 mg (84%) of thiocarbamate 2.106 as a colorless oil.

\[
\text{Ph}_3\text{CO} \quad \text{N} \quad \text{S} \quad \text{N} \quad \text{CO}_2\text{Bu}'
\]

\[R_f = 0.28 \text{ (6:1 hexanes/ethyl acetate)}; \quad [\alpha]^20_D = +16.4 ^\circ \text{ (c 1.65. CHCl}_3); \quad \text{IR (thin film)} 3129\text{w}, 3059\text{m}, 2978\text{s}, 2931\text{m}, 2872\text{m}, 2081\text{w}, 1960\text{w}, 1890\text{w}, 1738\text{s}, 1713\text{s}, 1652\text{s}, 1597\text{m}, 1531\text{m}, 1489\text{s}, 1463\text{s}, 1449\text{s}, 1391\text{s}, 1371\text{s}, 1323\text{s}, 1285\text{s}, 1242\text{s}, 1154\text{s}, 1095\text{s}, 1045\text{s}, 964\text{cm}^{-1}; \quad \text{^1H-NMR (300 MHz, CDCl}_3) \delta 8.33 \text{ (m, 1 H, ImH-5)}, 7.63 \text{ (m, 1 H, ImH-2)}, 7.41-7.19 \text{ (m, 15 H, Ar-H)}, 6.79 \text{ (ddd, J}_{3.2} = 15.6 \text{ Hz, J}_{3.4a} = 6.7 \text{ Hz, J}_{3.4b} = 6.6 \text{ Hz, 1 H, H-3)}, 7.05 \text{ (m, 1 H, ImH-4)}, 5.81-5.76 \text{ (m, 1 H, H-6)}, 5.70 \text{ (ddd J}_{2.3} = 15.6 \text{ Hz, J}_{2.4a} = 1.5 \text{ Hz, J}_{2.4b} = 1.3 \text{ Hz, 1 H, H-2)}, 3.45 \text{ (dd, J}_{gem} = 10.7 \text{ Hz, J}_{7a,6} = 3.4 \text{ Hz, 1 H, H-7a)}, 3.35 \text{ (dd, J}_{gem} = 10.7 \text{ Hz, J}_{7b,6} = 5.0 \text{ Hz, 1 H, H-7b)}, 2.23-1.95 \text{ (m, 4 H, H-4and H-5)}, 1.46 \text{ (s, 9 H, t-Bu); ^13C-NMR (75 MHz, CDCl}_3) \delta 183.7 \text{ (s, C=S)}, 165.7 \text{ (s, C-1)}, 145.5 \text{ (d, C-3)}, 143.5 \text{ (s, Ar-C)}, 137.1 \text{ (d, ImC-2)}, 131.0 \text{ (d, ImC-5)}, 128.6 \text{ (d, Ar-H)}, 128.1 \text{ (d, Ar-H)}, 127.4 \text{ (d, Ar-H)}, 124.2 \text{ (d, C-2)}, 118.0 \text{ (d, ImC-4)}, 87.0 \text{ (s, Ph}_3\text{CO)}, 82.5 \text{ (d, C-6)}, 80.4 \text{ (s, OCMe}_3), 63.6 \text{ (t, C-7)}, 29.2 \text{ (t, C-4)}, 28.3 \text{ (q, CMe}_3), 27.8 \text{ (t, C-5)}. \text{Anal. Calcd. For C}_{34}\text{H}_{36}\text{O}_2\text{N}_2\text{S: C, 71.80; H, 6.38; N, 4.93; S, 5.44. Obsd. C, 71.95; H, 6.38; N, 4.78; S, 5.44.}

Chapter 3 Experimental

Preparation of \textit{N}^\text{6}-Benzoyladenine (3.17) (Figure 3.4). 282 A 100 mL round-bottom flask equipped with a magnetic stirbar, water condenser and nitrogen inlet was charged with adenine (3.15, 2.50 g, 18.5 mmol) and 2.4 equivalents of benzoic anhydride (10.0 g, 44.2 mmol). The reaction was heated to 140 °C for 2 h to give a clear yellow solution. Absolute ethanol was added (70 mL) and the temperature maintained at 90 °C for an additional 1 h to give a yellow solution containing a white suspension. The reaction was cooled to 25 °C and vacuum filtered to give a light yellow solid. The solid was dried under high vacuum in the presence of P$_2$O$_5$ to yield 3.301 g (75%) of the previously reported \textit{N}^\text{6}-benzoyladenine (3.17).
Preparation of 4-Nitrophenyl Isothiocyanate. A 100 mL, 3-necked, round-bottom flask equipped with 2 addition funnels, a magnetic stirbar and nitrogen inlet was charged with a 0.2 M solution of 4-nitroaniline (1.00 g, 7.23 mmol) in acetone (36.0 mL) and the solution cooled to 0 °C. The first addition funnel was charged with 25% aqueous Na₂CO₃ (7.0 mL) and the second addition funnel was charged with a 0.06 M solution of thiophosgene (1.2 equiv., 660 µL, 8.68 mmol) in acetone (14.0 mL). Slow, dropwise addition of both the base and thiophosgene solutions over 15 minutes yielded a yellow solution with yellow suspension. When addition was complete, the cooling bath was removed and the reaction stirred at 25 °C for an additional 1 h until no further starting material was detected by TLC ($R_f = 0.55$, 20:1 CHCl₃/MeOH). Vacuum filtration provided a pale yellow solid which was dried under high vacuum in the presence of P₂O₅ to give 1.20 g (92%) of the previously reported 4-nitrophenyl isothiocyanate.

Mp = 106.0-108.0 °C [Lit. mp = 108-110 °C]¹⁷⁴; IR (CHCl₃) 3019m, 2027m(N=C=S), 1590m, 1522m, 1496w, 1424w, 1343s, 1215s, 851m, 757s cm⁻¹; ¹H-NMR (250 MHz, CDCl₃) δ 8.25 (d, $J = 14.5$ Hz, 2 H,
Preparation of O-(2,4-dinitrophenyl) chlorothioformate (3.68) (Scheme 3.18).\(^{174,201}\) A 100 mL, 3-necked, round-bottom flask equipped with a magnetic stir bar, two addition funnels and a nitrogen inlet was charged with 0.2 M solution of 2,4-dinitrophenol (3.70, 690 mg, 3.75 mmol) in acetone (19.0 mL) and cooled to 0 °C. The first addition funnel was charged with a 1.0 M aqueous solution of Na\(_2\)CO\(_3\) (5.6 mL) and the second addition funnel was charged with 0.06 M solution of thiophosgene (1.2 equiv., 350 \(\mu\)L, 4.2 mmol) in acetone (7.5 mL). Slow, dropwise addition of both the base and thiophosgene solutions over 15 minutes yielded a yellow solution with yellow suspension. When addition was complete, the cooling bath was removed and the reaction stirred at 25 °C for an additional 2 h. The reaction mixture was then extracted with chloroform (4 x 50 mL) and the combined organic extracts washed with water (50 mL), saturated brine (50 mL) and dried over anhydrous MgSO\(_4\). Vacuum filtration and concentration in vacuo yielded a pale syrup. Trituration with benzene yielded 490 mg (50 %) of the previously reported O-(2,4-dinitrophenyl) chlorothioformate (3.68) as a pale yellow solid.\(^{283}\)

\[
\begin{align*}
\text{O} & \quad \text{Cl} \\
\text{NO}_2 & \quad \text{NO}_2
\end{align*}
\]

Mp = 157.0-159.0 °C; IR (Nujol) 3111w, 2955s, 2920s, 2852s, 1934w, 1808w, 1704w, 1613m, 1541s, 1462s, 1411w, 1375s, 1347s, 1272s, 1247m, 1213m, 1169s, 1118m, 1064m \text{cm}^{-1}; \ ^1\text{H-NMR} (250 MHz, CDCl\(_3\)) \delta 9.08 (d, \(J_{3,5} = 2.7 \text{ Hz}, 1 \text{ H, H-3}\)), 8.70 (dd, \(J_{5,6} = 8.9 \text{ Hz}, J_{5,3} = 2.7 \text{ Hz}, 1 \text{ H, H-5}\)), 7.79 (d, \(J_{6,5} = 8.9 \text{ Hz}, 1 \text{ H, H-6}\)). \(^{13}\text{C-NMR} (75 MHz, CDCl\(_3\)) \delta 188.9 (s, C=S), 149.3 (s, C-1), 146.0 (s, C-4), 140.8 (s, C-2), 129.8 (d, C-3), 127.2 (d, C-5), 122.0 (d, C-6). \ HRMS (El) calcd for C\(_7\)H\(_3\)N\(_2\)O\(_5\)Cl (m-S): 231.988699. Obsd: 231.987579.
For comparative purposes, a sample of commercially available 1,1'-thiocarbonyldiimidazole (3.38) was characterized.

\[
\begin{array}{c}
\text{IR (Nujol)} 2968s, 2843s, 1465s, 1376s, 1293m, 1267m, 1098m, 1007m, 966m, 895m, 836m, 817m, \text{cm}^{-1}.  \\
\text{H-NMR (300 MHz, DMSO-}d_6) \delta 8.34 (s, 1 H, H-2), 7.81 (s, 1 H, H-5), 7.18 (s, 1 H, H-4). \text{^13C-NMR (75 MHz, DMSO-}d_6) \delta 174.0 (C=S), 138.9 (C-2), 131.3 (C-5), 121.67 (C-4).
\end{array}
\]

Preparation of 1,1'-Carbonothioylbis(1H-1,2,4-triazole) (3.38) (Scheme 3.11).

A 50 mL, 2-necked, round-bottom flask equipped with magnetic stirbar, Claisen head adapter, water condenser, and nitrogen inlet was charged with 1.0 equivalent of 1H-1,2,4-triazole (3.14, 3.83 g, 55.5 mmol) along with 1.0 equivalent of 1,1,1,3,3,3-hexamethyldisilazane (11.7 mL, 55.5 mmol) and 1 mol% ammonium sulfate (73 mg). The reaction was heated to 125 °C for 15 h to give a clear solution. The evolution of ammonia was monitored by an exhaust tube vented through a beaker of water and the pH levels monitored with pH paper or phenolphthalein indicator. The reaction flask was then cooled and fitted with a distillation head and the contents distilled under high vacuum (bp = 40.5 °C/1.2 mm Hg) to give 7.480 g (96%) of the previously reported 1-(trimethylsilyl)-1H-1,2,4-triazole as a clear liquid which matched data previously reported. \(^{236}\)

\[
\begin{array}{c}
\text{^1H-NMR (250 MHz, CDCl}_3) \delta 8.19 (s, 1 H, H-5), 8.08 (s, 1 H, H-3), 0.48 (s, 9 H, SiMe}_3); \text{^13C-NMR (62.9 MHz, CDCl}_3) \delta 154.4 (C-5), 148.5 (C-3), -0.7 (SiCH}_3).
\end{array}
\]

A 100 mL round-bottom flask equipped with a magnet stirbar, water condenser, and nitrogen inlet was charged with a 1.0 M solution of 1-(trimethylsilyl)-1H-1,2,4-triazole (7.48 g, 52.9 mmol) in benzene (50.0 mL). To this was added 0.4 equivalents of thiophosgene (2.00 mL, 26.0 mmol) in benzene (10 mL) and
the reaction stirred at 25 °C for 0.5 h then 60 °C for an additional 0.5 h. Vacuum filtration yielded 1.123

g of a fine yellow solid which on standing decomposed with the visible evolution of gas. The recovered

d orange filtrate was concentrated to give 2.335 g (49%) of an orange solid which was later determined to

be the previously reported 1,1'-thiocarbonyldi(1H-1,2,4-triazole) (3.38).

\[
\begin{array}{c}
\text{S} \\
\text{N} \\
\text{N} \\
\text{N}
\end{array}
\]

\text{Mp = 87.0-89.0 °C (decomp.), [Lit. Mp = 99-100 °C.]; IR (Nujol) 2902s, 1513m, 1463s, 1376s, 1299m,}

1234w, 1148w, 1119w, 1069w cm\(^{-1}\); \(\text{\textsuperscript{1}H-NMR (250 MHz, CDCl\textsubscript{3}/DMSO-d\textsubscript{6}) \delta 9.23 (s, 1 H), 8.18 (s, 1 H);}

\(\text{\textsuperscript{13}C-NMR (62.9 MHz, CDCl\textsubscript{3}/DMSO-d\textsubscript{6}) \delta 166.9 (C=S), 153.0 (C-3), 144.9 (C-5).}

\]

\text{Preparation of 3-\textit{O}-\textit{\beta}-(2,4-dinitrophenyl)cholest-5-ene (3.71) (Scheme 3.19). A 50 mL, 3-necked,}

round-bottom flask equipped with magnetic stir bar, addition funnel, and nitrogen inlet was charged with a

1.0 M solution of thiophosgene (152 µL, 2.00 mmol) in chloroform (2.0 mL). The addition funnel was

charged with a 0.5 M solution of 2,4-dinitrophenol (320 mg, 2.0 mmol) in water (4.0 mL) containing 1.0

equivalent of NaOH (80 mg, 2.0 mmol) and 2 mol% tetrabutylammonium bromide (13 mg). The sodium

phenoxide was added slowly over the course of 5 min and the reaction stirred vigorously at 25 °C for an

additional 1 h. The phases were then separated, and the organic phase washed with saturated sodium

bicarbonate, water, saturated brine and then dried over anhydrous MgSO\textsubscript{4}. Vacuum filtration and

concentration in vacuo yielded 383 mg (73%) of \textit{O}-(2,4-dinitrophenyl) chlorothioformate (3.68) as a

yellow oil which solidified on standing.\textsuperscript{283} The \textit{O}-(2,4-dinitrophenyl) chlorothioformate (3.68, 383 mg,}

1.45 mmol) was dissolved in pyridine (3.0 mL) and cooled to 0 °C. 3\textit{\beta}-Cholest-5-en-3-ol (3.40, 186 mg,}

0.48 mmol) was then added in small portions over several minutes and the reaction allowed to warm to 25

°C and stirred for 48 h until no further starting material was detected by TLC \((R_f = 0.45, 2:1)

hexanes/ethyl acetate). The reaction was concentrated and the residue flash chromatographed (silica gel,}

4:1 hexanes/ethyl acetate) to give 181 mg (68%) of 3\textit{\beta}-choles-5-en-3-\textit{O}-(2,4-dinitrophenyl) (3.71) as a

yellow solid.
[α]_{D}^{19} = -12.86° (c 1.78, CHCl₃). IR (CHCl₃) 2955s, 2920s, 2875s, 2860s, 1747s, 1541w, 1465s, 1373s,
1300w, 1238s, 1100w, 1044s cm⁻¹; ¹H-NMR (250 MHz, CDCl₃) δ 8.98 (d, J₅,₇ = 2.7 Hz, 1 H, H-3'), 8.53
(dd, J₅,₆ = 8.8 Hz, J₅,₃' = 2.7 Hz, 1 H, H-5'), 7.56 (d, J₆,₅' = 8.8 Hz, 1 H, H-6'), 4.69-4.56 (m, 1 H, H-3),
2.52-2.49 (m, 2 H, H-7); 2.05-0.97 (m, 27 H), 1.08 (s, 3 H, H-19), 0.92 (d, J = 6.5 Hz, 3 H, H-21), 0.87 (d,
J = 6.5 Hz, 6 H, H-26 and H-27), 0.69 (s, 3 H, H-18), ¹³C-NMR (75 MHz, CDCl₃) δ 150.8, 148.9, 145.3,
141.6, 138.8, 129.4, 126.4, 123.8, 122.0, 81.3, 56.8, 56.3, 50.2, 42.5, 39.9, 39.7, 37.9, 36.9, 36.7, 36.4,
35.9, 32.1, 28.4, 28.2, 27.6, 24.4, 24.0, 23.0, 22.7, 21.2, 19.4, 19.4, 18.9, 12.0; Anal. calcd for
C₃₃H₄₈O₃N₂: C, 71.71; H, 8.75; N, 5.07. Obsd: C, 68.50; H, 8.13; N, 4.67; S, 0.00.

Preparation of 3β-Cholest-5-en-3-0-[1H-(1,2,4-triazol-1-yl)-1-carbothioyl] (3.41) (Scheme 3.12).

A 50 mL round-bottom flask equipped with a magnetic stirbar, Claisen head adapter, water condenser and
nitrogen inlet was charged with a 0.15 M solution of 3β-cholest-5-en-3-ol (200 mg, 0.51 mmol) in THF
(4.0 mL) containing 1.1 equivalents of 1,1'-thiocarbonyldi(1H-1,2,4-triazole) (3.38, 102 mg, 0.57 mmol)
and the solution brought to reflux for 2 h with small amounts of additional 1,1'-thiocarbonyldi(1H-1,2,4-
triazole) added until no further starting material remained by TLC (Rf = 0.58, 2:1 hexanes/ethyl acetate).
The reaction was then cooled, concentrated in vacuo and flash chromatographed (silica gel, 5:1
hexanes/ethyl acetate) to give 146 mg (58%) of the desired thiocarbamate 3.41 as a white solid.
$R_f = 0.65$ (2:1 hexanes/ethyl acetate); $Mp = 201.0-203.0 \degree C$, $\lbrack \alpha \rbrack_{D}^{20} = -43.96 \degree$ (c 1.06, CHCl$_3$); IR (CHCl$_3$) 2957s, 2929s, 2870s, 2860s, 1734s, 1395w, 1375s, 1235w, 1299m, 1247s, 1193w, 1097w, 1047s cm$^{-1}$; $^1$H-NMR (250 MHz, CDCl$_3$) $\delta$ 9.06 (s, 1 H, triazole H-5), 8.04 (s, 1 H, triazole H-3), 5.47 (d, $J = 4.2$ Hz, 1 H, H-6), 5.41 (dd, $J = 8.8$ Hz, $J = 3.0$ Hz, 1 H, H-3), 2.63 (m, 2 H, H-7) 2.25-0.98 (m, 26 H), 1.08 (s, 3 H, H-19), 0.92 (d, $J = 6.5$ Hz, 3 H, H-21), 0.87 (d, $J = 6.5$ Hz, 6 H, H-26 and H-27), 0.69 (s, 3 H, H-18); $^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ 181.5 (C=S), 153.6, 145.9, 138.7, 124.1, 85.1, 56.8, 56.3, 50.2, 42.5, 39.9, 39.7, 37.2, 37.0, 36.8, 35.9, 32.1, 32.0, 28.4, 28.2, 27.1, 24.4, 24.0, 23.0, 22.7, 21.2, 19.4, 18.9, 12.0. Anal. calcd for C$_{30}$H$_{47}$OSN$_3$: C, 72.39; H, 9.52; N, 8.44; S, 6.44. Obsd: C, 72.25; H, 9.62; N, 8.42; S, 6.43.

**Preparation of 9H-(6-chloropurine) O-phenyl carbothioate (3.30) (Scheme 3.6).** A 25 mL round-bottom flask equipped with a magnetic stirbar and nitrogen inlet was charged with a 0.4 M solution of 6-chloropurine (3.16, 200 mg, 1.29 mmol) in pyridine (3.0 mL) and the solution cooled to 0 $\degree$C. Three equivalents of O-phenyl chlorothioformate (350 $\mu$L, 3.88 mmol) were added dropwise to yield a red solution which was allowed to warm slowly to 25 $\degree$C and stirred for 18 h. The reaction was then diluted with ethyl acetate (25 mL) and washed with 5% HCl (aq) (2 x 20 mL), water (20 mL), saturated brine (10 mL) and then dried over anhydrous MgSO$_4$. Vacuum filtration and concentration in vacuo yielded a red syrup which was flash chromatographed (silica gel, 15:1 hexanes/ethyl acetate) to give 73 mg (19%) of the desired 9H-(6-chloropurine) O-phenyl thiocarbamate (3.30) as a white solid along with recovered starting 6-chloropurine.
$R_f = 0.30, \text{(15:1 hexanes/ethyl acetate)}$; \text{Mp} = 151.0-152.0 °C; \text{IR (CHCl$_3$) 3018w, 1587m, 1562m, 1518w, 1489m, 1434w, 1376m, 1347w, 1328w, 1292w, 1252m, 1215s, 1183m, 1163w, 1138m, 1024w, 926m cm$^{-1}$:} \\
$^1$H-NMR (300 MHz, CDCl$_3$) δ 9.05 (s, 1 H, purine), 8.94 (s, 1 H, purine), 7.55-7.24 (m, 5 H, Ar); $^{13}$C-NMR (75 MHz, CDCl$_3$) δ 182.1 (s, C=S), 154.4 (d, C-2), 152.7 (s, C-6), 152.6 (s, Ar), 150.6 (s, C-4), 145.5 (d, C-8), 133.1 (s, C-5), 130.1 (d, Ar), 127.7 (d, Ar), 121.8 (d, Ar). Anal. calcd for C$_{12}$H$_{16}$N$_3$S: C, 49.58; H, 2.43; N, 19.27; S, 11.03. Obsd: C, 49.63; H, 2.37; N, 19.23; S, 11.05.

**Preparation of 3α-cholest-5-en-3-S-[1H-(1,2,4-triazol-1-yl)-1-carbamothioyl] (3.44a) (Scheme 3.13).**

A 50 mL round-bottom flask equipped with a magnetic stirbar, water condenser and nitrogen inlet was charged with a 0.1 M solution of 3β-cholest-5-en-3-O-[1H-(1,2,4-triazole)thiocarbamate] (3.41, 51 mg, 0.10 mmol) in 1,2-dichloroethane containing 2.0 equivalents of benzyl alcohol (20 µL, 0.20 mmol). The reaction was warmed to 80 °C for 12 h until no further starting material was detected by TLC ($R_f = 0.30, 9:1$ hexanes/ethyl acetate). The reaction was then concentrated and the residue flash chromatographed (silica gel, 10:1 hexanes/ethyl acetate) to give 8 mg (16%) of recovered starting material 3.41, 18 mg (35%) of the title compound 3.44a and 9 mg of unidentified material.

\[ R_f = 0.45, \text{(10:1 hexanes/ethyl acetate)} \] 
\[ \text{Mp} = 190-192 °C; \text{IR (CHCl$_3$) 3070m, 3035s, 3018s, 2940m, 1961w, 1817w, 1731w, 1700m, 1517m, 1478s, 1433w, 1371m, 1274w, 1215s, 1185m, 1119w, 1035m, cm$^{-1}$; }^1\text{H-NMR (300 MHz, CDCl$_3$) δ 8.82 (s, 1 H, triazole H-5), 8.01 (s, 1 H, triazole H-3), 5.41 (m, 1 H,} \]
H-6), 3.48 (m, 1 H, H-3), 2.46-2.44 (m, 2 H, H-7), 2.03-0.85 (m, 26 H), 1.03 (s, 3 H, H-19), 0.92 (d, J = 6.5 Hz, 3 H, H-26), 0.86 (d, J = 6.5 Hz, 6 H, H-27), 0.68 (s, 3 H, H-18); $^{13}$C-NMR (75 MHz, CDCl$_3$) δ 167.5 (s, C=S), 153.1 (d, C-5'), 142.3 (d, C-6), 140.6 (d, C-3'), 122.6 (s, C-5), 56.9 (d, C-14), 56.4 (d, C-17), 50.4 (d, C-9), 45.2 (d, C-3), 42.5 (s, C-13), 39.9 (t, C-16), 39.7 (t), 39.6 (t, C-24), 38.8 (t), 36.9 (t), 36.4 (t, C-22), 36.0 (d, C-20), 32.0 (d, C-8), 29.0 (t), 28.4 (t, C-12), 28.2 (d, C-25), 24.5 (t, C-15), 24.0 (t, C-23), 23.0 (q, C-26), 22.7 (q, C-27), 21.1 (t, C-11), 19.4 (q, C-19), 18.9 (q, C-21), 12.1 (q, C-18).
HRMS (EI) calcd for C$_{27}$H$_{44}$(M-SCON$_3$)$^+$: 368.344301. Obsd: 368.343933.

Preparation of 9H-(6-chloropurine) O-Phenylmethyl carbonothioate (3.33) (Scheme 3.7). A 50 mL round-bottom flask equipped with a magnetic stirbar, water condenser and nitrogen inlet was charged with 9H-(6-chloropurine) O-pentafluorophenyl thiocarbamate (3.32, 88 mg, 0.23 mmol) in benzonitrile (3.0 mL) containing 2.0 equivalents of benzyl alcohol (50 μL, 0.46 mmol) and the reaction slowly warmed to 60 °C for 24 h until no further starting material was detected by TLC ($R_f = 0.30$, 15:1 hexanes/ethyl acetate). The reaction was then diluted with dichloromethane and washed with water, saturated brine and then dried over anhydrous MgSO$_4$. Vacuum filtration and concentration in vacuo yield a colorless syrup which was flash chromatographed (silica gel, 9:1 hexanes/ethyl acetate) to yield 29 mg (55%) of the desired 9H-(6-chloropurine) O-phenylmethyl thiocarbamate (3.33) as a colorless oil.

\[
\begin{align*}
\text{Cl} & \quad \text{N} \\
\text{N} & \quad \text{O} \\
\text{S} & \quad \text{O} \\
\text{N} & \quad \text{N} \\
\text{Ph} & \quad \text{Cl}
\end{align*}
\]

$R_f = 0.25$, (15:1 hexanes/ethyl acetate); IR (CHC$_3$) 3018s, 1611w, 1571w, 1521w, 1475w, 1423w, 1388w, 1331w, 1215s, 1045w, 1005w cm$^{-1}$; $^1$H-NMR (250 MHz, CDCl$_3$) δ 8.92 (s, 1 H, purine), 8.63 (s, 1 H, purine), 7.60-7.41 (m, 5 H, Ph), 5.85, (s, 2 H, benzyl); $^{13}$C-NMR (75 MHz, CDCl$_3$) δ 182.9 (C=S), 158.3 (purine), 153.8 (purine C-8), 152.5 (purine), 144.4 (purine C-2), 133.5 (Ar), 129.2 (Ar), 129.0 (Ar), 128.6 (Ar), 120.1 (purine), 75.6 (benzyl). Thiocarbamate 3.33 did not provide satisfactory elemental analysis.
Preparation of 3β-cholest-5-en-3-ol O-(phenylmethyl) carbonothioate (3.43) (Scheme 3.13). A 2.0 mL conical vial equipped with a magnetic spinvane and nitrogen inlet was charged with a 0.3 M solution of 3β-cholest-5-en-3-O-[1H-(1,2,4-triazole)thiocarbamate] (3.41, 30 mg, 0.06 mmol) in acetonitrile (200 µL). To this was added a solution of 4.0 equivalents of benzyl alcohol (40 µL) and NaH (60% in mineral oil, 25 mg, 0.62 mmol) in acetonitrile (260 µL). The reaction was stirred for 2 h at 25 °C until no further starting material was detected by TLC (Rf = 0.45, 2:1 hexanes/ethyl acetate). The reaction was then diluted with ethyl acetate (10 mL), washed with water (5 mL) and dried over anhydrous MgSO4. Vacuum filtration and concentration in vacuo yielded a white film which was flash chromatographed (silica gel, 5:1 hexanes/ethyl acetate) to give 16 mg (50%) of the desired mixed thiocarbonate 3.43.

Rf = 0.90 (2:1 hexanes/ethyl acetate); IR (CHCl3) 3018m, 2950m, 2868m, 1521w, 1498w, 1466w, 1378w, 1350w, 1287m, 1215s, 1137w, 1083w, 1027w, 1003w, 990w cm⁻¹; ¹H-NMR (250 MHz, CDCl3) δ 7.39-7.34 (m, 5 H, Ar), 5.45 (s, 2 H, benzyl), 5.42-5.40 (m, 1 H, H-6), 5.09 (ddddd, J3,2α = J3,4α = 11.1 Hz, J3,2α = J3,4α = 4.8 Hz, 1 H, H-3), 2.56-2.42 (m, 2 H), 2.03-0.85 (m, 26 H), 1.03 (s, 3 H, H-19), 0.92 (d, J = 6.5 Hz, 3 H, H-26), 0.86 (d, J = 6.5 Hz, 6 H, H-27), 0.68 (s, 3 H, H-18); ¹³C-NMR (75 MHz, CDCl3) δ 194.6 (s, C=S), 139.4 (s, C-5), 134.8 (s, Ar), 128.8 (d, Ar) 128.7 (d, Ar), 123.3 (d, C-6), 83.4 (d, C-3), 74.4 (t, benzyl), 56.9 (d, C-14), 56.3 (d, C-17), 50.2 (d, C-9), 42.5 (s, C-13), 39.9 (t, C-16), 39.7 (t, C-24), 37.5 (t, C-1), 37.0 (t), 36.8 (s, C-10), 36.4 (t, C-22), 36.0 (d, C-20), 32.1 (t, C-7), 32.0 (d, C-8), 29.9 (s), 28.4 (t, C-12), 28.2 (d, C-28), 27.3 (t), 24.5 (t, C-15), 24.0 (t, C-23), 23.0 (q, C-27), 22.7 (q, C-26), 21.2 (t, C-11), 19.4 (q, C-19), 18.9 (q, C-21), 12.0 (q, C-18). Anal. calcd for C₃₅H₅₂O₂S: C, 78.30; H, 9.76; S, 5.97. Obsd: C, 78.37; H, 9.90; S, 5.82.
Preparation of O-phenyl O-phenylmethyl carbonothioate (3.31) (Scheme 3.31). A 2.0 mL conical flask equipped with a magnetic spinvane and nitrogen inlet was charged with a 0.5 M solution of 9H-(6-chloropurine) O-phenyl thiocarbamate (3.30, 30 mg, 0.10 mmol) in acetonitrile (200 µL). To this was added a solution of benzyl alcohol (40 µL) and NaH (60% in mineral oil, 25 mg, 0.62 mmol) in acetonitrile (260 µL). The reaction was stirred for 0.5 h at 25 °C until no further starting material was detected by TLC ($R_f = 0.25$, 2:1 hexanes/ethyl acetate). The reaction was then diluted with ethyl acetate (10 mL) and washed with water (5 mL) and dried over anhydrous MgSO₄. Vacuum filtration and concentration in vacuo yielded a white film which was flash chromatographed (silica gel, 5:1 hexanes/ethyl acetate) to give 13 mg (53%) of the previously reported O-phenyl O-benzyl thiocarbonate (3.31) as a colorless oil.

Mixture of rotamers: $^1$H-NMR (250 MHz, CDCl₃) δ 7.48-7.05 (m, 10 H, Ar), 5.51-5.47 (m, 2 H, benzyl); $^{13}$C-NMR (75 MHz, CDCl₃) δ 195.2 (s, C=S), 153.7 (s, Ar-O), 134.4 (s), 129.8-122.0 (11 doublets, Ar), 74.9 (t, benzyl).

Preparation of 1,1'-Carbonothioylbis(1H-benzimidazole) (3.39) (Scheme 3.11). A 50 mL, 2-necked, round-bottom flask equipped with magnetic stirbar, Claisen head adapter, water condenser, and nitrogen inlet was charged with 1.0 equivalent of benzimidazole (3.10, 4.25 g, 35.9 mmol) along with 1.0 equivalent of 1,1,1,3,3,3-hexamethyldisilazane (7.58 mL, 35.9 mmol) and 1 mol% ammonium sulfate (50 mg, 0.38 mmol). The reaction was warmed to heated to 125 °C for 15 h to give a clear brown solution. The evolution of ammonia was monitored by an exhaust tube passed through a beaker of water and the pH levels monitored with pH paper or phenolphthalein indicator. The flask was then cooled and fitted with a distillation head and the contents distilled under high vacuum (bp = 165 °C/1.0 mm Hg) to give 5.174 g (75%) of the previously reported 1-(trimethylsilyl)-1H-benzimidazole as a pale yellow solid.
A 100 mL round-bottom flask equipped with a magnet stir bar, addition funnel, water condenser, and nitrogen inlet was charged with a 1.3 M solution of 1-(trimethylsilyl)-1H-benzimidazole (5.174 g, 27.18 mmol) in benzene (20.0 mL) and the solution warmed gently until homogenous. The addition funnel was charged with 0.5 equivalents of thiophosgene (100 mL, 13.59 mmol) in benzene (5 mL) and then added dropwise to the 1-(trimethylsilyl)-1H-benzimidazole solution over the course of 40 minutes when a yellow precipitate was observed. Following addition, the addition funnel was rinsed with additional benzene (3 mL) and the reaction warmed slowly to 60 °C for 0.5 h and then cooled to 25 °C. Vacuum filtration yielded 1.741 g (46 %) of a bright yellow solid which was later determined to be the previously reported 1,1'-thiocarbonyldi(1H-benzimidazole) (3.39).

Preparation of 9H-(6-chloropurine) O-(pentafluorophenyl) carbothioate (3.32) (Scheme 3.8). A 25 mL round-bottom flask equipped with a magnetic stir bar and nitrogen inlet was charged with a 0.15 M solution of 6-chloropurine (3.16, 154 mg, 1.0 mmole) in pyridine (6.6 mL) containing 10 mol% 4-
dimethylaminopyridine (12 mg) and the solution cooled to 0 °C. Two equivalents of O-pentafluorophenyl chlorothioformate (320 μL, 2.0 mmole) were added dropwise and the reaction stirred at 0 °C for 1 h. The cooling bath was then removed and the reaction stirred at 25 °C for 12 h. The reaction was then diluted with ethyl acetate (50 mL) and washed with 5% HCl (25 mL), water (20 mL), saturated brine (20 mL) and then dried over anhydrous MgSO₄. Vacuum filtration and concentration in vacuo yielded a red syrup which was flash chromatographed (silica gel. 15:1 hexanes/ethyl acetate) to give 102 mg (27%) of the desired O-pentafluorophenyl thiocarbamate 3.32 as a yellow solid.

\[
\text{Rf} = 0.45 \text{ (9:1 hexanes/ethyl acetate); Mp} = 144.0-146.0 °C; \text{IR (CHCl₃)} 4210 \text{w}, 3018 \text{w}, 1612 \text{n}, 1576 \text{m}, 1518 \text{s}, 1474 \text{w}, 1450 \text{m}, 1394 \text{m}, 1360 \text{m}, 1329 \text{m}, 1303 \text{m}, 1271 \text{m}, 1215 \text{m}, 1175 \text{m}, 1125 \text{m}, 1064 \text{w}, 1034 \text{m}, 1006 \text{m}, 975 \text{w cm}^{-1}; \text{¹H-NMR (250 MHz, CDCl₃)} \delta 9.00 (s, 1 H), 8.97 (s, 1 H); \text{¹³C-NMR (62.9 MHz, CDCl₃)} \delta 178.2 (C=S), 158.7 (C-6), 154.4 (C-2), 152.8 (C-4), 144.0 (C-8), 122.6 (C-5); \text{¹⁹F-NMR (235 MHz, CDCl₃)} \delta -76.9 \text{ (dd, J = 22.0 Hz, J = 18.1 Hz, 2 F, F-3 and F-5)}, -83.3 \text{ (t, J = 22.0 Hz, 1 F, F-4)}, -86.7 \text{ (d, J = 18.1 Hz, 2 F, F-2 and F-6)}. \text{Thiocarbamate 3.32 did not give satisfactory elemental analysis.}

Preparation of 1,1-dimethylethyl 2,3-dideoxy-7-O-[1,1-dimethylethyl]dimethylsilyl]-4,5-O-(1-methylethylidene)-6-O-[1H-(1,2,4-triazol-1-yl)-1-carbamothioyl]-D-ribo-hept-2-enoate (3.60) (Scheme 3.14). A 25 mL, 2-necked round-bottom flask equipped with a magnetic stirbar, condenser and nitrogen inlet was charged with a 0.15 M solution of (Z)-tert-butyl 2,3-dideoxy-7-O-[tert-butyl]dimethylsilyl]-4,5-O-isopropylidene-D-ribo-hept-2-enoate (2.52, 325 mg, 0.80 mmol) in dimethoxymethane (5.0 mL) containing 3.0 equivalents of 1,1'-thiocarbonyldi(1H-1,2,4-triazole) (3.38, 40 mg, 2.4 mmol) and the reaction warmed slowly to 60 °C for 12 h. The reaction was then cooled and the solids removed by filtration through Celite. The filtrate was concentrated in vacuo and flash
chromatographed (15:1 hexanes/ethyl acetate) to give 163 mg (39%) of 1H-(1,2,4-triazole)thiocarbamate 3.60 as a light yellow oil along with unreacted starting material 2.52.

\[
R_f = 0.35 \text{ (4:1 hexanes/ethyl acetate); } [\alpha]_D^{20.5} = +98.5^\circ \text{ (c 1.03, CHCl}_3); \text{ IR (CHCl}_3) 2983, 2954, 2931, 2857, 1710, 1647, 1516, 1471, 1482, 1397, 1383, 1372, 1344, 1320, 1279, 1240, 1202, 1157, 1124, 1083, 1066, 967 \text{ cm}^{-1}; \text{ } ^1H-NMR (300 MHz, CDCl}_3) \delta 8.85 \text{ (s, 1 H, triazole H-5), 8.01 \text{ (s, 1 H, triazole H-3), 6.19 \text{ (dd, 1 H, J}_3.2 = 11.6 \text{ Hz, J}_3.4 = 7.7 \text{ Hz, 1 H, H-3), 5.78 \text{ (ddd, J}_3.4 = 7.7 \text{ Hz, J}_4.5 = 6.6 \text{ Hz, J}_4.2 = 1.5 \text{ Hz, 1 H, H-4), 5.72 \text{ (dd, J}_2.3 = 11.6 \text{ Hz, J}_2.4 = 1.5 \text{ Hz, 1 H, H-2), 5.63 \text{ (ddd, J = 7.5 Hz, J = 4.4 Hz, J = 3.2 Hz, 1 H), 4.88 \text{ (app. t, J = 7.0 Hz, 1 H), 4.06-3.96 \text{ (m, 2 H), 1.51 \text{ (s, 3 H, acetal), 1.41 \text{ (s, 3 H, acetal), 1.40 \text{ (s, 9 H, OBu}^t\text{), 0.83 \text{ (s, 9 H, SiBu}^t\text{), 0.03 \text{ (s, 3 H, SiMe), 0.01 \text{ (s, 3 H, SiMe);} ^13C-NMR (75 MHz, CDCl}_3) \delta 180.9 \text{ (s, C=S), 164.8 \text{ (s, C=O), 153.8 \text{ (d, triazole C-5), 143.9 \text{ (d, triazole C-3), 142.6 \text{ (d, C-3), 124.8 \text{ (C-2), 109.7 \text{ (s, acetal), 82.6 \text{ (d, 81.3 \text{ (s, OBu}^t\text{), 75.3 \text{ (d, 74.2 \text{ (d, 61.5 \text{ (t, C-7), 28.3 \text{ (q, OBu}^t\text{), 27.8 \text{ (q, acetal), 25.9 \text{ (q, SiBu}^t\text{), 25.3 \text{ (q, acetal), 18.3 \text{ (s, SiBu}^t\text{), -5.33 \text{ (q, SiMe}_2\text{).} \text{ Anal. calcd for C}_{23}H_{39}O_8N_5SSi: C, 53.77; H, 7.65; N, 8.18; S, 6.24. Obsd: C, 54.15; H, 7.62; N, 7.33; S, 6.25.}

**Preparation of (4S,5R,6R) 7-O-[(1,1-dimethylethyl)dimethylsilyl]-6-hydroxy-4,5-O-(1-methylethylidene)-hept-2-enoic acid, \(\varepsilon\)-lactone (3.34)** (Scheme 3.8). A 2.0 mL conical vial equipped with magnetic spin vane, water condenser and nitrogen inlet was charged with a 0.4 M solution of 9H-(6-chloropurine) \(\bigcirc\)-(pentafluorophenyl) thiocarbamate (3.32, 145 mg, 0.38 mmol) in dimethoxymethane (1.0 mL) containing 1.37 equivalents of \((Z)\)-tert-butyl 2,3-dideoxy-7-O-[tert-butyl(dimethyl)silyl]-4,5-O-isopropylidene-D-ribos-2-enolate (2.52, 210 mg, 0.52 mmol) and the reaction warmed slowly to reflux for 48 h until no further starting material remained by TLC \((R_f = 0.40, 10:1\text{ hexanes/ethyl acetate). The} \)
reaction was then concentrated and flash chromatographed (silica gel, 12:1 hexanes/ethyl acetate) to give 50 mg (40%) of what has been tentatively identified as (4S,5R,6R) 7-O-[tert-butyldimethylsilyl]-6-hydroxy-4,5-O-isopropylidene-hept-2-enoic acid, ε-lactone (3.34).

\[
\begin{align*}
\text{Bu'Me₂SiO} &
\end{align*}
\]

\[R_f = 0.35 \text{ (10:1 hexanes/ethyl acetate); } \mu_r^{28} = -66.1 \circ \text{ (c 0.13, CHCl}_3\text{); IR (CHCl}_3\text{) 3020m, 2991m, 2856m, 2930m, 2884m, 2857m, 1790m, 1759s, 1534m, 1518m, 1471m, 1463m, 1382m, 1374m, 1253m, 1216s, 1162m, 1140m, 1088s, 1041m, 1016m cm}^{-1}; ^1\text{H-NMR (300 MHz, CDCl}_3\text{) d 7.63 (dd, J}_{2.4} = 5.7 \text{ Hz, J}_{3.4} = 1.6 \text{ Hz, 1 H, H-3)}, 6.18 \text{ (dd, J}_{2.3} = 5.7 \text{ Hz, J}_{2.4} = 1.9 \text{ Hz, 1 H, H-2), 5.25 (ddd, J}_{4.3} = 7.8 \text{ Hz, J}_{4.2} = 1.9 \text{ Hz, J}_{4.3} = 1.6 \text{ Hz, 1 H, H-4), 4.30 (ddd, J}_{6.5} = 6.0 \text{ Hz, J}_{6.7b} = 5.0 \text{ Hz, J}_{7a} = 4.5 \text{ Hz, 1 H, H-6), 3.99 (dd, J}_{gem} = 11.5 \text{ Hz, J}_{7a,6} = 4.5 \text{ Hz, 1 H, H-7a), 3.94 (dd, J}_{gem} = 11.5 \text{ Hz, J}_{7b,6} = 5.0 \text{ Hz, 1 H, H-7b), 3.94 (dd, J}_{5.4} = 7.8 \text{ Hz, J}_{5.6} = 6.0 \text{ Hz, 1 H, H-5), 1.46 (s, 3 H, acetal), 1.34 (s, 3 H, acetal), 0.90 (s, 9 H, SiBu'}^3\text{), 0.10 (s, 6 H, SiMe)}_2; ^13\text{C-NMR (75 MHz, CDCl}_3\text{) $\delta$ 172.9 (C=O), 156.1 (C-3), 122.3 (C-2), 109.5 (acetal), 80.9, 78.07, 78.01, 61.5 (C-7), 27.5 (acetal), 26.1 (SiBu') , 25.2 (acetal), 18.5 (SiBu'), -3.8 (SiMe). Lactone 3.34 did not give satisfactory elemental analysis.}

Preparation of 2,3-O-(1-methylethylidene)-5-O-triphenylmethyl-D-ribose, O-methoxime (3.54) (Scheme 3.14). A 50 mL round-bottom flask equipped with a magnetic stirbar and nitrogen inlet was charged with a 1.0 M solution of 4,5-di-O-acetyl-2,3-O-isopropylidene-D-ribose, O-methoxime (2.49, 900 mg, 2.96 mmol) in absolute methanol (3.0 mL). To this was added a solution of prepared NaOMe in methanol and the reaction stirred at 25 °C for 4 h until no further starting material remained by TLC \(R_f = 0.9, 20:1 \text{ CHCl}_3/\text{MeOH}\). Amberlite IR-120 acidic resin was then added until the reaction was pH ≈ 7.0. The resin was then removed by filtration and the filtrate concentrated to give 640 mg of a clear syrup with was dissolved in CH₂Cl₂ (3.0 mL) and cooled to 0 °C. To this was added 1.05 equivalents of TrCl/DMAP

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(1.230 g, 3.0 mmol) in small portions over 30 min and then brought to reflux for 4 h. The reaction was concentrated and the residue flash chromatographed (silica gel, 10:1 hexanes/ethyl acetate) to give 365 mg (27%) of the previously reported 2,3-\(\text{O-}(1\text{-isopropylidene})\)-5-\(\text{O}\)-triphenylmethyl-D-ribose.

\(\text{O-methyloxime (3.54)}\) as a white solid along with 160 mg of unreacted starting material 2.49.

\[\begin{align*}
\text{Ph}_2\text{CO} & \quad \text{OH} \\
& \quad \text{NOMe}
\end{align*}\]

Mixture of isomers \(E/Z = 4\); \(R_f = 0.30\) (9:1 hexane/ethyl acetate); IR(CHCl\(_3\)) 3569br, 3060m, 2937m, 2249m, 1959w, 1900w, 1786m, 1734w, 1628w, 1597m, 1490s, 1448s, 1382s, 1374s, 1316m, 1219s, 1160m, 1044s cm\(^{-1}\); \(1^H\)-NMR (300 MHz, CDCl\(_3\)) \(\delta 7.54\)\-6.74 (m, 16 H, trityl and H-1), 4.74 (dd, \(J_{2,1} = 7.6\) Hz, \(J_{2.2} = 6.1\) Hz, 1 H, H-2), 4.20 (dd, \(J_{3.4} = 9.0\) Hz, \(J_{3.2} = 6.1\) Hz, 1 H, H-3), 3.84 (s, 3 H, OMe), 3.75 (ddd, \(J_{o.4} = 9.0\) Hz, \(J_{o.5b} = 6.0\) Hz, \(J_{4.5a} = 3.2\) Hz, 1 H, H-4), 3.38 (dd, \(J_{gem} = 9.7\) Hz, \(J_{sa.4} = 3.2\) Hz, 1 H, H-5a), 3.31 (dd, \(J_{gem} = 9.7\) Hz, \(J_{ba.4} = 6.0\) Hz, 1 H, H-5b), 2.70-2.40 (br s, 1 H, D\(_2\)O exch., OH), 1.37 (s, 3 H, acetal), 1.33 (s, 3 H, acetal); \(1^C\)-NMR (75 MHz, CDCl\(_3\)) \(\delta 149.3\) (s, Ph), 147.2 (d, C-1), 144.0 (s, Ph) 143.9 (s, Ph), 128.8 (d), 128.0 (d), 127.3 (d), 109.9 (s, acetal), 87.0 (s, CPh\(_3\)), 77.9 (d), 75.3 (d), 69.1 (d), 65.0 (t, C-5), 62.0 (q, OMe), 27.9 (q, acetal), 25.6 (q, acetal).

**Preparation of 2,3-\(\text{O-}(1\text{-methylethylidene})\)-4,5-di-\(\text{O}\)-thiocarbonate-D-ribofuranose, \(\text{O-methyloxime (3.76)}\)** (Scheme 3.22). A 50 mL round-bottom flask equipped with a magnetic stirbar and nitrogen inlet was charged with a 0.4 M solution of 4,5-di-\(\text{O}\)-acetyl-2,3-\(\text{O-}\)isopropylidene-D-ribofuranose, \(\text{O}\)-methyloxime (2.49, 260 mg, 0.84 mmol) in methanol (2.0 mL). To this was added a prepared solution of NaOMe/MeOH and the reaction stirred at 25 °C for 4 h. The solution was then neutralized to \(pH = 7.0\) by addition of IR-120 acidic resin. The solids were removed by filtration and the concentrate dissolved in dimethoxymethane (2.0 mL) to which was added 1.5 equivalents of 1,1'-thiocarbonyldi(1H-imidazole) (3.8, 224 mg, 1.26 mmol) and brought to reflux for 2 h. The reaction was cooled to 25 °C, concentrated in
vacuo and the residue flash chromatographed (silica gel, 10:1 hexanes/ethyl acetate) to yield 134 mg (65%) of the desired cyclic thiocarbonate 3.76 as a colorless oil.

Mixture of isomers ($E/Z = 1$): IR (CHCl$_3$) 3019m, 1319w, 1301w, 1288w, 1215s, 1164w, 1045m cm$^{-1}$; $^1$H-NMR (300 MHz, CDCl$_3$) δ 7.30 (d, $J_{1,2} = 6.7$ Hz, 0.46 H, H-1), 6.79 (d, $J_{1,2} = 3.9$ Hz, 0.54 H, H-1), 5.20 (dd, $J_{2,3} = 7.6$ Hz, $J_{2,1} = 3.9$ Hz, 0.54 H, H-2), 4.99 (ddd, $J_{4,3} = 7.6$ Hz, $J_{4,5a} = 7.6$ Hz, $J_{4,5b} = 5.5$ Hz, 0.46 H, H-4), 4.89 (app. t, $J_{2,1} = J_{2,3} = 6.7$ Hz, 0.46 H, H-2), 4.83-4.73 (m, 1 H), 4.64 (m, 1 H), 4.53 (m, 2 H, H-5), 1.55 (s, 3 H, acetal), 1.42 (s, 3 H, acetal). $^{13}$C-NMR (75 MHz, CDCl$_3$) Major isomer: δ 191.6 (C=S), 147.8 (C-1), 110.6 (acetal), 80.3, 76.6, 74.1, 69.5 (C-5), 62.5 (OMe), 26.4 (acetal), 24.2 (acetal); Minor isomer: δ 191.2 (C=S), 144.8 (C-1), 111.0 (acetal), 79.0, 75.8, 71.6, 70.5 (C-5), 63.0 (OMe), 27.2 (acetal). 24.9 (acetal). Anal. calcd for C$_{10}$H$_{15}$O$_3$NS: C, 45.97; H, 5.79; N, 5.36; S, 12.27. Obsd: C, 46.23; H, 5.96; N, 5.25; S, 12.03

**Preparation of 2,3-O-(1-methylethylidene)-4-O-[1H-(1,2,4-triazol-1-yl)-1-carbamothioyl]-5-O-triphenylmethyl-D-ribose, O-methyloxime (3.56) (Scheme 3.14).** In a glove box, a 10 mL scintillation vial containing a magnetic stirbar was charged with a 0.18 M solution of 2,3-O-isopropylidene-5-O-triphenylmethyl-D-ribose, O-methyloxime (3.54, 165 mg, 0.36 mmol) in dimethoxyethane (2.0 mL) containing 2.0 equivalents of thiocarbonyldi(1H-1,2,4-triazole) (3.38, 129 mg, 0.71 mmol) and the heterogeneous mixture cooled to -33 °C. In one portion, 1.02 equivalents of mineral oil free potassium hydride (15 mg, 0.37 mmol) was added with vigourous stirring and the visible evolution of hydrogen. The reaction was stirred at 25 °C for 3 h. The solids were then removed by filtration over Celite, and the filter pad rinsed with additional dimethoxyethane (2.0 mL). The filtrate was concentrated to yield an orange syrup which was flash chromatographed (silica gel, 8:1 hexanes/ethyl acetate) to give 42 mg
(20%) of the desired thiocarbamate 3.56 as a colorless syrup along with 100 mg (60%) of unreacted starting material. Thiocarbamate 3.56 was a mixture of rotational and stereoisomers and could not be fully characterized.

\[
\begin{align*}
\text{Ph}_3\text{CO} & \quad \text{NOMe} \\
\end{align*}
\]

IR (CHCl\textsubscript{3}) 3018\textsubscript{m}, 1517\textsubscript{w}, 1423\textsubscript{w}, 1397\textsubscript{w}, 1330\textsubscript{w}, 1278\textsubscript{w}, 1213\textsubscript{s}, 1125\textsubscript{w}, 1078\textsubscript{w}, 1049\textsubscript{w} cm\textsuperscript{-1}; \textsuperscript{1}H-NMR (200 MHz, CDCl\textsubscript{3}) \delta 8.95-8.85 (m, 1 H, triazole H-5), 8.12-7.97 (m, 1 H, triazole H-3), 7.53-6.64 (m, 16 H, trityl and H-1), 5.81-4.56 (m, 3 H), 3.77-3.56 (m, 4 H), 3.31-2.80 (m, 1 H), 1.70-1.38 (m, 6 H, acetal). \textsuperscript{13}C-NMR (75 MHz, CDCl\textsubscript{3}) \delta 182.0 (s, C=S) and 181.6 (s, C=S). Anal. calcd for C\textsubscript{31}H\textsubscript{32}O\textsubscript{5}N\textsubscript{4}S: C, 65.02; H, 5.63; N, 9.78; S, 5.60. Obsd: C, 64.97; H, 5.95; N, 9.07; S, 4.93.

2,3-O-(1-methylethylidene)-4-O-[(benzimidazol-1-yl)-1-carbamothioyl]-5-O-triphenylmethyl-D-ribose, O-methyloxime (3.57) (Scheme 3.14). In a glove box, a 10 mL scintillation vial containing a magnetic stirbar was charged with a 0.18 M solution of 2,3-O-isopropylidene-5-O-trityl-D-ribose, O-methyloxime (3.54, 183 mg, 0.40 mmol) in dimethoxyethane (2.0 mL) containing 1.9 equivalents of 1,1'-thiocarbonyldi(1H-benzimidazole) (3.39, 220 mg, 0.79 mmol) and the heterogeneous mixture cooled to -33 °C. In one portion, 1.05 equivalents of mineral oil free potassium hydride (16 mg, 0.41 mmol) was added with vigorous stirring and the visible evolution of hydrogen. The reaction was stirred at 25 °C for 3 h. The solids were then removed by filtration over Celite, and the pad rinsed with additional dimethoxyethane (2.0 mL). The filtrate was concentrated in vacuo to yield an orange syrup which was flash chromatographed (silica gel, 9:1 hexanes/ethyl acetate) to give 143 mg (58%) of the thiocarbamate 3.57 as a white solid along with 72 mg (29%) of slightly impure 3.57.
Mixture of isomers: $R_f = 0.25$ (9:1 hexanes/ethyl acetate); $M_p = 71.0-72.0^\circ C$; IR (CHCl$_3$) 3018m, 1516w, 1490w, 1448m, 1374m, 1318w, 1288w, 1247m, 1215s, 1160w, 1077w, 1046m cm$^{-1}$; $^1$H-NMR (300 MHz, CDCl$_3$) δ 8.75 (s, 1 H, benzimidazole H-2), 8.12 (d, $J = 6.9$ Hz, 1 H, benzimidazole), 7.77 (d, $J = 7.3$ Hz, 1 H, benzimidazole), 7.45 - 6.65 (m, 18 H, trityl, benzimidazole and H-1), 5.74 (ddd, $J_{4,3} = 8.9$ Hz, $J_{4,b} = 3.1$ Hz, $J_{4,a} = 2.4$ Hz, 1 H, H-4), 5.08 (dd, $J_{3,a} = 8.9$ Hz, $J_{3,2} = 6.2$ Hz, 1 H, H-3), 4.86 (dd, $J_{2,1} = 7.9$ Hz, $J_{2,2} = 6.2$ Hz, 1 H, H-2), 3.66 (dd, $J_{gem} = 11.2$ Hz, $J_{5,a,4} = 2.4$ Hz, 1 H, H-5a), 3.72 (dd, $J_{gem} = 11.2$ Hz, $J_{5,b,4} = 3.1$ Hz, 1 H, H-5b), 3.38 (s, 3 H, OMe), 1.48 (s, 6 H, acetal); $^{13}$C-NMR (125 MHz, CDCl$_3$) δ 183.5 (s, C=S), 145.7(d, C-1), 143.6 (s, trityl), 128.9 (d), 128.7 (d), 128.5 (d), 128.0 (d), 127.3 (d), 127.1 (d), 126.0 (d), 125.2 (d), 121.0 (d), 116.2 (d), 110.7 (s, acetal), 87.2 (s, CPh$_3$), 79.2(d), 75.3(d), 75.0 (d), 61.8 (q, OMe), 61.0 (t, C-5), 27.8 (q, acetal), 25.5 (q, acetal). Thiocarbamate 3.57 did not give satisfactory elemental analysis.

Preparation of (2Z)-1,1-dimethylethyl 6-O-[(1H-(benzimidazol-1-yl)-1-carbamothioyl]-2,3-dideoxy-7-O-[(1,1-dimethylethyl)dimethylsilyl]-4,5-O-(1-methylethylene)-D-ribo-hept-2-enoate (3.61) (Scheme 3.14). In a glove box, a 10 mL scintillation vial containing a magnetic stirbar was charged with a 0.25 M solution of (Z)-tert-butyl 2,3-dideoxy-7-O-(tert-butylmethylsilyl)-4,5-O-isopropylidene-D-ribo-hept-2-enoate (2.52, 200 mg, 0.49 mmol) in dimethoxethane (2.0 mL) containing 2.0 equivalents of 1,1'-thiocarbonyldi(1H-benzimidazole) (3.39, 277 mg, 0.99 mmol) and the heterogeneous mixture cooled to -33 °C. In one portion, 1.06 equivalents of mineral oil free potassium hydride (21 mg, 0.52 mmol) was added with vigourous stirring and the visible evolution of hydrogen. The reaction was stirred at 25 °C for 3 h. The solids were then removed by filtration over Celite, and the pad rinsed with additional
dimethoxyethane (2 mL). The filtrate was concentrated and flash chromatographed (silica gel, 8:1 hexanes/ethyl acetate) to give 175 mg (64%) of the desired thiocarbamate (Z)-3.61 along with 45 mg (16%) of the (E)-3.61 each as a colorless oil.

\[
\begin{align*}
Z\text{-isomer: } & R_f = 0.45 \text{ (6:1 hexanes/ethyl acetate)}; \ [\alpha]_D^{18.5} = + 64.1^\circ \text{ (c 0.82, CHCl}_3); \text{ IR (CHCl}_3 \text{) 3019s, } 2986m, 2930m, 2858w, 1708m, 1516m, 1472w, 1449m, 1415w, 1372s, 1347m, 1314m, 1287m, 1251s, 1215s, 1159m, 1102m, 1066m, 1038m \text{ cm}^{-1}; \text{ }^1\text{H-NMR (300 MHz, CDCl}_3 \delta 8.80 \text{ (s, 1 H, benzimidazole H-2), 8.19-8.16 \text{ (m, 1 H, benzimidazole), 7.76-7.72 \text{ (m, 1 H, benzimidazole), 7.38-7.32 \text{ (m, 2 H, benzimidazole), 6.20} \text{ (dd, } J_{3,2} = 11.6 \text{ Hz, } J_{3,4} = 7.9 \text{ Hz, 1 H, H-3), 5.82} \text{ (ddd, } J_{4,3} = 7.9 \text{ Hz, } J_{4,5} = 6.3 \text{ Hz, } J_{4,2} = 1.5 \text{ Hz, 1 H, H-4), 5.71} \text{ (ddd, } J_{6,5} = 8.5 \text{ Hz, } J_{6,7a} = 3.2 \text{ Hz, } J_{6,7b} = 2.4 \text{ Hz, 1 H, H-6), 5.65} \text{ (dd, } J_{2,3} = 11.6 \text{ Hz, } J_{2,4} = 1.5 \text{ Hz, 1 H, H-2), 4.99} \text{ (dd, } J_{5,6} = 8.5 \text{ Hz, } J_{5,4} = 6.3 \text{ Hz, 1 H, H-5), 4.08} \text{ (dd, } J_{gem} = 11.8 \text{ Hz, } J_{7a,6} = 3.2 \text{ Hz, 1 H, H-7a), 4.02} \text{ (dd, } J_{gem} = 11.8 \text{ Hz, } J_{7b,6} = 2.4 \text{ Hz, 1 H, H-7b), 1.54} \text{ (s, 3 H, acetal), 1.43} \text{ (s, 3 H, acetal), 1.18} \text{ (s, 9 H, OBu'), 0.86} \text{ (s, 9 H, SiBu'), 0.02} \text{ (s, 3 H, SiMe), -0.02} \text{ (s, 3 H, SiMe); }^13\text{C-NMR (75 MHz, CDCl}_3 \delta 184.3 \text{ (s, C=S), 164.5} \text{ (s, C=O), 144.8} \text{ (s, benzimidazole), 143.8} \text{ (s, benzimidazole), 142.3} \text{ (d, C-3), 126.0} \text{ (d), 125.1} \text{ (d), 124.6} \text{ (d), 120.8} \text{ (d), 116.5} \text{ (d), 109.6} \text{ (s, acetal), 81.0} \text{ (s, OBu'), 80.7} \text{ (d), 74.7} \text{ (d), 74.0} \text{ (d), 61.2} \text{ (t, C-7), 28.0} \text{ (q, OBu'), 27.9} \text{ (q, acetal), 25.9} \text{ (q, SiBu'), 25.4} \text{ (q, acetal), 18.4} \text{ (s, SiBu') -5.2} \text{ (q, SiMe), -5.4} \text{ (q, SiMe). Anal. calcd for } C_{28}H_{42}O_6N_2SSi: \text{ C, 59.76; H, 7.53 N, 4.98; S, 5.67. Obsd: C, 59.91; H, 7.60; N, 4.90; S, 5.53. }
\end{align*}
\]

E-isomer: [\alpha]_D^{18.5} = + 1.52 \text{ (c 0.33, CHCl}_3); \text{ IR (CHCl}_3 \text{) 3019m, 2985m, 2931m, 2858m, 1711m, 1660w, 1609w, 1517m, 1472w, 1448m, 1372s, 1346m, 1320m, 1287m, 1250m, 1250s, 1215s, 1158s, 1122m, 1102m, 1071m, 1042m, cm}^{-1}; \text{ }^1\text{H-NMR (250 MHz, CDCl}_3 \delta 8.80 \text{ (s, 1 H, benzimidazole H-2), 8.12-8.08 \text{ (m, 1 H, benzimidazole), 7.76-7.72 \text{ (m, 1 H, benzimidazole), 7.38-7.32 \text{ (m, 2 H, benzimidazole), 6.20} \text{ (dd, } J_{3,2} = 11.6 \text{ Hz, } J_{3,4} = 7.9 \text{ Hz, 1 H, H-3), 5.82} \text{ (ddd, } J_{4,3} = 7.9 \text{ Hz, } J_{4,5} = 6.3 \text{ Hz, } J_{4,2} = 1.5 \text{ Hz, 1 H, H-4), 5.71} \text{ (ddd, } J_{6,5} = 8.5 \text{ Hz, } J_{6,7a} = 3.2 \text{ Hz, } J_{6,7b} = 2.4 \text{ Hz, 1 H, H-6), 5.65} \text{ (dd, } J_{2,3} = 11.6 \text{ Hz, } J_{2,4} = 1.5 \text{ Hz, 1 H, H-2), 4.99} \text{ (dd, } J_{5,6} = 8.5 \text{ Hz, } J_{5,4} = 6.3 \text{ Hz, 1 H, H-5), 4.08} \text{ (dd, } J_{gem} = 11.8 \text{ Hz, } J_{7a,6} = 3.2 \text{ Hz, 1 H, H-7a), 4.02} \text{ (dd, } J_{gem} = 11.8 \text{ Hz, } J_{7b,6} = 2.4 \text{ Hz, 1 H, H-7b), 1.54} \text{ (s, 3 H, acetal), 1.43} \text{ (s, 3 H, acetal), 1.18} \text{ (s, 9 H, OBu'), 0.86} \text{ (s, 9 H, SiBu'), 0.02} \text{ (s, 3 H, SiMe), -0.02} \text{ (s, 3 H, SiMe); }^13\text{C-NMR (75 MHz, CDCl}_3 \delta 184.3 \text{ (s, C=S), 164.5} \text{ (s, C=O), 144.8} \text{ (s, benzimidazole), 143.8} \text{ (s, benzimidazole), 142.3} \text{ (d, C-3), 126.0} \text{ (d), 125.1} \text{ (d), 124.6} \text{ (d), 120.8} \text{ (d), 116.5} \text{ (d), 109.6} \text{ (s, acetal), 81.0} \text{ (s, OBu'), 80.7} \text{ (d), 74.7} \text{ (d), 74.0} \text{ (d), 61.2} \text{ (t, C-7), 28.0} \text{ (q, OBu'), 27.9} \text{ (q, acetal), 25.9} \text{ (q, SiBu'), 25.4} \text{ (q, acetal), 18.4} \text{ (s, SiBu') -5.2} \text{ (q, SiMe), -5.4} \text{ (q, SiMe). Anal. calcd for } C_{28}H_{42}O_6N_2SSi: \text{ C, 59.76; H, 7.53 N, 4.98; S, 5.67. Obsd: C, 59.91; H, 7.60; N, 4.90; S, 5.53. }
\]
(m, 1 H, benzimidazole), 7.80-7.77 (m, 1 H, benzimidazole), 7.40-7.35 (m, 2 H, benzimidazole), 6.64 (dd, \(J_{3,2} = 15.6\) Hz, \(J_{3,4} = 5.4\) Hz, 1 H, H-3), 5.94 (dd, \(J_{2,3} = 15.6\) Hz, \(J_{2,4} = 1.2\) Hz, 1 H, H-2), 5.54-5.51 (ddd, \(J_{6,5} = 8.7\) Hz, \(J_{6,7a} = 2.3\), \(J_{6,7b} = 2.1\) Hz, 1 H, H-6), 4.95-4.85 (m, 2 H, H-4 and H-5), 4.13 (dd, \(J_{\text{gem}} = 11.8\) Hz, \(J_{\text{gem}} = 11.8\) Hz, 1 H, H-7a), 4.03 (dd, \(J_{\text{gem}} = 11.8\) Hz, \(J_{\text{gem}} = 2.3\) Hz, 1 H, H-7b), 1.56 (s, 3 H, acetal), 1.44 (s, 3 H, acetal), 1.31 (s, 9 H, OBu'), 0.88 (s, 9 H, SiBu'), 0.05 (s, 3 H, SiMe), -0.02 (s, 3 H, SiMe); ^13C-NMR (50 MHz, CDCl\(_3\)) \(183.7\) (s, C=S), 164.7 (s, C=O), 144.9 (s), 144.1 (s), 139.1 (d), 131.3 (s), 126.0 (d), 125.2 (d), 121.2 (d), 115.9 (d), 110.0 (s, acetal), 100.2 (d), 80.7 (s, OBu'), 80.3 (d), 76.4 (d), 74.9 (d), 60.4 (t, C-7), 28.1 (q, OBu'), 28.0 (q, acetal), 26.0 (q, SiBu'), 25.6 (q, acetal), 18.4 (s, SiBu'), -5.2 (q, SiMe), -5.4 (q, SiMe).

Radical cyclization 2,3-O-(1-methylethylidene)-4,5-O-di-O-thiocarbonate-D-ribofuranose.

O-methyloxime (3.76): Preparation of 2- amino-2,5-anhydro-3,4-(1-methylethylidene)-D-allonothioic acid, \(\epsilon\)-lactone (3.78) (Scheme 3.23). A 50 mL round-bottom flask equipped with a magnetic stirrer, water cooled condenser and nitrogen inlet was charged with a 0.05 M solution of tributyltin hydride (215 \(\mu\)L, 0.80 mmol) in toluene (16.0 mL). Nitrogen gas was bubbled through the solution for 15 minutes and then warmed to 90 °C. A solution of 2,3-O-isopropylidene-4,5-O-di-O-thiocarbonate-D-ribofuranose, O-methyloxime (3.76, 100 mg, 0.38 mmol) in degassed toluene (5 mL) containing 0.2 equivalents of AIBN (12 mg, 0.076 mmol) was added via syringe pump over the course of 3 h and until no further oxime ether was detected by TLC (\(R_f = 0.80, 2:1\) hexanes/ethyl acetate w/triethyl amine). The reaction mixture was cooled and concentrated in vacuo to yield a light yellow oil which was flash chromatographed (silica gel, 1:1 hexanes/ethyl acetate w/triethylamine) yielded 52 mg (60%) of a white waxy solid which was identified as the 2-amino-2,5-anhydro-3,4-(1-methylethylidene)-D-allonothioic acid, \(\epsilon\)-lactone (3.78).
$R_f = 0.25$, (1:1 hexanes/ethyl acetate w/triethylamine); Mp = 122.5-123.5 ° C (decomp.); $[\alpha]_D^{18\circ} = + 24.2$

(c 0.15, CHCl$_3$); IR (CHCl$_3$) 4212w, 3018s, 1602w, 1518w, 1474w, 1422w, 1386w, 1372w, 1307w, 1244m, 1214s, 1160w, 1139w, 1111w, 1081w cm$^{-1}$; $^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 4.97 (dd, $J_{5,6} = 2.8$ Hz, $J_{5,6} = 2.0$ Hz, $J_{5,4b} = 0.7$ Hz, 1 H, H-5), 4.57 (dd, $J_{6,7} = 7.8$ Hz, $J_{6,5} = 2.0$ Hz, 1 H, H-6), 4.48 (d, $J_{7,6} = 7.8$ Hz, 1 H, H-7). 4.17 (dd, $J_{gem} = 10.5$ Hz, $J_{4a,5} = 2.8$ Hz, 1 H, H-4a), 4.00 (dd, $J_{gem} = 10.5$ Hz, $J_{4b,5} = 0.7$ Hz, 1 H, H-4b), 2.79 (br. s, 2 H, NH$_2$). 1.44 (s, 3 H, acetalt), 1.35 (s, 3 H, acetalt); $^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ 216.3 (s, C=S), 111.6 (s, acetalt), 86.5 (s, C-1), 77.4 (d, C-7), 76.4 (d, C-5), 73.8 (d, C-6), 64.1 (t, C-4), 26.0 (q, acetalt), 24.9 (q, acetalt). Anal. caled for C$_9$H$_{13}$NO$_4$S: C, 46.74; H, 5.67; N, 6.06; S, 13.86. Obsd: C, 47.16; H, 5.78; N, 6.01; S, 13.90.

The presence of the amino function was later confirmed by exposing the allonothiolactone 3.78 to standard acylating conditions (Ac$_2$O/pyr) to give the N-acetylated allonothiolactone 3.79.

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 7.53 (br. s, 1 H, NH), 5.85 (d, $J_{7,6} = 7.8$ Hz, 1 H, H-7), 5.02 (app t, $J_{5,4a} = 2.8$ Hz, $J_{5,6} = 2.0$ Hz, $J_{5,4b} = 0.8$ Hz, 1 H, H-5), 4.61 (dd, $J_{6,7} = 7.9$ Hz, $J_{6,5} = 2.0$ Hz, 1 H, H-6), 4.19 (dd, $J_{gem} = 10.4$ Hz, $J_{4a,5} = 2.8$ Hz, 1 H, H-4a), 4.12 (dd, $J_{gem} = 10.4$ Hz, $J_{4b,5} = 0.8$ Hz, 1 H, H-4b), 2.12 (s, 3 H, NC(O)CH$_3$), 1.41 (s, 3 H, acetalt), 1.33 (s, 3 H, acetalt); $^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ 213.0 (s, C=S), 170.0 (s, C=O), 111.4 (s, acetalt), 84.3 (s, C-1), 76.5 (d), 73.4 (d), 72.4 (d), 64.0 (t, C-4), 25.8 (q, NC(O)CH$_3$), 25.0 (q, acetalt), 24.7 (q, acetalt).
Cyclization of (2Z)-1,1-dimethylethyl 6-O-[(1H-(benzimidazol-1-yl)-1-carbamothioyl)-2,3-dideoxy-7-O-[(1,1-dimethylethyl)dimethylsilyl]-4,5-O-(1-methylethylidene)-D-ribo-hept-2-enoate (3.61): Preparation of 1-(2-[2-(1,1-dimethylethoxy)-2-oxoethyl]-6-O-[(1,1-dimethylethyl)dimethylsilyl]-1,2-dideoxy-3,4-O-(1-methylethylidene)-D-allopyranosyl) benzimidazole (3.90) and 1-(1,5-anhydro-2-[2-(1,1-dimethylethoxy)-2-oxoethyl]-6-O-[(1,1-dimethylethyl)dimethylsilyl]-2-deoxy-3,4-O-(1-methylethylidene)-D-ribo-hex-1-enopyranosyl) benzimidazole (3.91) (Figure 3.10).

A 25 mL round-bottom flask equipped with a magnetic stirrer, water cooled condenser and nitrogen inlet was charged with a 0.05 M solution of tributyltin hydride (100 μL, 0.31 mmol) in toluene (6.5 mL). Nitrogen gas was bubbled through the solution for 15 minutes and then the solution warmed to 90 °C. A solution of thiocarbamate 3.61 (109 mg, 0.20 mmol) in degassed toluene (4.0 mL) containing 0.2 equivalents of AIBN (6 mg, 0.04 mmol) was added via syringe pump over the course of 3 h and until no further starting material was detected by TLC ($R_f = 0.60$, 4:1 hexanes/ethyl acetate). The reaction mixture was cooled and concentrated in vacuo to yield a light yellow oil and flash chromatographed (silica gel, 3:1 hexanes/ethyl acetate) to yield 4 mg (4 %) of allopyranosyl benzimidazole 3.90 and 6 mg (6 %) (D-ribo-hex-1-enopyranosyl) benzimidazole 3.91 both as colorless oils.

![Chemical Structure](image)

$R_f = 0.1$ (4:1 hexanes/ethyl acetate); IR (thin film) 3018m, 2931m, 2858m, 1723m, 1459m, 1370m, 1215s, 1153m, 1061m cm⁻¹; ¹H-NMR (250 MHz, CDCl₃) δ 8.09 (s, 1 H, benzimidazole H-2), 7.83-7.80 (m, 1 H, benzimidazole), 7.50-7.46 (m, 1 H, benzimidazole), 7.32-7.28 (m, 2 H, benzimidazole), 6.15 (d, $J_{i,2} = 2.9$ Hz, 1 H, H-1), 4.42 (dd, $J = 5.1$ Hz, $J = 3.2$ Hz, 1 H, H-4), 4.31 (dd, $J = 9.0$ Hz, $J = 5.4$ Hz, 1 H), 3.95 (m, 1 H), 3.86-3.77 (m, 2 H, H-6), 3.10 (dddd, $J_{i,2,1} = 8.5$ Hz, $J_{i,2,1} = 5.8$ Hz, $J_{2,3} = 3.5$ Hz, $J_{2,1} = 2.9$ Hz, 1 H, H-2), 2.29 (dd, $J_{gem} = 17.0$ Hz, $J = 8.5$ Hz, 1 H, \(-\text{CH}_2\text{CO}_2\text{Bu}'\)), 2.21 (dd,
$J_{\text{gem}} = 17.0$ Hz, $J = 5.8$ Hz, 1 H -CH$_2$CO$_2$Bu', 1.46 (s, 3 H, acetal), 1.41 (s, 3 H, acetal), 1.28 (s, 3 H, OBut), 0.93 (s, 9 H, SiBu'), 0.11 (s, 3 H, SiMe), 0.09 (s, 3 H, SiMe); $^{13}$C-NMR (125 MHz, CDCl$_3$) δ 170.7 (C=O), 144.4, 143.4, 142.3 (benzimidazole), 133.4, 124.2 (benzimidazole), 123.4 (benzimidazole), 120.4 (benzimidazole), 112.3 (benzimidazole), 109.5 (acetal), 99.9 (anomeric), 81.9 (OCMe$_3$), 79.5 (C-5), 71.4 (C-3), 70.9 (C-4), 62.2 (C-6), 34.6 (CH$_2$CO$_2$Bu'), 28.4 (acetal), 28.0 (OBu'), 26.0 (SiBu'), 18.6 (SiBu'), -5.0 (SiMe); HRMS (EI) calcd for C$_{24}$H$_{33}$N$_2$O$_6$Si (M-CH$_2$): 475.226440. Obsd: 475.225952.

Preparation of (2Z)-1,1-dimethyl-2,3-dideoxy-4,5-O-(1-methylthioleuylidene)-6,7-di-O-thiocarbonate-D-ribo-hept-2-enoate (3.77) (Scheme 3.22): Method A. A 30 mL polypropylene bottle equipped with a magnetic stirbar and nitrogen inlet was charged with a 0.05 M solution of (Z)-tert-butyl
2,3-dideoxy-7-O-tert-butyldimethylsilyl-4,5-O-isopropylidene-D-ribo-hept-2-enoate (3.60, 55 mg, 0.096 mmol) in DME (2.0 mL) and cooled to 0 °C. Tetrabutylammonium fluoride (1.0 M in THF) was added dropwise periodically until no further starting material remained by TLC ($R_f = 0.5, 4:1$ hexanes/ethyl acetate). The reaction was quenched at 0 °C by addition of saturated NaHCO₃ (10 mL) and the phases separated. The aqueous phase was then extracted with diethyl ether (10 mL) and the combined organic phase washed with water (10 mL), saturated brine (10 mL) and then dried over anhydrous MgSO₄. Vacuum filtration and concentration in vacuo gave a yellow syrup which was flash chromatographed (silica gel, 5:1 hexanes/ethyl acetate) to give 15 mg (47%) of the desired cyclic thiocarbonate 3.77 as a white solid.

$$
\begin{align*}
\text{S} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\end{align*}
$$

$R_f = 0.28$ (5:1 hexanes/ethyl acetate) Mp = 132.0-134.0 °C, $[\alpha]^{19}_D = +165.0$ (c 0.23, CHCl₃), IR (CHCl₃) 3108s, 2984m, 2937w, 1643w, 1519w, 1474w, 1456w, 1408m, 1385m, 1369s, 1334s, 1299s, 1282s, 1243s, 1215s, 1159s, 1075w, 1052m, 1011w cm⁻¹; $^1$H-NMR (300 MHz, CDCl₃) δ 6.06 (dd, $J_{3,2} = 11.5$ Hz, $J_{3,4} = 6.1$ Hz, 1 H, H-3), 5.91 (dd, $J_{2,3} = 11.5$ Hz, $J_{2,4} = 1.9$ Hz, 1 H, H-2), 5.60 (ddd, $J_{4,5} = 7.6$ Hz, $J_{4,3} = 6.1$ Hz, $J_{4,4} = 1.9$ Hz, 1 H, H-4), 4.88 (dd, $J_{5,4} = 7.6$ Hz, $J_{5,6} = 3.5$ Hz, 1 H, H-5), 4.79 (ddd, $J_{6,7a} = 8.4$ Hz, $J_{6,7b} = 6.8$ Hz, $J_{6,5} = 3.5$ Hz, 1 H, H-6), 4.52 (dd, $J_{gem} = 11.8$ Hz, $J_{7a,6} = 6.8$ Hz, 1 H, H-7a), 4.47 (dd, $J_{gem} = 11.8$ Hz, $J_{7a,6} = 8.4$ Hz, 1 H, H-7a), 1.51 (s, 3 H, acetal), 1.49 (s, 9 H, Bu'), 1.40 (s, 3 H, acetal); $^{13}$C-NMR (75 MHz, CDCl₃) δ 191.8 (s, C=S), 164.9 (s, C=O), 143.1 (d, C-3), 125.4 (d, C-2), 110.0 (s, acetal), 82.1 (s, Bu'), 80.4 (d), 76.6 (d), 74.4 (d), 69.7 (t, C-7), 28.3 (q, Bu'), 26.8 (q, acetal), 24.4 (q, acetal). Anal. calcd for C₁₅H₂₇O₅S: C, 54.53; H, 6.72; S, 9.69. Obsd: C, 54.66; H, 6.70; S, 9.59.

Method B. 50 mL roundbottom flask equipped with magnetic stirbar, condenser and nitrogen inlet was charged with a 0.5 M solution of (Z)-tert-butyl 2,3-dideoxy-4,5-O-isopropylidene-D-ribo-hept-2-enoate
(2.43, 310 mg, 1.04 mmol) in dimethoxyethane (2.0 mL) containing 1.25 equivalents of 1,1'-thiocarbonyldiimidazole (3.8, 2.31 mg, 1.30 mmol) was warmed to reflux for 4 h until no further starting material was detected by TLC ($R_f = 0.25$, 1:1 hexanes/ethyl acetate). The reaction was concentrated in vacuo to give a golden syrup which was flash chromatographed (silica gel, 5:1 hexanes/ethyl acetate) to give 325 mg (94%) of desired cyclic thiocarbonate 3.77 as a white solid. Characterization of this material matched that reported in Method A above.

**Preparation of 2,3-O-(1-methylethylidene)-5-O-[(1,1-dimethylcyclohexyl)dimethylsilyl]-D-ribose, O-methyloxime (3.55) (Scheme 3.14).** A 100 mL round-bottom flask equipped with a magnetic stirbar and nitrogen inlet was charged with a 0.8 M solution of 2,3-O-isopropylidene-D-ribose, O-methyloxime (2.49, 890 mg, 4.07 mmol) in dimethylformamide (5.0 mL) and cooled to -10 °C. To this solution was added 1.5 equivalents of imidazole (415 mg, 6.10 mmol) followed by 1.0 equivalent of tert-butyltrimethylsilyl chloride (613 mg, 4.07 mmol) in small portions for the course of 40 minutes. Following addition, the reaction was maintained at -10 °C for an additional 1.5 h and then at 25 °C for 12 h. The reaction mixture was then diluted with chloroform (200 mL) and washed with water (50 mL). The aqueous layer was back extracted with chloroform (3 x 25 mL) and the combined organic phase was washed with saturated brine (20 mL) and dried over anhydrous MgSO\(_4\). Vacuum filtration and concentration in vacuo provided a clear yellow oil which was flash chromatographed (silica gel, 6:1 hexanes/ethyl acetate) to give 986 mg (72%) of the desired 5-O-(tert-butyltrimethylsilyl)-2,3-O-isopropylidene-D-ribose, O-methyloxime 3.55 as a yellow syrup ($E/Z = 6.0$)

![Chemical structure](image)

Mixture of isomers: $R_f = 0.35$, (4:1 hexanes/ethyl acetate); IR (thin film) 3522 br, 2987 s, 2956 s, 2932 s, 2884 s, 2857 s, 2819 w, 1795 s, 1741 w, 1629 w, 1471 s, 1468 s, 1382 s, 1255 s, 1219 s, 1170 s, 1154 s, 1117 s, 1047 s cm\(^{-1}\); \(^1\)H-NMR (300 MHz, CDCl\(_3\)) \(\delta 7.46\) (d, $J_{1,2} = 7.5$ Hz, 0.86 H, H-1), 6.87 (d, $J_{1,2} = 6.0$ Hz, 0.14
H, H-1), 5.30 (dd, J = 6.3 Hz, J = 6.4 Hz, 0.14 H), 4.76 (dd, J = 7.7 Hz, J = 6.2 Hz, 0.86 H), 4.72 (d, J = 2.0 Hz, 0.67 H), 4.60 (dd, J = 2.0 Hz, J = 1.5 Hz, 0.38 H), 4.24 (dd, J = 7.8 Hz, J = 6.4 Hz, 0.14 H), 4.12 (dd, J = 8.7 Hz, J = 6.0 Hz, 0.95 H), 3.92 (s, 2.53 H, OMe), 3.88 (s, 0.47 H, OMe), 3.84-3.75 (m, 1 H), 3.71-3.63 (m, 2 H), 3.56 (d, J = 11.8 Hz, 0.22 H), 2.73 (d, 3.9 Hz, 0.14 H), 2.63 (d, J = 4.8 Hz, 0.86 H), 1.47 (s, 3 H, acetal), 1.36 (s, 3 H, acetal), 0.91 (s, 9 H, Bu'), 0.09 (s, 6 H, SiMe); 13C-NMR (75 MHz, CDCl₃) δ 149.1 (d, C-1), 147.1 (d, C-1), 113.1 (s, acetal), 109.9 (s, acetal), 82.4 (d), 78.6 (d), 77.3 (d), 77.2 (d), 75.9 (d), 75.4 (d), 70.7 (d), 70.6 (d), 69.5 (d), 64.3 (t, C-5), 63.1(t, C-5), 62.4 (q, OMe), 62.0 (q, OMe), 27.9 (q, acetal), 27.7 (q, acetal), 26.9 (q, acetal), 18.4 (s, Bu'), 18.3 (s, Bu'), -5.1 (q, SiMe), -5.29 (q, SiMe), -5.4 (q, SiMe), -5.6 (q, SiMe). Compound 3.55 did not give satisfactory elemental analysis.

Preparation of 4-O-[(1H-imidazol-1-yl)-1-carbamoyl]-2,3-O-(1-methylethylidene)-5-O-[(1,1-dimethylethyl)dimehtylsilyl]-D-ribose, O-methyloxime (3.58) (Scheme 3.14). A 50 mL conical flask equipped with magnetic stirbar, condenser and nitrogen inlet was charged with a 0.2 M solution of 5-O-(tert-butyldimethylsilyl)-2,3-isopropylidene-D-ribose, O-methyloxime (3.55, 370 mg, 1.11 mmol) in THF (5.5 mL) containing 3.0 equivalents of 1,1'-thiocarbonyldiimidazole (3.8, 600 mg, 3.33 mmol) and the reaction warmed to reflux for 10 h until no further starting material was detected by TLC. The reaction was concentrated to give a golden syrup which was flash chromatographed (silica gel. 5:1 hexanes/ethyl acetate) to give 314 mg (64%) of 1H-imidazole thiocarbamate 3.58 as a colorless oil along with 40 mg (11%) of unreacted starting material.

Mixture of isomers: IR (thin film) 3133w, 2989m, 2953m, 2935m, 2897m, 2856m, 1739w, 1626w, 1531w, 1463m, 1391s, 1344m, 1323s, 1283s, 1246s, 1229s, 1109m, 1076m, 1042s cm⁻¹; 1H-NMR (300 MHz, CDCl₃) δ 8.30 (m, 1 H, imidazole), 7.61 (m, 1 H, imidazole), 7.27 (d, J₁,₂ = 7.7 Hz, 0.87 H, H-1), 7.01 (m,
1 H, imidazole), 6.80 (d, J, = Hz, 0.13 H, H-1), 5.55 (m, 0.87 H, ), 5.32 (dd, J = 6.4 Hz, J = 5.7 Hz, 0.13 H), 4.79 (m, 2 H), 4.12 (dd, J, = 11.9 Hz, J, = 2.6 Hz, 1 H, H-5a), 3.99 (dd, J, = 11.9 Hz, J, = 3.0 Hz, 1 H, H-5b), 3.67 (s, 0.5 H, OMe), 3.58 (s, 2.5 H, OMe), 1.51 (s, 3 H, acetal), 1.42 (s, 2.4 H, acetal), 1.40 (s, 0.6 H, acetal), 0.88 (s, 6.7 H, Bu'), 0.87 (s, 2.3 H, SiBu'), 0.4 (s, 3 H, SiMe), 0.01 (s, 3 H, SiMe): \(^1\)C-NMR (125 MHz, CDCl\(_3\)) \(\delta\) 182.0 (s, C=S), 145.9 (d, C-1), 137.0 (d, imidazole), 131.0 (d, imidazole), 118.1 (d, imidazole), 110.6 (s, acetal), 80.6 (d, C-2), 75.1 (d), 74.2 (d), 61.9 (q, OMe), 60.7 (t, C-5), 27.8 (q, acetal), 25.9 (q, Bu'), 25.3 (q, acetal), 18.4, (s, Bu'), -5.3 (q, SiMe). Anal. calcd for C\(_{51}\)H\(_{57}\)O\(_{15}\)S\(_{3}\)N: C, 51.44; H, 7.50; N, 9.47; S, 7.23. Obsd: C, 51.57; H, 7.61; N, 9.32; S, 7.11.

**Preparation of 3-O-[(1H-diisopropylamin-1-yi)-1-carbamothioyl]-1,2:5,6-di-O-(1-methylethylidene)-\(\alpha\)-D-glucofuranoside (3.66) (Scheme 3.17): Method A.** In a glovebox, a scintillation vial was charged with a 0.27 M solution of diacetyl glucose (140 mg, 0.538 mmol) in tetrahydrofuran (2.0 mL). To this was added 1.1 equivalents of mineral oil free potassium hydride (24 mg, 0.598 mmol) in one portion. The suspension was then stirred for 10 minutes until the evolution of hydrogen stopped and the solution became homogenous. The alkoxide solution was cooled to -30 °C and then added to a 1.2 M solution of distilled thiophosgene (4.6 equiv., 190 µL, 2.49 mmol) in tetrahydrofuran (2.0 mL) at -30 °C and the reaction stored at -30 °C for 18 h and then 25 °C for 2 h before excess thiophosgene was removed under high vacuum. \(^1\)H-NMR analysis of the crude reaction mixture showed the appearance of new low field hydrogens (ca. 5.50-5.59 ppm) indicating derivatization of the lone hydroxyl group of diacetyl glucose. Based upon subsequent reactions, this material has been tentatively identified as a mixture of thiocarbonate derived from diacetyl glucose (3.67, *vide infra*) and the expected chlorothioformate. The crude chlorothioformate was then dissolved in dichloromethane (1.0 mL) and cooled to 0 °C. To this was added a solution of diisopropyl amine (141 µL, 1.0 mmol) in dichloromethane (1.0 mL) and the reaction stirred at 25 °C for 18 h. The reaction was then quenched with water (5.0 mL) and the reaction extracted with diethyl ether (4 x 10.0 mL). The combined organic phase was then washed with saturated brine (10.0 mL) and dried over anhydrous MgSO\(_4\). Vacuum filtration and concentration in vacuo yielded a light yellow syrup which was flash chromatographed (silica gel, :1 hexanes/ethyl acetate) to give 45 mg.
(20%) of a light yellow oil identified as the desired diisopropylthiocarbamate 3.66 along with 43 mg
(14%) of material identified as the previously reported bis(1,2:5,6-di-O-isopropylidene-\(\alpha\)-D-
glucofuranoside)thiocarbonate 3.67.

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\begin{align*}
\text{\([\alpha]^{15.5}_{D} = -9.9^\circ (c 0.79, \text{CHCl}_3), \text{IR (CHCl}_3) 2981s, 2937m, 2890m, 1487s, 1452s, 1371s, 1345s, 1291m,
\end{align*}
\]
1229s, 1186m, 1163s, 1134s, 1077s, 1020s cm\(^{-1}\); \(\text{\[^1\text H-NMR (300 MHz, CDCl}_3\]}\) \(\delta\) 5.91 (d, J\(_{3,4}\) = 3.0 Hz, 1
H, H-3), 5.81 (d, J\(_{1,2}\) = 3.8 Hz, 1 H, H-1), 5.55-5.53 (m, 1 H, CHMe\(_2\)), 4.76 (d, J\(_{2,1}\) = 3.8 Hz, 1 H, H-2),
4.35 (ddd, J\(_{5,4}\) = 8.8 Hz, J\(_{5,6a}\) = 5.9 Hz, J\(_{5,6b}\) = 5.3 Hz, 1 H, H-5), 4.20 (dd, J\(_{4,3}\) = 3.0 Hz, J\(_{4,5}\) = 8.8 Hz, 1 H,
H-4), 4.14 (dd, J\(_{\text{gem}}\) = 8.6 Hz, J\(_{6a,5}\) = 5.9 Hz, H-6a), 3.98 (dd, J\(_{\text{gem}}\) = 8.6 Hz, J\(_{6b,5}\) = 5.3 Hz, 1 H, H-6b),
3.71-3.66 (m, 1 H, CHMe\(_2\)), 1.54 (s, 3 H, acetal), 1.42 (s, 3 H, acetal), 1.36 (d, J = 6.8 Hz, 3 H, Pr\(_\gamma\)), 1.32
(s, 3 H, acetal), 1.32 (d, J = 6.8 Hz, 3 H, Pr\(_\gamma\)), 1.29 (s, 3 H, acetal), 1.24 (m, 6 H, Pr\(_\gamma\)); \[^{13}\text C-NMR (50 MHz,
CDCl}_3\) \(\delta\) 187.3 (s, C=S), 112.3 (s, acetal), 109.7 (s, acetal), 104.8 (d, C-1), 83.9 (d), 82.7 (d), 80.2 (d),
72.5 (d), 68.2 (t, C-6), 54.4 (d, Pr\(_\gamma\)), 47.9 (d, Pr\(_\gamma\)), 26.9 (q, acetal), 26.8 (q, acetal), 26.4 (q, acetal), 25.3 (q,
acetal), 21.9 (q, Pr\(_\gamma\)), 21.2 (q, Pr\(_\gamma\)), 19.5 (q, Pr\(_\gamma\)), 19.2 (q, Pr\(_\gamma\)); Anal. calcd for C\(_{19}\)H\(_{33}\)O\(_6\)NS: C, 56.55; H,
8.24; N, 3.47; S, 7.94. Obsd: C, 56.30; H, 8.29; N, 3.28; S, 7.66.

Mp = 146.0-148.0 \(^\circ\) C (Lit. 145-148 \(^\circ\) C); \[^{206}\text{\([\alpha]^{15.5}_{D} = -36.9^\circ (c 0.28, \text{CHCl}_3)\]} \[^{1}\text H-NMR (300 MHz,
CDCl}_3\) \(\delta\) 5.88 (d, J\(_{1,2}\) = 3.8 Hz, 1 H, H-1), 5.62 (d, J\(_{3,4}\) = 2.5 Hz, 1 H, H-3), 4.66 (d, J\(_{2,1}\) = 3.8 Hz, 1 H, H-
2), 4.29-4.21 (m, 2 H), 4.10-4.01 (m, 2 H), 1.54 (s, 3 H, acetal), 1.42 (s, 3 H, acetal), 1.32 (s, 6 H, acetal);
\[^{13}\text C-NMR (75 MHz, CDCl}_3\) \(\delta\) 193.4 (s, C=S), 112.7 (s, acetal), 109.2 (s, acetal), 105.1 (d, C-1) 84.8 (d),

250
83.2 (d), 79.8 (d), 72.4 (d), 67.3 (t, C-6), 27.1 (q, acetal), 26.8 (q, acetal), 26.5 (q, acetal), 25.5 (q, acetal):
Anal. Calcd for C_{28}H_{38}O_{12}S: C, 53.37; H, 6.81; S, 5.57. Obsd. C, 53.34; H, 6.83; S, 5.57.

**Method B**

In a glovebox, a scintillation vial was charged with a 0.25 M solution of diacetone-α-D-glucopyranoside (130 mg, 0.50 mmol) in tetrahydrofuran (2.0 mL) containing 2.0 equivalents of 4-dimethylaminopyridine (122 mg, 1.00 mmol) and the solution cooled to -30 °C. This solution was then added to a solution of distilled thiophosgene (190 μL, 2.49 mmol) in tetrahydrofuran (2.0 mL) at -30 °C. The immediate precipitation of an orange solid was observed upon addition of the substrate. Following addition, the reaction was allowed to warm to 25 °C and stirred for an additional 18 h. Excess thiophosgene was then removed under high vacuum. The crude chlorothioformate was then dissolved in dichloromethane (1.0 mL) and cooled to 0 °C. To this was added a solution of diisopropyl amine (141 μL, 1.0 mmol) in dichloromethane (1.0 mL) and the reaction stirred at 25 °C for 18 h. The reaction was then quenched with water (5.0 mL) and the reaction extracted with diethyl ether (4 x 10 mL). The combined organic phase was then washed with saturated brine (10.0 mL) and dried over anhydrous MgSO₄. Vacuum filtration and concentration in vacuo yielded a light yellow syrup which was flash chromatographed (silica gel, 1:1 hexanes/ethyl acetate) to give 29 mg (14%) of a light yellow oil identified as the desired diisopropylthiocarbamate 3.66 above as the sole product isolated.

**Preparation of (2Z)-1,1-dimethylethyl 2,3-dideoxy-6-O-(methyl-1-carbonothioyl)-4,5-O-(1-methylethylidene)-6,7-di-O-thiocarbonate-D-ribo-hept-2-enoate (3.73) (Scheme 3.21).** In a glovebox, a 20 mL scintillation vial containing a stirbar was charged with a 0.12 M solution of (Z)-tert-butyl 2,3-dideoxy-4,5-O-isopropylidene-7-O-(tert-butyldimethylsilyl)-6-O-[(1H-1,2,4-triazole)thiocarbamate]-D-ribo-hept-2-enoate (3.60, 100 mg, 0.19 mmol) in dimethoxymethane (1.0 mL) containing 2.6 equivalents of absolute methanol (23μL, 0.57 mmol) and the solution cooled to -30 °C. To this was added 1.3 equivalents of mineral oil free potassium hydride (10 mg, 0.25 mmol) in small portions over 5 minutes. The reaction was allowed to come to 25 °C and stirred an additional 0.5 h to give a milky white solution. The reaction was removed from the glovebox and diluted with ethyl acetate (25 mL) and the reaction washed with saturated bicarbonate (25 mL). The aqueous phase was back extracted (25 mL) with ethyl...
acetate and the combined organic phases washed with water (20 mL), saturated brine (20.0 mL) and then dried over anhydrous MgSO₄. Vacuum filtration and concentration in vacuo provided a yellow syrup which was flash chromatographed (silica gel, 20:1 hexanes/ethyl acetate) to give 53 mg (61%) of the desired methyl thiocarbonate 3.73 along with unreacted starting material.

\[
\begin{align*}
R_f &= 0.65 \text{ (4:1 hexanes/ethyl acetate); IR (CHCl₃) 2978m, 2954m, 2991m, 2860m, 1713m, 1642w, 1448m, 1413w, 1366m, 1278m, 1249s, 1161s, 1108m, 1061m, 1025m cm}^{-1}; ^1H-NMR (500 MHz, CDCl₃) \delta 6.15 \text{ (dd, } J_{3,2} = 11.9 \text{ Hz, } J_{3,4} = 8.0 \text{ Hz, } 1 \text{ H, H-3}), 5.80-5.77 \text{ (m, } 2 \text{ H, H-2 and H-4}), 5.27 \text{ (ddd, } J_{6.5} = 7.3 \text{ Hz, } J_{6.7b} = 4.7 \text{ Hz, } J_{6.7a} = 2.8 \text{ Hz, } 1 \text{ H, H-6}), 4.72 \text{ (dd, } J_{5.6} = 7.3 \text{ Hz, } J_{5.4} = 6.8 \text{ Hz, } 1 \text{ H, H-5}), 3.98 \text{ (s, } 3 \text{ H, OMe}), 3.93 \text{ (dd, } J_{\text{gem}} = 11.8 \text{ Hz, } J_{\text{7a,6}} = 2.8 \text{ Hz, } 1 \text{ H, H-7a}), 3.88 \text{ (dd, } J_{\text{gem}} = 11.8 \text{ Hz, } J_{\text{7b,6}} = 4.7 \text{ Hz, } 1 \text{ H, H-7b}), 1.48 \text{ (s, } 9 \text{ H, OBut}'), 1.48 \text{ (s, } 3 \text{ H, acetal}), 1.37 \text{ (s, } 3 \text{ H, acetal}), 0.88 \text{ (s, } 9 \text{ H, SiBu}'), 0.02 \text{ (s, } 3 \text{ H, SiMe}), 0.01 \text{ (s, } 3 \text{ H, SiMe}); ^13\text{C-NMR (125 MHz, CDCl₃) } \delta 196.0 \text{ (s, C=S)}, 165.0 \text{ (s, C=O)}, 142.7 \text{ (d, C-3)}, 124.8 \text{ (d, C-2)}, 109.5 \text{ (s, acetal), 82.0 (d), 81.2 (s), 75.3 (d), 74.1 (d), 61.8 (t, C-7), 59.5 (q, OMe), 28.5 (q, OBut), 27.9 (q, acetal), 26.2 (q, SiBu'), 25.4 (q, acetal), 18.7 (s, SiBu'), -5.0 (q, SiMe).
\end{align*}
\]

Preparation of 9H-(6-methoxypurine) O-(pentafluorophenyl) carbonothioate (3.36) (Scheme 3.9). A 25 mL round-bottom flask equipped with magnetic stirbar was charged with a 1.0 M solution of 6-methoxypurine (500 mg, 3.14 mmol) in dichloromethane (3.2 mL) containing 0.25 equivalents of 4-dimethylaminopyridine (96 mg, 0.78 mmol) and the reaction cooled to 0 °C. Dropwise addition of 2.0 equivalents of O-pentafluorophenyl chlorothioformate (1.0 mL, 6.28 mmol) with vigorous stirring gave a bright yellow mixture which was stirred at 0 °C. After 1 h, the cooling bath was removed and the reaction stirred at 25 °C for an additional 12 h until no further starting material was detected by TLC (R_f = 0.15, 3% MeOH in CHCl₃). The reaction was then diluted with dichloromethane and the solids removed by
filtration. The organic phase was washed with water, saturated brine and then dried over anhydrous MgSO₄. Vacuum filtration and concentration in vacuo yielded a dark brown syrup which was flash chromatographed (silica gel, 1% MeOH in CHCl₃) to give 788 mg (71%) of the desired 9H-(6-methoxypurine)thiocarbamate 3.36 as a light yellow solid.

\[ \text{OMe} \]

\[ R_f = 0.35 \text{ (CHCl}_3/3\% \text{ MeOH)}; \text{Mp} = 129.0-131.0 ^\circ \text{C. IR (CHCl}_3) 3129w, 3018s, 2946w, 1653w, 1599s, 1581s, 1520s, 1483s, 1456m, 1425s, 1396s, 1362s, 1305s, 1289s, 1269s, 1216s, 1170m, 1126m, 1085m, 1010s \text{ cm}^{-1}; \text{^1H-NMR (400 MHz, CDCl}_3) \delta 8.80 \text{ (s, 1 H, H-2), 8.76 \text{ (s, 1 H, H-8)), 4.25 \text{ (s, 3 H, OMe):} \text{^{13}C-NMR (100 MHz, CDCl}_3) \delta 178.7 \text{ (s, C=S), 162.0 \text{ (s, C-6), 155.0 \text{ (d, C-2), 151.3 \text{ (s, C-4), 142.5 \text{ (m, Ar-F), 142.1 \text{ (d, C-8), 140.0 \text{ (m, Ar-F), 139.6 \text{ (m, Ar-F), 139.5 \text{ (m, Ar-F), 137.1 \text{ (m, Ar-F), 126.5 \text{ (Ar-F), 123.0 \text{ (s, C-5), 55.0 \text{ (q, OMe).}}}}}}}}

\text{Anal. calc for C}_{13}\text{H}_{23}\text{N}_{2}\text{F}_{3}\text{O}_{2}\text{S: C, 41.50; H, 1.34; N, 14.89; S, 8.52. Obsd. C, 41.60; H, 1.37; N, 14.86; S, 8.61.}}

Preparation of (2Z)-1,1-dimethylethyl 2,3-dideoxy-7-O-[(1,1-dimethylethyl)dimethylsilyl]-4,5-O-(1-methylethylidene)-6-O-[1,2:5,6-di-O-(1-methylethylidene)-α-D-glucofuranos-3-yl)-1-carbonothioyl]-D-ribo-hept-2-enoate (3.75) (Scheme 3.21). In a glovebox, a 20 mL scintillation vial containing a magnetic stirbar was charged with a 0.1M solution of (Z)-tert-butyl 2,3-dideoxy-7-O-(tert-butylidimethylsilyl)-4,5-O-isopropylidene-6-O-(1H-1,2,4-triazole)thiocarbamate D-ribo-hept-2-enoate (3.60, 63 mg, 0.12 mmol) in dimethoxymethane (1.0 mL) containing 1.5 equivalents diacetone-α-D-glucose (48 mg, 0.18 mmol) and the solution cooled to -30 °C. To this was added 1.5 equivalents of mineral oil free potassium hydride (7 mg, 0.18 mmol) in small portions over 5 minutes. The reaction was allowed to come to 25 °C and stirred an additional 1.5 h. The reaction was removed from the glovebox and diluted with ethyl acetate (25 mL) and the reaction washed with saturated bicarbonate (25 mL). The aqueous phase was back extracted with ethyl acetate and the combined organic phases washed with water.
(20 mL) and saturated brine (20 mL) and then dried over anhydrous MgSO₄. Vacuum filtration and concentration in vacuo provided a yellow syrup which was flash chromatographed (silica gel, 9:1 hexanes/ethyl acetate) to give 45 mg (52%) of the desired mixed thionocarbonate 3.75.

![Chemical Structure](image)

\[ R_f = 0.45 \text{ (3:1 hexanes/ethyl acetate); } [\alpha]_D^{19^\circ} = +63.7 \text{ (c 0.59, CHCl}_3\text{); IR (CHCl}_3\text{) 2985s, 2955s, 2935s, 2885s, 2857s, 1713s, 1646w, 1516w, 1472m, 1456m, 1410m, 1381s, 1372s, 1329s, 1215s, 1163s, 1066s, 1027s cm}^{-1}; \text{ } ^1{H}-\text{NMR (500 MHz, CDCl}_3\text{)} \delta 6.17 (dd, J = 7.4 Hz, J = 11.4 Hz, 1 H), 5.90 (d, J = 3.7 Hz, 1 H), 5.37-5.69 (m, 2 H), 5.50 (s, 1 H), 5.23 (dd, J = 7.4 Hz, J = 3.7 Hz, J = 3.0 Hz, 1 H), 4.72 (t, J = 7.0 Hz, 1 H), 4.56 (d, J = 3.7 Hz, 1 H), 4.20 (m, 2 H), 4.00 (m, 2 H), 3.90 (m, 2 H), 1.50 (s, 3 H, acetal), 1.46 (m, 12 H, acetal and OBu'), 1.37 (s, 3 H, acetal), 1.35 (s, 3 H, acetal), 1.31 (s, 3 H, acetal), 1.26 (s, 3 H, acetal), 0.84 (s, 6 H, SiMe₂); \text{ } ^{13}{C}-\text{NMR (125 MHz, CDCl}_3\text{)} \delta 193.6 \text{ (C=S), 164.8 (C=O), 142.8 (d, C-3), 124.6 (d, C-2), 112.7 (s, acetal), 109.7 (s, acetal), 109.4 (s, acetal), 105.3 (d, anomeric), 84.3 (d), 83.5 (d), 82.5 (d), 81.6 (s, OBU'), 80.0 (d), 75.1 (d), 74.5 (d), 72.4 (d), 67.3 (t, C-6'), 61.7 (t, C-7), 28.5 (q, OBU'), 27.8 (q, acetal), 27.2 (q, acetal), 27.1 (q, acetal), 26.7 (q, acetal), 26.2 (q, SiBu'), 25.6 (q, acetal), 25.4 (q, acetal), 18.6 (s, SiBu'), -4.99 (q, SiMe). Anal. calcd for C₃₃H₅₀O₁₂SSi: C, 56.23; H, 8.01; S, 4.55. Obsd: C, 55.73; H, 8.02; S, 4.42.}

**Preparation of (2Z)-1,1-dimethylethyl 7-O-[(1,1-dimethylethyl)dimethylsilyl]-6-O-[1-(5-O-[(1,1-dimethylethyl)dimethylsilyl]-2,3-O-(1-methylethyldiene)-α-D-ribofuranos-1-yl)-1-carbonothioyl]-2,3-dideoxy-4,5-O-(1-methylethyldiene)-D-ribo-hept-2-enoate (3.74)** (Scheme 3.21). In a glovebox, a 20 mL scintillation vial containing a stirbar was charged with a 0.12 M solution of 1H-1,2,4-
triazole thiocarbonate (3.60, 65 mg, 0.12 mmol) in dimethoxymethane (1.0 mL) containing 1.5 equivalents of 5-O-(tert-butyltrimethylsilyl)-2,3-0-isopropylidene-α-D-ribofuranose (57 mg, 0.19 mmol) and the solution cooled to -30 °C. To this was added 1.6 equivalents of mineral oil free potassium hydride (8 mg, 0.20 mmol) in small portions over 5 minutes. The reaction was allowed to come to 25 °C and stirred an additional 1.5 h. The reaction was removed from the glovebox and diluted with ethyl acetate (25 mL) and the reaction washed with saturated bicarbonate (25 mL). The aqueous phase was back extracted with ethyl acetate and the combined organic phases washed with water (20 mL), saturated brine (20 mL) and dried over anhydrous MgSO₄. Vacuum filtration and concentration in vacuo provided a yellow syrup which was flash chromatographed (silica gel, 9:1 hexanes/ethyl acetate) to give 72 mg (76%) of the desired mixed thiocarbonate 3.74.

![Chemical Structure](image)

1H-NMR (500 MHz, CDCl₃) δ 6.38 (m, 1 H, H-1'), 6.15 (dd, J₃,₂ = 11.8 Hz, J₃,₄ = 7.0 Hz, 1 H, H-3), 5.83 (dd, J₂,₃ = 11.8 Hz, J₂,₄ = 1.5 Hz, 1 H, H-2), 5.74 (ddd, J₄,₅ = 7.5 Hz, J₄,₇ = 7.0 Hz, J₅,₂ = 1.5 Hz, 1 H, H-4), 5.37 (ddd, J₆,₇ = 6.0 Hz, J₆,₉ = 5.2 Hz, J₆,₁₀ = 2.9 Hz, 1 H, H-6), 4.73 (m, 2 H, H-2' and H-3'), 4.67 (dd, J₅,₆ = 7.0 Hz, J₅,₇ = 5.2 Hz, 1 H, H-5), 4.29 (dd, J₄',₅a' = 9.6 Hz, J₄',₅b' = 5.1 Hz, 1 H, H-4'), 3.85 (dd, J₆,₇ = 11.8 Hz, J₆,₈ = 6.0 Hz, 1 H, H-7a), 3.79 (dd, J₆,₇ = 11.8 Hz, J₆,₈ = 2.9 Hz, 1 H, H-7b), 3.65 (dd, J₆,₇ = 10.5 Hz, J₇a,₈ = 5.0 Hz, 1 H, H-5b'), 3.47 (dd, J₆,₇ = 10.5 Hz, J₇a,₈ = 9.6 Hz, 1 H, H-5a'), 1.47 (s, 3 H, acetal), 1.45 (s, 9 H, OBU'), 1.44 (s, 3 H, acetal), 1.33 (s, 3 H, acetal), 1.31 (s, 3 H, acetal), 0.86 (s, 9 H, SiBu'), 0.84 (s, 9 H, SiBu'), 0.03 (s, 6 H, SiMe), 0.00 (s, 6 H, SiMe); 13C-NMR (125 MHz, CDCl₃) δ 192.6 (s, C=S), 164.9 (s, C=O), 142.4 (d, C'-3), 124.7 (d, C'-2), 113.0 (s, acetal), 109.9 (d, anomeric), 109.2 (s, acetal), 89.1 (d), 85.3 (d), 82.4 (d), 81.7 (d), 81.2 (s, OBU'), 76.1 (d), 74.0 (d), 63.2 (t), 61.7 (t), 28.3 (q, Bu'), 27.3 (q, acetal), 26.6 (q, acetal), 26.0 (q, Bu'), 25.2 (q, acetal), 25.1 (q, acetal), 18.4 (s, SiBu'), -5.0
Preparation of (2Z)-1,1-dimethylethyl 2,3-dideoxy-7-O-[(1,1-dimethylethyl)dimethylsilyl]-4,5-O-(1-methylethylidene)-6-O-[(9H-6-methoxypurin-1-yl)-1-carbamothioyl]-D-ribo-hept-2-enoate (3.37) (Scheme 3.10) Method A. In a glovebox, a 20 mL scintillation vial containing a stirbar was charged with a 0.1 M solution of 1H-(1,2,4-triazole)thiocarbamate (3.60, 50 mg, 0.097 mmol) in dimethoxyxymethane (1.0 mL) containing 3.0 equivalents of 6-methoxypurine (45 mg, 0.30 mmol) and the solution cooled to -30 °C. To this was added 2 equivalents of mineral oil free potassium hydride (8 mg, 0.20 mmol) in small portions over 5 minutes. The reaction was allowed to come to 25 °C and stirred an additional 1.5 h. The reaction was removed from the glovebox and diluted with ethyl acetate (25 mL) and the reaction washed with saturated bicarbonate (25 mL). The aqueous phase was back extracted with ethyl acetate and the combined organic phases washed with water (20 mL), saturated brine (20 mL) and dried over anhydrous MgSO₄. Vacuum filtration and concentration in vacuo provided a yellow syrup which was flash chromatographed (silica gel, 9:1 hexanes/ethyl acetate) to yield 5 mg (9%) of 9H-(6-methoxypurine)thiocarbamate 3.37.

Method B. A 10 ml roundbottom flask equipped with a magnetic stirbar, condenser and nitrogen inlet was charged with a 0.25 M solution of (Z)-tert-butyl 7-O-(tert-butyldimethylsilyl)-2,3-dideoxy-4,5-O-isopropylidene-D-ribo-hept-2-enoate (2.52, 100 mg, 0.25 mmol) in tetrahydrofuran (1.0 mL) or benzonitrile (1.0 mL) containing 0.8 equivalents of 9H-(6-methoxypurine) O-(pentafluorophenyl) thiocarbamate (3.36, 75 mg, 0.20 mmol) and the reaction warmed to reflux for 8 h and 12 h respectively until no further starting material was detected by TLC (Rf = 0.80, 3:1 hexanes/ethyl acetate). The reaction was concentrated in vacuo and flash chromatographed (silica gel, 5:1 hexanes/ethyl acetate) to provide 22 mg (16 %) and 17 mg (14 %) respectively of desired 9H-(6-methoxypurine) thiocarbamate 3.37.

Method C. In a glovebox, a 20 mL scintillation vial containing a magnetic stirbar was charged with a 0.1 M solution of (Z)-tert-butyl 7-O-(tert-butyldimethylsilyl)-2,3-dideoxy-4,5-O-isopropylidene-D-ribo-hept-
2-enoate (2.52, 115 mg, 0.28 mmol) in dimethoxymethane (1.0 mL) containing 0.8 equivalents of 9H-(6-methoxypurine) O-(pentafluorophenyl) thiocarbamate (3.36, 86 mg, 0.23 mmol) and the solution cooled to -30 °C. To this was added 1.05 equivalents of mineral oil free potassium hydride (12 mg, 0.30 mmol) in small portions over 5 minutes. The reaction was allowed to come to 25 °C and stirred an additional 0.5 h. The reaction was removed from the glovebox warmed slowly to 50 °C until no further starting material was detected by TLC (R$_f$ = 0.80, 3:1 hexanes/ethyl acetate). The reaction was then cooled, concentrated in vacuo and flash chromatographed (silica gel, 9:1 hexanes/ethyl acetate) to give 22 mg (16%) of the desired 9H-(6-methoxypurine) thiocarbamate 3.37.

![Chemical Structure]

R$_f$ = 0.55 (2:1 hexanes/ethyl acetate); [α]$^{20}_{D}$ = + 50.9 ° (c 0.09, CHCl$_3$), IR (thin film) 2989s, 2931s, 2884m, 2848m, 1789m, 1760m, 1711s, 1643m, 1599s, 1575s, 1535s, 1517s, 1480s, 1462m, 1424m, 1410m, 1383s, 1354s, 1330s, 1283s, 1249s, 1157s, 1088s, 1066s, 1041s cm$^{-1}$; $^1$H-NMR (500 MHz, CDCl$_3$) δ 8.70 (s, 1 H, H-2'), 8.60 (s, 1 H, H-8'), 6.23 (dd, J$_{3,2}$ = 11.4 Hz, J$_{3,4}$ = 8.1 Hz, 1 H, H-3), 5.81 (dd, J$_{2,3}$ = 11.4 Hz, J$_{2,4}$ = 2.0 Hz, 1 H, H-2), 5.73-5.71 (m, 2 H, H-4 and H-6), 4.92 (app t, J = 6.9 Hz, 1 H, H-5), 4.20 (s, 3 H, OMe), 4.04 (m, 2 H, H-7), 1.52 (s, 3 H, acetal), 1.42 (s, 3 H, acetal), 1.31 (s, 9 H, OBU'), 0.83 (s, 9 H, SiBU'), 0.00 (s, 3 H, SiMe), -0.03 (s, 3 H, SiMe); $^{13}$C-NMR (125 MHz, CDCl$_3$) δ 180.9 (s, C=S), 164.8 (s, C-1), 161.7 (s, C-6'), 154.3 (d, C-2'), 151.7 (s, C-4'), 142.5 (d, C-3), 141.2 (d, C-8'), 124.8 (d, C-2), 122.9 (s, C-5'), 109.7 (s, acetal), 81.5 (d), 75.3 (d), 74.0 (d), 61.5 (t, C-7), 54.7 (q, OMe), 28.1 (q, OBU'), 27.9 (q, acetal), 25.9 (q, SiBU'), 25.4 (q, acetal), 18.3 (s, SiBU'), -5.29 (q, SiMe), -5.33 (q, SiMe). HRMS (El) calcd for C$_{23}$H$_{33}$O$_6$N$_4$Si (M-OC$_4$H$_9$)$^+$: 521.189010. Obsd: 521.187835.
Cyclization of (2Z)-1,1-dimethylencyt 2,3-dideoxy-7-O-[(1,1-dimethylethyl)dimethylsilyl]-4,5-O-(1-methylethylidene)-6-O-[1,2:5,6-di-O-(1-methylethylidene)-α-D-glucofuranos-3-yl]-1-carbonothioyl-D-ribo-hept-2-enoate (3.75): preparation of thioester (3.94) (Scheme 3.12). A 25 mL round-bottom flask equipped with a magnetic stirbar, condenser with septum and nitrogen inlet was charged with a 0.05 M solution of tributyltin hydride (2.5 equiv., 89 μL, 0.33 mmol) in benzene (6.6 mL, degassed) cooled to 0 °C and irradiated with a 500W halogen lamp. A 0.14 M solution (degassed) of mixed thiocarbonate (3.75, 94 mg, 0.13 mmol) in benzene (2.6 mL, degassed) containing 0.5 equivalents of AIBN (11 mg) was added via syringe pump over the course of 1 h and the reaction monitored by TLC. Following complete addition of the substrate, the cooling bath was allowed to warm slowly under continuous irradiation with continuous monitoring by TLC. Starting material was consumed at t ≥ 45 °C. The reaction mixture was concentrated and chromatographed (silica gel, 9:1 hexanes/ethyl acetate) to yield 17 mg (18%) of aliphatic thioester 3.94 along with an additional 9 mg (15%) of material which has been tentatively identified as thiolactone 3.95.

\[
\text{IR (CHCl}_3\text{) 3532br, 2984s, 2933s, 2885m, 2857m, 1730s, 1472m, 1458m, 1381m, 1373m, 1331m, 1304m, 1254s, 1217s, 1161s, 1075s, 1024s cm}^{-1};\text{ }^{1}H\text{-NMR (400 MHz, CDCl}_3\text{) }\delta \text{ 5.85 (d, } J = 3.8 \text{ Hz, 1 H, H-1')}, 5.71 (d, J = 3.0 \text{ Hz, 1 H, H-3'}), 4.69 (dd, J = 8.4 Hz, J = 5.5 Hz, 1 H), 4.66 (d, J = 3.8 Hz, 1 H, H-2'), 4.37-4.34 (m, 1 H), 4.31 (dd, J = 9.4 Hz, J = 3.0 Hz, 1 H), 4.17 (dd, J = 8.5 Hz, J = 5.8 Hz, 1 H), 4.08 (dd, J = 9.3 Hz, J = 5.5 Hz, 1 H), 4.03 (dd, J = 8.5 Hz, J = 5.0 Hz, 1 H), 3.79 (dd, J = 9.5 Hz, J = 2.6 Hz, 1 H, H-4), 3.74-3.67 (m, 2 H, H-5), 3.63 (dd, J = 9.5 Hz, J = 5.5 Hz, 1 H, H-5), 2.70 (m, 2 H, CH₂CO₂R), 2.48 (d, J = 5.6 Hz, 1 H, D₂O exch., OH), 1.53 (s, 3 H, acetal), 1.42 (s, 9 H, Bu'), 1.40 (s, 3 H, acetal), 1.37 (s,
3 H, acetal), 1.32 (s, 3 H, acetal), 1.31 (s, 3 H, acetal), 1.30 (s, 3 H, acetal), 0.89 (s, 9 H, Bu'), 0.07 (s, 6 H, SiMe); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 221.5 (s, C=S), 170.7 (s, C=O), 112.7 (s, acetal), 108.6 (s, acetal), 105.6 (d, C-1') 83.0 (d), 82.5 (d), 80.7 (d), 80.2 (d), 79.4 (d), 72.5 (d), 69.0 (d), 67.6 (t), 64.6 (t), 51.7 (d, C-2), 39.1 (t, CH$_2$CO$_2$R), 28.3 (q), 27.8 (q), 27.0 (q), 26.9 (q), 26.5 (q), 26.1 (q, SiBu'), 25.6 (q), 25.4 (q), 18.7 (s, SiBu'), -4.9 (q, SiMe), -5.0 (q, SiMe); HRMS (El) calcd for C$_{25}$H$_{48}$O$_{12}$SiS (M-OC$_4$H$_9$)$^+$: 649.271402. Obsd: 649.271926.

Tentative: $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 4.20-4.08 (m, 2 H), 4.01-3.88 (m, 2 H), 3.85-3.72 (m, 1 H), 3.57-3.52 (m, 1 H), 2.98-2.81 (m, 1 H, CH$_2$CO$_2$R), 2.65-2.55 (m, 1 H, CH$_2$CO$_2$R) 1.50-1.20 (m, 15 H, acetals and OBu'), 0.95 (s, 9 H, SiBu'), 0.0 (m, 6 H, SiMe); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 218.6 (C=S), 170.8 (C=O), 111.5 (acetal), 82.7, 81.0 (OCMe$_3$) 76.9, 75.1, 62.2 (C-6), 51.1 (C-2), 37.3 (CH$_2$CO$_2$R), 28.3 (OBU'), 27.1 (acetal), 26.1 (SiBu'), 24.8 (acetal), 18.6 (SiCMe$_3$), -5.0 (SiMe$_2$).
APPENDIX B

NMR SPECTRA

This appendix contains the NMR spectra of new compounds and selected intermediates prepared in the course of this work. They are reported in the order in which they appear in the document. Each spectrum is an exact reproduction of the original data.

Each spectrum has a notebook reference number located at the upper left hand corner of the page consisting of: my initials (BIB), the notebook number (2 or 3), the page number, and compound identifier (A, B, C, ...). The majority of spectra have also been saved electronically to a file name listed just below the Bruker trademark in the upper right corner of the page. The file names consist of my initials (BB), the spectrum type (H for proton, C for carbon), followed by notebook and page number.
B118-2-276 13C BROADBAND DECOUPLED

Chemical shift (δ): 1.108

Compound: BnO→OBn

NMR spectrum with peaks at various ppm values.
1.112
mixture of isomers
1.112
mixture of isomers
818-2-153 recovered

1.113

Current Data Parameters
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PROCNO 1

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BIB-3-40 PERACETYLATED

2.43 Acetylated
Acetylated

2.43
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Mixture of isomers
2.49 Mixture of isomers
2.49
Acetylated mixture of isomers
Acetylated mixture of isomers

BIB-3-18 PERACETYLATED
Mixture of isomers

2.51
Mixture of isomers

![Chemical structure diagram]

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2.68b
BIB-3-78 FOLLOWING WITTIG OLEFINATION

Ph₃CO

2.101
2.105
3.34
(Tentative)
3.34
(Tentative)
BIB-3-145R IN CDCl3/DMSO-6 ORANGE FILTRATE SOLID

3.38

336

10 0 9 0 8 0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0
BIB-3-160A-B IN CDCl3

3.42

PPM

9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
3.54
Mixture of isomers
3.54 Mixture of isomers
3.55
Mixture of isomers
TBDMSO

\[ \text{3.55} \]

Mixture of isomers
Mixture of isomers
3.56
Mixture of isomers
3.57 Mixture of isomers
3.57
Mixture of isomers
3.58
Mixture of isomers
BIB-3-758 13C-H correlation

3.60
3.76 Mixture of isomers
3.76
Mixture of isomers