I. Synthesis of Conformationally Restricted Nucleosides. II. Studies Toward the Total Synthesis of (-)-Neplanocin A

DISSERTATION

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

By

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*****

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ABSTRACT

The recent spurt of interest in conformationally restricted nucleosides has brought into focus concern for the development of spirocyclic nucleosides as potential drug candidates and as potential modulators of DNA conformation and stability. Herein a convenient synthesis a number of spirocyclic nucleosides is detailed. This new class of nucleosides has examples in four different series; sddN, sd4N, sN (RNA), and sdN (DNA). Three unique synthetic strategies were utilized in the development of all four series, with incorporation of all five natural nucleobases.

The pyrimidine bases uracil and thymine were introduced via Vorbrüggen glycosidation conditions utilizing a C2í sulfide to give the beta anomer exclusively. These sulfides were used in a divergent manor to produce three series, sddN, sd4N, and sN by using the sulfide as a handle for further functionalization about the tetrahydrofuran ring. For the synthesis of these same three series with the purine bases adenine and guanine, use was made of SN2 displacement of two different anomeric chlorides with the sodium salt of the adenine and guanine precursors.

The final series sdN or DNA analogues began with an α,β-unsaturated lactone. The olefin was dihydroxylated and selectively deoxygenated to give the C2í deoxy
system. Introduction of thymine, cytosine and adenine via Vorbrüggen glycosidation conditions resulted in anomeric mixtures.

A study toward the synthesis of (-)-neplanocin A was undertaken. The synthesis began by the conversion of methyl D-glucopyranoside into a fully protected methyl D-allopyranoside. The protected allopyranoside was then converted into a vinyl sugar needed for a zirconocene mediated ring contraction.
DEDICATION

To my wife Holly,
without whom I never would have achieved all that I have
ACKNOWLEDGMENTS

I would like to express my gratitude to Dr. Leo A. Paquette for giving me the opportunity to work in his research group for the past two years. Thank you, Doc, for your support and guidance on these projects.

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I must thank my parents for being supportive over all of my years through school. Finally, I must thank my wife Holly. She has been the one who has proofread everything that I have written. She has also been extremely patient with me and has helped me when I have been frustrated. I could not have accomplished the things that I have without her support.
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<tr>
<td>α</td>
<td>alpha</td>
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<tr>
<td>[α]</td>
<td>specific rotation</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>br</td>
<td>broad (IR and NMR)</td>
</tr>
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<tr>
<td>CSA</td>
<td>(1S)-(+)10-camphorsulfonic acid</td>
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<tr>
<td>δ</td>
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<td>DMF</td>
<td>N,N-dimethylformamide</td>
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DMSO  dimethylsulfoxide

eq.  equivalent

Et  ethyl

γ  gamma

g  gram(s)

h  hour(s)

IR  infrared

J  coupling constant in Hz (NMR)

k  kilo

KHMD  potassium hexamethyldisilazide

L  liter(s)

LDA  lithium diisopropylamide

m  milli; multiplet (NMR)

μ  micro

M  moles per liter

Mc  chloromethylsulfonyl

Me  methyl

MHz  megahertz

min  minute(s)

mol  mole(s)

Ms  methanesulfonyl

MS  mass spectrometry; molecular sieves

m/z  mass to charge ratio (MS)
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<td>NMO</td>
<td>4-methylmorpholine N-oxide</td>
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<tr>
<td>NMR</td>
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<td>$p$</td>
<td>para</td>
</tr>
<tr>
<td>Ph</td>
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</tr>
<tr>
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<td>$p$-methoxybenzyl</td>
</tr>
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<td>parts per million</td>
</tr>
<tr>
<td>py</td>
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</tr>
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</tr>
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</tr>
<tr>
<td>s</td>
<td>singlet (NMR); second(s)</td>
</tr>
<tr>
<td>SEM</td>
<td>2-(trimethylsilyl)ethoxymethyl</td>
</tr>
<tr>
<td>$t$</td>
<td>tertiary (tert)</td>
</tr>
<tr>
<td>t</td>
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CHAPTER 1

INTRODUCTION

1.1 Background and Significance

The molecule responsible for the storage and replication of genetic information in living systems is deoxyribonucleic acid (DNA) and it exists as a duplex consisting of two complementary strands. These strands are interwound to form a right-handed helix encoded by the specific Watson-Crick hydrogen bonding patterns of the adenine/thymine (A/T) and guanine/cytosine (G/C) base pairs. The information stored by DNA is used to direct and control the synthesis of proteins. Almost all cells contain one or two complete copies of this genetic information, which is utilized by being transcribed into messenger ribonucleic acid (mRNA). This single stranded molecule carries information from DNA to the ribosomes where proteins are manufactured within the cell.\(^1\)

Inhibition of gene expression at either translation or transcription by the selective complexation of single stranded RNA or double stranded DNA has received much attention of late.\(^2-5\) This research activity into synthetic oligonucleotides has been motivated by diagnostic and therapeutic goals. These results are of potential importance in the basic scientific study of biochemical and biophysical structure and function. The antisense oligonucleotides (AO) would bind with enhanced affinity to their mRNA
counterpart, thus suppressing translation. The antisense principle approach is to target mRNA by duplex formation with a short oligonucleotide in order to prevent translation of the mRNA into proteins. Any genetic sequence, and thus any disease with a genetic origin, should be subject to selective targeting in this manner. In 1998, twenty-one years after the introduction of the antisense approach, the first oligonucleotide was introduced in the pharmaceutical marketplace. Ultimate proof of principle consisted of the phosphorothioate ISIS-2922 (Fomivirsen), prescribed for use against CMV retinitis.

The use of oligomers containing conformationally restricted monomers has been a successful approach to achieving high binding affinity in antisense approaches. Several oligonucleotide analogues containing bi- and tricyclic carbohydrate mimics have displayed enhanced duplex stabilities as compared to unmodified oligonucleotide strands. Substitution of the natural furanose sugar moiety results in a reduction of conformational freedom. This reduction can have an overall effect by increasing the thermodynamic stability of the DNA/RNA heteroduplex.

The impact of prior work in the chemically modified antisense oligonucleotide arena indicates that the antisense strategy is general, attractive, and worthy of pursuit, especially when compared with the individual developments involving traditional drugs acting at the protein level. Without doubt the demand for such agents is high. It is a general opinion that the structure and functions of DNA can be successfully mimicked by consideration of steric factors, proper conformational adjustment within the furanose mimic, hydratability, and pharmacokinetic behavior. It was the goal of this Ph.D. research to develop a series of nucleosides involving a spirocyclic sugar analogue.
1.2 Preliminary Studies

Several years ago the first examples of oxonium ion-initiated pinacolic ring expansion were reported from within the Paquette group.\textsuperscript{21-23} From these examples, it was noted that 1.1 (Figure 1.1) could serve as a sugar mimic after a series of transformations. What was initially attractive about 1.1 was that once it was converted to nucleoside 1.2 the molecule would be conformationally biased, but not conformationally locked. Another advantage of the spirocyclic system was in the incorporation of a quaternary center at C4i. The quaternary center should result in resistance toward enzymatic transformations (e.g. by nucleases). A third advantage was that the hydroxyl group on C5i could be synthesized with a defined stereochemistry, thus resulting in two different DNA analogues.

![Figure 1.1. Spirosugar mimic](image)

Before pursuing the transformation of 1.1 into a spironucleoside, several molecular modeling calculations were performed.\textsuperscript{24,25} Modeling of a natural thymidine 1.3, the anti-configured 1.4, and syn-configured 1.5 was performed. When all three structures have been fully minimized in Amber for the gas phase (Figure 1.2), the overlay of 1.4 with the natural thymidine 1.3 results in a root mean square (RMS) value of 0.058.
The overlay of 1.5 with natural 1.3 is a remarkable RMS of 0.007, indicating almost no distortion about the sugar framework between the two systems.

Figure 1.2. Computer modeling of monomers

In addition to modeling of the monomeric units, modeling of a 13-mer of a DNA strand and its complementary chain was also performed (Figures 1.3, 1.4 and 1.5). Figure 1.3 shows the computer modeling of the natural thymidine 1.3, with an expansion of the center of the strand. The central sugar unit in the expansion was then replaced with the modified spirocompounds as shown in Figures 1.4 and 1.5. In Figure 1.4, the syn-configured spirocycle 1.5 is shown. What should be noted is that incorporation of the spirocyclic nucleoside results in little to no distortion about the DNA backbone. What is also of note is that when compared with Figure 1.3, the distortion of the thymine base from the plane within the helix is minimal. The incorporation of the anti-configured base in Figure 1.5 again shows little to no distortion of the DNA sugar backbone when compared to the natural system. However, with the incorporation of 1.4 into the DNA strand, there is some distortion of the thymine base from the plane within the double helix. Although the computer modeling provides no insight into reduced conformational
flexibility, enhanced stability is anticipated as a consequence of the structural preorganization provided by the spirocyclic architecture.

Figure 1.3. Computer modeling of DNA with natural thymidine 1.3
Figure 1.4. Computer modeling of DNA with syn configured thymidine

Figure 1.5. Computer modeling of anti configured thymidine
It was the molecular modeling that brought about the first efforts toward the synthesis of spirocyclic nucleosides. Two post-doctoral researchers, Todd Bibart and Dafydd Owen, made the first attempts at the conversion of a spirocyclic ketone to a spirocyclic sugar mimic and part of their synthetic route is shown in Scheme 1.1. Coupling of 2-lithiodihydrofuran with cyclobutanone, followed by N-bromosuccinimide-initiated pinacol rearrangement gave spiroketone 1.6. Resolution of the racemic ketones was facilitated with Johnson’s (S)-(−)-sulfoximine to give 1.7 after chromatography. Removal of the chiral auxiliary was brought about by fragmentation elimination, and reduction of the ketone gave bromo alcohol 1.8. Protection of the hydroxyl group and dehydrobromination resulted in the formation of 1.9. Finally, 1.9 was subjected to regioselective oxidation for arrival at 1.10.

Scheme 1.1. Previous synthesis of $\alpha,\beta$-unsaturated MOM lactone
Their preparation of 1.10 allowed for a divergent synthesis toward four classes of spirocyclic nucleosides as shown in Figure 1.6. Although the main goal of the project was to synthesize spiro-DNA analogues, it was also planned to access three other series as well. Compound 1.11 is the spirocyclic didehydronucleoside (sddN) sometimes to be referred as the saturated nucleoside. The next example 1.12 is spirocyclic didehydro-dideoxynucleoside (sd4N) also known as the unsaturated analogue. Finally 1.13 is the spirocyclic nucleoside (sN) or RNA and 1.4 spirocyclic deoxynucleoside (sdN) or DNA. There are many examples of nucleosides without the C2í and C3í hydroxyl groups that have had potent biological activity.3,27,28 It was hoped that the spironucleosides shown in Figure 1.6 would possess some biological activity.

Figure 1.6. Spirocyclic targets

The synthetic strategy pursued by Bibart and Owen suffered from some drawbacks, the first and most important of which was the low yield during the introduction of the chiral auxiliary to give 1.7. A 45% yield in the second transformation is a major hindrance in a lengthy linear synthesis. The second drawback was that no C2í
substituent was present to give an enhanced anomeric ratio during the glycosidation. The development of a new synthetic strategy to solve these problems was the focus of my M.S. thesis.\textsuperscript{29}

The new strategy (Scheme 1.2) began again with 2,3-dihydrofuran, which was lithiated and coupled with cyclobutanone. There followed an acid-mediated pinacol rearrangement to give spiroketone \textit{1.14}. Resolution of the enantiomers was accomplished by formation of the chiral ketal from (R)-mandelic acid and chromatographic separation to give \textit{1.15}. Removal of the ketal with lithium hydroxide followed by either a Meerwein-Ponndorf-Verley reduction or reduction by L-selectride and subsequent protection as the \textit{tert}-butyldimethylsilyl (TBS) ether gave anti-configured \textit{1.16} and the syn-configured \textit{1.17}, respectively. Oxidation of the furan to the $\gamma$-lactone was accomplished with ruthenium tetroxide to give \textit{1.18} and \textit{1.19}. Treatment of either \textit{1.18} or \textit{1.19} with excess LHMDS followed by phenyl benzenethiosulfonate resulted in the $\alpha,\alpha$-disulfide which was desulfurized with ethylmagnesium bromide to give \textit{1.20} and \textit{1.21} as diastereomeric mixtures. Finally oxidation of the sulfide followed by thermal extrusion of phenylsulfenic acid furnished \textit{1.22} and \textit{1.23}. 
Scheme 1.2. Synthetic route from M.S. thesis

This new synthetic strategy has solved some of the problems that were present in the previous synthesis. Most notable are the nearly quantitative yields for the formation and removal of the chiral ketals. This synthesis also allows for the use of the C2í sulfide as a tool for introduction of the nucleobases during the glycosidation reactions. The focus of this dissertation is to demonstrate how compounds 1.20, 1.21, and 1.22 have been utilized in the synthesis of the four nucleoside target series.
CHAPTER 2

SYNTHESES OF SDDN, SD4N, AND SN

2.1 Introduction

Subsequent to the development of an efficient route to γ-butyrolactones 1.18 and 1.19 (Figure 2.1), work could begin on the synthesis of spironucleosides. These lactones were to serve as useful synthons for the introduction of the DNA bases.

![Diagram of 1.18 and 1.19]

**Figure 2.1.** Spirolactones

The key issues associated with 1.18 and 1.19 such as their production in enantiomerically pure form and incontrovertible assignment of absolute configuration have been solved.25,26,29,30 This chapter details the conversion of these and related building blocks into a broad range of spironucleosides defined by \textit{sddN}, \textit{sd4N}, and \textit{sN} shown in Figure 2.2.
2.2 Synthesis of spirocyclic thymidine and uridine analogues

The synthetic approach toward the target spirocyclic nucleosides takes advantage of the feasibility of generating the phenylthio-substituted lactone 2.1.1, which had been previously synthesized. As shown in Scheme 2.1, submission of 2.1.1 to the action of diisobutylaluminum hydride followed by acylation gave 2.2 as an anomeric mixture in 94% yield. Treatment of 2.2 at -78 °C with a Lewis acid (TMSOTf or SnCl₄) in the presence of persilylated thymine gave the target 2.3 in moderate yield (54-59%).

Scheme 2.1. Vorbr, ggen glycosidation
The choice of Lewis acid was very important to the selectivity of the glycosidation, as shown in Scheme 2.2. The use of TMSOTf as the Lewis acid resulted in an anomeric \( \beta:\alpha \) ratio of 2:1. When tin tetrachloride was used as the Lewis acid, a large increase was observed in the anomeric ratio in that no alpha anomer was observed by \( ^1\text{H} \) NMR. The effect of Lewis acid is not as prevalent in glycosidations where the C2i directing group is an oxygen source.\(^{31}\)

The use of the 2-phenylthio substituent results in two possible modes of action, depending on the choice of Lewis acid. The first mechanistic aspect of the reaction is the transient intervention of an episulfonium ion intermediate\(^{34}\), as shown in Figure 2.3. The formation of the episulfonium ion could occur regardless of the choice of Lewis acid. The second mechanistic aspect of the reaction is complexation of the sulfur atom to the tin Lewis acid in advance of oxonium ion formation\(^{35}\) to foster selective formation of a 1,2-trans glycosyl bond.\(^{36-39}\)

\[
\begin{align*}
\text{OTBS} & \quad \text{OTBS} \\
\text{2.2} & \quad \text{2.2} \\
\text{SPh} & \quad \text{SPh} \\
\text{OAc} & \quad \text{OAc} \\
\text{OTBS} & \quad \text{OTBS} \\
\text{2.3} & \quad \text{2.3} \\
\text{B} & \quad \text{B} \\
\end{align*}
\]

\[\text{TMSOTf, } -78 \text{ to rt}\]

\[\text{TMS2-Base, CH2Cl2}\]

\[\text{SnCl4, } -78 \text{ to rt}\]

Scheme 2.2. Effect of Lewis acid on anomeric ratio
Chelation of the sulfur atom is not possible with trimethylsilyl triflate, \(^{35}\) thus the only control results from the episulfonium ion. The observed 2:1 anomeric ratio indicates that the formation of the episulfonium ion is either not complete, or that the nucleophilic addition of the base occurs faster than formation of the episulfonium ion.

![Episulfonium and Chelation](image)

**Figure 2.3.** Mode of selectivity

With the appropriate conditions developed for formation of the thymine nucleosides with stereocontrol, attention was turned to the introduction of other pyrimidine bases, namely uracil and 5-fluorouracil (Scheme 2.3). The other natural DNA bases will be discussed in section 2.4. Treatment of 2.3 with SnCl\(_4\) in the presence of a persilylated base gave the desired targets 2.3, 2.4, and 2.5 in approximately 60% yield. The selectivity of uracil was slightly diminished as compared to thymine, but this is in line with customary steric effects.

Elimination of the 2-phenylthio substituent in 2.3, 2.4, and 2.5 was next accomplished by controlled oxidation with the Davis oxaziridine reagent.\(^{40}\) The impure sulfoxides were heated in a mixture of xylenes and pyridine to bring about the thermal elimination of phenylsulfenic acid and deliver 2.6-2.8 in high yield. Finally, removal of the TBS protecting group was carried out with potassium fluoride and 18-crown-6 to give
2.9 and 2.10. The excellent yield of the thymidine example reflects its exceptional stability under these conditions. In contrast, epimerization was encountered in both examples when recourse was made to TBAF for desilylation.

Scheme 2.3. Synthesis of sd4N pyrimidines

The route to the saturated spirocyclic nucleosides appeared to be straightforward from sulfides 2.3 and 2.4. However, treatment of either sulfide with Raney Ni\(^{41}\) or nickel boride\(^{42-44}\) resulted in hydrogenation of the olefin in the uracil and thymine rings. The alternative route to these same saturated nucleosides can be seen in Scheme 2.4. The unsaturated spirocycles 2.6 and 2.7 were treated with hydrogen in the presence of 5% palladium on charcoal to give the saturated compounds 2.11 and 2.12, respectively. Deprotection was realized by the use of 18-crown-6 and potassium fluoride in THF, to give 2.13 and 2.14 in 83% yield.\(^{45,46}\)
Scheme 2.4. Synthesis of sddN pyrimidines

The third series of nucleosides that could be easily obtained from this synthetic strategy were the RNA analogues. The synthesis again began with the unsaturated nucleosides 2.6-2.8, as seen in Scheme 2.5. Dihydroxylation of the olefin with osmium tetroxide proved very reliable when the base was uracil or thymine, giving 2.15 and 2.16 in 90 and 100% yields, respectively.

Scheme 2.5. Synthesis of sN pyrimidines

Treatment of the 5-fluorouracil adduct 2.8 with osmium tetroxide did not give the desired diol. Multiple products were isolated from the reaction mixture, and their
structures could not be determined beyond a reasonable doubt. Finally, removal of the TBS protecting group was achieved upon treatment of 2.15 and 2.16 with TBAF in THF.

2.3 The syn-configured spirocycles

Before attempts were made to introduce of the other DNA bases in the anti series, efforts to apply the same synthetic strategy to the syn-configured spirocycle were investigated. Treatment of lactone 2.20.1 with diisobutylaluminum hydride followed by acylation of the lactol gave two compounds. Scheme 2.6 depicts the isolated compounds. The first compound was the desired anomeric acetate 2.21, while the other product, 2.22, was the result of overreduction. The reduction conditions were later optimized by Alexandra Kahane, who later synthesized several nucleosides in this diastereomeric series.47

![Scheme 2.6](image)

**Scheme 2.6.** Difficulty with Dibal-H reduction

With the anomeric acetate 2.21 in hand, the synthesis of an RNA analogue was continued as shown in Scheme 2.7. Treatment of 2.21 with persilylated thymine in the presence of tin tetrachloride gave the desired thymidine 2.23 in 40% yield. As with the anti series, only the beta anomer was observed by $^1$H NMR. Elimination of the
2-phenylthio substituent in 2.23 was next accomplished by controlled oxidation with the Davis oxaziridine reagent\textsuperscript{40} and subsequent thermal extrusion of phenylsulfenic acid by heating in xylenes containing pyridine to give 2.24.

![Chemical structures](image)

**Scheme 2.7.** Formation of syn-sN thymidine

The olefin 2.24 was treated with osmium tetroxide and NMO to give the desired diol in 36\% yield. It is noteworthy that the dihydroxylation of the anti analogue 2.7 proceeded in quantitative yield, whereas the dihydroxylation of 2.24, proceeded poorly. During the dihydroxylation of 2.24, multiple products were observed and could not be fully identified. Deprotection was realized with a combination of PPTS and concentrated HCl to give the desired RNA analogue 2.26.
2.4 Synthesis of spirocyclic cytidine and adenosine analogues

With the completion of the three nucleoside series for the bases thymine and uracil, attention was turned toward the introduction of the remaining DNA bases, the first being cytosine. Acetate 2.2 (Scheme 2.8) was treated with persilylated cytosine in the presence of tin tetrachloride as the Lewis acid to give 2.27 in 67% yield, with only the beta anomer being observed by $^1$H NMR. As with the previous nucleosides, the synthesis was to involve the selective oxidation of the sulfide followed by thermal extrusion of phenylsulfinic acid. Treatment of 2.27 with the Davis oxaziridine reagent$^{40}$ followed by heating in xylenes gave products of depurination and not the expected olefin 2.28.

![Scheme 2.8. Glycosidation with cytosine](image)

Loss of the cytosine base during thermolysis is a known side reaction associated with cytosine and the purine bases.$^{32}$ Direct efforts to curb this undesired reaction by
performing the thermolysis in the presence of a variety of bases failed. In another effort to prevent depurination, 2.28 was converted into the N-acyl analogue shown in Scheme 2.9 by treatment with acetic anhydride in pyridine. Oxidation was again performed using the oxaziridine reagent and the resulting sulfoxide 2.30 was isolated in 69% yield. The pure sulfoxide was then heated in a mixture of xylenes and pyridine to give the desired product in less than 10% yield. As was previously observed, the major product was that of depurination and efforts to increase the yield of 2.31 proved unsuccessful.

![Scheme 2.9](image)

**Scheme 2.9.** Oxidation and thermolysis of cytosine derivative

As the reactions with cytosine were being explored, the introduction of adenine was also pursued (Scheme 2.10). Treatment of acetate 2.2 with persilylated benzoyladenine and tin tetrachloride in acetonitrile gave the deprotected nucleoside 2.32 in 50% yield with none of the alpha anomer detected by $^1$H NMR. The choice of solvent
was very important for the selective introduction of adenine. The use of dichloromethane or a mixture of dichloromethane and acetonitrile resulted in mixtures of the alpha and beta anomers in different ratios. It should be noted that the use of acetonitrile allowed for the simultaneous removal of the TBS protecting group during the glycosidation conditions. Deprotection was not observed in previous trials with dichloromethane as the solvent. Unfortunately, as with the cytosine spirocycles, the two-step oxidation and thermolysis of \(2.32\) to give olefin \(2.33\) proved unsuccessful, resulting in depurination. Spirocyclic nucleosides containing cytosine, adenine and guanine would have to be synthesized by an alternative route, which will be discussed in Chapter 4.

![Scheme 2.10. Introduction of adenine](image_url)
2.5. Summary

In conclusion, syntheses of the first spirocyclic nucleosides featuring both syn and anti-hydroxyl substituents at C5i have been achieved for the nucleobases uracil, 5-fluorouracil and thymine. A divergent pathway to three different target series, sd4N, sdN and sN was developed. In each case, high beta/alpha anemic ratios were obtained. An alternate route to these same targets incorporating purine nucleobases would be developed later.

All of the nucleosides that were synthesized above were sent to the National Institutes of Health to be screened for biological activity. Two of the compounds, 2.18 and 2.19 (Figure 2.4) possessed striking activity against the Epstein-Barr virus (EBV). Compound 2.18 was found to have an EC₅₀ of <0.08 µg/mL, while 2.19 has an EC₅₀ of 0.34 µg/mL.

![2.18 and 2.19](image)

**Figure 2.4.** Biologically active compounds
CHAPTER 3

MOM GLYCOSIDATIONS AND DNA ANALOGUES

3.1 Introduction

Following the development of an efficient synthesis of \( \gamma \)-butyrolactones 1.22\(^{29} \) and 1.10\(^{26,29} \) (Figure 3.1), work began on the synthesis of spironucleosides with a DNA configuration. These lactones would serve as useful templates for the introduction of nucleobases. The following chapter will detail efforts toward the synthesis of the DNA analogues of spironucleosides.

![Figure 3.1. \( \alpha,\beta \)-Unsaturated lactones](image)

3.2 Glycosidations of MOM protected spirocycles

During initial studies toward the synthesis of spirocyclic nucleosides, the MOM protecting group was used. It was observed by Bibart and Owen\(^{48} \) that when performing
the glycosidation reaction, the results were frequently not reproducible. Sometimes the desired nucleoside would be obtained as the sole product, while in other instances, multiple products were obtained. It was at this point that they pursued the use of a different protecting group, and made good use of the p-methoxybenzyl group.25

It was decided to reinvestigate the glycosidations within the MOM protected spirocycles to investigate what was occurring during this reaction. Synthesis of the necessary anomeric acetate began with α,β-unsaturated lactone 3.1, shown in Scheme 3.1. Dihydroxylation of 1.10 with osmium tetroxide gave the desired diol in 93% yield, which was treated with excess diisobutylaluminum hydride to furnish the desired lactol. The reaction mixture was quenched with acetic anhydride and pyridine and warmed to room temperature. After work-up and column chromatography, triacetate 3.1 was isolated. Failure to execute this protocol leads instead to tight complexation of the aluminum ion to the triad of hydroxyl groups.

Scheme 3.1. Glycosidation on MOM-spirocycle
The anomeric mixture of acetates was treated under Vorbrüggen glycosidation conditions\textsuperscript{31} with persilylated thymine\textsuperscript{49} and TMSOTf as the Lewis acid. The desired thymine adduct was obtained in 60\% yield. This reaction was repeated multiple times in the hope of observing and identifying the multiple products observed by Bibart and Owen.\textsuperscript{48}

After unsuccessful attempts to obtain the side products, time was spent analyzing their notebook pages pertaining to this glycosidation. It was noted that when they performed the glycosidation initially, only product 3.2 was observed. However, when they performed the same reaction weeks or months later, other products were indicated by TLC. It quickly became apparent that during the later glycosidation attempts they did not freshly distill the trimethylsilyl triflate prior to use. The presence of triflic acid in the TMSOTf would have a great effect on the MOM protecting group. During all of the attempts to reproduce their results, freshly distilled trimethylsilyl triflate had been used.

To test this theory, triacetate 3.1 was treated with persilylated thymine and freshly distilled TMSOTf (Scheme 3.2). Thirty minutes after the addition of trimethylsilyl triflate, TLC indicated that 3.2 and free thymine were the only products in the reaction mixture. At this point, one drop of triflic acid was added to the reaction mixture. After another 30 min, two new products were observed by TLC.

After chromatography it was determined that the two new products were that of MOM deprotection 3.2 and the structurally unusual dithymidine 3.4. The isolation of both of these compounds indicated that the triflic acid is causing the removal of the MOM protecting group during the course of the reaction. Production of the dithymidine
presumably arises from the reaction of excess silylated base with intermediate oxonium ion 3.5 during the MOM deprotection (Figure 3.2)

Scheme 3.2. Addition of TfOH to the glycosidation

When a larger excess of silylated base was used with a mix of TMSOTf and triflic acid, elevated proportions of 3.4 were isolated. This observation is further proof that a second oxonium ion is formed during the course of the reaction. Further reactions were run on MOM protected spirocycles and it was found that glycosidations of the MOM protecting group were not limited to the spirocyclic sugar itself, but is general for the β-oriented MOM series (Scheme 3.3).
Figure 3.2. A second oxonium ion formation

Treatment of lactone 3.6 with bis(trimethylsilyl)adenine\textsuperscript{49} in the presence of trimethylsilyl triflate with a catalytic amount of triflic acid resulted in the formation of 3.7 in 25% yield. Optimization of these conditions was not explored. It is believed that 3.4 and 3.7 represent prototypes of a unique series of nucleoside mimics that have not been accorded prior attention.\textsuperscript{50}

Scheme 3.3. MOM glycosidation with adenine

3.3 Synthesis of spiro-DNA analogues

The final target series for spironucleoside mimics is that of the DNA analogues. The synthesis of these analogues began with α,β-unsaturated lactone 1.22, shown in
Scheme 3.4. Initial attempts at dihydroxylation utilizing osmium tetroxide met with limited success in that after seven days conversion to the diol was less than 10%, whereas the MOM protected spirocycle 1.10 gave 97% yield for these same conditions. This observation shows how the protecting group has a large effect on the overall reactivity of the system. The dihydroxylation was performed with ruthenium tetroxide, generated \textit{in situ} from ruthenium(III) chloride and sodium periodate. The conditions devised by Shing and co-workers involved a two-phase solvent system and the reaction required only five minutes for completion.\textsuperscript{51} The desired diol 3.8 was obtained in 75% yield. The unfortunate limitation of these reaction conditions is that only two hundred milligrams can be reacted at one time. If more material is submitted, products of over-oxidation are observed.

The diol was then selectively deoxygenated with use of excess samarium(II) iodide.\textsuperscript{52-54} The desired 2-deoxy compound 3.9 was obtained in quantitative yield. It was found unnecessary to protect the diol prior to treatment with SmI\textsubscript{2}, thus eliminating a sometimes necessary masking. Attempts were made to change the additive from HMPA to DMPU. However, when DMPU was used, the reaction failed to proceed to completion even when large excesses of SmI\textsubscript{2} were used.

The protection of the C3\textsubscript{i} hydroxy group proved to be very difficult. Initial strategy involved protecting the C3\textsubscript{i} hydroxy group as either the N,N-diethythiocarbamate\textsuperscript{55,56} or as the 2-(phenylthio)ethyl ether.\textsuperscript{57-59} Both of these protecting groups have previously been utilized in 2-deoxy systems as participants in the oxonium ion during glycosidation, thus blocking the alpha face and giving the beta nucleoside. Unfortunately, the introduction of these protecting groups proved to be unsuccessful.
The unreactive nature of the hydroxyl group is not completely unexpected considering that the hydroxyl group is adjacent to a pseudo-neopentyl center. The free hydroxyl was then protected as the TBS ether. Again the hydroxy group proved to be unreactive. Treatment of 3.9 with TBSCI and imidazole resulted in no reaction. However, when a change was made to tert-butyldimethylsilyl triflate and 2,6-lutidine, the desired protected lactone 3.10 was obtained in 50% yield. Finally, the lactone was reduced in the presence of diisobutylaluminum hydride to give the lactol, which was immediately protected as the anomeric acetate 3.11.

![Scheme 3.4](image)

**Scheme 3.4. Synthesis of 2-deoxyspirocycle**

The inability to introduce a protecting group on the C3i hydroxyl that would serve as a directing group during the glycosidation partially led to the choice of TBS as the protecting group. It was hoped that the bulky TBS group would partially block the α-face giving the β-anomer as the major product. Treatment of acetate 3.11 with
persilylated thymine in the presence of SnCl₄ as the Lewis acid resulted in the formation of only one product (Scheme 3.5).

Scheme 3.5. Introduction of thymine

With the formation of only one anomer, it was initially believed that the steric bulk of the TBS group did indeed block the α-face. To prove this, recourse was made to nOe studies. Unfortunately, a 1.5% enhancement was observed between the C1í and C5í protons. Although this enhancement is not very large, the same minute enhancement is observed in 3.13 for which an X-ray crystal structure is also available.⁴⁷,⁶⁰

Figure 3.3. nOe evidence for α-configuration and X-ray for syn-series
With the undesired anomer being the only product obtained from the thymine glycosidation, it seemed unlikely that introduction of the other bases would be successful. In an effort to change the selectivity, the solvent used in the glycosidation reaction conditions was changed for the introduction of cytosine and adenine (Scheme 3.6). It was hoped that the use of a polar solvent would reduce the chelation between the tin and the silylated base, thus lowering the steric demand of the reacting nucleophile and increasing the yield of the β-anomer. Acetate 3.11 was treated with persilylated cytosine in dry acetonitrile at -40 °C, neat tin tetrachloride serving as the Lewis acid. The desired nucleoside 3.14 was obtained in 65% yield as an inseparable 1:1 mixture. Similar treatment of 3.11 with bis(trimethylsilyl)adenine in acetonitrile also gave rise to a 1:1 mixture of anomers in 50% yield. In this case, the anomers of 3.15 were separable by careful chromatography on silica gel with a mixture of benzene and ethyl acetate as the eluent.

Scheme 3.6. Introduction of cytosine and adenine
Since the adenine adducts proved separable, nOe data was collected on each substrate. One of the products 3.15.1 had no nOe between the C1\(1\) and the C5\(1\) protons, while the other compound 3.15.2 had a 1.0% enhancement between these same two protons. Compound 3.15.1 was also crystalline. At the time of the writing of this dissertation attempts were being made to grow a suitable crystal for X-ray analysis.

3.4 Summary

A new series of nucleosides utilizing oxonium ion formation within the MOM protecting group as the reactive center has been described. The glycosidation of MOM protected spirocycles could be controlled to achieve nucleoside introduction only at the anomeric center by making use of freshly distilled TMSOTf. The MOM spirocycles could also be made to react at the MOM protecting group by the addition of triflic acid. In addition to the MOM glycosides, three DNA mimics 3.12, 3.14, and 3.15 have also been synthesized. A six-step sequence from the known \(\alpha,\beta\)-unsaturated lactone 1.22 was developed. The unfortunate formation of the \(\alpha\)-anomer as the major product was a major detriment to the grand scope of the project. Efforts to overcome this selectivity problem are currently being pursued within the syn series in the Paquette group.\(^{61}\)
CHAPTER 4

SPIROCYCLIC PURINE ANALOGUES

4.1 Introduction

The application of Vorbrüggen glycosidations\textsuperscript{31} for the synthesis of the spirocyclic nucleoside analogues proceeded very well with all five natural DNA bases, as was discussed in Chapter 2. Unfortunately, as seen in Scheme 4.1, oxidation and thermolysis of the sulfide to enable further functionalization about the spirocyclic core met with difficulty. In order to achieve the goal of all of the nucleobases on the four target series, a new synthetic strategy would have to be developed, and is discussed herein.

Scheme 4.1. Sulfide route to spirocyclic purine nucleosides
4.2 A New Route to Purine Analogues

The strategy used for the synthesis of spirocyclic purine analogues involved the SN2-type displacement of a glycosyl halide with the sodium salt of purines. The known lactone \( \text{1.18} \) (Scheme 4.2) was reduced to the corresponding lactol \( \text{4.1} \) with Dibal-H. The crude lactol was converted to glycosyl chloride \( \text{4.2} \) by treatment with triphenylphosphine in a mixture of carbon tetrachloride and THF at 60 °C. The crude glycosyl chloride was cannulated into a mixture of 6-chloropurine and sodium hydride in THF. Following purification, purine analogues \( \text{4.3.1} \) and \( \text{4.3.2} \) were isolated in 31% and 18% yields, respectively. Although flash chromatography enabled the separation of the anomers, it was found that upon standing in solution, epimerization occurred and a 1.7:1 mixture resulted. It is believed that this interconversion proceeds by transient formation of the oxonium ion and that the \( \beta/\alpha \) distribution represents the thermodynamic equilibrium ratio.

Proton NMR studies of \( \text{4.3.1} \) and \( \text{4.3.2} \) failed to establish the configuration of the major product beyond a reasonable doubt. Recourse was made to MM3 calculations for assessing the relative thermodynamic stabilities of the four possible isomers including the N7 and N9 options. Figure 4.1 depicting the Monte Carlo simulations (MacroModel version 5.0) of 1500 different conformers in each situation revealed that \( \text{4.3.1} \) was the global minimum, albeit by a very small margin relative to \( \text{4.3.2} \) (0.4 kcal/mol).
Scheme 4.2. S\textsubscript{N}2 displacement of anomeric chloride

![Scheme 4.2](image)

Figure 4.1. MM3 calculations of the four isomers

![Figure 4.1](image)
Although these calculations are still not definitive proof of structure, comparison of 4.3.1 and 4.3.2 was made both by the calculations and available X-ray analysis for the C5’ diastereomer 4.4 shown in Figure 5.2. The same MM3 calculations predicted that the minor component would be the α-anomer. X-ray analysis of the minor component 4.4.2 revealed that the structure was indeed the α-anomer. With the calculations of 4.4.1 and 4.4.2 being corroborated by X-ray analysis, it seemed that the calculations involving 4.3.1 and 4.3.2 could be used for the final structural assignment.

![MM3 steric energies of C5i diastereomer](image-url)

**Figure 4.2.** MM3 steric energies of C5i diastereomer

With the configurational issues resolved, substitutive amination was accomplished by heating 4.3.1 and 4.3.2 at 100 °C with methanolic ammonia in a sealed vessel for 6 h as shown in Scheme 4.3. After careful column chromatography, two mixtures of products were isolated. The minor compounds were a 1.7:1 mixture of the methoxy substituted purine 4.5, while the major products were the desired adenine adducts 4.6 also in a 1.7:1 anomeric ratio. The production of 4.5 as a mixture of anomers
was favored at shorter reactions times. When heating was prolonged, the presence of 4.5 was not observed, but losses arising from decomposition became clearly apparent. Deprotection of the hydroxyl groups gave rise to 4.7 as a 3:1 anomic mixture.

Scheme 4.3. Conversion to adenine

With a viable route to the saturated spirocyclic nucleosides, focus was turned to the synthesis of the unsaturated (sd4N) and RNA (sN) series and is shown in Scheme 4.4. The known α,β-unsaturated lactone 1.22 was treated as previously described to give the desired glycosyl chloride 4.9. Sn2 displacement of the glycosyl halide was facilitated with the sodium salt of 2-amino-6-chloropurine to give 4.10.1 and 4.10.2 as an inseparable 2.3:1 anomic mixture. Column chromatography enabled the acquisition of enriched samples of both anomers. When the enriched 4.10.1 and 4.10.2 were allowed to stand at room temperature for 12 h, reconversion to the 2.3:1 mixture occurred in both
cases. The structural assignments to 4.10.1 and 4.10.2 was again based on MM3 calculations.

![Diagram]

**Scheme 4.4. Formation of unsaturated purine analogue**

The guanine precursor 4.10 was utilized in two strategies. The first was in conversion of the 2-amino-6-chloropurine to guanine, thus giving the unsaturated spirocycle (Scheme 4.5). Treatment of 4.10, as the mixture, with 2-mercaptoethanol and sodium methoxide in a mixture of methanol and water resulted not in the direct formation of guanine\(^{70,71}\) as expected, but in conversion to sulfide 4.11. Prolonged reaction times and/or addition of more water and sodium methoxide did not promote formation of the desired guanine adduct 4.12. Upon consideration of the proposed reaction mechanism,\(^{71}\) it was believed that elevated temperatures would facilitate guanine formation. To investigate this, a solvent change from methanol to dioxane was utilized. Within 30 min
of heating to reflux, the reaction was complete. The desired product 4.12 was precipitated out of solution by the addition of acetic acid, then collected by vacuum filtration. Removal of the TBS protecting group was not accomplished. Compound 4.12 was subjected to a long list of conditions reported for the removal of silyl ethers including TBAF, HF-pyr, KF/18-crown-6, CsF, and others. In all cases, the result was either no reaction or decomposition. When recourse was made to heating those reaction mixtures, where no reaction was observed, decomposition of the material occurred rapidly.

![Chemical structures](image)

**Scheme 4.5.** Conversion to guanine

With the synthesis of the unsaturated purine analogues developed, efforts turned to the synthesis of RNA analogues (Scheme 4.6). Dihydroxylation of 4.10, as the mixture, was performed with ruthenium tetroxide in a two-phase solvent system of ethyl
acetate, acetonitrile, and water as devised by Shing and coworkers.\textsuperscript{51} The conversion required five minutes for completion. It was anticipated that the speed of the reaction would promote dihydroxylation from the $\alpha$-face, thus giving only two products. Separation of the anomeric products 4.13 and 4.14 was accomplished with MPLC on silica gel.

\textbf{Scheme 4.6.} Synthesis of RNA configured guanine precursor

Efforts toward the completion of the guanine sN analogue are shown in Scheme 4.7. The chloropurine 4.14 was treated with 2-mercaptoethanol, sodium methoxide in methanol, and water.\textsuperscript{70,71} Unfortunately, under these reaction conditions none of the desired guanine analogue was isolated, nor was any of the sulfide intermediate.

\textbf{Scheme 4.7.} Conversion to guanine
With the lack of success in obtaining the RNA configured guanine from the diol 4.14 an alternative route was developed and is shown in Scheme 4.8. It was decided to first begin with the unsaturated guanine analogue 4.12 and perform dihydroxylation of the olefin with osmium tetroxide. The use of hydrogen sulfide to reduce the osmate ester was necessary so as to avoid an aqueous workup. After column chromatography, an inseparable mixture of three products was obtained in a ratio of 4:1:1, with the major product having the configuration depicted by 4.16 as determined by nOe.

Scheme 4.8. Dihydroxylation of unsaturated guanine

4.3 Summary

A viable approach to the synthesis of spirocyclic nucleosides possessing adenine and guanine as the nucleobases has been developed. The methodology takes advantage of the availability of saturated and unsaturated glycosyl chlorides and their susceptibility to $S_N2$-type displacement with sodium salts of 6-chloropurine and 2-amino-6-chloropurine. Although the glycosylations are not stereocontrolled, it was found that the rapid epimerization about the anomeric center would have resulted in a mixture from any attempt at diastereomeric control as was attempted in Chapter 2.
CHAPTER 5

(-)-NEPLANOCIN A

5.1 Introduction

(-)-Neplanocin A (5.1) is a carbocyclic nucleoside\textsuperscript{72} as seen in Figure 5.1, isolated from *Ampullariella regularis* in 1981\textsuperscript{73} and has S-adenosylhomocysteine hydrolase inhibitory activity.\textsuperscript{74} To date, several examples of the total synthesis of neplanocin A have been reported. These approaches have involved the chemoenzymatic desymmetrization of bicyclic Diels-Alder adducts derived from cyclopentadiene;\textsuperscript{75,76} palladium-mediated rearrangement;\textsuperscript{77} construction of the five-membered ring by an intramolecular Horner-Wadsworth-Emmons or Wittig reaction,\textsuperscript{78-80} and a C-H insertion reaction, respectively.\textsuperscript{81,82}

![Figure 5.1. Structure of (-)-Neplanocin A](image)

Figure 5.1. Structure of (-)-Neplanocin A
Neplanocin A and other carbocyclic nucleosides are of synthetic interest because of their antitumor or antiviral activities.83-86 Due to the absence of a true glycosidic bond, carbocyclic nucleosides are chemically more stable and not subject to the action of the enzymes that cleave this linkage in conventional nucleosides.83-86 As with nucleosides, these carbocyclic pseudonucleosides exhibit remarkable differences in biological activity when modifications are made to the cyclopentane ring.73 It is these modifications that have promoted the quest for a new synthetic strategy toward neplanocin A and possible analogues, via a zirconocene-mediated ring contraction.

5.2 Background and significance of zirconocene-mediated ring contractions of vinyl pyranosides.

The development of new synthetic methodologies brought by organozirconium compounds provides a number of possibilities for the efficient preparation of a vast array of organic molecules.87 Of great importance is the discovery by Negishi's group that the highly reactive complex 5.2 as seen in Scheme 5.1, can be readily generated in situ simply by warming a solution of Cp₂Zr(n-Bu)₂ in THF. This has allowed easy access to this useful zirconium reagent, commonly known as \( \text{Cp}_2\text{Zr}^- \).88

![Scheme 5.1. Formation of zirconocene equivalent](image_url)
The ability of 5.2 to participate in ligand exchange with unsaturated compounds has proven to be very useful. If the substrate is an allylic ether, the oxophilicity of the zirconium subsequently reveals itself via β-elimination of the alkoxy group as in intermediate 5.3 with formation of the allylzirconocene 5.4.89

The Taguchi group has demonstrated a clever extrapolation of this process, in that when carbohydrates containing a terminal olefin such as 5.5 are subjected to iCp₂Zr and boron trifluoride etherate, they are cleanly and efficiently transformed into stereochemically pure vinyl cyclopentanols exemplified by 5.6 (Scheme 5.2).90,91 As a consequence of diastereofacial discrimination and adoption of chair-like transition states, the vinyl and hydroxyl groups in the product are invariably cis oriented. This stereoselectivity is a consequence of the minimization of non-bonded steric interactions as C-C bond formation is initiated.

Scheme 5.2. First example of zirconocene ring contraction

In order to gain unambiguous understanding of the stereochemical bias of this rearrangement, attention was focused on the currently accepted mechanism proposed by Taguchi and coworkers.90 This proposed mechanism can be seen in Scheme 5.3. First,
ligand exchange between the 5-vinyl pyranoside and iCp₂Zr⁻ occurs, followed by β-elimination of the alkoxy group to generate the Z-allylic zirconium intermediate 5.7. The structural features of this intermediate were exhaustively studied by proton NMR. The olefinic proton coupling constant was found to be 10.3 Hz, which is in line with a Z-configuration. In addition to the coupling constant, a strong nuclear Overhauser effect (nOe) was found between the protons alpha to the double bond (Figure 5.2).

Scheme 5.3. Mechanism of zirconocene-mediated ring contraction reaction

The addition of boron trifluoride etherate promotes the decomposition of zirconium hemiacetal 5.7 to oxocarbenium ion 5.8, which subsequently cyclizes to give the product. Examination of the two possible transition states 5.8.1 and 5.8.2 gives clear indication why product formation has a strong stereochemical preference.
Figure 5.2. NMR studies of 5.7

Figure 5.3. Two possible transition states

With high stereoselectivity control and a well accepted mechanism, it became apparent that the carbocyclic core of neplanocin A could be synthesized utilizing the zirconocene-mediated ring contraction. A vinyl sugar with a C3 configuration different from that utilized by Taguchi would need to be utilized, but the stereochemistry of this center should have little effect on the success of the ring contraction based on the proposed mechanism.
5.3 Synthesis of (-)-Neplanocin A

(-)-Neplanocin A (5.1) would arise from alcohol 5.9 by conversion of the olefin to the aldehyde followed by elimination of the alcohol. The α,β-unsaturated aldehyde would be reduced and protected. Introduction of the adenine via Mitsunobu conditions and a global deprotection would provide the natural product. The cyclopentane core would be synthesized using a zirconocene-mediated ring contraction reaction on the vinyl sugar 5.10. The choice of protecting groups is important for the zirconium-mediated ring contraction. Benzyl and p-methoxybenzyl groups have both been found to be stable to the ring contraction conditions. Vinyl sugar 5.10 would be synthesized from the known epoxy sugar 5.11, which can be obtained from D-glucose in four steps.

**Scheme 5.4. Retrosynthetic approach to (-)-Neplanocin A**

In order to obtain all of the necessary stereocenters for 5.1, the vinyl sugar must have an α-D-allopyranoside configuration. The necessary fully protected allopyranoside
could be obtained two ways, either by starting with D-allose or by inversion of the C3 stereocenter in D-glucose. The cost associated with using D-allose ($70 for 0.25 g) as the starting material in a lengthy synthesis is prohibitive, so it was decided to begin the synthesis with D-glucose ($24 for 3 kg).\(^{93}\)

To enable inversion of the C3 stereocenter in glucose, it must first be converted into the known 2,3-anhydropyranoside 5.11. The synthesis of 5.11 (Scheme 5.5) begins with the conversion of D-glucose to the corresponding α-methylglucopyranoside by treatment with methanolic hydrochloric acid.\(^{94}\) Next, protection of C4 and C6 by formation of the 4,6-\(\text{O}\)-benzylidene derivative is accomplished by treatment with benzaldehyde and zinc(II) chloride.\(^{94}\) The resulting diol is first converted to the ditosyl pyranoside,\(^{95}\) which is then treated with sodium methoxide to give the 2,3-anhydro-allopyranoside 5.11.\(^{94}\)

\[
\text{D-Glucose} \xrightarrow{1. \text{MeOH, } H^+} \xrightarrow{2. \text{PhCHO, ZnCl}_2} \xrightarrow{3. \text{TsCl, NaOH, K}_2\text{CO}_3} \xrightarrow{4. \text{NaOMe, MeOH, CHCl}_3} \text{5.11}
\]

Scheme 5.5. Synthesis of epoxypyranoside 5.11

Opening of the epoxide via an \(S_N\)2 mechanism would result in inversion of the C3 stereocenter giving the desired axial alcohol. To facilitate this, epoxy sugar 5.11 was dissolved in boiling allyl alcohol, which had first been treated with sodium hydride (Scheme 5.6). The desired altropyranoside was obtained cleanly. However, an allopyranoside is required for the zirconocene ring contraction. To attain the necessary
allopyranoside stereochemistry, inversion of the C2 center also proved necessary. Prior to this, further protecting group modifications within the altropyranoside were necessary.

The planned synthesis utilizes the same protecting group on the C3 and C4 hydroxyls. To accomplish this, the benzylidene acetal must be selectively opened to free the C4 hydroxyl and generate the 6-O-benzyl altropyranoside. A variety of methods exist for the selective opening of benzylidene acetals including LiAlH₄·AlCl₃, NaCNBH₃·HCl, and others. However, these methods are not compatible with free hydroxyl groups. Treatment of the crude alcohol from the epoxide ring opening with triethylsilane and trifluoroacetic acid was found to be compatible with the unprotected alcohol and give the desired diol. The resulting crude diol was then benzyolated to give 5.12 after purification.

Scheme 5.6. Conversion to allopnyranoside

With the fully protected sugar in hand, inversion of the C2 center could be pursued. The allyl protecting group in 5.12 was removed by sequential treatment with Wilkinson’s catalyst to isomerize the double bond, followed by oxymercuration to give the desired alcohol 5.13. The planned inversion at C2 involved oxidation to the
ketone, followed by selective reduction to give the equatorial alcohol. Unfortunately, treatment of 5.13 with TPAP\textsuperscript{105,106} did not give the desired ketone, but resulted in formation of the β-eliminated product 5.14. A survey of oxidants including TPAP, PCC, Dess-Martin, and Swern was undertaken. All resulted in delivery of 5.14 as the major product.

To work around this problem, a change of protecting groups was sought, as seen in Scheme 5.7. Dibenzoate 5.12 was saponified with sodium methoxide in methanol to give diol 5.15 in high yield. The diol was then transformed into the acetonide using 2,2-dimethoxypropane and catalytic \( p \)-toluenesulfonic acid to give 5.16 in good yield. After isolation of the newly protected sugar, removal of the allyl protecting group was performed as previously described to give alcohol 5.17 in 85% yield.

Treatment of alcohol 5.17 with TPAP resulted in clean conversion to the desired ketone 5.18. Formation of the β-eliminated product was not observed. Inversion of C2 was completed by treatment of 5.18 with sodium borohydride to give the desired equatorial alcohol 5.19 as the exclusive product.\textsuperscript{107} Finally, protection of the resulting alcohol as the 2-(trimethylsilyl)ethoxymethyl (SEM) ether\textsuperscript{108} was accomplished by treatment with oil-free potassium hydride and SEMCl to give 5.20. The yield of this protection suffered greatly if the potassium hydride was not free from oil, usually giving less than 60% yield and no recovered starting material.
Scheme 5.7. New strategy to allopyranoside

The most direct route to the desired vinyl allopyranoside 5.10 would be to introduce the double bond immediately, remove the acetonide and reprotect the diol as the di-PMB ether. To pursue this route (Scheme 5.8), the benzyl functionality was removed by hydrogenolysis over 10% palladium on charcoal to give primary alcohol 5.21.

Scheme 5.8. First attempt at aldehyde formation
The conversion of alcohol 5.21 to desired aldehyde 5.22 proved to be unsuccessful. The oxidants investigated included PCC, Dess-Martin, IBX, TPAP, and Swern. In all cases, the ability to monitor the reaction by TLC proved to be difficult. The co-formation of at least five different compounds was evident. Proton NMR spectroscopy of the crude reaction mixtures never revealed the presence of a diagnostic aldehyde signal. It is known that the C6 aldehyde in pyranosides is sometimes very unstable, especially when the pyranoside is unable to undergo ring flip. When the C5 proton is fixed in an axial orientation, decomposition appears to happen more readily. To overcome this problem, it became apparent that the acetonide protecting group must be removed prior to the oxidation of the primary alcohol.

Primary alcohol 5.21 was converted to benzoate 5.23 (Scheme 5.9), thus allowing for removal of the acetonide by treatment with 80% acetic acid in water. During removal of the acetonide, the reaction must be monitored carefully so as not to remove the SEM protecting group at the same time. With careful control of the reaction time, the desired diol 5.24 can be obtained in good yield.

![Scheme 5.9](image-url)

**Scheme 5.9.** New protecting group strategy
The next transformation was to protect the diol as the di-PMB ether 5.25. To accomplish this, compound 5.24 was treated with oil-free potassium hydride and \( p \)-methoxybenzyl bromide. The desired compound 5.25 was isolated in trace amounts, usually less than 10%. Additives such as \( n \)-Bu\(_4\)NI and 18-crown-6 were also used, but without much success. In addition to the low yield, purification of the desired compound proved to be difficult in that 5.25 co-eluted with \( p \)-methoxybenzyl alcohol during column chromatography. In light of these difficulties, an alternative protecting group strategy was sought.

The new route (Scheme 5.10) started with the fully protected sugar 5.20, the acetonide was first removed with 80% acetic acid in water to give 5.26. As with the previous acetonide removal, the reaction must be carefully monitored or deprotection of the SEM group also occurs. It was found to be best when the reaction was stopped after 4 h regardless of scale. In this time frame, the reaction usually proceeds to 80% conversion, with 100% yield based on recovered starting material. The diol was submitted to hydrogenolysis over 10% palladium on charcoal. After removal of the catalyst and evaporation of the solvent, the resulting triol was converted directly to monoTBS ether 5.27 by treatment with one equivalent of TBSCl and imidazole.

Masking of the remaining hydroxy groups as PMB ethers proved to be problematic. Standard conditions utilizing sodium or potassium hydride in THF with PMBBBr gave a mixture of products. In addition to the desired compound 5.28, monoadducts were obtained as were products of silyl migration. Changing the solvent or recourse to crown ethers did not remedy the situation. An attempt at PMB protection using \( p \)-methoxybenzyl trichloroacetimidate and \( p \)-toluene sulfonic acid was investigated.
As with the basic protections, multiple products were observed. The protection problem was remedied by changing the base from a hydride source to an amide source. The use of NaHMDS and PMBB Br with a catalytic amount of n-Bu₄NI gave desired product 5.28 in 70% yield. The sugar moiety 5.28 now possesses all of the desired protecting groups for further functionalization after the zirconocene ring contraction. All that remained was the conversion of the primary TBS ether to the vinyl sugar 5.10.

Scheme 5.10. Conversion to vinyl-allopyranoside

The TBS group was removed by treatment with tetrabutylammonium fluoride in THF to furnish in high yield the desired alcohol 5.29, which was oxidized with TPAP and NMO as the cooxidant. This reaction sequence was difficult to follow by TLC in that the aldehyde was not stable to either silica gel or alumina TLC plates and multiple products were seen. The reaction mixture was quenched after 2 h and filtered through a plug of Florisil. Proton NMR analysis indicated that one product had formed, and that it contained a diagnostic aldehyde signal. To this aldehyde was added a solution of n-BuLi
and methyltriphenylphosphonium iodide in THF at 0 °C to give the desired vinyl alloglycoside 5.10 in good yield. When the aldehyde was added to the ylide, the yield suffered and multiple decomposition products were observed.

With the synthesis of vinyl alloglycoside 5.10 complete, efforts to perform the key step of the synthesis were undertaken, as seen in Scheme 5.11. Cyclopentadienylzirconium dichloride was treated with two equivalents of n-BuLi at 0 °C. After 1 h, a solution of 5.10 was added and the solution was stirred for 30 min prior to the addition of boron trifluoride etherate. Unfortunately, the adaptation of these conditions did not give the desired carbocycle. Only products of decomposition were isolated with one of them being p-methoxybenzyl alcohol.

Scheme 5.11. Zirconocene-mediated ring contraction

The isolation of PMBOH from the ring contraction conditions has led to the belief that this may not be a suitable protecting group for this transformation. Current studies are being pursued where the PMB protecting groups have been replaced by benzyl protecting groups. It is hoped that the benzyl ethers will be more stable toward the ring contraction conditions.
**5.4 Summary and Future Plans for the Completed Synthesis**

Synthesis of the carbocyclic core of neplanocin A utilizing a zirconocene-mediated ring contraction has been approached. Beginning from relatively inexpensive D-glucose, a fifteen-step sequence to the carbocycle was developed. Of those fifteen steps, nine of them involve protection or deprotection of the alcohols. Although the preceding work had several synthetic strategies, the most direct path from D-glucose can be seen in Scheme 5.12.

![Scheme 5.12. Complete route to vinyl allopypanoside](image-url)
The epoxy sugar was opened with the sodium salt of allyl alcohol, and selective opening of the benzylidene acetal to give 5.15 in good yield for the two steps. The diol was then protected as the acetonide with 2,2-dimethoxypropane, followed by removal of the allyl protecting group to give the desired alcohol 5.17. Conversion of the altropyranoside to the allopypanoside was facilitated by use of TPAP as the oxidant, followed by reduction with NaBH₄ to give 5.19. Protection of 5.19 as the SEM ether 5.20 proceeded without incident in high yield. Removal of the acetonide, hydrogenolysis of the benzyl protecting group and mono-protection of the triol as the TBS ether gave 5.27 in 68% yield for the three steps. The diol was converted to di-PMB ether 5.28, which was deprotected using TBAF to give 5.29. Finally, the primary alcohol was oxidized with TPAP and a Wittig olefination provided the desired vinyl allopypanoside 5.10 in 70% yield. With the direct synthesis of the vinyl pyranoside completed, progress toward the total synthesis requires more advanced investigation.\textsuperscript{110}
CHAPTER 6

EXPERIMENTAL

All manipulations were performed under an inert atmosphere unless otherwise indicated. All solvents were reagent grade and were pre-dried when necessary. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium/benzophenone, while dichloromethane (CH$_2$Cl$_2$) was distilled from calcium hydride.

Melting points were measured using a Thomas-Hoover capillary melting point apparatus and all melting points are uncorrected. Infrared spectra were recorded with a Perkin-Elmer FT-IR and are reported in reciprocal centimeters (cm$^{-1}$). Optical rotations were recorded with a Perkin-Elmer Model 241 polarimeter fitted with a sodium lamp and concentrations are reported in g/100 mL. Proton nuclear magnetic resonance spectra ($^1$H) were recorded at 300 or 500 MHz on a Brucker AC-300 or Br, ker DRX-500 instrument, and chemical shifts are reported in parts per million ($\delta$). Splitting patterns for proton NMR are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Carbon nuclear magnetic resonance spectra ($^{13}$C) were recorded at either 75 MHz with a Br, ker AC-300 or at 125 MHz with a Br, ker DRX-500 instrument. Chemical shifts for carbon NMR are also reported in parts per million ($\delta$). Mass spectra were recorded at The Ohio State University Chemistry Department facility. Elemental analyses were performed by Atlanta Microlab, Inc., Norcross, Georgia, USA.

Ethylmagnesium bromide (6.0 mL of 2.70 M, 16.2 mmol) was added to a solution of disulfide (4.91 g, 10.0 mmol) in dry THF (75 mL) at -10°C. After 1 h, the reaction mixture was quenched with saturated NH₄Cl solution (150 mL) and extracted with ether (3 x 75 mL). The combined organic layers were washed with brine (25 mL), dried, and evaporated prior to chromatography of the residue on silica gel. Elution with 14:1 petroleum ether/ether gave 1.80 g each (combined yield of 95%) of the levorotatory diastereomers of 2.1, both as colorless oils.

For diastereomer A: IR (CHCl₃, cm⁻¹) 1768; ¹H NMR (300 MHz, CDCl₃) δ 7.52-7.49 (m, 2 H), 7.31-7.25 (m, 3 H), 4.07-3.97 (m, 2 H), 2.95 (dd, J = 13.4, 9.4 Hz, 1 H), 1.98-1.90 (m, 3 H), 1.71-1.63 (m, 3 H), 1.57-1.40 (m, 1 H), 0.83 (s, 9 H), 0.03 (s, 3 H), 0.02 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 174.7, 132.8 (2C), 132.6, 129.1 (2C), 128.1, 92.6, 77.8, 46.3, 35.2, 34.6, 31.3, 25.6 (3C), 18.4, 17.8, -4.7, -5.1; ES MS m/z (M + Na)⁺ calcd 401.1583, obsd 401.1585; [α]₁⁸D -2.4 (c 2.09, CHCl₃).

For diastereomer B: IR (CHCl₃, cm⁻¹) 1768; ¹H NMR (300 MHz, CDCl₃) δ 7.56-7.53 (m, 2 H), 7.32-7.26 (m, 3 H), 4.01-3.93 (m, 2 H), 2.49 (dd, J = 13.7, 9.1 Hz, 1 H), 2.36 (dd, J = 13.7, 9.1 Hz, 1 H), 2.05-1.93 (m, 1 H), 1.87-1.83 (m, 2 H), 1.79-1.63 (m, 2 H), 1.58-1.43 (m, 1 H), 0.84 (s, 9 H), 0.03 (s, 3 H), 0.00 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 174.3, 133.1 (2C), 132.6,
Isomerization of β-sulfide 2.1.2

Sulfide 2.1.2 (1.00 g) was dissolved in dry THF (40 mL) and treated with 1 drop of DBU. The solution was stirred for 2 h and quenched with saturated NH₄Cl solution (5 mL). The layers were separated and the aqueous layer was extracted with ether (3 × 10 mL). The combined organic phases were washed with brine (10 mL), dried over MgSO₄ and evaporated. Column chromatography of the residue on silica gel (14:1 hexane/ether) gave 0.73 g (73%) of sulfide 2.1.1 and 0.21 g (21%) of sulfide 2.1.2.

Acetic Acid 6-(tert-Butyldimethylsilanyloxy)-3-phenylsulfanyl-1-oxaspiro[4.4]non-2-yl Ester (2.2).

Lactone 2.1.1 (0.47 g, 1.20 mmol) was dissolved in CH₂Cl₂ (25 mL), cooled to -78 °C, and treated with Dibal-H (2.40 mL of 1.0 M, 2.40 mmol). After 30 min of stirring, a saturated solution of Rochelle's salt (40 mL) was introduced, the reaction mixture was allowed to warm to rt, and the separated aqueous layer was extracted with CH₂Cl₂ (3 x 20 mL). The organic phases were combined, dried, and evaporated to leave an oil that was dissolved in CH₂Cl₂ (20 mL) and treated sequentially with pyridine (4.05 mL, 49.5 mmol), acetic anhydride (1.55 mL, 16.5 mmol), and a catalytic quantity of DMAP. After 30 min, the reaction mixture was poured into saturated NaHCO₃ solution (30 mL) and the separated aqueous phase was extracted with CH₂Cl₂ (2 x 20 mL). The combined organic layers were washed with
water (15 mL) and brine (15 mL) prior to drying and solvent evaporation. There was obtained 0.48 g (94%) of 2.2 as an anomeric mixture that was used without further purification.

**General Glycosidation Procedure for 2.3.** For the glycosidations of pyrimidine bases, CH$_2$Cl$_2$ is the solvent of choice. When purine bases are involved, CH$_3$CN is the preferred reaction medium. The sample of 2.2 and the heterocyclic base must be dissolved in the same solvent in order to realize good stereoselectivity. The persilylated base (1.5 equiv) was placed in the appropriate solvent (0.06 mmol/mL) and SnCl$_4$ (2.0 equiv) was added, at which time the base dissolved. The SnCl$_4$ used was 1 M in CH$_2$Cl$_2$ for thymine, cytosine, and uracil, and neat for adenine. The solution was stirred at rt for 1.5 h, cannulated into a cold (-78 °C) solution of 12 (0.03 mmol/mL), maintained at -78 °C for 30 min, warmed to rt, and stirred for 30 min prior to being quenched with saturated NaHCO$_3$ solution. The separated aqueous layer was extracted with ethyl acetate and the combined organic phases were dried and evaporated.

**1-[6-(tert-Butyldimethylsilanyloxy)-3-phenylsulfanyl-1-oxaspiro[4.4]non-2-yl]-5-methyl-1H-pyrimidine-2,4-dione (2.3).**

Product 2.3: from 0.30 g (0.71 mmol) of 2.2 and 0.29 g (1.1 mmol) of persilylated thymine (0.29 g, 1.1 mmol), there was isolated 0.22 g (59%) of 2.3 with a diastereomeric purity in excess of 97:3 after chromatography on silica gel (elution with 3:2 hexane/ether); colorless syrup; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.94 (s, 1 H), 7.44-7.40 (m, 2 H), 7.27-
7.21 (m, 3 H), 6.88 (d, \( J = 1.2 \) Hz, 1 H), 5.99 (d, \( J = 8.6 \) Hz, 1 H), 4.03 (t, \( J = 7.3 \) Hz, 1 H), 3.62 (dt, \( J = 10.8, 8.3 \) Hz, 1 H), 2.82 (dd, \( J = 12.8, 8.1 \) Hz, 1 H), 2.00-1.57 (m, 10 H), 0.94 (s, 9 H), 0.12 (s, 3 H), 0.10 (s, 3 H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 163.2, 150.3, 134.6, 133.5 (2C), 132.2, 129.0 (2C), 128.1, 111.2, 91.0, 88.3, 78.5, 49.6, 36.8, 36.1, 31.7, 25.9 (3C), 18.5, 18.0, 12.2, -3.9, -4.6; ES HRMS \( m/z \) (M+Na)\(^+\) calcd 511.2057, obsd 511.2009; \([\alpha]_D^{18}\) -6.7 (c 0.6, C\(_2\)H\(_5\)OH).

1-[6-(tert-Butyldimethylsilyloxy)-3-phenylsulfanyl-1-oxaspiro[4.4]non-2-yl]-1H-pyrimidine-2,4-dione (2.4).

Product 2.4: from 0.30 g (0.71 mmol) of 2.2 and 0.28 g (1.1 mmol) of persilylated uracil, there was obtained 0.22 g (61%) of 2.4 as a 9:1 \( \beta:\alpha \) anomic mixture after chromatography on silica gel (elution with 3:2 hexane/ether); colorless syrup; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 9.06 (s, 1 H), 7.47-7.43 (m, 2 H), 7.28-7.22 (m, 4 H), 6.09 (d, \( J = 8.2 \) Hz, 1 H), 5.58 (dd, \( J = 8.1, 2.0 \) Hz, 1 H), 4.05 (t, \( J = 7.2 \) Hz, 1 H), 3.65 (dt, \( J = 10.6, 8.1 \) Hz, 1 H), 2.81 (dd, \( J = 12.9, 8.0 \) Hz, 1 H), 2.00-1.60 (m, 7 H), 0.93 (s, 9 H), 0.11 (s, 3 H), 0.10 (s, 3 H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 163.0, 150.3, 139.2, 133.4 (2C), 131.9, 129.0 (2C), 128.1, 102.8, 91.5, 88.5, 78.5, 50.3, 36.9, 35.6, 31.3, 25.8 (3C), 18.0, 17.9, -4.0, -4.7; ES HRMS \( m/z \) (M+Na)\(^+\) calcd 497.1901, obsd 497.1913; \([\alpha]_D^{18}\) +8.8 (c 1.5, C\(_2\)H\(_5\)OH).

Anal. Calcd for C\(_{24}\)H\(_{34}\)N\(_2\)O\(_4\)SSi: C, 60.73; H, 7.22. Found: C, 60.83; H, 7.17.
1-[6-(tert-Butyldimethylsilyloxy)-3-phenylsulfanyl-1-oxaspiro[4.4]non-2-yl]-5-fluoro-1H-pyrimidine-2,4-dione (2.5).

Product 2.5: from 0.30 g (0.71 mmol) of 2.2 and 0.29 g (1.1 mmol) of persilylated 5-fluorouracil, there was isolated 0.23 g (63%) of 2.5 with a diastereomeric purity in excess of 97:3 after chromatography on silica gel (elution with 3:2 hexane/ether); colorless syrup; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.95 (br s, 1 H), 7.45 (d, $J = 6.5$ Hz, 1 H), 7.30-7.24 (m, 3 H), 7.01-6.99 (m, 2 H), 6.35 (d, $J = 7.8$ Hz, 1 H), 4.81 (q, $J = 9.2$ Hz, 1 H), 4.28 (m, 1 H), 2.97 (dd, $J = 8.0$, 9.2 Hz, 1 H), 1.94-1.85 (m, 4 H), 1.78-1.47 (m, 3 H), 0.94 (s, 9 H), 0.18 (s, 3 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 156.9 (d, $J = 25.1$ Hz, 1C), 150.8, 140.2 (d, $J = 235.6$ Hz, 1C), 133.2, 132.7 (2C), 128.9 (2C), 127.7, 121.9 (d, $J = 32.6$ Hz, 1C), 94.1, 89.4, 77.2, 44.1, 36.0, 35.9, 33.1, 25.8 (3C), 20.6, 17.9, -4.5, 4.8; $^{19}$F NMR (235 MHz, CHCl$_3$) $\delta$ -162.83; ES HRMS m/z (M+Na)$^+$ calcd 515.1807, obsd 515.1806; $[\alpha]_{D}^{18}$ -4.7 (c 0.8, C$_2$H$_5$OH).

**General Procedure for Sulfoxidation and Thermolysis.** The glycosidated sulfide (1.0 equiv) was dissolved in CHCl$_3$ (50 mL) and treated with the Davis oxaziridine (1.1 equiv). After 16-24 h of stirring, the solvent was evaporated to leave a residue that was taken up in xylenes (125 mL) containing 2-3 equiv of pyridine. The solution was refluxed for 4 h, cooled, and freed of solvent under reduced pressure. The residue was dissolved in ethyl acetate, washed with sodium thiosulfate solution, dried, and evaporated.
1-[6-(tert-Butyldimethylsilyl)oxy]-1-oxaspiro[4.4]non-3-en-2-yl]-1H-pyrimidine-2,4-dione (2.6).

Product 2.6: from 0.22 g (0.46 mmol) of 2.4, there was isolated 0.16 g (90%) of 2.6 as a colorless syrup following chromatography on silica gel (elution with 3:2 hexane/ether); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.95 (br s, 1 H), 7.95-7.91 (m, 1 H), 7.35 (d, \(J = 8.1\) Hz, 1 H), 6.98 (t, \(J = 1.4\) Hz, 1 H), 6.41 (dd, \(J = 5.9, 4.8\) Hz, 1 H), 5.74-5.69 (m, 2 H), 5.13 (br s, 1 H), 3.99 (t, \(J = 5.3\) Hz, 1 H), 2.09-1.54 (series of m, 6 H), 0.88 (s, 9 H), 0.06 (s, 3 H), 0.04 (s, 3 H); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 163.4, 150.8, 140.0, 138.9, 123.7, 102.7, 101.1, 89.2, 80.1, 35.2, 33.6, 25.7 (3C), 20.4, 17.9, -4.2, -4.7; ES HRMS \(m/z\) (M+Na\(^+\) calcd 387.1701, obsd 387.1745; \([\alpha]_{D}^{18}\) -39 (c 1.2, CHCl\(_3\)).

1-[6-(tert-Butyldimethylsilyl)oxy]-1-oxaspiro[4.4]non-3-en-2-yl]-5-methyl-1H-pyrimidine-2,4-dione (2.7).

Product 2.7: from 0.22 g (0.46 mmol) of 2.3, there was isolated 0.15 g (88%) of 2.7 as a colorless syrup following chromatography on silica gel (elution with 3:2 hexane/ether); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.55 (br s, 1 H), 7.26 (s, 1 H), 7.03 (s, 1 H), 6.43 (dd, \(J = 5.9, 1.6\) Hz, 1 H), 5.72 (dd, \(J = 5.9, 0.9\) Hz, 1 H), 3.93 (dd, \(J = 4.8, 2.7\) Hz, 1 H), 2.12-1.58 (series of m, 9 H), 0.91 (s, 9 H), 0.07 (s, 6 H); \(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 163.4, 150.6, 139.2, 135.3, 124.0, 111.1, 101.2, 89.3, 80.6, 35.4, 34.1, 25.8 (3C), 21.3, 18.0, 17.5, -4.3, -4.8; ES HRMS \(m/z\) (M+Na\(^+\) calcd 401.1873, obsd 401.1852; \([\alpha]_{D}^{18}\) -34 (c 0.4, CHCl\(_3\)).
1-(6-Hydroxy-1-oxaspiro[4.4]non-3-en-2-yl)-1H-pyrimidine-2,4-dione (2.9).

A solution of 2.6 (0.07 g, 0.19 mmol) in THF (3 mL) was treated with the 18-crown-6/CH3CN complex (0.18 g, 0.58 mmol) and potassium fluoride (0.03 g, 0.58 mmol), stirred at rt for 3 days, quenched with water (10 mL), and extracted with ethyl acetate (3 x 10 mL). The combined organic phases were dried and evaporated to leave a residue that was chromatographed on silica gel. Elution with ether gave 0.04 g (57%) of 2.9 as a white foam; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.64 (br s, 1 H), 7.57 (d, $J = 8.1$ Hz, 1 H), 6.96 (t, $J = 1.4$ Hz, 1 H), 6.45 (dd, $J = 5.9$, 1.8 Hz, 1 H), 5.78 (dd, $J = 5.9$, 1.2 Hz, 1 H), 5.71 (dd, $J = 8.1$, 1.8 Hz, 1 H), 4.14-4.10 (m, 1 H), 2.27-1.59 (series of m, 6 H) (OH not observed);
$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 163.1, 150.7, 140.6, 137.3, 124.4, 102.5, 100.4, 89.7, 79.1, 34.9, 32.9, 19.6; ES HRMS $m/z$ (M+Na)$^+$ calcd 273.0846, obsd 273.0866; $[\alpha]_{D}^{18}$ -13.0 (c 0.10, C$_2$H$_5$OH).

1-(6-Hydroxy-1-oxaspiro[4.4]non-3-en-2-yl)-5-methyl-1H-pyrimidine-2,4-dione (2.10).

A solution of 2.7 (0.13 g, 0.34 mmol) in THF (30 mL) was treated with the 18-crown-6/CH$_3$CN complex (1.05 g, 3.4 mmol) and potassium fluoride (0.20 g, 3.4 mmol), stirred at rt for 7 days, quenched with water (20 mL), and extracted with ethyl acetate (3 x 20 mL). The combined organic phases were dried and evaporated to leave a residue that was chromatographed on silica gel. Elution with ether furnished 0.03 g (33%) of 2.10 as a white foam, and returned 0.09 g (68%) of unreacted 2.7. For 2.10: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.44 (br s, 1 H), 7.40 (d, $J = 1.0$ Hz, 1 H), 7.00 (s, 1 H), 6.49 (dd, $J = 5.9$, 1.7 Hz, 1 H), 5.83 (d, $J = 5.9$ Hz, 1 H), 4.19-4.16 (m, 1 H), 2.40-1.47 (series of m, 9 H) (OH not observed); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 163.7, 150.6, 137.8, 136.7, 125.2, 100.7, 90.0, 79.7, 35.4, 33.3, 30.8, 20.1, 12.9; ES HRMS $m/z$ (M+Na)$^+$ calcd 287.1002, obsd 287.1011; $[\alpha]_{D}^{18}$ -3.0 (c 0.10, C$_2$H$_5$OH).
1-[6-(tert-Butyldimethylsilanyloxy)-1-oxaspiro[4.4]non-2-yl]-1H-pyrimidine-2,4-dione (2.11).

A 0.17 g (0.47 mmol) sample of 2.6 was dissolved in ethanol (15 mL) and admixed with 5% palladium on charcoal (0.042 g). H₂ was bubbled through the suspension for 5 min, after which a balloon of H₂ was attached to the flask. The mixture was stirred for 24 h, filtered through a pad of Celite, and evaporated to give 0.13 g (90%) of 2.11 as a white foam; ¹H NMR (500 MHz, CDCl₃) δ 8.18 (br s, 1 H), 7.68 (d, J = 8.1 Hz, 1 H), 6.08-6.06 (m, 1 H), 5.68 (d, J = 8.1 Hz, 1 H), 4.17 (t, J = 7.3 Hz, 1 H), 2.48-2.42 (m, 1 H), 2.27-2.20 (m, 1 H), 2.02-1.85 (m, 3 H), 1.76-1.45 (m, 5 H), 0.91 (s, 9 H), 0.09 (s, 6 H); ¹³C NMR (125 MHz, CDCl₃) δ 162.9, 144.3, 140.0, 101.7, 94.9, 85.4, 77.9, 34.3, 32.5, 31.7, 27.7, 25.8 (3C), 18.3, 18.0, -4.0, -4.6; ES HRMS m/z (M+Na)+ calcd 389.1867, obsd 389.1872; [α] D¹⁸ -12.0 (c 0.2, CHCl₃).

1-[6-(tert-Butyldimethylsilanyloxy)-1-oxaspiro[4.4]non-2-yl]-5-methyl-1H-pyrimidine-2,4-dione (2.12).

A sample of 2.7 (0.13 g, 0.34 mmol) was dissolved in ethanol (15 mL) and admixed with 5% palladium on charcoal (0.042 g). Hydrogen gas was bubbled through the suspension for 5 min, after which a balloon of H₂ was attached to the flask. The mixture was stirred for 24 h, filtered through a pad of Celite, and evaporated to give 2.12 (0.13 g, 100%), as a white foam; ¹H NMR (300 MHz, CDCl₃) δ 8.10 (br s, 1 H), 7.25 (s, 1 H), 6.07 (t, J = 5.9 Hz, 1 H), 4.10 (t, J = 6.4 Hz, 1 H), 2.47-2.24 (m, 2 H), 2.06-1.61 (series of
m, 11 H), 0.91 (s, 9 H), 0.10 (s, 3 H), 0.09 (s, 3 H); \^1^3^C NMR (75 MHz, CDCl\textsubscript{3}) \text{\delta} 163.8, 150.4, 135.2, 110.6, 94.3, 84.7, 77.9, 35.1, 32.0, 32.4, 29.2, 25.8 (3C), 19.1, 18.0, 12.6, -4.1, -4.7; ES HRMS m/z (M+Na\textsuperscript{+}) calcd 403.2023, obsd 403.2044; \([\alpha]_D^{18}\) +17.0 (c 0.3, CHCl\textsubscript{3}).

1-(6-Hydroxy-1-oxaspiro[4.4]non-2-yl)-1H-pyrimidine-2,4-dione (2.13).

A solution of 2.11 (0.09 g, 0.25 mmol) in THF (20 mL) was treated with the 18-crown-6/CH\textsubscript{3}CN complex (0.77 g, 2.5 mmol) and potassium fluoride (0.15 g, 2.5 mmol), stirred at rt for 7 days, and worked up as described earlier. Elution with ether afforded 2.13 as a white foam (0.05 g, 83%); \(^1^H\) NMR (500 MHz, CD\textsubscript{3}OD) \text{\delta} 7.95 (d, \(J = 8.1\) Hz, 1 H), 6.03 (dd, \(J = 6.4, 4.1\) Hz, 1 H), 5.66 (d, \(J = 8.1\) Hz, 1 H), 4.11 (t, \(J = 7.1\) Hz, 1 H), 2.51-2.42 (m, 1 H), 2.35-2.25 (m, 1 H), 2.12-2.00 (m, 2 H), 1.85-1.64 (m, 5 H), 1.58-1.50 (m, 1 H), (NH and OH not observed); \(^1^3^C\) NMR (125 MHz, CD\textsubscript{3}OD) \text{\delta} 166.4, 152.3, 142.4, 102.0, 96.2, 87.1, 77.6, 35.8, 33.1, 32.2, 28.7, 19.5; ES HRMS m/z (M+Na\textsuperscript{+}) calcd 275.1002, obsd 275.1017; \([\alpha]_D^{18}\) +3.5 (c 0.4, C\textsubscript{2}H\textsubscript{5}OH).

1-(6-Hydroxy-1-oxaspiro[4.4]non-2-yl)-5-methyl-1H-pyrimidine-2,4-dione (2.14).

A solution of 2.12 (0.10 g, 0.26 mmol) in THF (30 mL) was treated with the 18-crown-6/CH\textsubscript{3}CN complex (0.79 g, 2.6 mmol) and potassium fluoride (0.15 g, 2.6 mmol), stirred at rt for 7 days, and
worked up as described earlier. Elution with ether gave 2.14 as a white foam (0.06 g, 83%); 1H NMR (500 MHz, CD3OD) δ 7.81 (d, J = 1.1 Hz, 1 H), 6.05 (dd, J = 6.5, 4.2 Hz, 1 H), 4.12 (t, J = 7.3 Hz, 1 H), 2.50-2.38 (m, 1 H), 2.33-2.25 (m, 1 H), 2.10-1.98 (m, 2 H), 1.87 (d, J = 1.1 Hz, 3 H), 1.80-1.62 (m, 5 H), 1.58-1.50 (m, 1 H) (NH and OH not observed); 13C NMR (125 MHz, CD3OD) δ 166.5, 152.4, 138.2, 111.0, 95.8, 86.7, 77.6, 35.8, 32.9, 32.1, 28.7, 19.4, 12.4; ES HRMS m/z (M+Na)+ calcd 289.1159, obsd 289.1164; [α]D\textsuperscript{18} -1.5 (c 0.8, C2H5OH).

**General Procedure for Dihydroxylation.** Either 2.6 or 2.7 (1 equiv) was dissolved in a 5:1 acetone-water mixture (15 mL), treated with osmium tetroxide (30 mol %) and N-methylmorpholine-N-oxide (2.5 equiv), stirred for 48 h, quenched with a saturated solution of Na2S2O3 (15 mL), and stirred for 30 min. The black mixture was extracted with ethyl acetate (3X), and the combined organic layers were dried and evaporated. Chromatography of the residue on silica gel (elution with hexane/ether 3:2) gave the desired diol.

1-\{6-(\textit{tert}-Butyldimethylsilanyloxy)-3,4-dihydroxy-1-oxaspiro[4.4]non-2-yl\}-1H-pyrimidine-2,4-dione (2.15).

For 2.15: from 0.14 g (0.40 mmol) of 2.6, there was isolated 0.13 g (87%) of 2.15 as a colorless syrup; 1H NMR (300 MHz, CDCl3) δ 9.96 (br s, 1 H), 7.57 (d, J = 8.2 Hz, 1 H), 5.75 (d, J = 8.4 Hz, 1 H), 5.71 (d, J = 4.5 Hz, 1 H), 4.39 (br s, 1 H), 4.34-4.31 (m, 2 H), 4.06 (t, J = 6.9 Hz, 1 H), 3.03 (br s, 1 H), 2.05-1.96 (m, 1 H), 1.82-1.55 (m, 5 H), 0.87 (s, 9 H),
0.08 (s, 3 H), 0.05 (s, 3 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 163.1, 151.5, 139.7, 102.3, 97.2, 91.1, 79.0, 77.2, 71.1, 32.3, 29.0, 25.8 (3C), 18.7, 17.9, -4.0, -4.8; ES HRMS m/z (M+Na)$^+$ calcld 421.1765; $[\alpha]_{D}^{18}$ -45.0 (c 1.4, CHCl$_3$).

1-[6-(tert-Butyldimethylsilyloxy)-3,4-dihydroxy-1-oxaspiro[4.4]non-2-yl]-5-methyl-1$H$-pyrimidine-2,4-dione (2.16).

For 2.16: reaction of 0.17 g (0.45 mmol) of 2.7 afforded 0.14 g (85%) of 2.16 as a colorless syrup; $^1$H NMR (500 MHz, CD$_3$OD) δ 7.40 (s, 1 H), 5.80 (d, $J = 7.4$ Hz, 1 H), 4.27-4.25 (m, 1 H), 4.21 (d, $J = 5.3$ Hz, 1 H), 4.15-4.10 (m, 1 H), 2.29-2.24 (m, 1 H), 2.01-1.92 (m, 1 H), 1.84 (s, 3 H), 1.65-1.56 (m, 3 H), 1.55-1.45 (m, 1 H), 0.89 (s, 9 H), 0.10 (s, 3 H), 0.08 (s, 3 H) (OH and NH not observed); $^{13}$C NMR (125 MHz, CD$_3$OD) δ 165.3, 151.9, 136.9, 110.9, 95.5, 88.1, 79.1, 74.0, 70.7, 32.7, 30.0, 25.6 (3C), 18.7, 18.0, 11.6, -4.7, -5.3; ES HRMS m/z (M+Na)$^+$ calcld 435.1928, obsd 435.1882; $[\alpha]_{D}^{18}$ -20.0 (c 0.20, C$_2$H$_5$OH).

1-(3,4,6-Trihydroxy-1-oxaspiro[4.4]non-2-yl)-1$H$-pyrimidine-2,4-dione (2.18).

A solution of 2.15 (0.10 g, 0.25 mmol) in THF (20 mL) was treated with TBAF (1.25 mL of 1 M in THF, 1.25 mmol), stirred for 1 h, admixed with silica gel (0.05 g), and freed of solvent. The residue was placed atop a column of silica gel and the product was eluted with ethyl acetate to give 0.02 g (50%) of 2.18 as a white solid, mp 198-200 °C dec; $^1$H NMR (300 MHz, CD$_3$OD) δ 7.82 (d, $J = 8.1$ Hz, 1 H), 5.93 (d, $J = 7.0$ Hz, 1 H), 5.72 (d, $J = 8.1$ Hz, 1 H), 4.39 (dd, $J = 7.0$, 5.1 Hz, 1 H), 4.23 (d, $J = 5.1$ Hz, 7.0 Hz, 1 H), 4.04 (d, $J = 7.0$ Hz, 1 H).
1 H), 4.04 (t, J = 7.3 Hz, 1 H), 2.28-1.40 (series of m, 6 H) (3 OH and 1 NH not observed); \(^{13}\)C NMR (125 MHz, CD\(_3\)OD) δ 166.1, 152.8, 142.6, 103.1, 96.6, 89.2, 78.9, 75.9, 71.7, 32.3, 30.7, 19.2; ES HRMS m/z (M+Na\(^+\)) calcd 307.0901, obsd 307.0898; [\(\alpha\)]\(_D\)\(^{18}\) -31.0 (c 0.5, C\(_2\)H\(_5\)OH).

5-Methyl-1-(3,4,6-trihydroxy-1-oxaspiro[4.4]non-2-yl)-1H-pyrimidine-2,4-dione (2.19).

Diol 2.16 (60 mg, 0.15 mmol) was dissolved in THF (20 mL) and treated with TBAF (1.25 mL of 1 M in THF, 1.25 mmol), stirred for 1 h, and processed in the predescribed manner to furnish 21 mg (50%) of 2.19 as a white solid, mp 205-207 C dec; \(^1\)H NMR (500 MHz, CD\(_3\)OD) δ 7.88 (br s, 1 H), 7.65 (d, J = 1.1 Hz, 1 H), 5.91 (d, J = 7.1 Hz, 1 H), 4.40 (dd, J = 7.1, 5.2 Hz, 1 H), 4.22 (d, J = 5.2 Hz, 1 H), 4.05 (t, J = 7.4 Hz, 1 H), 2.40-2.30 (m, 1 H), 2.11-2.03 (m, 1 H), 1.89 (d, J = 1.1 Hz, 3 H), 1.75-1.65 (m, 3 H), 1.60-1.52 (m, 1 H) (3 OH not observed); \(^{13}\)C NMR (125 MHz, CD\(_3\)OD) δ 166.3, 153.0, 138.3, 112.0, 96.3, 89.0, 78.9, 75.6, 71.6, 32.4, 30.7, 19.2, 12.4; ES HRMS m/z (M+Na\(^+\)) calcd 321.1057, obsd 321.1061; [\(\alpha\)]\(_D\)\(^{18}\) -11.0 (c 0.10, C\(_2\)H\(_5\)OH).


Spirolactone 1.19\(^{29}\) (5.00 g, 18.4 mmol) dissolved in dry THF (60 mL) was cooled to -78 C, treated with lithium hexamethyldisilazide (45.0 mL of 1.0 M in THF, 45.0 mmol), and stirred for 1 h in the cold. After
the introduction of phenyl benzenethiosulfonate (11.58 g, 47.2 mmol) as a solution in dry THF (40 mL), the reaction mixture was held at -78 °C for 3 h, allowed to warm to rt overnight, and quenched with saturated NH₄Cl solution (50 mL) prior to extraction with ether (3 x 100 mL). The combined organic phases were dried and concentrated to leave a residue that was purified by chromatography on silica gel (elution with 6% ether in hexane) to give **1.21.0** (7.74 g, 86%) as a colorless solid, mp 115.0-115.8 °C; ^1^H NMR (300 MHz, CDCl₃) δ 7.73-7.64 (m, 4 H), 7.43-7.33 (m, 6 H), 3.61 (t, J = 7.1 Hz, 1 H), 2.64 (d, J = 14.3 Hz, 1 H), 2.17 (d, J = 14.3 Hz, 1 H), 2.09 (t, J = 9.3 Hz, 1 H), 1.83-1.69 (m, 3 H), 1.51-1.43 (m, 2 H), 0.86 (s, 9 H), 0.06 (s, 6 H); ^^1^C NMR (75 MHz, CDCl₃) δ 172.1, 136.4 (2C), 135.8 (2C), 131.1, 130.6, 130.0 (2C), 129.5 (2C), 129.0 (2C), 90.0, 77.4, 63.0, 42.8, 33.9, 30.2, 25.8 (3C), 18.2, 18.1, -4.4, -4.6; ES HRMS m/z (M+Na)^+ calcd 509.1616, obsd 509.1612; [α]_D^20 -47.9 (c 1.09, CHCl₃).

**Monophenylthio Lactones 2.20.1 and 2.20.2.** To a solution of **1.21.0** (7.74 g, 15.8 mmol) in dry THF (100 mL) was added ethylmagnesium bromide (9.5 mL of 3.0 M in ether, 28.5 mmol) at -10 °C. After 2 h of stirring in the cold, the reaction mixture was quenched by the dropwise addition of saturated NH₄Cl solution (50 mL) and extracted with ether (3 x 100 mL). The combined organic layers were dried and concentrated to leave a residue that was purified by chromatography on silica gel. Elution with 4% ether in hexane provided **2.20.1** (3.75 g) and **2.20.2** (1.24 g) as colorless oils in a combined 83% yield.

For 2.20.1: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.53-7.50 (m, 2 H), 7.33-7.28 (m, 3 H), 4.18 (dd, $J = 9.3$, 10.6 Hz, 1 H), 3.83 (dd, $J = 7.4$, 9.0 Hz, 1 H), 2.53 (dd, $J = 9.0$, 9.3 Hz, 1 H), 2.20 (dd, $J = 10.7$, 12.0 Hz, 1 H), 1.86-1.78 (m, 4 H), 1.65-1.60 (m, 2 H), 0.83 (s, 9 H), 0.04 (s, 3 H), 0.02 (s, 3 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 175.0, 132.9, 132.7 (2C), 129.1 (2C), 128.0, 90.7, 79.6, 46.4, 37.0, 33.1, 30.5, 25.7 (3C), 18.5, 17.8, -4.2, -5.1; ES HRMS m/z (M+Na)$^+$ calcd 401.1583, obsd 401.1588; $[\alpha]_{D}^{20}$ $+$26.2 (c 1.05, CHCl$_3$).

For 2.20.2: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.56-7.53 (m, 2 H), 7.35-7.29 (m, 3 H), 4.03 (t, $J = 9.9$ Hz, 1 H), 3.75 (t, $J = 7.4$ Hz, 1 H), 2.39 (dd, $J = 9.6$, 13.0 Hz, 1 H), 2.24 (dd, $J = 10.2$, 13.0 Hz, 1 H), 2.02-1.58 (series of m, 6 H), 0.86 (s, 9 H), 0.03 (s, 6 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 174.5, 133.0, 132.9 (2C), 129.4 (2C), 128.3, 91.1, 77.4, 46.4, 36.6, 33.8, 30.6, 26.1 (3C), 18.4, 18.3, -4.2, -4.4; ES HRMS m/z (M+Na)$^+$ calcd 401.1583, obsd 401.1595; $[\alpha]_{D}^{20}$ $+$19.0 (c 0.57, CHCl$_3$).

Equilibration of 2.20.2 with 2.20.1. A solution of 2.20.2 (1.34 g, 3.5 mmol) in THF (15 mL) was treated with DBU (0.05 mL, 0.3 mmol), stirred overnight at rt, diluted with 10% HCl (2 mL), and extracted with ethyl acetate (2 x 15 mL). The combined organic phases were washed with brine (3 mL), dried, and concentrated. Chromatography of the
residue on silica gel (elution with 3% ether in hexanes) afforded 2.20.1 (1.10 g, 83%) in addition to unreacted 2.20.2 (0.15 g, 12%).

**Acetic Acid 6-(tert-Butyldimethylsilanyloxy)-3-phenylsulfanyl-1-oxaspiro[4.4]non-2-yl Ester (2.21).**

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

A solution of 2.20.1 (100 mg, 0.26 mmol) in dry CH$_2$Cl$_2$ (16 mL) was treated with Dibal-H (0.3 mL of 1 M, 0.30 mmol) at -78 °C, stirred at this temperature for 2 h, quenched with saturated Rochelle's salt solution (16 mL), and stirred overnight. The separated aqueous phase was extracted with CH$_2$Cl$_2$ (3 x 10 mL) and the combined organic layers were dried and evaporated to provide the crude lactol that was immediately acetylated.

The above material was dissolved in pyridine (2 mL), treated with acetic anhydride (0.5 mL) at rt, stirred overnight, and evaporated to dryness under high vacuum. The residue was dissolved in ethyl acetate (10 mL), washed sequentially with saturated CuSO$_4$ solution (5 mL), water (5 mL), and brine (5 mL), dried, and concentrated. Purification of the residue by chromatography on silica gel (elution with 95:5 petroleum ether/ether) gave 46 mg (51%) of 2.21 and 15 mg (20%) of 2.22.

For 2.21 (as anomeric mixture): $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.41-7.38 (m, 2 H), 7.31-7.23 (m, 3 H), 6.22 (d, $J = 1.7$ Hz, 1 H), 3.90-3.85 (m, 1 H), 3.74-3.70 (m, 1 H), 2.37 (dd, $J = 13.3$, 7.6 Hz, 1 H), 2.25-1.50 (series of m, 10 H), 0.90 (s, 9 H), 0.06 (s, 3 H), 0.05 (s, 3 H); $^{13}$C NMR (75 MHz, CDCl$_3$) (as major diastereomer) $\delta$ 170.0, 134.3, 131.5 (2C), 128.9 (2C), 127.2, 102.4, 93.9, 78.1, 51.5, 37.3, 34.6, 30.8, 25.7 (3C), 21.3, 18.4, 18.1,
-4.5, -4.7; ES HRMS m/z (M+Na)+ calcd 445.1839, obsd 445.1814; $[\alpha]_D^{20} +28$ (c 2.0, CHCl₃) (for the diastereomeric mixture).

**Acetic Acid 3-[2-(tert-Butyldimethylsilanyloxy)-1-hydroxy-cyclopentyl]-2-phenylsulfanyl-propyl Ester (2.22).**

For 2.22: $^1$H NMR (300 MHz, CDCl₃) $\delta$ 7.48-7.44 (m, 2 H), 7.31-7.20 (m, 3 H), 4.24 (dd, $J = 5.7$, 1.1 Hz, 2 H), 3.76 (t, $J = 6.9$ Hz, 1 H), 3.68 (pent, $J = 5.6$ Hz, 1 H), 2.67 (s, 1 H), 2.02 (s, 3 H), 1.98-1.45 (series of m, 8 H), 0.88 (s, 9 H), 0.06 (s, 3 H), 0.04 (s, 3 H); $^{13}$C NMR (75 MHz, CDCl₃) $\delta$ 170.8, 134.5, 132.1 (2C), 128.9 (2C), 127.1, 79.4, 78.6, 66.7, 43.1, 40.4, 35.3, 31.3, 25.8 (3C), 20.8, 19.4, 17.9, -4.3, -4.9; ES HRMS m/z (M+Na)+ calcd 447.1996, obsd 447.1981; $[\alpha]_D^{19} +6.4$ (c 2.9, CHCl₃).

**1-[6-(tert-Butyldimethylsilanyloxy)-3-phenylsulfanyl-1-oxaspiro[4.4]non-2-yl]-5-methyl-1H-pyrimidine-2,4-dione (2.23).**

Silylated thymine (1.0 mmol) and 2.21 (202 mg, 0.48 mmol) were dissolved in CH₂Cl₂ (2.5 mL), cooled to -78 °C, and treated with tin tetrachloride (1.9 mL of 1 M in CH₂Cl₂, 2 equiv). The reaction mixture was maintained at -78 °C for 15 min, allowed to warm to rt, quenched with saturated NaHCO₃ solution (3 mL), and extracted with CH₂Cl₂. The combined organic layers were dried and concentrated to leave a residue that was chromatographed on silica gel (elution with 3:1 hexane/ether) to give 0.09 g (40%) of 2.23 as a white solid, mp 167.2-168.4 °C; $^1$H NMR (300 MHz, CDCl₃), $\delta$ 7.85 (br s, 1 H),
7.55 (d, $J = 1.2$ Hz, 1 H) 7.43-7.40 (m, 2 H), 7.24-7.22 (m, 3 H), 6.08 (d, $J = 8.8$ Hz, 1 H), 3.82 (t, $J = 7.4$ Hz, 1 H), 3.74-3.65 (m, 1 H), 2.35 (dd, $J = 7.4$, 12.9, Hz, 1 H), 2.09 (t, $J = 12.9$ Hz, 1 H), 1.85-1.53 (series of m, 6 H), 1.81 (d, $J = 1.2$ Hz, 3 H), 0.96 (s, 9 H), 0.14 (s, 3 H), 0.13 (s, 3 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 163.1, 150.2, 135.3, 133.5 (2C), 132.2, 129.0 (2C), 128.1, 111.0, 88.7, 87.3, 79.9, 50.2, 37.7, 34.3, 30.2, 29.7, 26.0 (3C), 18.2, 12.2, -4.2, -4.7; ES HRMS m/z (M+Na)$^+$ calcd 511.2057, obsd 511.2030; $[\alpha]_{D}^{20} +44$ (c 0.50, CHCl$_3$).

1-[6-(tert-Butyldimethylsilyloxy)-1-oxaspiro[4.4]non-3-en-2-yl]-5-methyl-1H-pyrimidine-2,4-dione (2.24).

Sulfide 2.23 (0.12 g, 0.25 mmol, 1.0 eq) was dissolved in CHCl$_3$ (10 mL) and treated with the Davis oxaziridine (0.07 g, 0.27 mmol, 1.1 eq). After 16 h of stirring, the solvent was evaporated to leave a residue that was taken up in xylenes (125 mL) containing 2-3 equiv of pyridine. The solution was refluxed for 4 h, cooled, and freed of solvent under reduced pressure. The residue was dissolved in ethyl acetate, washed with sodium thiosulfate solution, dried, and evaporated. Column chromatography of the residue on silica gel (3:1 hexane/ethyl acetate) gave 2.24 (0.09 g, 100%) as white foam; $^1$H NMR (300 MHz, CDCl$_3$) δ 8.21 (bs, 1 H), 7.70 (d, $J = 1.1$ Hz, 1 H), 6.83 (t, $J = 1.4$ Hz, 1 H), 6.05 (dd, $J = 5.9$, 1.9 Hz, 1 H), 5.91 (dd, $J = 5.9$, 1.1 Hz, 1 H), 4.06 (t, $J = 7.1$ Hz, 1 H), 2.07-1.70 (m, 9 H), 0.88 (s, 9 H), 0.07 (s, 3 H), 0.05 (s, 3 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 163.7, 153.5,136.6 (2C), 127.1, 109.9, 98.8, 98.4, 77.2, 36.4, 33.7, 25.8 (3C), 18.6, 18.3, 12.7, -4.3, -4.5; ES HRMS m/z (M+Na)$^+$ calcd. 401.1867, obsd 401.1886.
1-[6-(tert-Butyldimethylsilyloxy)-3,4-dihydroxy-1-oxaspiro[4.4]non-2-yl]-5-methyl-1H-pyrimidine-2,4-dione (2.25).

Olefin 2.24 (1 eq) (0.10 g, 0.26 mmol, 1.0 eq) was dissolved in 6 mL of 8:1 acetone:water. To this was added OsO₄ (8.0 mg, 0.032 mmol, 0.12 eq) and NMO (92.2 mg, 0.80 mmol, 3.1 eq). The yellow solution was stirred for 24 h, quenched with a saturated solution of Na₂S₂O₄ and stirred for 30 min. The black solution was extracted three times with ethyl acetate, dried over Na₂SO₄ and evaporated. Column chromatography of the residue on silica gel (1.5:1 hexane:EtOAc) gave diol 2.25 (40 mg, 36%) as a white foam; ¹H NMR (300 MHz, CDCl₃) δ 9.10 (bs, 1 H), 7.80 (d, J = 1.2 Hz, 1 H), 5.76 (d, J = 5.7 Hz, 1 H), 4.90 (bs, 1 H), 4.34 (t, J = 5.3 Hz, 1 H), 4.08 (d, J = 5.1 Hz, 1 H), 3.96 (dd, J = 10.3, 7.2 Hz, 1 H), 3.24 (bs, 1 H), 2.08-1.61 (m, 9 H), 0.84 (s, 9 H), 0.06 (s, 3 H), 0.05 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 163.8, 152.0, 136.6, 109.8, 96.6, 91.3, 77.6, 77.2, 74.8, 31.3, 29.2, 25.7 (3C), 18.0, 17.9, 12.7, -4.5, -4.9; ES HRMS m/z (M+Na)+ calcd 435.1922, obsd 435.1936.

5-Methyl-1-(3,4,6-trihydroxy-1-oxaspiro[4.4]non-2-yl)-1H-pyrimidine-2,4-dione (2.26).

Compound 2.25 (0.02 g, 0.05 mmol, 1.0 eq) was dissolved in absolute ethanol (4 mL). PPTS (0.02 g, 0.084 mmol, 1.7 eq) was added followed by 1 drop of concentrated HCl. The solution was heated to 60°C overnight, cooled, treated with silica gel (0.3 g), and freed of solvent. The solid was loaded onto a column of silica gel and eluted with 9:1 EtOAc/MeOH to give 2.26 (6.0 mg, 60%) as a white solid, mp 254.5-257.5°C (dec); IR
(CH$_3$CN, cm$^{-1}$) 3628, 3537, 1695, 1634; $^1$H NMR (300 MHz, CD$_3$OD) $\delta$ 8.11 (d, $J = 1.2$ Hz, 1 H), 5.92 (d, $J = 6.1$ Hz, 1 H), 4.33 (dd, $J = 5.8$, 5.3 Hz, 1 H), 4.01 (d, $J = 5.1$ Hz, 1 H), 3.91 (t, $J = 8.0$ Hz, 1 H), 2.09-1.54 (series of m, 9 H) (OH and NH not observed); $^{13}$C NMR (75 MHz, CD$_3$OD) $\delta$ 166.6, 153.1, 139.5, 111.5, 94.8, 89.8, 77.2, 75.6, 74.5, 32.3, 31.1, 19.4, 12.6; ES HRMS (M + Na)$^+$ calcd 321.1057, obsd 321.1037.

4-Amino-1-[6-(tert-Butyldimethylsilanyloxy)-3-phenylsulfanyl-1-oxaspiro[4.4]non-2-yl]-1H-pyrimidin-2-one (2.27).

The general glycosylation procedure for 2.2 was followed. From 0.30 g (0.71 mmol) of 2.2, 0.28 g (1.1 mmol) of persilylated cytosine and 1.40 mL of 1 M SnCl$_4$ in CH$_2$Cl$_2$, there was produced 0.23 g (67%) of 2.27 (>97:3 $\beta$:\(\alpha\) isomeric purity) after chromatography on silica gel (elution with benzene/ethyl acetate 1:1); colorless gum; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.42-7.38 (m, 2 H), 7.26 (d, $J = 7.4$ Hz, 1 H), 7.22-7.15 (m, 3 H), 6.18 (d, $J = 7.6$ Hz, 1 H), 5.79 (d, $J = 7.4$ Hz, 1 H), 4.01 (t, $J = 6.4$ Hz, 1 H), 3.61 (q, $J = 8.0$ Hz, 1 H), 2.75 (dd, $J = 13.0$, 7.9 Hz, 1 H), 1.98-1.25 (series of m, 7 H), 0.87 (s, 9 H), 0.06 (s, 6 H) (NH$_2$ protons not seen); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 165.4, 155.9, 140.0, 133.0, 132.9 (2C), 129.0 (2C), 127.6, 95.6, 91.8, 88.8, 78.4, 51.1, 37.2, 35.8, 31.7, 25.8 (3C), 18.6, 17.9, -4.0, -4.7; ES HRMS $m/z$ (M+Na)$^+$ calcd 496.2061, obsd 496.2046; [$\alpha$]$^\text{D}$ +20.0 (c 1.9, C$_2$H$_5$OH).
**N-{1-[6-(**tert**-Butyldimethylsilanyloxy)-3-phenylsulfanyl-1-oxaspiro[4.4]non-2-yl]-2-oxo-1,2-dihydropyrimidin-4-yl}acetamide (2.29).**

The above nucleoside 2.27 (0.16 g, 0.34 mmol) was dissolved in CH$_2$Cl$_2$ (20 mL), treated with acetic anhydride (0.13 mL, 1.4 mmol), pyridine (0.28 mL, 3.4 mmol), and DMAP (8 mg - catalytic), and stirred for 1 h prior to being quenched with saturated NaHCO$_3$ solution (30 mL). The product was extracted with ethyl acetate (3 x 15 mL), the combined organic phases were dried and evaporated, and the residue was chromatographed on silica gel. Elution with hexane/ether 1:2 furnished 0.16 g (89%) of 2.29 as a white solid, mp 190-192 °C dec; $^1$H NMR (500 MHz, CDCl$_3$) δ 10.33 (br s, 1 H), 7.72 (d, $J$ = 7.6 Hz, 1 H), 7.43-7.22 (m, 6 H), 6.19 (d, $J$ = 7.2 Hz, 1 H), 4.10 (t, $J$ = 6.9 Hz, 1 H), 3.70 (q, $J$ = 7.9 Hz, 1 H), 2.78 (dd, $J$ = 13.1, 7.9 Hz, 1 H), 2.28 (s, 3 H), 2.05-1.40 (series of m, 7 H), 0.89 (s, 9 H), 0.10 (s, 3 H), 0.09 (s, 3 H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 171.5, 162.9, 155.0, 144.0, 133.0 (2C), 132.9, 129.1 (2C), 127.9, 97.2, 93.1, 89.9, 78.4, 52.0, 37.3, 35.8, 31.6, 25.9 (3C), 24.9, 18.5, 17.9, -4.0, -4.6; ES HRMS m/z (M+Na)$^+$ calcd 538.2166, obsd 538.2165; [$\alpha$]$^\text{D}_{18}$ +45.0 (c 2.8, CHCl$_3$).

**N-{1-[3-Benznesulfinyl-6-(**tert**-butyldimethylsilanyloxy)-1-oxaspiro[4.4]non-2-yl]-2-oxo-1,2-dihydropyrimidin-4-yl}acetamide (2.30).**

Sulfide 2.29 (0.16 g, 0.31 mmol) was dissolved in CHCl$_3$ (20 mL) and treated with the Davis oxaziridine (0.09 g, 0.34 mmol). After 4 h the solvent was evaporated, the residue was chromatographed on silica gel. Elution with hexane/ether 1:2 furnished 0.11 g (69%) of 2.30 as a
colorless glass; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.48 (br s, 1 H), 7.65-7.63 (m, 2 H), 7.51-7.45 (m, 3 H), 7.29 (d, $J = 7.5$ Hz, 1 H), 7.13-7.11 (m, 1 H), 5.94 (d, $J = 6.5$ Hz, 1 H), 4.24-4.18 (m, 2 H), 2.93 (dd, $J = 9.6$, 13.5 Hz, 1 H), 2.25 (s, 3 H), 1.92-1.48 (series of m, 1 H), 0.93 (s, 9 H), 0.16 (s, 3 H), 0.12 (s, 3 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 171.5, 163.4, 155.5, 144.7, 131.8, 131.4, 129.6 (2C), 124.4 (2C), 97.4, 96.0, 88.7, 78.5, 70.8, 65.1, 35.2, 32.2, 26.2 (3C), 25.4, 18.9, 18.2, -3.5, -4.4.

$N$-[9-(6-Hydroxy-3-phenylsulfanyl-1-oxaspiro[4.4]non-2-yl)-9$H$-purin-6-yl]-benzamide (2.33).

Into a solution of persilylated benzoyladenine (0.11 g, 0.36 mmol) in dry acetonitrile (10 mL) was introduced neat SnCl$_4$ (0.11 mL, 0.96 mmol) and this mixture was stirred for 1 h before being slowly added to a -40 $^\circ$C solution of 2.2 (0.10 g, 0.24 mmol) in the same solvent (15 mL). After 30 min, warming to rt was allowed to occur slowly and stirring was maintained for another 6 h prior to quenching with saturated NaHCO$_3$ solution (20 mL). The separated aqueous layer was extracted with ethyl acetate (3 x 15 mL), and the combined organic solutions were dried and evaporated. Chromatography of the residue on silica gel (elution with 1:1 benzene/ethyl acetate) furnished 60 mg (50%) of 2.33 as a colorless syrup; $^1$H NMR (500 MHz, C$_6$D$_6$) $\delta$ 8.53 (br s, 1 H), 7.70-7.68 (m, 2 H), 7.27 (s, 1 H), 7.05-7.02 (m, 3 H), 6.95-6.92 (m, 3 H), 6.73-6.69 (m, 3 H), 5.54 (d, $J = 8.0$ Hz, 1 H), 5.04-5.00 (m, 1 H), 4.27 (t, $J = 8.7$ Hz, 1 H), 3.04 (dd, $J = 12.6$, 7.5 Hz, 1 H), 2.03-1.89 (m, 3 H), 1.59-1.51 (m, 1 H), 1.41-1.32 (m, 3 H) (OH not observed); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 164.2, 152.0, 150.2, 143.0, 139.5, 133.0, 132.2 (2C), 131.8,
129.0 (2C), 128.9 (2C), 128.3, 128.0, 127.8 (2C), 94.1, 93.1, 78.0, 48.5, 38.5, 36.0, 28.6, 17.4 (C4 of adenine not observed); ES HRMS m/z (M+Na)$^{+}$ calcd 510.1577, obsd 510.1626; $[\alpha]_{D}^{19}$ -14.0 (c 0.30, CHCl$_3$).

**Acetic Acid 2,3-Diacetoxy-6-methoxymethoxy-1-oxaspiro[4.4]non-4-yl Ester (3.1).**

A solution of 1.10$^{25,29}$ (0.26 g, 1.11 mmol) in dry CH$_2$Cl$_2$ (50 mL) was cooled to -78 °C under N$_2$, treated dropwise via syringe with a solution of Dibal-H in hexanes (8.0 mL of 1 M, 8.0 mmol), and stirred at this temperature for 1.5 h prior to the addition of acetic anhydride (10 mL). After 2 h, pyridine (12.1 mL) was introduced and the mixture was stirred overnight with slow warming to room temperature. A saturated solution of Rochelle's salt (20 mL) was added and one hour later the product was extracted into CH$_2$Cl$_2$, dried, and concentrated to furnish 3.1 as a clear oil (0.40 g, 61%) that was used directly.

Triacetate 3.1 (0.10 g, 0.27 mmol) and persilylated thymine (0.14 g, 0.50 mmol) were dissolved in THF (25 mL) at 0 °C, trimethylsilyl triflate (110 mg, 0.50 mmol) was added, and the reaction mixture was stirred at room temperature overnight prior to quenching with 1 M NaHCO$_3$ and extraction with ethyl acetate. The organic phase was washed with brine, dried and evaporated to give 28% of 3.2, 15% of 3.3 and 34% of 3.4 after chromatographic purification. These yields varied as a function of reaction conditions and particularly the purity of the trimethylsilyl triflate. Compound 3.2 proved to be labile to chromatography and was not fully characterized.
Acetic Acid 4-Acetoxy-6-hydroxy-2-(5-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-1-oxaspiro[4.4]non-3-yl Ester (3.3).

For 3.3: white solid, mp 195-199 C; ¹H NMR (300 MHz, CDCl₃) δ 8.70 (s, 1 H), 7.30 (d, J = 1.1 Hz, 1 H), 5.95 (d, J = 6.6 Hz, 1 H), 5.75-5.70 (m, 2 H), 4.21 (t, J = 7.5 Hz, 1 H), 2.17 (s, 3 H), 2.16-2.00 (m, 4 H), 1.93 (s, 3 H), 1.83-1.57 (m, 5 H), (OH proton missing); ¹³C NMR (75 MHz, CDCl₃) δ 169.9, 169.7, 163.3, 150.6, 136.4, 111.8, 94.0, 87.2, 78.3, 72.9, 71.0, 31.4, 30.2, 20.6, 20.5, 18.2, 12.6; ES MS m/z (M + Na)⁺ calcd 405.1274, obsd 405.1271.

Acetic Acid 4-Acetoxy-2-(5-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-6-(5-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethoxy)-1-oxaspiro[4.4]non-3-yl Ester (3.4).

For 3.4: white solid, mp 112-117 C; IR (CHCl₃, cm⁻¹) 3390, 1751, 1695; ¹H NMR (300 MHz, C₆D₆) δ 10.70 (s, 1 H), 10.37 (s, 1 H), 6.60 (s, 1 H), 6.57 (s, 1 H), 6.19 (d, J = 5.2 Hz, 1 H), 6.14-6.10 (m, 1 H), 5.76 (d, J = 6.4 Hz, 1 H), 5.17 (d, J = 10.6 Hz, 1 H), 4.56-4.53 (m, 1 H), 4.48 (d, J = 10.6 Hz, 1 H), 1.97 (s, 3 H), 1.90-1.60 (m, 15 H); ¹³C NMR (75 MHz, C₆D₆) δ 169.4, 169.1, 165.0, 164.3, 152.4, 150.8, 139.0, 137.8, 112.2, 111.4, 94.4, 90.2, 83.6, 74.7, 73.0, 72.0, 32.4, 31.9, 20.8, 20.1, 20.0, 12.4 (2C); ES MS m/z (M + Na)⁺ calcd 543.1705, obsd 543.1735.

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Acetic Acid 4-Acetoxy-6-methoxymethoxy-2-oxo-1-oxaspiro[4.4]non-3-yl Ester (3.6).

A solution of 1.10 (0.16 g, 0.69 mmol) in CH₂Cl₂ (5.0 mL) containing DMAP (10 mg) was cooled to ñ40 °C and treated sequentially with acetic anhydride (3.0 mL, 32 mmol) and pyridine (4.0 mL, 49 mmol). The reaction mixture was allowed to warm to room temperature after 3 h, quenched with saturated NaHCO₃ solution (30 mL), and extracted with CH₂Cl₂ (2 x 20 mL). The combined organic phases were washed with 1M HCl (20 mL) and brine (20 mL), then dried and evaporated. Chromatography of the residue on silica gel (elution with 3:2 petroleum ether-ether) gave 100 mg (48%) of 3.6 as a colorless oil; ¹H NMR (300 MHz, CDCl₃) δ 5.92 (d, J = 5.3 Hz, 1 H), 5.77 (d, J = 5.3 Hz, 1 H), 4.68 (d, J = 6.8 Hz, 1 H), 4.60 (d, J = 6.8 Hz, 1 H), 4.05 (t, J = 5.8 Hz, 1 H), 3.38 (s, 3 H), 2.20-2.08 (m, 7 H), 2.06-1.98 (m, 2 H), 1.80-1.70 (m, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 170.2, 169.5, 168.7, 95.1, 93.6, 81.6, 70.4, 67.7, 55.8, 29.8, 29.0, 20.2, 19.9, 18.6; ES MS m/z (M + Na)+ calcd 339.1056, obsd 339.1048.

Acetic Acid 4-Acetoxy-6-(6-amino-purin-9-ylmethoxy)-2-oxo-1-oxaspiro[4.4]non-3-yl Ester (3.7).

A solution of 3.6 (100 mg, 0.32 mmol) in CH₂Cl₂ (5.0 mL) containing bis(trimethylsilyl)adename (160 mg, 0.57 mmol) was treated with trimethylsilyl triflate (0.16 mL, 0.83 mmol). After 5 min, triflic acid (0.02 mL, 0.23 mmol) was introduced. Five minutes later, a white precipitate formed and the reaction mixture was quenched by the addition of saturated
NaHCO₃ solution (15 mL). The separated aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL), and the combined organic phases were washed with brine (10 mL), dried, and evaporated. Column chromatography of the residue on silica gel (elution with 100% ethyl acetate) returned 40 mg of unreacted 3.6 and furnished 20 mg (25%) of 3.7 as a white solid; ¹H NMR (300 MHz, CDCl₃) δ 8.38 (s, 1 H), 8.13 (s, 1 H), 5.72-5.64 (m, 4 H), 4.10-4.06 (m, 1 H), 2.12 (s, 3 H), 2.11 (s, 3 H), 2.09-1.98 (m, 3 H), 1.80-1.68 (m, 3 H) (NH₂ protons not observed); ¹³C NMR (125 MHz, CDCl₃) δ 169.7, 169.6, 169.0, 152.5, 149.4, 146.8, 142.3, 119.1, 93.3, 84.4, 71.9, 70.0, 67.6, 30.3, 29.2, 20.4, 20.1, 19.1; ES MS m/z (M + H)⁺ calcd 420.1519, obsd 420.1502.

6-(tert-Butyldimethylsilanyloxy)-3,4-dihydroxy-1-oxaspiro[4.4]nonan-2-one (3.8).

Lactone 1.22²⁹ (0.20 g, 0.75 mmol) was dissolved in a combination of acetonitrile (4 mL), ethyl acetate (4 mL) and water (1.2 mL). The reaction mixture was cooled to 0 °C and treated sequentially with sodium periodate (0.17 g, 0.79 mmol) and 5 min later with RuCl₃H₂O (10 mg, 0.047 mmol). After an additional 5 min of stirring, a saturated solution of sodium thiosulfate (25 mL) was introduced and the product was extracted into ethyl acetate (3 x 15 mL). The combined organics were dried over Na₂SO₄ and evaporated to leave a residue that was filtered through a silica plug (elution with ether) to give pure 3.8 (0.17 g, 75%) as a colorless glass; ¹H NMR (300 MHz, C₆D₆) δ 4.95 (d, J = 5.1 Hz, 1 H), 4.54 (d, J = 5.1 Hz, 1 H), 3.89 (t, J = 6.3 Hz, 1 H), 2.57-1.95 (m, 1 H), 2.00-1.90 (m, 1 H), 1.78-1.25 (series of m, 4 H), 0.93 (s, 9 H), 0.02 (s, 3 H), -0.04 (s, 3 H); ¹³C NMR (75 MHz, C₆D₆)
δ 177.2, 96.6, 78.3, 71.1, 70.1, 325, 29.2, 26.0 (3C), 18.6, 18.0, -4.7, -5.0; ES HRMS m/z (M+Na)+ calcd 325.1447, obsd 325.1441; [α]D\text{18} -12.0 (c 1.0, CHCl₃).


Diol 3.8 (0.05 g, 0.17 mmol) was dissolved in THF (2 mL) and treated with ethylene glycol (0.11 mL, 2.0 mmol) and dry HMPA (0.15 mL). Argon was bubbled through the solution for 10 min prior to the addition of SmI₂ (0.1M in THF, 8.5 mL, 0.85 mmol). The reaction mixture was quenched by the addition of hexane (10 mL), filtered through a plug of silica gel, and evaporated to give 3.9 (0.05 g, 100%) as a colorless oil; ¹H NMR (300 MHz, CDCl₃) δ 4.58 (dd, J = 4.6, 6.8 Hz, 1 H), 4.04 (t, J = 5.3 Hz, 1 H), 2.88 (dd, J = 6.8, 17.6 Hz, 1 H), 2.52 (dd, J = 4.6, 17.6 Hz, 1 H), 2.33-1.98 (m, 3 H), 1.82-1.72 (m, 2 H), 1.66-1.55 (m, 1 H), 0.88 (s, 9 H), 0.08 (s, 3 H), 0.07 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 174.6, 97.8, 79.0, 69.0, 38.3, 32.7, 28.0, 25.7, 19.6 (3C), 17.8, -4.6, -5.0; ES HRMS m/z (M+Na)+ calcd 309.1589, obsd 309.1591.

4,6-Bis-(\textit{tert}-Butyldimethylsilanyloxy)-1-oxaspiro[4.4]nonan-2-one (3.10).

Alcohol 3.9 (0.40 g, 1.4 mmol) was dissolved in CH₂Cl₂ (10 mL), 2,6-lutidine (0.50 mL, 4.2 mmol) was added, and the solution was cooled to 0 °C. TBSOTf (0.40 mL, 1.7 mmol) was added and the reaction mixture was quenched after 30 min with saturated bicarbonate solution (5 mL). The product was extracted into CH₂Cl₂ (2 X 10 mL), and the combined organic layers were
dried over Na₂SO₄ and evaporated. The residue was purified by column chromatography on silica gel (8:1 hexane/ether) to give 3.10 (0.28 g, 50%); IR (CHCl₃, cm⁻¹) 1771, 1259; 

¹H NMR (500 MHz, CDCl₃) δ 4.63 (dd, J = 1.9, 6.0 Hz, 1 H), 4.04 (t, J = 6.3 Hz, 1 H), 2.86 (dd, J = 6.0, 17.5 Hz, 1 H), 2.42 (dd, J = 2.0, 17.4 Hz, 1 H), 2.28-2.23 (m, 1 H), 2.08-2.03 (m, 1 H), 1.91-1.86 (m, 1 H), 1.78-1.71 (m, 2H), 1.64-1.58 (m, 1 H), 0.93 (s, 9 H), 0.92 (s, 9 H), 0.13 (s, 3 H), 0.12 (s, 3 H), 0.11 (s, 3 H), 0.09 (s, 3 H); 

¹³C NMR (125 MHz, CDCl₃) δ 175.8, 99.3, 78.4, 69.4, 40.1, 32.8, 28.8, 26.1 (3C), 26.0 (3C), 19.1, 18.4, 18.3, -4.2 (2C), -4.5, -4.7; ES HRMS m/z (M+Na)+ calcd 429.2357, obsd 423.2357; 

[α]¹₈D -11.6 (c 1.0, CHCl₃).

Acetic Acid 4,6-Bis-(tert-Butyldimethylsilanyloxy)-1-oxaspiro[4.4]non-2-yl Ester (3.11).

A solution of 3.10 (0.28 g, 0.70 mmol) in dry CH₂Cl₂ (20 mL) was treated with Dibal-H (0.9 mL of 1 M, 0.90 mmol) at -78 °C, stirred at this temperature for 2 h, quenched with saturated Rochelle's salt solution (16 mL), and stirred for 4 h. The separated aqueous phase was extracted with CH₂Cl₂ (3 x 10 mL) and the combined organic layers were dried and evaporated to provide the crude lactol that was immediately acetylated.

The above material was dissolved in CH₂Cl₂ (10 mL) and pyridine (1 mL), treated with acetic anhydride (0.13 mL, 1.4 mmol), and DMAP (0.01 g), stirred at rt for 30 min, and evaporated to dryness under high vacuum. The residue was dissolved in ethyl acetate (10 mL), washed sequentially with saturated CuSO₄ solution (5 mL), water (5 mL), and brine (5 mL), dried, and concentrated. Purification of the residue by column
chromatography on silica (9:1 hexane/ether) gave 3.11 (0.23 g, 73%) as a colorless oil; 1H NMR (500 MHz, CDCl₃) δ 6.30 (dd, J = 4.0, 5.3 Hz, 0.8 H), 6.19 (dd, J = 1.1, 5.5 Hz, 0.2 H), 4.66 (t, J = 5.1 Hz, 0.8 H), 4.48-4.47 (m, 0.2 H), 4.06 (t, J = 5.7 Hz, 0.8 H), 3.92 (s, 7.2 H), 0.91 (s, 1.8 H), 0.10 (br s, 12 H); 13C NMR (125 MHz, CDCl₃) δ 170.9, 170.8, 98.7, 98.6, 98.5, 98.2, 78.6, 78.3, 71.6, 70.4, 42.3, 42.2, 33.7, 32.5, 30.6, 30.0, 26.3 (3C), 26.2 (3C), 26.1 (3C), 26.0 (3C), 21.8 (2C), 19.9, 19.0, 18.4 (2C), 18.3 (2C), -4.1 (2C), -4.2, -4.4 (2C), -4.5 (2C), -4.7; ES HRMS m/z (M+Na)+ calcd 467.2619, obsd 467.2634; [α]D 18 -20.7 (c 0.7, CHCl₃).

1-[4,6-Bis-(tert-Butyldimethylsilanyloxy)-1-oxaspiro[4.4]non-2-yl]-5-methyl-1H-pyrimidine-2,4-dione (3.12).

Silylated thymine (0.12 g, 0.44 mmol) and 3.11 (100 mg, 0.22 mmol) were dissolved in CH₂Cl₂ (2.5 mL), cooled to -78 °C, and treated with neat tin tetrachloride (0.05 mL, 2 equiv). The reaction mixture was maintained at -78 °C for 15 min, allowed to warm to rt, quenched with saturated NaHCO₃ solution (3 mL), and extracted with CH₂Cl₂. The combined organic layers were dried and concentrated to leave a residue that was chromatographed on silica gel (elution with 3:2 hexane/ether) to give 0.06 g (52%) of 3.12. 1H NMR (500 MHz, CDCl₃) δ 8.15 (br s, 1 H), 7.67 (s, 1 H), 6.19 (d, J = 6.6 Hz, 1 H), 4.51 (d, J = 5.2 Hz, 1 H), 3.82 (t, J = 4.3 Hz), 2.75-2.69 (m, 1 H), 2.25-2.20 (m, 1 H), 2.08-2.03 (m, 1 H), 1.95 (s, 3 H), 1.91-1.85 (m, 1 H), 1.81-1.74 (m, 2 H), 1.64-1.58 (m, 1 H), 0.94 (s, 9 H), 0.92 (s, 9 H), 0.14 (s, 3 H), 0.11 (s, 3 H), 0.10 (s, 3 H), 0.09 (s, 3 H);
$^{13}$C NMR (125 MHz, CDCl$_3$) δ 164.0, 150.7, 137.6, 110.2, 101.0, 85.0, 78.1, 72.0, 42.8, 33.6, 30.3, 30.1, 26.1 (3C), 26.0 (3C), 20.1, 18.4, 18.3, 13.0, -4.0, -4.4, -4.5, -4.6; ES HRMS m/z (M+Na)$^+$ calcd 533.2837, obsd 533.2830; $[\alpha]^D_{18}$ -5.5 (c 0.2, CHCl$_3$).

4-Amino-1-[4,6-Bis-(tert-Butyldimethylsilanyloxy)-1-oxaspiro[4.4]non-2-yl]-1H-pyrimidin-2-one (3.14).

Silylated cytosine (0.11g, 0.44 mmol) and 3.11 (100 mg, 0.22 mmol) were dissolved in CH$_3$CN (2.5 mL), cooled to -40 °C, and treated with neat tin tetrachloride (0.05 mL, 2 equiv). The reaction mixture was maintained at -40 °C for 15 min, allowed to warm to rt, quenched with saturated NaHCO$_3$ solution (3 mL), and extracted with ethyl acetate. The combined organic layers were dried and concentrated to leave a residue that was chromatographed on silica gel (elution with ethyl acetate) to give 0.07 g (60%) of 3.14. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.86 (d, $J$ = 6.5 Hz, 0.5 H), 7.68 (d, $J$ = 6.5 Hz, 0.5 H), 6.20-5.85 (series of multiplets, 2 H), 4.56 (t, $J$ = 5.7 Hz, 0.5 H), 4.46 (d, $J$ = 4.5 Hz, 0.5 H), 4.11 (t, $J$ = 7.1 Hz, 0.5 H), 3.85-3.80 (m, 0.5 H), 2.72-2.65 (m, 0.5 H), 2.46-2.43 (m, 0.5 H), 2.25-2.14 (m, 1 H), 2.08-1.53 (series of multiplets, 6 H), 0.94 (s, 4.5 H), 0.93 (s, 4.5 H), 0.92 (s, 4.5 H), 0.86 (s, 4.5 H), 0.12 (s, 1.5 H), 0.11 (s, 3 H), 0.10 (s, 3 H), 0.09 (s, 1.5 H), 0.08 (s, 1.5 H), 0.00 (s, 1.5 H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 164.9 (2C), 143.0 (2C), 140.9 (2C), 128.7 (2C), 101.4 (2C), 96.6 (2C), 86.3, 85.3, 78.0 (2C), 72.2 (2C), 42.7, 42.0, 33.7, 32.6, 30.5, 29.5, 26.3 (3C), 26.2 (3C), 26.1 (6C), 20.2, 18.9, 18.4 (2C), 18.2 (2C), -3.7, -3.9, -
4.0, -4.2, -4.3, -4.5, -4.6, -4.7; ES HRMS m/z (M+Na)⁺ calcd 518.2841, obsd 518.2833;
[α]D¹⁸ +15.3 (c 0.9, CHCl₃).

9-[4,6-Bis-(tert-Butyldimethylsilanyloxy)-1-oxaspiro[4.4]non-2-yl]-9H-purin-6-ylamine (3.15).

Silylated adenine (1.12 g, 0.44 mmol) and 23 (100 mg, 0.22 mmol) were dissolved in CH₃CN (2.5 mL), cooled to -40 °C, and treated with neat tin tetrachloride (1.9 mL, 2 equiv). The reaction mixture was maintained at -40 °C for 15 min, allowed to warm to rt, quenched with saturated NaHCO₃ solution (3 mL), and extracted with ethyl acetate. The combined organic layers were dried and concentrated to leave a residue that was chromatographed on silica gel (elution with 1:2 benzene/ethyl acetate) to give compound 3.15.1 (29 mg, 25%) and compound 3.15.2 (28 mg, 25%).

For 3.15.1: ¹H NMR (500 MHz, C₆D₆) δ 8.59 (s, 1 H), 8.40 (s, 1 H), 6.40 (d, J = 6.9 Hz, 1 H), 5.49 (br s, 2 H), 4.51 (d, J = 5.2 Hz, 1 H), 3.67 (t, J = 4.9 Hz, 1 H), 2.57-2.48 (m, 1 H), 2.27-2.17 (m, 2 H), 1.99-1.81 (m, 2 H), 1.67-1.58 (m, 2 H), 1.51-1.65 (m, 2 H), 0.89 (s, 9 H), 0.81 (s, 9 H), -0.02 (s, 3 H), -0.03 (s, 3 H), -0.04 (s, 3 H), -0.15 (s, 3 H);
¹³C NMR (125 MHz, C₆D₆) δ 156.2, 153.4, 150.3, 139.8, 120.5, 100.2, 83.8, 78.4, 72.2, 42.6, 33.3, 30.2, 26.0 (3C), 25.9 (3C), 19.8, 18.2, 18.1, -4.5, -4.7, -4.8, -5.1; ES HRMS m/z (M+Na)⁺ calcd 542.2953, obsd 542.2955; [α]D¹⁸ -8.2 (c 0.6, CHCl₃).
For 3.15.2: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.38 (s, 1 H), 6.42 (d, $J = 7.2$ Hz, 1 H), 4.62 (d, $J = 5.1$ Hz, 1 H), 3.92 (t, $J = 5.0$ Hz, 1 H), 2.86-2.82 (m, 1 H), 2.37-2.34 (m, 1 H), 2.30-2.25 (m, 1 H), 2.11-2.07 (m, 1 H), 1.93-1.89 (m, 1 H), 1.80-1.74 (m, 2 H), 1.62-1.58 (m, 1 H), 0.95 (s, 9 H), 0.88 (s, 9 H), 0.13 (s, 9 H), 0.01 (s, 3 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 155.3, 152.6, 149.8, 140.8, 120.0, 101.0, 83.8, 78.6, 72.2, 43.0, 33.5, 30.4, 30.1, 26.3 (3C), 26.2 (3C), 20.0, 18.4, 18.3, -4.0, -4.4, -4.5, -4.7; ES HRMS $m/z$ (M+Na)$^+$ calcd 542.2953, obsd 542.2945; [$\alpha$]$^D_{18}$ +10.3 (c 0.4, CHCl$_3$).


A cold (-78 $^\circ$C) solution of 1.18$^{29}$ (0.50 g, 1.8 mmol) in CH$_2$Cl$_2$ (20 mL) was treated with Dibal-H (2.2 mL of 1 M in hexanes, 2.2 mmol), stirred at this temperature for 30 min, and quenched with saturated Rochelle's salt solution (50 mL). The separated aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 15 mL), and the combined organic phases were dried and evaporated. The resulting lactol 4.1 was dissolved in dry THF (20 mL), treated with triphenylphosphine (0.97 g, 3.7 mmol) and carbon tetrachloride (2 mL), and heated at 60 $^\circ$C for 3 h. The reaction mixture was cooled to rt, at which point the supernatant was transferred via cannula to a solution of 6-chloropurine (0.56 g, 3.7 mmol) and sodium hydride (0.15 g, 3.7 mmol) in dry DMF (20 mL) at 0 $^\circ$C. After 5 h of stirring, the solvent was removed under reduced pressure and the residue was taken up in CH$_2$Cl$_2$.
(200 mL). This solution was washed with water (40 mL), dried, and evaporated. Chromatography of the residue on silica gel (elution with 5:1 hexane/ether) furnished 0.23 g of **4.3.1** and 0.13 g of **4.3.2** (49% total).

**4.3.1**: white solid, mp 108.0-110 °C; $^1$H NMR (500 MHz, CDCl$_3$) δ 8.77 (s, 1 H), 6.40-6.38 (m, 1 H), 4.18 (t, $J = 6.0$ Hz, 1 H), 2.65-2.63 (m, 1 H), 2.56-2.51 (m, 2 H), 2.03-1.72 (series of m, 6 H), 1.59-1.54 (m, 1 H), 0.92 (s, 9 H), 0.10 (s, 3 H), 0.08 (s, 3 H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 152.2, 151.5, 151.4, 143.9, 132.7, 96.5, 85.8, 78.0, 35.2, 32.9, 32.8, 28.8, 26.2 (3C), 19.6, 18.4, -3.9, -4.3; ES HRMS m/z (M+Na)$^+$ calcd 431.1640, obsd 431.1664; $[^\alpha]_D^{18}$ -32.1 (c 1.0, CHCl$_3$).

**4.3.2**: colorless glass; $^1$H NMR (500 MHz, CDCl$_3$) δ 8.77 (s, 1 H), 6.38-6.36 (m, 1 H), 4.05 (t, $J = 6.2$ Hz, 1 H), 2.71-2.67 (m, 1 H), 2.59-2.51 (m, 2 H), 2.03-1.87 (m, 4 H), 1.78-1.71 (m, 2 H), 1.59-1.54 (m, 1 H), 0.95 (s, 9 H), 0.14 (s, 3 H), 0.13 (s, 3 H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 152.2, 151.4, 151.3, 143.8, 132.8, 96.8, 86.9, 78.4, 35.4, 33.6, 32.2, 29.0, 26.2 (3C), 19.5, 18.4, -4.1, -4.5; ES HRMS m/z (M+Na)$^+$ calcd 431.1640, obsd 431.1659; $[^\alpha]_D^{18}$ -21.5 (c 1.0, CHCl$_3$).
The chloropurines 4.3.1 and 4.3.2 (0.37 g of a 1.7:1 mixture, 0.90 mmol) were dissolved in methanol that had been saturated with NH₃ (40 mL) and stirred in a sealed heavy wall glass tube at 100 °C for 6 h. After the removal of solvent, the residue was subjected to chromatography on silica gel (elution with 3:2 hexane/ether). There was isolated 1.7:1 mixtures of the dimethoxy compounds 4.5 (0.02 g, 5%) and the amino derivatives 4.6 (0.17 g, 48%).

**9-[6-(tert-Butyldimethylsilyloxy)-1-oxaspiro[4.4]non-2-yl]-6-methoxy-9H-purine (4.5).**

For 4.5: colorless syrup; ¹H NMR (500 MHz, C₆D₆) δ 8.63 (s, 0.6 H), 8.62 (s, 0.4 H), 7.97 (s, 0.6 H), 7.87 (s, 0.4 H), 6.12-6.09 (m, 0.4 H), 5.96-5.94 (m, 0.6 H), 4.08 (t, J = 5.2 Hz, 0.6 H), 3.87 (s, 1.2 H), 3.85 (s, 1.8 H), 3.79 (t, J = 5.8 Hz, 0.4 H), 2.36-2.17 (m, 4 H), 1.92-1.35 (series of m, 6 H), 0.91 (s, 3.6 H), 0.90 (s, 5.4 H), 0.01 (s, 1.8 H), 0.00 (s, 1.2 H), -0.01 (s, 1.2 H), -0.04 (s, 1.8 H); ¹³C NMR (125 MHz, C₆D₆) δ 161.8, 161.7, 152.2 (2C), 152.1 (2C), 141.0, 140.5, 123.1 (2C), 95.6 (2C), 85.9, 85.4, 78.1, 78.0, 53.8, 53.7, 35.2, 35.1, 32.9 (2C), 32.1, 31.8, 28.9, 28.7, 26.1 (3C), 26.0 (3C), 19.9, 19.5, 18.2 (2C), -4.3, -4.5, -4.7, -4.8; ES HRMS m/z (M+Na)⁺ calcd 427.2976, obsd 427.2154; [α]¹⁸_D -22.9 (c 1.0, CHCl₃).

For 4.6: white solid, mp 205.2-207.0 °C dec; ¹H NMR (500 MHz, CDCl₃) δ 8.38 (br s, 1 H), 8.10 (s, 0.63 H), 8.02 (s, 0.37 H), 6.34-6.31 (m, 1 H), 6.03 (br s, 2 H), 4.17 (t, J = 5.8 Hz, 0.63 H), 4.03 (t, J = 6.0 Hz, 0.37 H), 2.66-2.57 (m, 1 H), 2.54-2.30 (m, 2 H), 2.04-1.71 (series of m, 6 H), 1.58-1.52 (m, 1 H), 0.94 (s, 3.3 H), 0.92 (s, 5.7 H), 0.13 (s, 1.1 H), 0.12 (s, 1.1 H), 0.09 (s, 1.9 H), 0.08 (s, 1.9 H); ¹³C NMR (125 MHz, CDCl₃) δ 155.7 (2C), 152.9 (2C), 149.8 (2C), 139.2, 139.0, 120.5 (2C), 96.4, 96.0, 86.2, 85.1, 78.2, 78.1, 35.5, 35.3, 33.7, 32.9, 32.8, 32.4, 29.1, 29.0, 26.3 (3C), 26.2 (3C), 19.7, 19.6, 18.4 (2C), -3.9, -4.1, -4.3, -4.5; ES HRMS m/z (M+Na)⁺ calcd 390.2320, obsd 390.2328; [α]₁⁸D -31.4 (c 1.50, CHCl₃).


A 0.04 g (0.10 mmol) sample of the 4.6 mixture generated above was dissolved in dry THF (3 mL) and treated with TBAF (0.2 mL of 1 M in THF, 0.2 mmol). The reaction mixture was stirred for 3 h, quenched with water (10 mL), and extracted with ethyl acetate (3 x 10 mL). The combined organic phases were dried and evaporated. The residue was triturated with ether (3 x 5 mL) to give 4.7 as a 3:1 mixture (0.02 g, 67%); white solid, mp 159.5-161.0 °C; ¹H NMR (500 MHz, CDCl₃) δ 8.39 (s, 0.25 H), 8.37 (s, 0.75 H), 8.01 (s, 0.25 H), 7.88 (s, 0.75 H), 6.58 (br s, 0.75 H), 6.36-6.34 (m, 0.25 H), 6.14 (dd, J =
6.4, 8.2 Hz, 0.75 H), 5.73 (br s, 1.5 H), 5.64 (br s, 0.5 H), 4.26 (t, \( J = 8.8 \) Hz, 0.75 H), 4.11 (t, \( J = 5.7 \) Hz, 0.25 H), 3.10-3.02 (m, 0.75 H), 2.79-2.74 (m, 0.75 H), 2.70-2.41 (series of m, 1.75 H), 2.20-1.98 (series of m, 3 H), 1.90-1.57 (m, 4 H); \(^{13}\text{C}\) NMR (125 MHz, CDCl\(_3\)) \( \delta \) 156.3, 155.7, 153.3, 152.8, 148.9, 148.5, 141.1, 138.9, 121.8 (2C), 96.6, 95.1, 87.9, 85.7, 78.4, 78.0, 36.6, 35.3, 33.3, 32.5, 32.1, 31.8, 28.8, 28.7, 19.7, 18.2; EI HRMS \( m/z \) (M\(^+\)) calcd 275.1377, obsd 275.1378; \([\alpha]^{18}_D \) -27.1 (c 0.7, C\(_2\)H\(_5\)OH).


Lactone 1.22\(^{29}\) (0.50 g, 1.7 mmol) was dissolved in CH\(_2\)Cl\(_2\) (20 mL), cooled to -78 \( ^\circ \)C, and treated with Dibal-H (2.1 mL, 1 M in hexanes, 2.1 mmol). After 30 min, the reaction mixture was quenched with saturated Rochelle’s salt solution (50 mL), the separated aqueous phase was extracted with CH\(_2\)Cl\(_2\) (3 x 15 mL), and the combined organic layers were dried and evaporated. The resulting lactol 4.8 was dissolved in dry THF (20 mL), treated with triphenylphosphine (0.97 g, 3.7 mmol) and carbon tetrachloride (2 mL), and heated at 60 \( ^\circ \)C for 3 h. The reaction mixture was cooled to rt, at which point the supernatant was transferred via cannula to a solution of 2-amino-6-chloropurine (0.63 g, 3.7 mmol) and sodium hydride (0.15 g, 3.7 mol) in dry DMF (20 mL) at 0 \( ^\circ \)C. After 5 h of stirring, the solvent was taken up in CH\(_2\)Cl\(_2\) (200 mL) prior to a water wash (40 mL), drying, and solvent evaporation. Chromatography of the residue on silica gel (elution with 3:1 hexane/ether) furnished an inseparable mixture of 4.10.1 and 4.10.2 (ratio 2.3:1) (0.37 g, 50%) as a colorless glass; \(^1\text{H}\) NMR (500 MHz, C\(_6\)D\(_6\)) \( \delta \)
7.72 (s, 0.32 H), 7.48 (s, 0.68 H), 6.74-6.73 (m, 0.68 H), 6.70-6.68 (m, 0.32 H), 6.10 (dd, J = 1.7, 5.9 Hz, 0.32 H), 6.06 (dd, J = 1.7, 5.9 Hz, 0.68 H), 5.20-5.18 (m, 1 H), 4.64 (br s, 0.64 H), 4.58 (br s, 1.36 H), 3.87-3.58 (m, 0.68 H), 3.81-3.79 (m, 0.32 H), 1.87-1.74 (m, 2 H), 1.64-1.35 (m, 4 H), 0.90 (s, 6.12 H), 0.88 (s, 2.88 H), -0.03 (s, 2.04 H), -0.04 (s, 2.04 H), -0.06 (s, 0.96 H), -0.12 (s, 0.96 H); 13C NMR (125 MHz, C6D6) δ 159.8 (2C), 154.2, 154.1, 152.2, 152.1, 139.7, 139.6, 138.5, 138.4, 126.5, 126.4, 123.7 (2C), 101.6, 87.6 (2C), 81.3, 81.0, 35.4, 35.2, 34.0, 33.7, 26.0 (6C), 21.4, 21.2, 18.2, 18.1, -4.4, -4.6, -4.8 (2C); ES HRMS m/z (M+Na)+ calcd 444.1593, obsd 444, 1588; [α]18D -75.9 (c 0.75, CHCl3).


Compound 4.10, (0.20 g, 0.48 mmol) was dissolved in methanol (4 mL). Sodium methoxide (0.10 g, 2.0 mmol) and 2-mercaptoethanol (0.16 mL) were added to the mixture. After the addition of two drops of water, the mixture was heated under reflux for 1.5 h. Another portion of sodium methoxide (0.08 g, 1.5 mmol) was added and heating was continued for another 1 hour. All volatile materials were removed in vacuo. The residue was purified by column chromatography on silica gel (1:3 hexane/ether) to give 4.11 (0.20 g, 90%) as a colorless oil; 1H NMR (500 MHz, CDCl3) δ 7.76 (s, 0.7 H), 7.72 (s, 0.3 H), 6.95-6.94 (m, 0.7 H), 6.93-6.92 (m, 0.3 H), 6.55 (dd, J = 1.8, 5.9 Hz, 0.7 H), 6.52 (dd, J = 1.7, 5.9 Hz, 0.3 H), 5.99-5.96 (m, 1 H), 5.09 (br
s, 2 H), 4.06-4.01 (m, 2.3 H), 3.91-3.89 (m, 0.7 H), 3.53-3.51 (m, 2 H), 2.14-1.59 (series of m, 6 H), 0.94 (s, 6.3 H), 0.93 (s, 2.7 H), 0.09 (br s, 6 H), (OH not observed); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 161.6, 159.1, 151.2, 151.1, 139.5, 139.3, 138.9, 138.8, 126.4, 126.3, 123.8, 123.7, 116.8, 116.4, 102.3, 102.2, 87.6, 85.5, 81.5, 81.2, 63.7 (2C), 35.6, 35.4, 34.2, 34.0, 32.9, 32.8, 26.2 (3C), 26.1 (3C), 21.6, 21.5, 18.4, 18.3, -4.0, -4.2, -4.3, -4.4; ES HRMS m/z (M+Na)$^+$ calcd 486.1966, obsd 486.1971; $\left[\alpha\right]_{D}^{18}$ -48.3 (c 1.4, CHCl$_3$).


Compound 4.11, (0.20 g, 0.48 mmol) was dissolved in methanol (4 mL). Sodium methoxide (0.10 g, 2.0 mmol) and 2-mercaptoethanol (0.16 mL) were added to the mixture. After the introduction of two drops of water, the mixture was heated under reflux for 1.5 h. Another portion of sodium methoxide (0.08 g, 1.5 mmol) was added and heating was continued for another 1 h. All volatile materials were removed in vacuo. The residue was dissolved in water (2 mL) and acidified with acetic acid. The resulting solid was collected by vacuum filtration and washed with water to give 4.12 (0.06 g, 35%) as a white solid, mp 175.0-180.2 $\circ$C; $^1$H NMR (500 MHz, C$_5$D$_5$N) $\delta$ 7.92 (s, 1 H), 7.11-7.09 (m, 1 H), 6.49 (dd, $J = 1.8$, 6.0 Hz, 0.38 H), 6.46 (dd, $J = 1.7$, 5.9 Hz, 0.62 H), 6.03-6.00 (m, 1 H), 4.04-4.02 (m, 1 H), 3.08-2.85 (m, 2 H), 2.11-1.55 (series of m, 4 H), 0.90 (s, 5.6 H), 0.89 (s, 3.4 H), 0.07 (br s, 4.8 H), 0.01 (s, 1.2 H); $^{13}$C NMR (125 MHz, C$_5$D$_5$N) $\delta$ 160.3, 160.2, 156.9, 156.8, 153.6, 153.5, 150.7 (2C), 139.5, 139.3, 136.4, 96
136.1, 120.1, 120.0, 102.8, 102.7, 89.0, 88.9, 82.6, 82.5, 36.7, 36.6, 35.3, 34.9, 27.3 (3C), 27.2 (3C), 22.7, 22.5, 19.5, 19.4, -3.1, -3.3, -3.4, -3.5; ES HRMS m/z (M+Na)+ calcd 426.1932, obsd 426.1914; [α]D 18 79.1 (c 0.1, CHCl3).


Following the dissolution of the 4.10 mixture in a combination of acetonitrile (4 mL), ethyl acetate (4 mL), and water (1.2 mL), the reaction mixture was cooled to 0 °C, and treated sequentially with sodium periodate (0.15 g, 0.70 mmol) and 5 min later RuCl3·H2O (10 mg, 0.047 mmol). After an additional 5 min of stirring, a saturated solution of sodium thiosulfate (25 mL) was introduced and the products were extracted into ethyl acetate (3 x 15 mL). The combined organic layers were dried and evaporated to leave a residue that was chromatographed on silica gel (elution with 1:2 hexane/ether) to give pure samples of 4.13 (82 mg, 38%) and 4.14 (48 mg, 22%).

For 4.13: white solid, mp 190.5-192 °C; 1H NMR (500 MHz, CDCl3) δ 7.95 (s, 1 H), 5.84 (d, J = 5.8 Hz, 1 H), 5.19 (br s, 2 H), 4.73 (t, J = 5.3 Hz, 1 H), 4.55 (d, J = 4.7 Hz, 1 H), 4.09 (t, J = 5.7 Hz, 1 H), 2.41-2.35 (m, 1 H), 2.06-2.02 (m, 1 H), 1.89-1.76 (m, 3 H), 1.63-1.58 (m, 1 H), 0.86 (s, 9 H), 0.08 (s, 3 H)
(neither OH is observed); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 158.9, 153.1, 152.5, 140.9, 125.9, 98.2, 90.2, 79.6, 76.6, 72.1, 33.1, 30.8, 26.1 (3C), 19.6, 18.2, -3.9, -4.5; ES HRMS $m/z$ (M+Na)$^+$ calcd 478.1653, obsd 478.1594; $[\alpha]_{D}^{18}$ -22.9 (c 0.35, CHCl$_3$).

For 4.14: white solid, mp 195-197.2 $\infty$C; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.91 (s, 1 H), 5.95 (d, $J$ = 6.2 Hz, 1 H), 5.16 (br s, 2 H), 4.89 (dd, $J$ = 4.5, 6.2 Hz, 1 H), 4.85 (br s, 1 H), 4.47 (d, $J$ = 4.5 Hz, 1 H), 4.44 (t, $J$ = 5.6 Hz, 1 H), 2.07-2.03 (m, 2 H), 1.99-1.77 (m, 4 H), 0.98 (s, 9 H), 0.23 (s, 3 H), 0.19 (s, 3 H) (1 OH not observed) $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$158.9, 153.1, 152.5, 140.9, 125.8, 98.3, 90.3, 79.6, 76.7, 72.1, 33.1, 30.8, 26.1 (3C), 19.6, 18.2, -3.9, -4.5 ;ES HRMS $m/z$ (M+Na)$^+$ calcd 478.1653, obsd 478.1593; $[\alpha]_{D}^{18}$ -17.0 (c 0.2, CHCl$_3$).

2-(2-Amino-6-Chloropurin-9-yl)-6-Hydroxy-1-oxaspiro[4.4]nonane-3,4-diol (4.16).

Compound 4.12 (0.0075 g, 0.02 mmol) was dissolved in a 4:1 mixture of THF/pyridine (1 mL) and osmium tetroxide (0.005 g, 0.02 mmol) was added. The resulting brown solution was stirred for 2 h, at which point no starting material was observed by TLC. The reaction mixture was quenched by bubbling H$_2$S gas through for 10 min. The reaction mixture was filtered through a plug of Celite, and evaporated. The residue was purified by column chromatography on silica gel with 20% methanol in benzene to give 4.16 (0.007 g, 80%) as a white solid mp 91-112 $\infty$C; $^1$H NMR (500 MHz,
Methyl 2-\textit{O}-Allyl-3,4-di-\textit{O}-benzoyl-6-\textit{O}-benzyl-\textalpha-D-altropyranoside (5.12).

Epoxide 5.11 (10.00 g, 37.8 mmol, 1 eq) was dissolved in allyl alcohol (500 mL), treated with NaH (1.36 g, 56.8 mmol, 1.5 eq), and heated to reflux for 48 h. The solution was cooled, and excess allyl alcohol was removed by evaporation under reduced pressure. The residue was dissolved in EtOAc (200 mL) and saturated NH$_4$Cl solution (150 mL) was added. The aqueous layer was extracted with EtOAc (3 x 75 mL), the combined organics were washed with brine (75 mL), dried over Na$_2$SO$_4$ and evaporated. The crude material was dissolved in CH$_2$Cl$_2$ (500 mL), cooled to 0°C, and treated with triethylsilane (30.0 mL, 189 mmol, 5 eq) and trifluoroacetic acid (14.6 mL, 189 mmol, 5 eq). The resulting solution was stirred at 0°C
for 1 h, then warmed to room temp for 2 h. The reaction mixture was quenched slowly by addition of saturated NaHCO₃ solution (300 mL), the layers were separated, and the aqueous layer was extracted with EtOAc (3 x 75 mL). The organic phases were combined, washed with brine (75 mL), dried over Na₂SO₄ and evaporated. The crude oil was then dissolved in CH₂Cl₂ (200 mL). Pyridine (30.8 mL, 378 mmol, 10 eq) and benzoyl chloride (20.9 mL, 189 mmol, 5 eq) was then added. The reaction mixture was stirred for 48 h prior to quenching with water (200 mL). The separated aqueous layer was extracted with EtOAc (3 x 75 mL). The organic layers were combined, washed with brine (75 mL), dried over Na₂SO₄, and evaporated. The residual oil was purified by column chromatography on silica gel (3:1 hexane/ether) to give 5.12 as a colorless oil (8.19 g, 41% three steps); IR (neat, cm⁻¹) 1727, 1602; ¹H NMR (500 MHz, CDCl₃) δ 8.11-8.06 (m, 3 H), 7.94-7.89 (m, 2 H), 7.63-7.18 series of m, 10 H), 6.03-5.95 (m, 1 H), 5.80-5.76 (m, 1 H), 5.65 (dd, J = 3.4, 9.5 Hz, 1 H), 5.40-5.26 (m, 2 H), 4.88 (s, 1 H), 4.69-4.56 (m, 3 H), 4.33-4.23 (m, 2 H), 3.88-3.86 (m, 1 H), 3.84-3.83 (m, 2 H), 3.53 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 166.1, 165.6, 138.4, 134.5, 134.4 (2C), 133.7 (2C), 133.6 (2C), 133.5 (2C), 128.9 (2C), 128.8 (2C), 128.7 (2C), 128.6, 118.5, 100.7, 75.5, 74.1, 72.3, 69.9, 68.7; ES HRMS m/z (M+Na)⁺ calcd 555.1989, obsd 555.1978; [α]₁⁸D +111.8 (c 2.9, CHCl₃).
Methyl 2-\textit{O}-\textit{Allyl}-4,6-\textit{O}-benzylidene-\textit{\textalpha}-\textit{D}-altropyanoside (5.11.1).

A sample of the intermediate resulting from the opening of the epoxide 5.11 was purified by column chromatography on silica gel (1:1 hexane/ether) to give 5.11.1 as a colorless oil; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.52-7.48 (m, 2 H), 7.38-7.33 (m, 3 H), 5.97-5.84 (m, 1 H), 5.63 (s, 1 H), 5.35-5.21 (series of m, 2 H), 4.71 (s, 1 H), 4.32 (dd, $J = 5.1$, 10.2 Hz, 1 H), 4.22-4.08 (series of m, 4 H), 3.93 (dd, $J = 3.0$, 9.8 Hz, 1 H), 3.83 (t, $J = 10.2$ Hz, 1 H), 3.65 (dd, $J = 0.5$, 3.0 Hz, 1 H), 3.43 (s, 3 H), 2.92 (br s, 1 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 137.3, 133.8 (2C), 129.0 (2C), 128.1, 126.2, 118.0, 102.1, 100.1, 76.6 (2C), 71.6, 69.1, 67.0, 58.1, 55.5; EI HRMS m/z (M)$^+$ calcd 322.1411, obsd 322.1393; $[\alpha]_{D}^{18}$ +63.1 (c 3.5, CHCl$_3$).

Methyl 3,4-\textit{Di-\textit{O}-benzoyl}-6-\textit{O}-benzyl-\textit{\textalpha}-\textit{D}-altropyanoside (5.13).

Allyl sugar 5.12 (0.24 g, 0.45 mmol, 1 eq) was dissolved in a mixture of ethanol/benzene/water (7:3:1, 30 mL), and treated with Wilkinson's catalyst (0.07 g, 0.08 mmol, 0.17 eq) and DABCO (0.03 g). The mixture was heated to reflux for 36 h, cooled and evaporated. The residue was dissolved in a mixture of acetone/water (9:1, 30 mL) whereupon HgCl$_2$ (1.30 g) was added. To this mixture was added HgO (1.30 g) in portions over 5 min. The mixture was stirred for 24 h, filtered through Celite and evaporated. The residue was dissolved in ether (50 mL) and stirred with saturated potassium iodide solution (30 mL) for 30 min. The separated aqueous layer was extracted with ether (2 x 10 mL). The combined organic phases were washed
with brine (15 mL), dried over Na₂SO₄ and evaporated. The residue was purified by column chromatography on silica gel (1.5:1 hexane/ether) to give 5.13 (0.20 g, 90%) as a white solid, mp 103.0-103.5 °C; IR (CHCl₃, cm⁻¹) 3479, 1724; ¹H NMR (500 MHz, CDCl₃) δ 8.04 (d, J = 7.3 Hz, 2 H), 7.93 (d, J = 7.3 Hz, 2 H), 7.60-7.22 (series of m, 11 H), 5.74 (d, J = 6.0 Hz, 2 H), 4.88 (d, J = 2.5 Hz), 4.68 (ABq, 2 H, J = 12.1 Hz, ∆ν = 34.1 Hz), 4.55-4.53 (m, 1 H), 4.17 (br s, 1 H), 3.81-3.78 (m, 2 H), 3.56 (s, 3 H), 2.94 (br s, 1 H); ¹³C NMR (125 MHz, CDCl₃) δ 166.3, 165.8, 138.2, 133.6 (2C), 130.3 (2C), 130.2 (2C), 130.0 (2C), 128.8 (2C), 128.7 (4C), 128.1 (2C), 128.0, 102.1, 74.1, 71.0, 69.9, 69.7, 68.8, 67.5, 56.3; ES HRMS m/z (M+Na)+ calcd 515.1676, obsd 515.1690; [α]¹⁸D +70.4 (c 7.0, CHCl₃).

**Benzoic Acid 6-benzyloxymethyl-2-methoxy-3-oxo-3,6-dihydro-2H-pyran-4-yl Ester (5.14).**

Compound 5.13 (0.10 g, 0.20 mmol) was dissolved in CH₂Cl₂ (2 mL), 4Å molecular sieves (0.10 g) were added followed by NMO (35 mg, 0.30 mmol) and TPAP (3.5 mg, 0.01 mmol). The mixture was stirred for 1 h, filtered through a plug of silica gel, and purified by column chromatography on silica gel (3:1 hexane/ether) to give 5.14 (60 mg, 80%) as a white solid, mp 83.0-83.5 °C; IR (CHCl₃, cm⁻¹) 1748, 1719; ¹H NMR (500 MHz, CDCl₃) δ 8.17-8.15 (m, 2 H), 7.66-7.64 (m, 1 H), 7.54-7.50 (m, 2 H), 7.41-7.40 (m, 4 H), 7.32-7.30 (m, 1 H), 6.89 (d, J = 1.7 Hz, 1 H), 5.01-4.99 (m, 3 H), 4.68 (d, J = 1.1 Hz, 1 H), 3.84 (dd, J = 2.7, 9.9 Hz, 1 H), 3.73 (dd, J = 2.7, 9.9 Hz, 1 H), 3.63 (s, 3 H); ¹³C NMR (125 MHz, CDCl₃)
CDCl₃) δ 183.1, 164.2, 142.0, 137.9, 134.9, 130.8 (2C), 129.0 (3C), 128.9, 128.4, 128.2 (3C), 99.8, 74.2, 71.5, 68.9, 57.4; ES HRMS m/z (M+Na)+ calcd 391.1152, obsd 391.1137; [α]¹D +6.6 (c 0.7, CHCl₃).

Methyl 2-O-Allyl-6-O-benzyl-α-D-altropyranoside (5.15).

Compound 5.12 (3.00 g, 5.6 mmol) was dissolved in methanol (50 ml) and cooled to 0 °C. To this solution was added 30% NaOMe/MeOH (2.8 mL, 14.1 mmol), and the reaction mixture was allowed to warm to room temperature. After 1 h, the solvent was evaporated and the residue was dissolved in ethyl acetate (100 mL), washed with saturated NaHCO₃ solution (30 mL), dried over Na₂SO₄, and evaporated. The material was purified by column chromatography of the residue on silica gel (1:2 hexane/ether) to give 5.15 (1.37 g, 76%) as a colorless oil; IR (neat, cm⁻¹) 3476, 1737; ¹H NMR (500 MHz, CDCl₃) δ 7.37-7.26 (m, 5 H), 5.92-5.85 (m, 1 H), 5.31-5.26 (m, 1 H), 5.21-5.19 (m, 1 H), 4.75 (s, 1 H), 4.62 (s, 2H), 4.08-4.07 (m, 2 H), 3.99 (br s, 1 H), 3.88-3.84 (m, 2 H), 3.79-3.73 (m, 2 H), 3.63-3.62 (m, 1 H), 3.42 (s, 3 H), 3.02 (br s, 1 H); ¹³C NMR (125 MHz, CDCl₃) δ 138.8, 134.6, 128.7 (2C), 128.0 (2C), 127.9, 118.1, 99.8, 76.0, 73.9, 71.7, 70.9, 69.3, 68.5, 65.7, 55.7; ES HRMS m/z (M+Na)+ calcd 347.1465, obsd 347.1451; [α]¹D +56.3 (c 5.0, CHCl₃).
Methyl 2-\textit{O}-Allyl-6-\textit{O}-benzyl-3,4-\textit{O}-isopropylidine-\textalpha-\textit{D}-altropyranoside (5.16).

Diol 5.15 (1.27 g, 4.27 mmol) was dissolved in acetone (12 mL) and 2,2-dimethoxypropane (0.57 mL, 4.65 mmol) was added followed by a catalytic amount of TsOH (0.012 g). The solution was stirred for 1 h and evaporated to dryness. After CH$_2$Cl$_2$ (50 mL) was added, the organic layer was washed with saturated NaHCO$_3$ solution (10 mL), dried over Na$_2$SO$_4$ and evaporated. Column chromatography of the residue on silica gel (2:1 hexane/ether) gave 5.16 (1.27 g, 81\%) as a colorless oil; IR (neat, cm$^{-1}$) 1454, 1382, 1213; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.41-7.36 (m, 4 H), 7.34-7.30 (m, 1 H), 6.02-5.94 (m, 1 H), 5.35 (ddd, $J$ = 1.6, 3.2, 17.3 Hz, 1 H), 5.23 (dd, $J$ = 1.4, 10.4 Hz, 1 H), 4.66 (s, 2 H), 4.64 (d, $J$ = 4.7 Hz, 1 H), 4.30-4.19 (m, 4 H), 3.92-3.89 (m, 1 H); 3.78 (dd, $J$ = 2.5, 10.9 Hz, 1 H), 3.68-3.65 (m, 1 H), 3.57 (dd, $J$ = 4.7, 7.2 Hz, 1 H), 3.48 (S, 3 H), 1.52 (s, 3 H), 1.39 (s, 3 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 138.6, 135.1, 128.8 (2C), 128.0 (2C), 127.9, 117.8, 110.6, 102.1, 79.9, 76.9, 73.8, 72.6, 72.3, 70.9, 70.4, 55.7, 28.0, 25.8; ES HRMS $m/z$ (M+Na)$^+$ calcd 387.1778, obsd 387.1772; $[\alpha]_D^{18}$ +46.8 (c 1.0, CHCl$_3$).

Methyl 6-\textit{O}-Benzyl-3,4-\textit{O}-isopropylidine-\textalpha-\textit{D}-altropyranoside (5.17).

Compound 5.16 (1.00 g, 1.9 mmol) was dissolved in a 7:4:1 mixture of ethanol/benzene/H$_2$O (92 mL). DABCO (0.09 g, 0.84 mmol) and Wilkinson's catalyst (0.23 g, 0.25 mmol) were added. The solution was heated to reflux for 18 h, cooled to room temperature and evaporated. The residue was dissolved in a 9:1 mixture of acetone:H$_2$O (40 mL). Yellow HgO (0.90 g) was first
added followed by the slow addition of HgCl₂ (0.90 g). After 30 min of stirring the mixture was filtered through Celite and the solvent was evaporated. The residue was dissolved in ether (100 mL), washed with saturated potassium iodide solution, dried over Na₂SO₄ and evaporated. The residue was purified by column chromatography of the residue on silica gel (3:2 hexane/ether) to give 5.17 (0.52 g, 85%) as a light yellow oil; IR (neat, cm⁻¹) 3462, 1497, 1454; ¹H NMR (300 MHz, CDCl₃) δ 7.37-7.28 (m, 5 H), 4.62 (s, 2 H), 4.56 (d, J = 5.4 Hz, 1 H), 4.31 (dd, J = 7.2, 8.7 Hz, 1 H), 4.13 (t, J = 7.5 Hz, 1 H), 3.92-3.80 (m, 1 H), 3.78-3.72 (m, 2 H), 3.62 (dd, J = 5.4, 10.9 Hz, 1 H), 3.54 (S, 3 H), 2.69 (d, J = 4.4 Hz, 1 H), 1.48 (s, 3 H), 1.35 (s, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 138.4, 128.8 (2C), 128.0 (2C), 127.9, 111.0, 102.3, 77.2, 73.9, 73.4, 72.6, 70.9, 70.8, 56.0, 27.9, 25.7; ES HRMS m/z (M+Na)+ calcd 347.1465, obsd 347.1450; [α]D⁰ +26.7 (c 2.4, CHCl₃).

4-Benzylxymethyl-6-methoxy-2,2-dimethyl-dihydro[1,3]dioxolo[4,5-c]pyran-7-one
Methyl 6-O-benzyl-3,4-O-isopropylidene-2-oxo-α-D-altropyranoside (5.18).

Alcohol 5.17 (0.40 g, 1.2 mmol) was dissolved in CH₂Cl₂ (10 mL).

4= molecular sieves (0.60 g) were added, followed by NMO (0.22 g, 1.8 mmol) and TPAP (0.021 g, 0.06 mmol). The mixture was stirred for 1 h and filtered through a plug of silica gel (elution with 1:1 CH₂Cl₂/ether) to give 5.18 (0.40 g) in quantitative yield; IR (neat, cm⁻¹) 1794, 1759, 1673; ¹H NMR (300 MHz, CDCl₃) δ 7.37-7.31 (m, 5 H), 4.90 (s, 1 H), 4.77-4.64 (m, 4 H), 3.97-3.91 (m, 1 H), 3.82-3.70 (m, 2 H), 3.50 (s, 3 H), 1.47 (s, 3 H), 1.38 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ
201.8, 137.7, 128.4 (2C), 127.8, 127.6 (2C), 112.7, 99.0, 77.6, 74.7, 73.5, 72.7, 69.7, 55.9, 27.1, 25.5; ES HRMS \(m/z\) (M+Na)\(^+\) calcd 345.1309, obsd 345.1302; \([\alpha]_{D}^{18}\) +9.8 (c 0.8, CHCl\(_3\)).

**Methyl 6-O-Benzyl-3,4-O-isopropylidene-\(\alpha\)-D-allopyranoside (5.19).**

Ketone 5.18 (0.40 g, 1.2 mmol) was dissolved in EtOH (10 mL), cooled to 0 \(^\circ\)C and treated with NaBH\(_4\) (0.07 g, 2.0 mmol). After 30 min, the reaction mixture was quenched by the addition of acetone (3 mL) and the solvent was evaporated. The residue was dissolved in ether (30 mL), washed with brine (10 mL), dried over Na\(_2\)SO\(_4\) and evaporated prior to purification by column chromatography on silica gel (3:2 hexane/ether) to give 5.19 (0.35 g, 88\%) as a light yellow oil; IR (neat, cm\(^{-1}\)) 3490, 1451; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.37-7.30 (m, 5 H), 4.76 (d, \(J = 4.7\) Hz, 1 H), 4.60 (d, \(J = 1.8\) Hz, 2 H), 4.45 (t, \(J = 4.9\) Hz, 1 H), 4.11 (dd, \(J = 5.1, 9.6\) Hz, 1 H), 3.89-3.79 (m, 2 H), 3.73 (dd, \(J = 2.2, 10.8\) Hz, 1 H), 3.61 (dd, \(J = 5.4, 10.8\) Hz, 1 H), 3.46 (s, 3 H), 1.50 (s, 3 H), 1.36 (s, 3 H) (OH not observed); \(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 138.6, 128.8 (2C), 128.0 (3C), 110.6, 98.7, 74.6, 74.0, 72.1, 69.9, 67.3, 67.0, 56.4, 28.7, 26.6; ES HRMS \(m/z\) (M+Na)\(^+\) calcd 347.1465, obsd 347.1474; \([\alpha]_{D}^{18}\) +92.4 (c 1.0, CHCl\(_3\)).
Methyl 6-O-Benzyl-3,4-O-isopropylidene-2-O-(2-trimethylsilanyloxyethyl)-α-D-allopyranoside (5.20).

Alcohol 5.19 (0.35 g, 1.08 mmol) was dissolved in THF (20 mL), oil-free KH (0.09 g, 2.16 mmol) was added followed by SEMCl (0.38 mL, 2.16 mmol). After 1 h, the reaction mixture was quenched with H2O (10 mL). The aqueous layer was extracted with ether (2 x 20 mL), washed with brine (10 mL), dried over Na2SO4 and evaporated. The residue was purified by column chromatography on silica gel (2:1 hexane/ether) to give 5.20 (0.39 g, 80%) as a colorless oil; IR (neat, cm⁻¹) 1497, 1454; ¹H NMR (500 MHz, CDCl₃) δ 7.40-7.30 (m, 5 H), 4.90-4.84 (m, 3 H), 4.65 (AB, 2 H, J = 12.2 Hz, ΔνAB = 10.6 Hz), 4.57 (t, J = 4.6 Hz, 1 H), 4.15 (dd, J = 4.9, 9.6 Hz, 1 H), 3.92-3.89 (m, 2 H), 3.79-3.73 (m, 3 H), 0.99-0.95 (m, 2 H), 0.05 (s, 9 H); ¹³C NMR (125 MHz, CDCl₃) δ 138.6, 128.8 (2C), 128.0 (2C), 127.9, 110.9, 98.2, 95.1, 74.0, 73.8, 72.4, 72.2, 69.9, 67.2, 66.2, 56.3, 29.0, 26.6, 18.7, -1.0 (3C); ES HRMS m/z (M+Na)⁺ calcd 477.2279, obsd 477.2250; [α]₁₈<sub>D</sub> +40.8 (c 2.4, CHCl₃).

Methyl 3,4-O-Isopropylidene-2-O-(2-trimethylsilanyloxyethyl)-α-D-allopyranoside (5.21).

Compound 5.20 (0.15 g) was dissolved in ethanol (10 mL); 10 % Pd-C (0.04 g) was introduced and H₂ was bubbled through for 5 min. The mixture was stirred for another 30 min., filtered through Celite and evaporated to give 5.21 (0.11 g) in quantitative yield as a colorless oil; IR (neat, cm⁻¹) 3508, 1455; ¹H NMR (500 MHz, CDCl₃) δ 4.87-4.83 (m, 3 H), 4.54 (t, J = 4.6 Hz, 1 H),
4.06 (dd, $J = 5.0, 9.4$ Hz, 1 H), 3.89-3.85 (m, 2 H), 3.80-3.68 (m, 4 H), 3.45 (s, 3 H), 2.03 (br s, 1 H), 1.55 (s, 3 H), 1.37 (s, 3 H), 0.98-0.94 (m, 2 H), 0.03 (s, 9 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 111.0, 98.2, 95.2, 73.3, 72.4, 72.3, 68.0, 66.2, 62.9, 56.3, 29.0, 26.6, 18.7, -1.0 (3C); ES HRMS $m/z$ (M+Na$^+$) calcd 387.1810, obsd 387.1799; $[\alpha]^\text{D}_{18}$ $+22.0$ (c 2.0, CHCl$_3$).

**Methyl 6-$O$-Benzoyl-3,4-$O$-isopropylidene-2-$O$-(2-trimethylsilanylethoxymethyl)-$\alpha$-$D$-alloyanoside (5.23).**

Alcohol 5.21 (0.11 g, 0.3 mmol) was dissolved in CH$_2$Cl$_2$ (10 mL) in advance of the addition of pyridine (1.0 mL), DMAP (0.01 g), and benzoyl chloride (0.06 g, 0.05 mmol). After 1 h the reaction mixture was quenched with saturated NaHCO$_3$ solution (5 mL) and the layers were separated. Following extraction with CH$_2$Cl$_2$ (3 x 10 mL), the combined organic layers were dried over Na$_2$SO$_4$ and evaporated. Column chromatography of the residue on silica gel (3:2 hexane/ether) gave 5.23 (0.14 g, 93%) as a colorless oil; IR (neat, cm$^{-1}$) 1725, 1275; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.06-8.03 (m, 2 H), 7.56-7.53 (m, 1 H), 7.45-7.40 (m, 2 H), 4.85-4.83 (m, 3 H), 4.61-4.58 (m, 2 H), 4.49-4.40 (m, 1 H), 4.07-4.05 (m, 2 H), 3.89 (t, $J = 4.4$ Hz, 1 H), 3.74-3.68 (m, 2 H), 3.44 (s, 3 H), 1.56 (s, 3 H), 1.37 (s, 3 H), 0.96-0.92 (m, 2 H), 0.01 (s, 9 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 166.3, 133.0, 130.0, 129.6 (2C), 128.4 (2C), 110.8, 97.8, 94.9, 73.3, 72.3, 71.8, 65.8, 65.8, 65.6, 64.1, 55.8, 28.6, 26.2, 18.3, -1.4; ES HRMS $m/z$ (M+Na$^+$) calcd 491.2072, obsd 491.2053; $[\alpha]^\text{D}_{18}$ +34.6 (c 1.4, CHCl$_3$).
Methyl 6-O-Benzoyl-2-O-(2-trimethylsilanylethoxymethyl)-α-D-allopyranoside (5.24).

Compound 5.23 (0.14 g, 0.3 mmol) was dissolved in 80% aqueous acetic acid (20 mL) and stirred for 4 h. The material was evaporated to dryness, and the residue was purified by column chromatography on silica gel (1:2 hexane/ether) to give 5.24 (0.08 g, 65%) as a colorless glass; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.09-8.07 (m, 1 H), 7.61-7.58 (m, 1 H), 7.48-7.45 (m, 2 H), 4.91 (d, \(J = 3.5\) Hz, 1 H), 4.85 (ABq, 2 H, \(J = 7.1\) Hz, \(\Delta \nu_{AB} = 26.1\) Hz), 4.76 (dd, \(J = 1.9, 11.9\), 1 H), 4.62-4.58 (m, 1 H), 4.28-4.26 (m, 1 H), 4.00-3.97 (m, 1 H), 3.78-3.67 (m, 3 H), 3.62-3.57 (m, 1 H), 3.49 (s, 3 H), 3.40 (d, \(J = 8.5\) Hz, 1 H), 2.93 (d, \(J = 10.3\) Hz, 1 H), 1.01-0.94 (m, 2 H), 0.05 (s, 9 H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 166.9, 133.5, 130.4, 130.1 (2C), 128.8 (2C), 99.8, 94.3, 73.1, 70.4, 67.6, 67.0, 66.2, 64.5, 56.2, 18.6, -1.0 (3C); ES HRMS \(m/z\) (M+Na\(^+\)) calcd 451.1759, obsd 451.1742; \([\alpha]_D^{18}\) +44.2 (c 3.7, CHCl\(_3\)).

Methyl 6-O-Benzyl-2-O-(2-trimethylsilanylethoxymethyl)-α-D-allopyranoside (5.26).

Compound 5.20 (1.20 g) was dissolved in 30 mL of 80% acetic acid and stirred at room temperature for 4.5 h, after which the acetic acid was evaporated and the water was removed by azeotropic distillation with benzene (2 x 50 mL). The residue was purified by column chromatography on silica gel (1:1 hexane/ether) to give 5.26 (0.88 g, 80%) as a colorless glass; IR (neat, cm\(^{-1}\)) 3487, 1057; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.40-7.35 (m, 4 H), 7.32-7.29 (m, 1 H), 4.92 (d, \(J = 3.5\) Hz, 1 H), 4.84 (AB, 2 H, \(J = 7.1\) Hz, \(\Delta \nu_{AB} = 26.2\) Hz), 4.65 (s, 2 H), 4.24-4.21
(m, 1 H), 3.88-3.85 (m, 1 H), 3.80-3.59 (series of multiplets, 6 H), 3.49 (s, 3 H), 3.40 (d, \(J = 8.8\) Hz, 1 H), 2.77 (d, \(J = 10.3\) Hz, 1 H), 1.01-0.95 (m, 2 H), 0.05 (s, 9 H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 138.6, 128.8 (2C), 128.0, 127.9 (2C), 100.0, 94.2, 74.0, 73.1, 70.5, 69.9, 68.1, 67.4, 66.1, 56.2, 18.6, -1.0; ES HRMS \(m/z\) (M+Na)\(^+\) calcd 437.1966, obsd 437.1955; \([\alpha]^{18}_{\text{D}}\) +21.9 (c 2.6, CHCl\(_3\)).

Methyl 6-\(O\)-\(\text{ tert-Butyl}dimethylsilyl\)-2-\(O\)-(2-trimethylsilanyloxyethyl)-\(\alpha\)-\(D\)-allopynanoside (5.27).

Diol 5.26 was dissolved in absolute ethanol (75 mL) and 10% Pd-C (0.05 g) was added. H\(_2\) gas was bubbled through the mixture for 5 min, and the mixture was stirred under a H\(_2\) filled balloon for another hour. After filtration through a pad of Celite, solvent evaporation gave 0.57 g (84%), of crude triol, which was directly dissolved in CH\(_2\)Cl\(_2\) (30 mL) and treated with imidazole (0.16 g, 1.3 eq) and TBSCl (0.29 g, 1.1 eq). The reaction mixture was stirred for 1 h and quenched with saturated NH\(_4\)Cl solution (10 mL). The separated aqueous layer was extracted with CH\(_2\)Cl\(_2\) (10 mL) and the combined organic phases were dried over Na\(_2\)SO\(_4\) and evaporated. Column chromatography of the residue on silica gel (1:1 hexane/ether) gave 5.27 (0.69 g, 90%) as a colorless oil; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 4.90 (d, \(J = 3.4\) Hz, 1 H), 4.86 (ABq, 2 H, \(J = 7.2\) Hz, \(\Delta\nu_{\text{AB}} = 25.2\) Hz), 4.22 (br s, 1 H), 4.01 (dd, \(J = 2.4, 11.2\) Hz, 1 H), 3.88 (dd, \(J = 5.4, 11.2\) Hz, 1 H), 3.77-3.62 (m, 4 H), 3.52-3.49 (m, 4 H), 0.99-0.94 (m, 11 H), 0.13 (s, 6 H), 0.06 (s, 9 H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 199.8, 94.3, 73.3, 70.6, 69.3, 69.3, 67.6, 66.1, 63.5, 56.0, 26.4 (3C), 18.8, 18.6, -1.0 (3 C), -4.9
Methyl 6-\textit{O-}\textit{t}err-Butyldimethylsilyl-3,4-di-\textit{O-}(4-methoxybenzyl)-2-\textit{O-}(2-trimethylsilylethoxymethyl)-\alpha-\textit{D-}alloyranoside (5.28).

Diol 5.27 (0.40 g, 0.91 mmol) was dissolved in THF (20 mL), cooled to 0 °C, and treated with NaHMDS (2.70 mL, 2.70 mmol). After 1 h, PMBBBr (0.46 g, 2.3 mmol) and a catalytic amount of Bu4NI were added. The ice bath was removed and the solution was stirred for 3 d. The reaction mixture was quenched by the addition of water (10 mL). The separated aqueous layer was extracted with ether (3 x 10 mL), and the combined organic solutions were dried over Na2SO4 and evaporated. Column chromatography of the residue on silica gel 3:1 hexane/ether gave 5.28 0.43 g (70%) as a colorless oil; IR (neat, cm\(^{-1}\)) 1613, 1514; \(^1\)H NMR (300 MHz, CDCl3) \(\delta\) 7.30 (d, \(J = 8.7\) Hz, 2 H), 7.20 (d, \(J = 8.7\) Hz, 2 H), 6.85 (d, \(J = 8.7\) Hz, 2 H), 6.79 (d, \(J = 8.7\) Hz, 2 H), 4.78 (d, \(J = 3.6\) Hz, 2 H), 4.73 (d, \(J = 4.0\) Hz, 1 H), 4.66 (ABq, 2 H, \(J = 7.1\) Hz, \(\Delta\nu_{AB} = 13.1\) Hz), 4.43 (ABx, 2 H, \(J = 11.3\) Hz, \(\Delta\nu_{AB} = 23.7\) Hz), 4.12-4.05 (m, 2 H), 3.89-3.69 (series of multiplets, 10 H), 3.61-3.56 (m, 2 H), 3.42 (s, 3 H), 0.90 (br s, 11 H), 0.06 (s, 6 H), 0.02 (s, 9 H); \(^13\)C NMR (75 MHz, CDCl3) \(\delta\) 159.1 (2C), 131.4, 130.5, 129.3 (2C), 129.0 (2C), 113.7 (2C), 113.4 (2C), 98.6, 93.2, 74.9, 74.0, 73.3, 72.3, 71.0, 67.2, 65.4, 62.5, 55.6, 55.2 (2C), 26.0 (3C), 18.3, 18.1, -1.5 (3C), -5.2, -5.4; ES HRMS \(m/z\) (M+Na)\(^+\) calcd 701.3512, obsd 701.3470; \([\alpha]_{D}^{18}\) +34.8 (c 2.3, CHCl3).
Methyl 3,4-Di-O-(4-methoxybenzyl)-2-O-(2-trimethylsilylethoxymethyl)-α-D-allopyranoside (5.29).

Compound 5.28 (0.10 g, 0.15 mmol) was dissolved in THF (10 mL) and TBAF (1M in THF, 0.15 mL) was added and the solution was stirred at room temperature for 2 h. The reaction mixture was quenched by the addition of water (5 mL) and the separated aqueous phase was extracted with ether (2 x 10 mL). The combined organics were dried over Na₂SO₄ and evaporated. Column chromatography of the residue on silica gel (2:3 hexane/ether in 100% ether) gave 5.29 (0.07 g, 88%) as a colorless oil; IR (neat, cm⁻¹) 3493, 1613, 1514; ¹H NMR (300 MHz, CDCl₃) δ 7.32 (d, J = 8.6 Hz, 2 H), 7.20 (d, J = 8.7 Hz, 2 H), 6.85 (d, J = 8.7 Hz, 2 H), 6.81 (d, J = 8.6 Hz, 2 H), 4.85-4.64 (series of multiplets, 5 H), 4.40 (ABq, 2 H, J = 11.5 Hz, ΔνAB = 42.5 Hz), 4.15-4.10 (m, 2 H), 3.85-3.61 (m, 10 H), 3.61-3.53 (m, 1 H), 1.87 (dd, J = 5.4, 7.4 Hz, 1 H), 0.96-0.89 (m, 2 H), 0.01 (s, 9 H); ¹³C NMR (75 MHz, CDCl₃) δ 159.3, 158.9, 131.3, 129.4 (3C), 129.3 (2C), 113.8 (2C), 113.5 (2C), 98.9, 93.5, 74.9, 74.2, 73.3, 72.0, 70.7, 66.4, 65.5, 62.2, 55.9, 55.3, 55.2, 18.2, -1.4 (3C); ES HRMS m/z (M+Na)⁺ calcd 587.2647, obsd587.2688; [α]D¹⁸ +37.0 (c 3.1, CHCl₃).

{2-[2-Methoxy-4,5-bis(4-methoxybenzyl)oxy]-6-vinyltetrahydropyran-3-yloxymethoxy]ethyl}trimethyl-1-silane (5.10).

Compound 5.29 (0.20 g, 0.35 mmol) was dissolved in CH₂Cl₂ (5 mL) and treated with 4≈ sieves (0.20 g), NMO (0.06 g, 0.53 mmol) and TPAP (0.006 g, 0.02 mmol). The mixture was stirred for 2 h, filtered

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through a plug of silica gel and evaporated. The aldehyde was dissolved in dry THF (5 mL) and cooled to 0 °C. Into the cold solution was cannulated a solution prepared from methyltriphenylphosphonium iodide (0.36 g, 0.89 mmol) and n-BuLi (0.7 mL, 0.89 mmol) in THF (5 mL) which had stirred for 1 h at 0 °C. The reaction mixture was warmed to room temperature, and after 3 h quenched with water. The separated aqueous layer was extracted with ether (2 x 10 mL), and the combined organic phases were dried over Na₂SO₄ and evaporated. Column chromatography of the residue on silica gel (2:1 hexane/ether) gave 5.10 (0.10 g, 48%) as a colorless syrup; ¹H NMR (500 MHz, CDCl₃) δ 7.36 (d, J = 8.5 Hz, 2 H), 7.23 (d, J = 8.5 Hz, 2 H), 6.89 (d, J = 8.6 Hz, 2 H), 6.85 (d, J = 8.6 Hz, 2 H), 6.02-5.95 (m, 1 H), 5.50-5.46 (m, 1 H), 5.30-5.28 (m, 1 H), 4.84 (s, 2 H), 4.78 (d, J = 4.1 Hz, 1 H), 4.70 (ABx, 2 H, J = 7.1 Hz, Δν = 26.6 Hz), 4.60-4.57 (m, 1 H), 4.43 (ABq, 2 H, J = 11.5 Hz, Δν_{AB} = 34.1 Hz), 4.15-4.14 (m, 1 H), 3.85 (s, 3 H), 3.82 (s, 3 H), 3.80-3.74 (m, 1 H), 3.69-3.67 (m, 1 H), 3.63-3.56 (m, 1 H), 3.47 (s, 3 H), 3.20 (dd, J = 2.6, 9.7 Hz, 1 H), 1.02-0.94 (m, 2 H), 0.05 (s, 9 H); ¹³C NMR (125 MHz, CDCl₃) δ 159.6, 159.3, 136.1, 131.7, 130.6, 129.9 (2C), 129.6 (2C), 117.8, 114.1 (2C), 113.9 (2C), 99.2, 93.7, 79.4, 74.3, 73.7, 72.7, 71.6, 67.3, 65.9, 56.4, 55.7, 31.3, 18.6, -1.0 (3C); ES HRMS m/z (M+Na)⁺ calcd 583.2698, obsd 583.2690; [α]D ¹⁸ +34.0 (c 0.6, CHCl₃).
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