An Efficient, General Asymmetric Synthesis of Carbocyclic Nucleosides: Application of an Asymmetric Aldol/Ring-Closing Metathesis Strategy

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A general and efficient synthesis of carbocyclic and hexenopyranosyl nucleosides has been developed. The strategy combines three key transformations: an asymmetric aldol addition to establish the relative and absolute configuration of the pseudosugar, a ring-closing metathesis to construct the pseudosugar ring, and a Trost-type palladium(0)-mediated substitution to assemble the pseudosugar and the aromatic base. Carbovir, abacavir, and their 2′-methyl derivatives as well as hexenopyranosyl nucleoside analogues have been prepared by this sequence.

Introduction

The development of agents that function as nontoxic, selective inhibitors of kinases and polymerases for the control of viral diseases has been the focus of intense research.[1] However, despite significant progress, the need continues for new replication inhibitors of the human immunodeficiency virus (HIV), herpes simplex virus (HSV), Epstein−Barr virus (EBV), human cytomegalovirus (CMV), hepatitis B virus (HBV), and other viruses. The ongoing problem of drug resistance adds substantially to this need.[2] Nucleoside analogues that are good substrates for cellular kinases, but resistant to other host enzymes, such as phosphorylases, are essential for the development of useful therapeutic agents. Replacement of the oxygen in the sugar portion of the nucleoside with a methylene unit results in carbocyclic nucleoside analogues that are highly resistant to phosphorylases.[3] While the carbocyclic analogue of adenosine was first described by Shealy[4] in 1966, the discovery that the natural carbocyclic nucleosides aristeromycin[5,6] and neplanocin A[7] display antibiotic and antitumor activity sparked the search for other carbocyclic nucleoside analogues with biological activity. Subsequently, other synthetic carbocyclic nucleosides have shown significant potential as new antiviral (as well as antitumor) agents.[8] Particularly, carbovir (**1**)[9] and abacavir (Ziagen, **2**)[10] have been shown to be inhibitors of HIV replication, the causative agent for the acquired immune deficiency syndrome (AIDS).[13] Herdewijn has also prepared two series of pyranosyl analogues **3** and **4**, which, like carbocyclic nucleosides, lack the labile anomeric linkage to the aromatic base.[11,12]

Many synthetic approaches to carbocyclic nucleosides rely on the use of cyclopentadiene for the source of the carbocyclic sugar.[13] The advantages of using cyclopenta-

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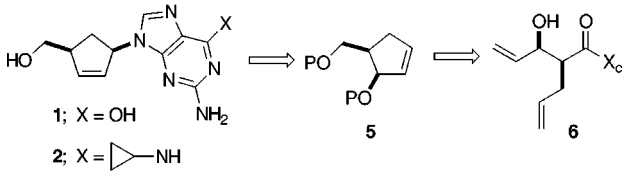
Scheme 1

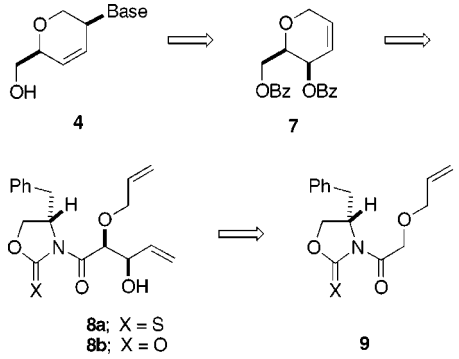


diene are that the five-membered carbocyclic structure is already intact and it is a very inexpensive starting material. There are disadvantages as well. To accomplish an enantioselective synthesis, introduction of chirality upon the carbocyclic ring must be accomplished by means of an asymmetric bond forming reaction, by a desymmetrization process of a meso intermediate, or by classical resolution. The ability to prepare a variety of substituted analogues is also somewhat limited.

We recently reported an efficient and general strategy for the synthesis of carbocyclic nucleosides **1** and **2** based on an asymmetric aldol/ring-closing metathesis strategy. This strategy holds the advantage of establishing the asymmetry of the molecule prior to ring closure, thus opening the possibility of introduction of substitution on the five-membered ring.[14] We sought to exploit the aldol-metathesis approach to allow greater flexibility in the preparation of a variety of 2′ substituted analogues as well as heterocyclic analogues. Our approach to carbocyclic nucleoside analogues involves a combination of three powerful reactions in retrosynthetic order: (1) Trost-type allylic substitution of an allylic ester with the purine or pyrimidine base to assemble the nucleoside base and the pseudo-sugar,[15] (2) ring-closing metathesis (RCM) to form the pseudo sugar ring,[16] and (3) asymmetric aldol addition to control the relative and absolute stereochemistry of the pseudo-sugar[17] (Scheme 1). The palladium-catalyzed coupling of the pseudosugar fragment **5** (or its allylic regioisomer) with an aromatic base via an π-allyl intermediate is a well-established, convergent approach to nucleosides.[18] The appropriate functionalized precursors **5** have been previously prepared by a variety of methods from cyclopentadiene,[6b,13d,e,f,i,19] but can also be formed in a straightforward manner by RCM of a diene **6**, the stereochemistry of which is established through an asymmetric aldol addition.

The strategy described above might also be applied to the construction of other nucleoside analogues by incorporation of a heteroatom into the sugar moiety as illustrated in Scheme 2. Initiating the strategy with a glycolate chiral auxiliary **9** could allow the stereoselective preparation of the diene **8**. Metathesis of the diene **8** would provide the allylic ester **7**, which could result in

Scheme 2



the rapid assembly of hexenopyranosyl nucleosides **4** through a palladium(0)-mediated substitution. Herein, we report the details concerning the use of this strategy in the synthesis of carbocyclic as well as other substituted nucleoside analogues.

Results

Synthesis of Carbovir 1 and Abacavir 2. The synthesis of carbocyclic nucleosides **1** and **2** began with acylation of the lithium anion of (*S*)-4-benzyl-2-oxazolidinone with 4-pentenoic pivalic mixed anhydride to afford **10** in nearly quantitative yield (Scheme 3). Use of our titanium tetrachloride and (−)-sparteine protocol[20] to generate the chlorotitanium enolate of **10** followed by addition of acrolein resulted in diastereoselective syn aldol addition to produce the aldol adduct **11** in 82% yield [>99% de, $[\alpha]^{24}_D$ +50.6 (c = 0.89, $CHCl_3$)]. Exposure of **11** to 1 mol % $(PCy_3)_2Cl_2Ru{=}CHPh$ in CH_2Cl_2 at 25 °C led to cyclopentenol **12** (97% yield), which was then reduced to diol **13** in 78% yield with $LiBH_4$ (>99.6% ee by chiral HPLC of the bis-(*p*-toluate) ester).[21] While allylic alcohols have been known to undergo isomerization in the presence of the Grubbs catalyst,[22] the presence of the allylic alcohol in **11** does not adversely effect the ring-closing metathesis in this case. Diol **13**[13l] was readily converted to the diacetate **14**[6b] by exposure to acetic anhydride, triethylamine and 4-(dimethylamino)pyridine. The dicarbonate **15** was accessed by treatment of the diol with methyl chloroformate in dichloromethane with pyridine as the base.[13l] Interestingly, if triethylamine was

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(21) It was imperative to remove trace amounts of ruthenium from the metathesis reaction since any residual ruthenium catalyzed hydrogenation of the cyclopentene olefin in the during the lithium borohydride reduction. Apparently, the hydrogen generated during the reduction, in combination with the trace ruthenium resulted in hydrogenation of the alkene.

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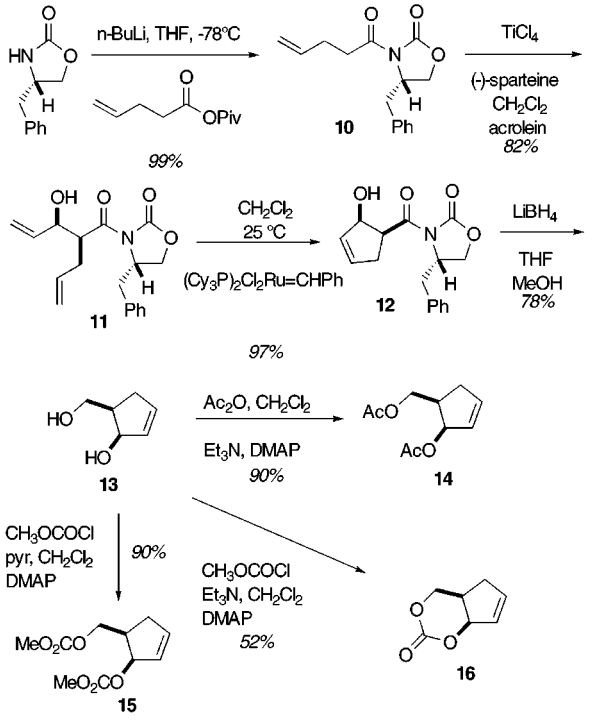
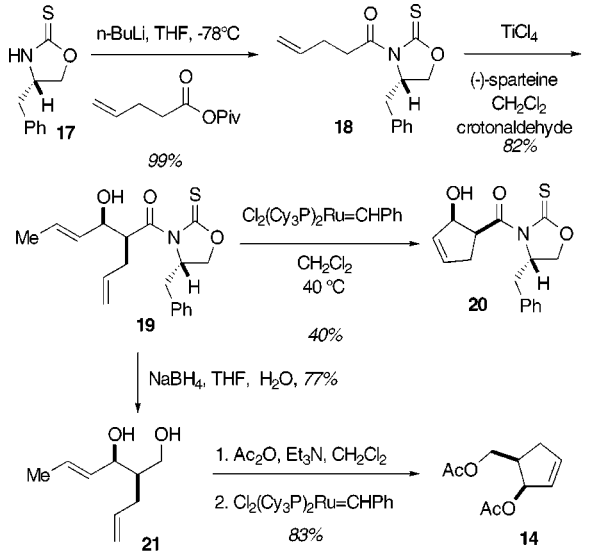
Scheme 3



Scheme 4



used as the base in the methyl chloroformate acylation, cyclic carbonate **16**[13d] resulted.

In an effort to avoid the use of lithium borohydride to remove the oxazolidinone auxiliary because of the cost, the use of the oxazolidinethione **17** as the chiral auxiliary was investigated since oxazolidinethiones are known to be more easily cleaved.[23] Attachment of the 4-pentenoate proceeded as before to give the acyl oxazolidinethione **18** in 99% yield (Scheme 4). Again, through the use of (−)-sparteine as the base with titanium tetrachloride as the Lewis acid, the Evans syn aldol **19** resulted in high yield with excellent diastereoselectivity. Unfortunately, attempts to execute the Grubbs metathesis on diene **19** were disappointing. Yields were generally low due to poor conversion. The thiocarbonyl of the oxazolidinethione was

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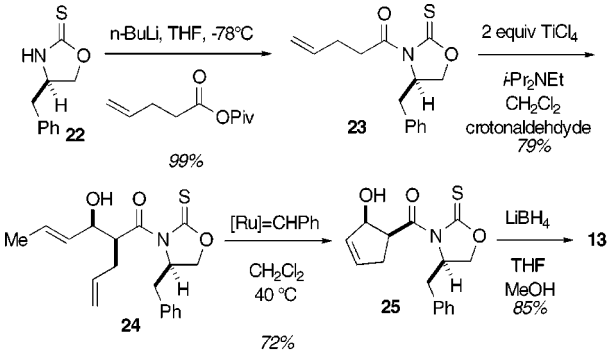
Scheme 5



thought to be coordinating to the metal center, thus stabilizing the intermediate ruthenium alkylidine. Since the next step was to remove the auxiliary, we opted to reverse the order of the sequence and reductively remove the auxiliary prior to the olefin metathesis. Exposure of aldol adduct **19** to sodium borohydride in aqueous THF produced the diol **21** in 77% yield. Acetylation of the diol with acetic anhydride followed by treatment of the diacetate with the Grubbs catalyst produced the diacetate **14** in 83% overall yield.

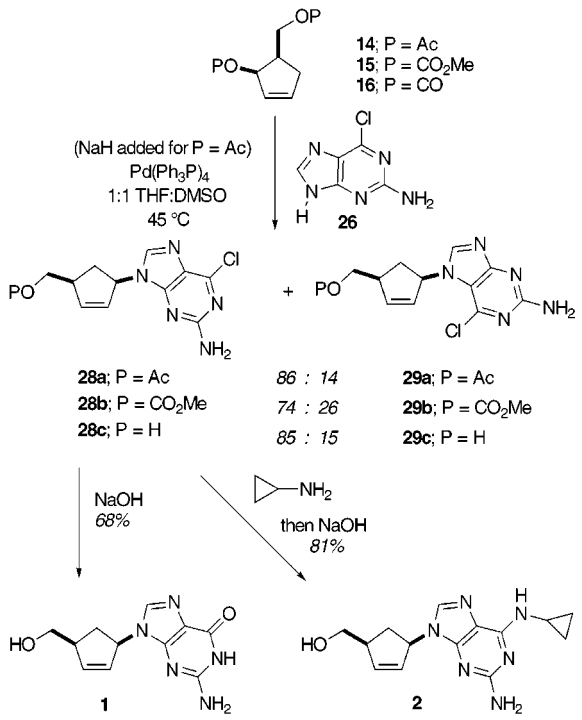
In a similar approach, the non-Evans syn aldol adduct **24** was prepared in 79% yield by enolization of the acyl oxazolidinethione **23** with 2 equiv of titanium tetrachloride in the presence of diisopropylamine followed by addition of crotonaldehyde. In contrast to the Evans syn aldol adduct **19**, the diene **24** underwent efficient ring-closing metathesis when treated with $Cl_2(PCy_3)_2Ru$=CHPh. There is apparently a difference in the ability of the thiocarbonyl to coordinate to the metal in the intermediate alkylidine in the Evans syn and non-Evans syn diastereomers **19** and **24**. The ultimate result is that the non-Evans syn diastereomer **24** can be processed to the required diol **13** as shown in Scheme 5 by metathesis of the diene **24** followed by reductive removal of the auxiliary.

With ready access to the diacetate **14**, the dicarbonate **15** and the cyclic carbonate **16**, evaluation of the Pd-catalyzed coupling with both 2-amino-6-chloropurine **26** and 2-amino-6-(cyclopropylamino)purine **27** was investigated (Schemes 6 and 7). While Pd(0)-catalyzed assembly of carbocyclic nucleosides from allylic acetates and carbonates and purine bases is well-established,[18] the use of cyclopropylaminopurine **27** had not been previously investigated. Reaction of diacetate **14** with 2-amino-6-chloropurine in the presence of $Pd(PPh_3)_4$ and NaH in 1:1 THF/DMSO at 45 °C yielded an 86:14 mixture of the chloropurine acetate **28a**[13m] and its N7 isomer **29a** (65% isolated yield of **28a**). The analysis of the N7 and N9 coupling products is readily accomplished by ^{1}H NMR, since the proton at the 8-position of the purine is well separated and easily distinguished in the two regioisomers. The C-8 proton of the N9 isomer (ca. δ 7.85 ppm) is typically upfield of the N7 isomer (ca. δ 8.05 ppm). The problem of N9−N7 regioselectivity is a common problem in classic Vorbruggen coupling of purines with sugars,[24] but the issue has only recently been recognized in Pd-catalyzed couplings.

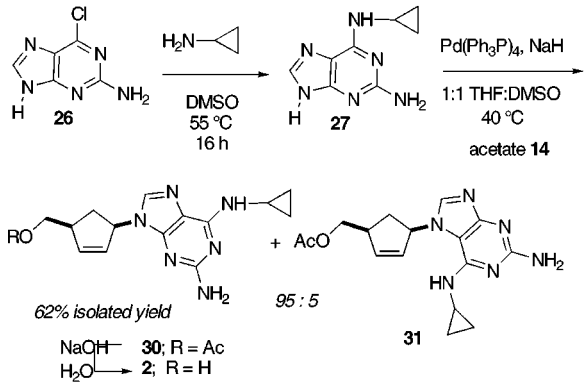
This extremely important observation was noted by Benneche and Gunderson.[19e−f] They noted that not only

(24) (a) Vorbruggen, H.; Krolikiewicz, K.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1234−1255. (b) Vorbruggen, H.; Hofle, G. *Chem. Ber.* **1981**, *114*, 1256−1268.

Scheme 6



Scheme 7



did coupling of purines with allylic esters and carbonates give a mixture of N9 and N7 isomers of the products, but also incorporation of larger groups at the 6 position of the purine can substantially alter the regioselectivity of the coupling reaction. Earlier and some subsequent reports fail to recognize this limitation of the direct coupling, although it is a common problem in natural nucleoside synthesis. As expected, use of the cyclic carbonate **16** in the coupling reaction with **26** led to a similar result (71% yield of an 85:15 N9/N7 mixture of **28c**:[13d]**29c** as determined by ^{1}H NMR), but the dicarbonate **15** gave only a 74:26 mixture, albeit in higher yield (68% of N9 isomer **28b**[13f] after purification) and at room temperature without the need for external base. Treatment of the chloropurine **28a** with cyclopropylamine in EtOH followed by hydrolysis of the acetate (NaOH, H_2O) produced abacavir **2** in 81% overall yield identical to that previously reported.[10,13] Alternatively, direct hydrolysis of **28a** with NaOH produced carbovir **1** in 68% yield consistent with reported literature data.[9,13]

On the basis of the observations of Benneche and Gundersen,[19e,f] it was anticipated that the N9/N7 regioselectivity might be improved by first incorporating the cyclopropylamino group at the 6-position. Thus, 2-amino-6-(cyclopropylamino)purine **27** was utilized as the nucleophile in the coupling reaction. Exposure of **27** and diacetate **14** to 10 mol % $Pd(PPh_3)_4$ and NaH in DMSO resulted in a 95:5 mixture of N9/N7 regioisomers **30** and **31** (Scheme 7). The N9 isomer **30** was obtained in 62% yield after silica gel chromatography and was readily hydrolyzed to **2** with NaOH.

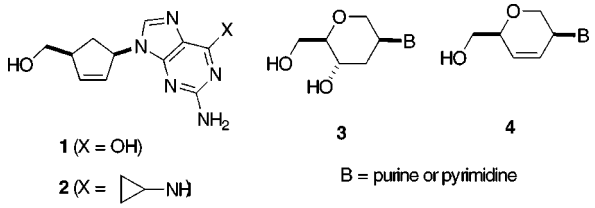


Figure 1. Nucleoside analogues.

Synthesis of 2′-Methyl Derivatives of Carbovir and Abacavir. The advantages of enzymatic stability and improved bioavailability of carbocyclic nucleosides is counter-balanced by substantial changes in the conformation of carbocyclic nucleosides relative to natural nucleosides and their analogues. Removal of the ring oxygen eliminates the possibility for anomeric stabilization of the axially oriented C−N bond and also removes the gauche interaction between the C4′−O bond and the C3′−OH bond. The result is a dramatic change in the conformation obtained in the five membered ring pseudorotational cycle. The preferential C2′-endo,3′-exo (southern) and C3′-endo,2′-exo (northern) conformations are not favored in analogous carbocyclic nucleosides.[25] The 1′-exo conformation that places the base in a pseudoequatorial orientation is preferred. This conformational change is a likely reason for the lack of biological activity of many carbocyclic nucleosides, possibly due to poor processing to the triphosphates by cellular or viral kinases or because of poor recognition of the triphosphate by the appropriate polymerase. As a consequence of the noted conformational observations, the activity of carbocyclic nucleoside antiretroviral agents has been correlated with conformation.[26] For example, Marquez and co-workers demonstrated that Carba-T, a conformationally unrestricted pyrimidine carbocyclic nucleoside, showed poor activity against HSV-I and II (Figure 1).[27] Locking the system into a northern $_2E$ conformation by cyclopropane annulation led to pronounced antiretroviral activity of N-methano Carba-T (Figure 2). A similar annulation that biased the system into a southern ^2E conformation produced poor antiretroviral activity for S-methano Carba-T in the same assay. Additionally, it has been demonstrated by Painter that AZT-triphosphate and thymidine triphosphate both adopt a similar (northeastern) 4′-exo conformation when bound to reverse transcriptase; thus, conformationally biased carbocyclic nucleosides that exist in a northern or northern-like 4′-exo conformation could be viable antivirals.[28−30]

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(26) It should be noted that the action of nucleoside drugs involves multiple enzymatic steps, each of which may exhibit distinct conformational selectivity. For a comprehensive review of the defining terms for nucleoside conformations, see: Saenger, W. *Principles of Nucleic Acid Structure*; Springer-Verlag: New York, 1984.

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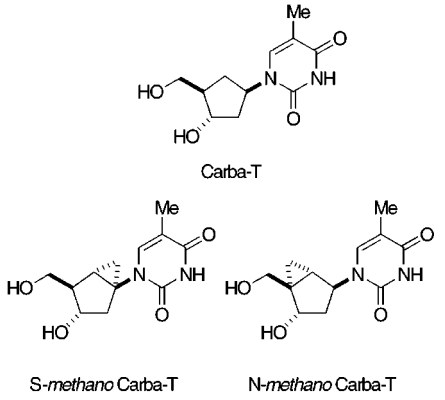


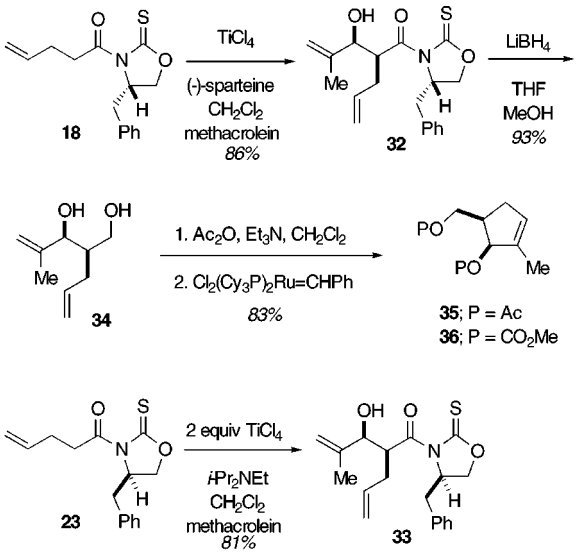
Figure 2. Conformationally restricted carbocyclic nucleosides.

Figure 3. Conformations of 2′-substituted cyclopentenes.

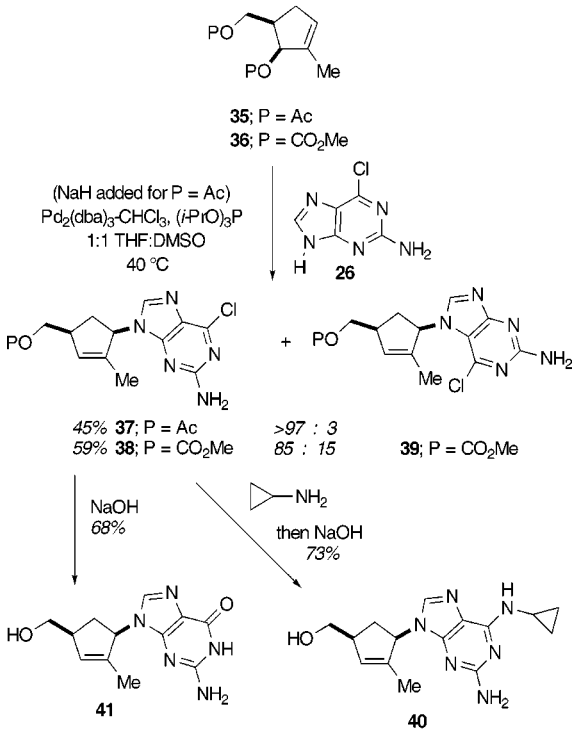
We thus set out to bias abacavir and carbovir into more northern-like conformations, which would require a pseudoaxially oriented base. We anticipated that the addition of a 2′-methyl group would lead to enhanced $A^{1,2}$ strain with the purine and force the base to be pseudoaxial. Molecular modeling on a simple system (*cis*-3-amino-5-methylcyclopentene) supports this argument:[31] with no olefinic substitution, the conformation possessing pseudoequatorial substituents is thermodynamically favored by 0.4 kcal mol^{-1} over the pseudoaxial conformation by calculated MM2 energies (Figure 3). Addition of a 2′-methyl group reverses the conformational bias; the pseudoaxial conformation is favored by 0.4 kcal mol^{-1}. In the carbocyclic nucleoside systems of interest, the presence of purine ring systems instead of a simple amino group should lead to additional conformation bias, and the $\Delta\Delta G$ of 0.8 kcal mol^{-1} in the model system should serve as a lower limit.

Construction of 2′-methyl analogues would be difficult through traditional strategies for carbocyclic nucleoside synthesis, because of their reliance upon cyclopentadiene as starting material. However, 2′-alkyl derivatives were thought to be accessible by the previously described aldol/RCM route through the use of methacrolein or other α-substituted acroleins in the aldol reaction. Thus, the synthesis of 2′-methyl derivatives of abacavir and carbovir began with the formation of the titanium enolate of **18** with 1.1 equiv $TiCl_4$ and 2.5 equiv (−)-sparteine followed by exposure to methacrolein to form the Evans syn aldol adduct **32** in 86% yield (Scheme 8).[20] Alternatively, under slightly different conditions for the aldol addition (2.1 equiv of $TiCl_4$ and 1.1 equiv of EtN-*i*-Pr_2), the non-Evans syn aldol adduct **33** was obtained in 81% yield. Reductive removal of the chiral auxiliary in **32**

Scheme 8



Scheme 9



or **33** was accomplished with $LiBH_4$ to form diol **34** which was acylated to provide the corresponding diacetate or dicarbonate. Lithium borohydride was utilized since $LiBH_4$ gives slightly higher yields than sodium borohydride in some cases. Ring-closing metathesis under standard conditions provided methylcyclopentenes **35** and **36**, respectively.

Both the diacetate **35** and dicarbonate **36** were utilized in the Pd-catalyzed coupling with 2-amino-6-chloropurine (Scheme 9). Initial results with $Pd(PPh_3)_4$ showed significantly lower yields than in analogous reactions of **14** and **15**. Yields were slightly increased by employing $Pd_2(dba)_3$·$CHCl_3$/PPh_3 as the catalyst, but optimized conditions for both **35** and **36** involved $Pd_2(dba)_3$·$CHCl_3$/$P(Oi\text{-}Pr)_3$ catalyst system and led to 45% isolated yield of chloropurine acetate **37** and 59% isolated yield of chloropurine carbonate **38**. ^{1}H NMR analysis of the crude

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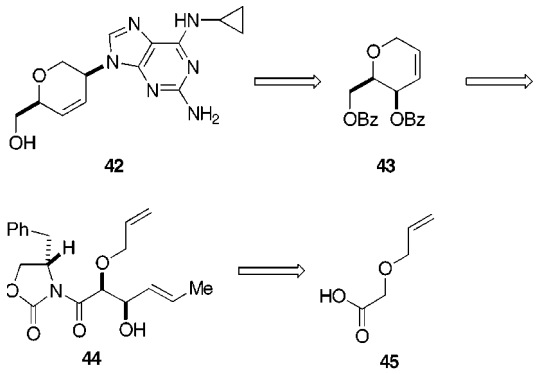
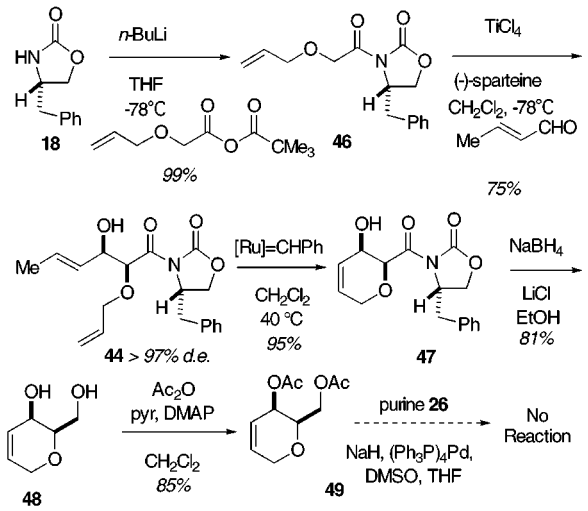
(30) Birnbaum, G. I.; Giziewicz, J.; Gabem, E. J.; Lin, T.-S.; Prusoff, W. H. *Can. J. Chem.* **1987**, *65*, 2135−2139.
(31) Molecular mechanics calculations were performed with MM2 parameters.

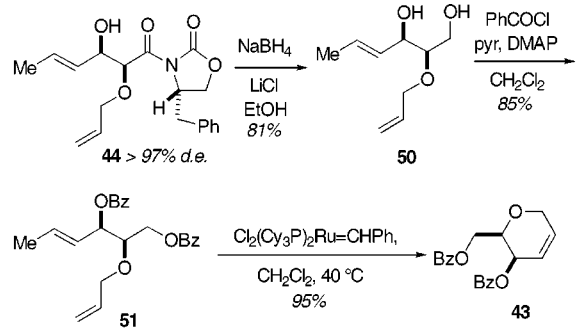
Scheme 10



Scheme 11



Scheme 12



product mixtures indicated no N7 isomer was formed in the reaction of **35** whereas an 85:15 N9/N7 isomer ratio resulted in the reaction of **36**. Again, the C-8 purine proton was diagnostic in analysis of the regioisomers. Functionalization of **37** and **38** to the 2′-methyl derivatives of abacavir and carbovir proceeded as in the earlier synthesis. Thus, exposure of **37** to cyclopropylamine in EtOH at reflux followed by basic hydrolysis formed **40** in 73% yield. Direct hydrolysis of **38** afforded **41** in 68% yield.

The issue of N9/N7 regioselectivity in the purine coupling step is influenced by the steric properties of the incoming nucleophile as well as those of the allylic intermediate. Increased steric interaction upon approach of the purine nucleophile, such as the 6-cyclopropylamino group in **27** or the 2′-methyl group of **35**, favors the desired N9 isomer. Additionally, the nature of the leaving group affected the N9/N7 selectivity; with the allylic acetates **14** and **35**, NaH was used to form the purine anion prior to π-allyl formation while the purine anion was generated in situ during reactions with allylic carbonates (such as **15** and **36**). Preformation of the purine anion may limit the extent of reversibility of nucleophilic attack on the π-allyl complex, suggesting the N9 isomer is the kinetic product.

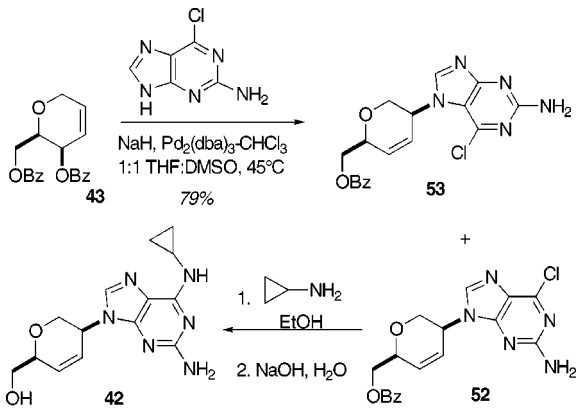
Synthesis of a D-*threo*-Hex-3′-enopyranosyl Nucleoside. With a general strategy to the synthesis of carbocyclic nucleosides completed, it was thought that a similar approach might be applied to other nucleoside analogues. The initial approach to the synthesis of hex-3′-enopyranosyl nucleoside analogue **42** was based on the strategy employed in the synthesis of the carbocyclic nucleoside analogues as shown in Scheme 10. A palladium-catalyzed coupling of a substituted purine with dibenzoate **43** was planned for the convergent construction of the nucleoside analogue. Dibenzoate **43** would be prepared in high enantiomeric purity from the asymmetric aldol adduct **44** by a ring-closing metathesis reaction. The aldol product **44** was to be obtained through an asymmetric aldol addition to establish the relative and absolute configuration of the new stereogenic centers. The required acyl oxazolidinone or oxazolidinethione would be obtained from allyloxy acetic acid **45** and the appropriate chiral auxiliary.

The allyloxyacetic acid was readily prepared by exposure of allyl alcohol to sodium hydride in THF followed by treatment with the sodium carboxylate of bromoacetic acid. The resultant carboxylic acid was quantitatively converted to the mixed anhydride by exposure to pivaloyl chloride in THF-diethyl ether (Scheme 11). The oxazolidinone **18** was acylated with α-allyloxyacetyl pivaloyl anhydride in high yield to provide the acyl oxazolidinone **46**. Enolization of **46** with titanium tetrachloride and (−)-sparteine followed by addition of crotonaldehyde produced the aldol adduct **44** in 75% yield with a diastereoselectivity of >97:3. Exposure of diene **44** to 5 mol percent of Grubbs' ruthenium carbene gave the cyclic ether **47** in 95% yield. Reductive removal of the auxiliary with sodium borohydride−lithium chloride provided the somewhat water-soluble diol **48**. Conversion of the diol **48** to the diacetate **49** with acetic anhydride and pyridine set the stage for the palladium catalyzed coupling to the purine base. Unfortunately, attempts to couple 2-amino-6-chloropurine **26** and diacetate **49** in the presence of $(Ph_3P)_4Pd$ were completely unsuccessful.

At this juncture it seemed appropriate to address not only the issue of the palladium catalyzed coupling, but also the problem of the water solubility of diol **48**. Due to the water solubility of diol **48** it was decided to remove the chiral auxiliary and protect the diol prior to the ring closing metathesis reaction. Thus, reduction of the acyl oxazolidinone **44** with sodium borohydride−lithium chloride gave diol **50** (81% yield) which was significantly less water-soluble than diol **48**. Acylation of the diol with benzoyl chloride gave the dibenzoate **51** in 85% yield. The diene **51** smoothly underwent ring-closing metathesis to yield the dibenzoate **43** in 95% yield upon exposure to the Grubbs catalyst (Scheme 12).

With ready access to the dibenzoate **43**, the palladium catalyzed coupling with 2-amino-6-chloropurine was again attempted. While use of $(Ph_3P)_4Pd$ once again failed to produce the nucleoside analogue, use of $Pd_2(dba)_3$−$CHCl_3$ as the palladium (0) source resulted in isolation of the coupling product **52** in 79% yield, based on recovered

Scheme 13



starting material. Subsequent exposure of **52** to cyclopropylamine in ethanol at reflux followed by basic hydrolysis of the benzoate provided the nucleoside **42** in good yield (Scheme 13).

Conclusion

An efficient, enantioselective synthesis of carbocyclic nucleoside and hex-3′-enopyranosyl nucleoside analogues has been accomplished by exploiting a novel asymmetric aldol−olefin metathesis sequence for the asymmetric construction of the sugar fragment of the nucleoside. A direct palladium catalyzed coupling of the sugar to the purine allows for the highly convergent assembly of the nucleoside analogue. The general approach described here should be adaptable to a variety of nucleoside analogues.

Experimental Section

General Procedures. All reactions involving air- and/or water-sensitive reagents were carried out under an atmosphere of N_2 using oven-dried glassware. Unless otherwise noted, reagents were obtained from commercial suppliers and used without further purification. $Cl_2(PCy_3)_2Ru{=}CHPh$ was prepared according to a modified procedure of Grubbs and co-workers.[32] Et_2O, THF, and CH_2Cl_2 were purified according to the method of Grubbs and co-workers.[33] Et_3N, $EtN{i}\text{-}Pr_2$, DMSO, and pyridine were distilled from CaH_2. Purification by silica gel chromatography was performed by the method of Still using Scientific Adsorbents Incorporated 40 micron flash silica gel.[34] Optical rotations were measured at ambient temperature.

4*S*-Benzyl-3-pent-4-enoyloxazolidin-2-one (10). To a cooled solution (−78 °C) of 4-pentenoic acid (10.0 g, 100 mmol) and 14.7 mL (105 mmol) of triethylamine in 800 mL of diethyl ether was added 12.35 mL (100 mmol) of pivaloyl chloride. After 5 min, the bath was removed and replaced by an ice−water bath. The heterogeneous mixture was mechanically stirred at 0 °C for 1 h. In a separate flask, a solution of 17.7 g (100 mmol) of (*S*)-4-benzyl-2-oxazolidinone in 120 mL of THF was cooled to −78 °C whereupon 63.1 mL (101 mmol) of 1.6 M *n*-butyllithium in hexanes was added slowly. This solution was stirred for 10 min at −78 °C. The flask containing the mixed anhydride was cooled to −78 °C, and the lithiated oxazolidinone was transferred via cannula into the mixed anhydride. After being stirred at −78 °C for 15 min, the reaction mixture was warmed to 0 °C and stirred for 30 min. After the reaction was quenched with water, the layers were separated and the aqueous layer was washed with ether. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by filtration through a pad of silica gel (3:1 hexanes/ethyl acetate) to give 25.88 g (100%) of the title compound **10** as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 2.42 (m, 2H); 2.72 (dd, J = 9.7, 13 Hz, 1H); 3.03 (m, 2H); 3.29 (dd, J = 13, 4 Hz, 1H); 4.15 (m, 2H); 4.65 (m, 1H); 5.07 (m, 2H); 5.86 (m, 1H); 7.12−7.37 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.17, 34.78, 37.9, 55.14, 66.2, 115.7, 127.3, 128.9, 129.4, 135.2, 136.7, 153.4, 172.5. IR (film): 1790, 1708 cm^{-1}. $[\alpha]^{24}_D$: +64.2° (c = 0.83, $CHCl_3$). Anal. Calcd for $C_{15}H_{17}O_3N$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.20; H, 6.65; N, 5.33.

[3(2*S*,3*R*),4*S*]-3-(2-Allyl-3-hydroxypent-4-enoyl)-4-benzyloxazolidin-2-one (11). A solution of the 4*S*-benzyl-3-pent-4-enoyloxazolidin-2-one **10** (4.00 g, 15 mmol) in 70 mL of dichloromethane was cooled to 0 °C. Titanium tetrachloride (1.86 mL, 17 mmol) was added dropwise, producing a yellow precipitate. After 5 min, (−)-sparteine (8.85 mL, 39 mmol) in 10 mL of dichloromethane was added dropwise, resulting in a red-black solution. The solution was stirred at 0 °C for 20 min and then cooled to −78 °C. Freshly distilled acrolein (1.54 mL, 23 mmol) in 2 mL of dichloromethane was then added dropwise. When addition was complete, the mixture was warmed to 0 °C for 30 min. Half-saturated ammonium chloride was added, the mixture was filtered through Celite, and the layers were separated. The aqueous layer was extracted twice with dichloromethane. The combined organic extracts were dried over sodium sulfate and concentrated. Purification of the residue by flash chromatography (3:1 hexanes/ethyl acetate) afforded 3.98 g (82%) of **11** as a viscous, colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 2.38−2.61 (band, 3H); 2.62 (dd, J = 10.5, 13 Hz, 1H); 3.28 (dd, J = 13, 4 Hz, 1H); 4.13 (m, 2H); 4.22 (m, 1H); 4.42, (m, 1H); 4.69 (m, 1H); 4.98−5.37 (m, 4H); 5.72−5.96 (m, 2 H); 7.12−7.34 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 31.89, 37.87, 47.23, 55.4, 65.88, 73.13, 116.6, 117.1, 127.2, 128.8, 129.3, 135.1, 135.2, 137.2, 153.4, 174.3. IR (film): 3500, 1780 cm^{-1}. $[\alpha]^{24}_D$: +50.6° (c = 0.89, $CHCl_3$). Anal. Calcd for $C_{18}H_{21}O_4N$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.65; H, 6.74; N, 4.40.

[3(1*R*,2*R*)4*S*]-4-Benzyl-3-(2-hydroxycyclopent-3-enecarbonyl)oxazolidin-2-one (12). To a solution of the [3(2*S*,3*R*),4*S*]-3-(3-hydroxy-2-allyl-1-oxo-4-pentenyl)-4-benzyl-2-oxazolidinone **11** (767 mg. 2.43 mmol) in 15 mL of dichloromethane under argon was added 40 mg of benzylidine(bistricyclohexylphosphine)ruthenium(II) dichloride. The dark mixture was stirred at 25 °C for 30 min, whereupon TLC showed complete reaction. Air was bubbled through the mixture for 3 h to oxidize the remaining catalyst. The solution was concentrated, and the residue was purified by flash chromatography to give 679 mg (97%) of **12** as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 2.00 (br, 1H); 2.48 (m, 1H); 2.76 (dd, J = 10.5, 13 Hz, 1H); 3.12 (m, 1H); 3.31 (dd, J = 13, 4 Hz, 1H); 4.15 (m, 2H); 4.45 (m, 1H); 4.69 (m, 1H); 5.09, (m, 1H); 5.74 (m, 1H); 6.02 (m, 1H); 7.15−7.36 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 33.19, 38.07, 47.03, 55.49, 66.2, 77.23, 127.2, 128.8, 129.3, 131.1, 134.7, 135.4, 153.6, 172.1. IR (film): 3480, 1780, 1700 cm^{-1}. $[\alpha]^{24}_D$: −92.5° (c = 0.795, $CHCl_3$). Anal. Calcd for $C_{16}H_{17}O_4N$: C, 66.88; H, 5.96; N, 4.88. Found: C, 66.79; H, 5.92; N, 4.79.

(1*R*,5*R*)-5-Hydroxymethyl-2-cyclopenten-1-ol (13). A solution of [3(1*R*,2*R*)4*S*]-4-benzyl-3-[(2-hydroxy-3-cyclopenten-1-yl)carbonyl]-2-oxazolidinone **12** (339 mg, 1.18 mmol) in 11 mL of THF was cooled to 0 °C, and 0.105 mL of methanol was added. Lithium borohydride solution (1.30 mL of a 2 M solution, 2.6 mmol) was added, and gas evolution was observed. After being stirred for 1 h at 0 °C, the reaction was quenched by the addition of 3.5 mL of 10% sodium hydroxide solution. Diethyl ether was added, and the layers were separated. The aqueous layer was extracted with ethyl acetate, and the combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated. Flash chromatography of the residue provided 102 mg (78%) of the diol **13** as a pale yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 2.03−2.49 (band, 3H); 3.33 (br s, 2H); 3.71 (m, 2H); 4.82 (m,

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(33) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.
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1H); 5.74 (m, 1H); 5.92 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 33.54, 42.49, 62.59, 77.61, 132.4, 135.0. IR (film): 3600−3000 (broad) cm^{-1}. $[\alpha]^{24}_D$: −125.1° (c = 0.47, CH_2Cl_2). The sample was identical in all respects to an authentic sample. The diol was converted to its bis-*p*-toluate and analyzed by chiral HPLC on a Chiralcel OD column eluting with 4% ethanol−heptane. Optical purity was determined to be >99% by this method. *S*,*S*-Enantiomer elution time = 5.9 min; *R*,*R*-enantiomer elution time = 7.6 min.

Diacetate 14, Cyclic Carbonate 16, and Dicarbonate 15. To a solution of diol **13** in CH_2Cl_2 at 0 °C under nitrogen was added 2.2 equiv of either triethylamine (for the diacetate and the cyclic carbonate) or pyridine (for the dicarbonate). The acylating agent (3.0 equiv) was then added dropwise followed by a catalytic amount of *N*,*N*-dimethylaminopyridine (DMAP). After 1.5−2.0 h, the reaction was quenched with 5% HCl solution and the layers were separated. The organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over sodium sulfate, filtered, and concentrated. The residue was purified by flash chromatography (15% EtOAc/Hexanes) to give diacetate **14** (90% yield), cyclic carbonate **16** (52% yield), or dicarbonate **15** (90% yield).

Diacetate 14.[6b] ^{1}H NMR (250 MHz, $CDCl_3$) δ: 2.0 (s, 3H); 2.02 (s, 3H); 2.14−2.30 (m, 1H); 2.39−2.55 (m, 1H); 2.58−2.78 (m, 1H); 4.02−4.28 (dd, J = 6.8, 8.1, 11.1 Hz, 2H); 5.68−5.75 (m, 1H); 5.79−5.85 (m, 1H); 6.02−6.10 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.9, 170.5, 136.7, 129.4, 78.04, 63.34, 39.49, 34.61, 21.01, 20.83. IR: 1740 (broad), 1370, 1235, 1035. $[\alpha]^{24}_D$: −178.0° (c = 0.45, CH_2Cl_2).

Cyclic Carbonate 16.[13d] ^{1}H NMR (250 MHz, $CDCl_3$) δ: 2.31−2.48 (m, 1H); 2.57−2.73 (m, 1H); 2.84−3.01 (m, 1H); 4.01 (dd, J = 5.1, 11.0 Hz, 1H); 4.31 (dd, J = 4.3, 11.0 Hz, 1H); 5.46−5.55 (m, 1H); 5.79−5.87 (m, 1H); 6.08−6.15 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.5, 137.5, 128.9, 87.45, 68.2, 35.01, 33.77. IR: 1750, 1620 cm^{-1}. $[\alpha]^{24}_D$: −145.2° (c = 0.44, CH_2Cl_2).

Dicarbonate 15.[13l] ^{1}H NMR (250 MHz, $CDCl_3$) δ: 2.20−2.32 (m, 1H); 2.42−2.57 (m, 1H); 2.66−2.81 (m, 1H); 3.73 (s, 3H); 3.77 (s, 3H); 4.20 (dd, J = 5.9, 11.0 Hz, 1H); 4.33 (dd, J = 6.9, 11.0 Hz, 1H); 5.60 (m, 1H); 5.88−5.92 (m, 1H); 6.10−6.15 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.7, 155.3, 137.7, 129.0, 82.05, 66.81, 54.79, 54.68, 39.89, 34.58. IR: 1745 (broad), 1440. $[\alpha]^{24}_D$: −148.5° (c = 0.46, CH_2Cl_2).

4*S*-1-(4-Benzyl-2-thioxooxazolidin-3-yl)pent-4-en-1-one 18. To a cooled solution (−78 °C) of 4-pentenoic acid (2.26 g, 22.6 mmol) and 3.30 mL (23.7 mmol) of triethylamine in 180 mL of diethyl ether was added 2.78 mL (22.6 mmol) of pivaloyl chloride. After 5 min, the bath was removed and replaced by an ice−water bath. The heterogeneous mixture was mechanically stirred at 0 °C for 1 h. In a separate flask, a solution of 4.9 g (22.6 mmol) of (*S*)-4-benzyl-2-oxazolidinethione in 27 mL of THF was cooled to −78 °C, whereupon 14.25 mL (22.8 mmol) of 1.6 M *n*-butyllithium in hexanes was added slowly. This solution was stirred for 10 min at −78 °C. The flask containing the mixed anhydride was cooled to −78 °C, and the lithiated oxazolidinethione was transferred via cannula into the mixed anhydride. After being stirred at −78 °C for 15 min, the reaction mixture was warmed to 0 °C and stirred for 30 min. Water was added, the layers were separated, and the aqueous layer was washed with ether. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated. The residue was purified by filtration through a pad of silica gel (3:1 hexanes/ethyl acetate) to give 4.74 g (81%) of the title compound **18** as a pale yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.28 (m, 5H); 5.91 (m, 1H); 5.0−5.18 (m, 2H); 3.22−3.62 (m, 3H); 2.75 (dd, J = 10, 13.3 Hz, 1H); 2.48 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.07, 36.557, 37.32, 59.6, 70.1, 115.4, 127.1, 128.7, 129.1, 135.0, 136.4, 172.9, 185.1. IR (film): 1700 cm^{-1}. $[\alpha]^{24}_D$: +119.8 ° (c = 0.99, CH_2Cl_2). Anal. Calcd for $C_{15}H_{17}NO_2S$: C, 65.43; H, 6.22; N, 5.09. Found: C, 65.32; H, 6.23; N, 5.00.

[3(2*S*,3*R*),4*S*]-3-(2-Allyl-3-hydroxy-4-methylhex-4-enoyl)-4-benzyloxazolidin-2-thione 19. To a stirring solution of acyloxazolidinethione **18** (313 mg, 1.21 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added $TiCl_4$ (0.146 mL, 1.33 mmol). The reaction mixture immediately turned dark red. After 5 min, (−)-sparteine (0.69 mL, 3.02 mmol) was added and the reaction mixture darkened further. The solution was stirred for 20 min to ensure complete enolate formation before cooling to −78 °C. Freshly distilled crotonaldehyde (0.15 mL, 1.81 mmol) was added dropwise. Clean formation of a more polar species was observed after 20 min. The reaction was quenched by addition of half-saturated NH_4Cl and was extracted with CH_2Cl_2. The organic extracts were dried over $MgSO_4$, concentrated under vacuum, and purified by silica gel chromatography to yield **19** as a white crystalline solid, 313 mg, 78%. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.28 (m, 5H); 5.51−6.02 (m, 3H); 5.35 (dt, J = 5.7, 8.5 Hz, 1H); 5.0−5.19 (m, 1H); 4.94 (m, 1H); 4.42 (brt, J = 5.7 Hz, 1H); 4.26 (m, 2H); 3.24 (dd, J = 3, 12 Hz, 1H); 2.69 (dd, J = 12, 9.5 Hz, 1H); 2.38−2.52 (m, 3H); 1.72 (d, J = 6 Hz, 3H).

[3(2*S*,3*R*),4*R*]-3-(2-Allyl-3-hydroxy-4-methylhex-4-enoyl)-4-benzyloxazolidin-2-thione 24. To a stirring solution of acyloxazolidinethione **23** (247 mg, 0.897 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added $TiCl_4$ (0.20 mL, 1.79 mmol). The solution immediately turned red and was allowed to stir for 5 min before the addition of EtN-*i*-Pr_2 (0.19 mL, 1.08 mmol). After 20 min, the reaction mixture was cooled to −78 °C, and freshly distilled crotonaldehyde (0.11 mL, 1.35 mmol) was added. After being stirred for 1 h at −78 °C and an additional 1 h at 0 °C, the reaction was quenched by the addition of half-saturated NH_4Cl and was extracted with CH_2Cl_2. The organic fractions were dried over $MgSO_4$, concentrated under vacuum, and purified by silica gel chromatography to yield **24** as a white crystalline solid, 227 mg, 73%. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.29 (m, 5H); 5.57−5.91 (m, 3H); 5.28 (dt, J = 5.7, 8.5 Hz, 1H); 4.95−5.0.14 (m, 1H); 4.94 (m, 1H); 4.53 (brt, J = 5.7 Hz, 1H); 4.28 (m, 2H); 3.26 (dd, J = 3, 12 Hz, 1H); 2.75 (dd, J = 12, 9.5 Hz, 1H); 2.41−2.65 (m, 3H); 1.72 (d, J = 6 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ: 17.27, 31.86, 37.09, 47.03, 59.5, 69.71, 72.93, 116.3, 126.8, 128.0, 128.4, 128.9, 130.01, 134.7, 135.0, 174.4, 185.1; IR (film): 3450, 1690 cm^{-1}. $[\alpha]^{24}_D$: +153.6 ° (c = 1.39, CH_2Cl_2). Anal. Calcd for $C_{19}H_{23}NO_3S$: C, 66.06; H, 6.71; N, 4.05. Found: C, 65.79; H, 6.63; N, 4.01.

[4*S*,2*R*,3*R*]-(4-Benzyl-2-thioxooxazolidin-3-yl)(2-hydroxycyclopent-3-enyl)methanone 25. To a solution of the aldol adduct **24** (3.715 g, 10.8 mmol) in 74 mL of dichloromethane under argon was added 177 mg of benzylidine(bis-tricyclohexylphosphine)ruthenium(II) dichloride. The dark mixture was stirred at 40 °C for 1 h, whereupon TLC showed complete reaction. Air was bubbled through the mixture for overnight to oxidize the remaining catalyst. Concentration followed by flash chromatography gave 2.43 g (74%) of cyclopentene **25** as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.28 (m, 5H); 6.03 (m, 1H); 5.80 (m, 1H); 5.49 (brt, J = 7 Hz, 1H); 5.16 (m, 1H); 4.97 (m, 1H); 4.29 (m, 2H); 3.32 (dd, J = 3, 12 Hz, 1H); 3.11 (m, 1H); 2.75 (dd, J = 12, 9.5 Hz, 1H); 2.49 (m, 1H); 2.22 (d, J = 8.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 33.87, 37.0, 46.52, 59.88, 69.85, 78.0, 126.8, 128.4, 129.0, 130.07, 133.6, 135.1, 172.6, 185.1. IR (film): 3450, 1690 cm^{-1}. $[\alpha]^{24}_D$: +396.2° (c = 0.84, CH_2Cl_2). Anal. Calcd for $C_{16}H_{17}NO_3S$: C, 63.35; H, 5.65; N, 4.62. Found: C, 63.42; H, 5.70; N, 4.58.

Chloropurine Acetate 28a.[13m] To a solution of hexane-washed sodium hydride (3.04 mmol, 0.122 g of 60% NaH) in 5 mL of dimethyl sulfoxide under nitrogen was added 2-amino-6-chloropurine (2.89 mmol, 0.490 g). The mixture was heated at 45 °C for 15 min. After the mixture was cooled to room temperature, tetrakis(triphenylphosphine)palladium(0) (5.0 mol %, 0.15 mmol, 0.167 g) was added followed by the addition of diacetate **14** (2.89 mmol, 0.573 g) in 5 mL of THF. The mixture was heated at 45 °C overnight. The mixture was allowed to cool to room temperature and was quenched with water. The solution was extracted five times with ethyl acetate. The combined organic layers were washed with water and concentrated. Purification by flash chromatography afforded 0.275 g of starting material and 0.298 g 65% based on recovered starting material) of the N-9 isomer **28a**.[13m] ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.59−1.76 (m, 1H); 2.20 (s, 3H); 2.71−2.90 (m, 1H); 3.08−3.21 (m, 1H); 4.50−4.61 (dd, J = 4.3, 4.7, 10.0 Hz, 2H); 5.31 (m, 2H); 5.49−5.59 (m, 1H); 5.82−5.90 (m,

1H); 6.09−6.14 (m, 1H); 7.79 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.9, 159.0, 153.4, 151.2, 140.4, 137.8, 129.8, 125.5, 66.11, 59.44, 44.4, 34.52, 20.83. IR: 3560−3060, 1735 cm^{-1}. $[\alpha]^{24}_D$: −88.6° (c = 0.43, CH_2Cl_2).

Chloropurine Carbonate 28b[13f] and Chloropurine Alcohol 28c. To a solution of 2-amino-6-chloropurine (0.378 mmol, 0.064 g) in 1 mL of dimethyl sulfoxide under nitrogen was added tetrakis(triphenylphosphine)palladium(0). Dicarbonate **15** (0.378 mmol, 0.087 g) or cyclic carbonate **9** was then added in 1 mL of THF. After being stirred for 2 h, the reaction was quenched with water. The mixture was extracted five times with ethyl acetate. The combined organic layers were washed with water and concentrated. Purification by flash chromatography afforded 0.083 g (68%) of chloropurine carbonate **28b**. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.68−1.79 (m, 1H); 2.74−2.90 (m, 1H); 3.10−3.24 (m, 1H); 3.75 (s, 3H); 4.19 (dd, J = 5.3, 10.6 Hz, 1H); 4.29 (dd, J = 4.7, 10.6 Hz, 1H); 5.21 (m, 2H); 5.50−5.60 (m, 1H); 5.82−5.89 (m, 1H); 6.08−6.12 (m, 1H); 7.83 (s, 1H) ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.8, 155.7, 153.3, 151.1, 140.7, 137.1, 130.2, 125.5, 69.26, 59.30, 54.85, 44.43, 34.00. IR (film): 3500−3100(br), 1745 cm^{-1}. $[\alpha]^{24}_D$: −64.6° (c = 0.28, CH_2Cl_2).[13f]

Chloropurine Alcohol 28c.[13d] Same procedure as above. Yields range from 61% to 65%. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.90−2.03 (m, 1H); 2.69−2.89 (m, 1H); 3.00−3.18 (m, 1H); 3.66−3.90 (m, 3H); 5.20 (m, 2H); 5.41−5.58 (m, 1H); 5.75−5.82 (m, 1H); 6.10−6.19 (m, 1H); 7.89 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.7, 153.1, 151.2, 141.8, 139.1, 129.6, 125.5, 64.61, 60.66, 47.66, 33.19. IR: 3560−3000, 1610 cm^{-1}. $[\alpha]^{24}_D$: −80.0° (c = 0.62, CH_3OH).[13d]

(−)-1592U89 2.[10] To a stirred solution of chloropurine acetate **28a** (0.117 mmol, 0.036 g) in 1 mL of ethanol was added cyclopropylamine (1.17 mmol, 0.081 mL). The mixture was heated at reflux for 5 h. After the mixture was cooled to room temperature, 0.234 mL of a 1 N NaOH solution was added. The mixture was stirred overnight and concentrated. Purification by flash chromatography provided 0.027 g (81%) of 1592U89 **2** identical to that previously reported.[9] ^{1}H NMR (250 MHz, DMSO-d_6) δ: 0.50−0.70 (m, 4H); 1.49−1.63 (m, 1H); 2.52−2.69 (m, 1H); 2.83 (br m, 1H); 3.01 (br m, 1H); 3.42 (m, 2H); 4.75 (m, 1H); 5.38 (m, 1H); 5.78−5.90 (m, 3H); 6.02−6.12 (m, 1H); 7.29 (d, J = 4.2 Hz, 1H); 7.59 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 159.9, 155.8, 150.9, 137.8, 134.7, 129.9, 113.5, 63.98, 58.01, 47.58, 34.19, 23.76, 6.324. IR (film): 3590−3000 (br), 1590 (br) cm^{-1}. $[\alpha]^{24}_D$: −37.5° (c = 0.51, CH_3OH).

(−)-Carbovir 1.[9] A solution of chloropurine acetate **28a** (0.286 mmol, 0.088 g) in 5 mL of a 0.5 N NaOH solution was heated at reflux for 5 h. After being cooled to room temperature, the solution was neutralized with 5 mL of a 0.5 M HCl solution. Concentration and purification by column chromatography afforded 0.048 g (68%) of (−)-carbovir **1** identical to that previously reported.[9] ^{1}H NMR (250 MHz, DMSO-d_6) δ: 1.49−1.61 (m, 1H); 2.50−2.65 (m, 1H); 2.78−2.90 (m, 1H); 3.38−3.48 (m, 2H); 4.68−4.74 (m, 1H); 5.28−5.39 (m, 1H); 5.80−5.89 (m, 1H); 6.06−6.12 (m, 1H); 6.42 (s, 2H); 7.58 (s, 1H); 10.52 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 156.7, 153.3, 150.6, 138.1, 134.9, 129.6, 116.6, 63.9, 58.39, 47.59, 34.24.

Acetate−Cyclopropylaminopurine 30. To a stirred solution of sodium hydride (0.375 mmol, 0.009 g) in 1 mL of dimethyl sulfoxide under nitrogen was added 2-amino-6-cyclopropylaminopurine (0.313 mmol, 0.059 g). The solution was heated at 45 °C for 15 min. After the mixture was cooled to room temperature, tetrakis(triphenylphosphine)palladium(0) (0.031 mmol, 0.036 g) was added followed by the addition of diacetate **14** (0.313 mmol, 0.062 g) in 1 mL of THF. The mixture was heated at 45 °C overnight. The mixture was allowed to cool to room temperature and was quenched by the addition of water. The mixture was extracted five times with ethyl acetate. The combined organic layers were washed with water and concentrated. Purification by flash chromatography provided 0.064 g (62%) of acetate **30**. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 0.55−0.62 (m, 2H); 0.79−0.90 (m, 2H); 1.57−1.70 (m, 2H); 2.03 (s, 3H); 2.73−2.90 (m, 1H); 2.91−3.04 (m, 1H); 3.05−3.19 (m, 1H); 4.02−4.20 (dd, J = 4.7 Hz, 5.3, 10.1, 2H); 4.73−4.88 (m, 1H); 5.48−5.58 (m, 1H); 5.63−5.72 (m, 1H); 5.85−5.91 (m, 1H); 6.03−6.10 (m, 1H); 7.49 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.8, 159.9, 156.1, 150.8, 136.8, 135.1, 130.6, 114.7, 66.37, 58.52, 44.25, 35.01, 23.55, 20.72, 7.23. IR (film): 3580−3000(br), 1735 cm^{-1}. $[\alpha]^{24}_D$: −41.0° (c = 0.39, CH_2Cl_2).

[3(2*S*,3*R*),4*S*]-3-(2-Allyl-3-hydroxy-4-methylpent-4-enoyl)-4-benzyloxazolidine-2-thione (32). To a stirring solution of acyloxazolidinethione **18** (8.30 g, 30.1 mmol) in CH_2Cl_2 (200 mL) at 0 °C was added $TiCl_4$ (3.46 mL, 31.6 mmol). The reaction mixture immediately turned dark red. After 5 min, (−)-sparteine (17.3 mL, 75.4 mmol) was added, and the reaction mixture darkened further. The solution was stirred 20 min to allow complete enolate formation before being cooled to −78 °C. Freshly distilled methacrolein (2.74 mL, 33.2 mmol) was added dropwise. Clean formation of a more polar species (R_f 0.16, 25% EtOAc in hexanes) was observed after 20 min. The reaction was quenched by addition of half-saturated NH_4Cl and was extracted with CH_2Cl_2. The organic fractions were dried over $MgSO_4$, concentrated under vacuum, and purified by silica gel chromatography (30−50% EtOAc in hexanes elution) to yield **32** as a white crystalline solid, 8.94 g, 86%. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.78 (s, 3); 2.41−2.73 (m, 3); 2.67 (dd, 1, J = 13.4, 10.6 Hz); 3.26 (dd, 1, J = 13.3, 3.1 Hz); 4.17−4.32 (m, 2); 4.42−4.46 (m, 1); 4.86−5.16 (m, 5); 5.36−5.45 (m, 1); 5.84−6.05 (m, 1); 7.18−7.36 (m, 5). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.21, 31.09, 37.70, 44.64, 60.32, 70.04, 74.60, 112.46, 117.31, 127.42, 129.01, 129.37, 135.19, 135.30, 144.09, 175.90, 185.22. IR (film): 3500, 1685 cm^{-1}. $[\alpha]_D$: +38.2 (c 0.44, CH_2Cl_2). Anal. Calcd for $C_{19}H_{23}NO_3S$: C, 66.06; H, 6.71. Found: C, 66.29; H, 6.89.

[3(2*S*,3*R*),4*R*]-3-(2-Allyl-3-hydroxy-4-methylpent-4-enoyl)-4-benzyloxazolidin-2-thione (33). To a stirring solution of acyloxazolidinethione **23** (1.31 g, 4.76 mmol) in CH_2Cl_2 (30 mL) at 0 °C was added $TiCl_4$ (1.04 mL, 9.52 mmol). The solution immediately turned red and was allowed to stir for 5 min before the addition of EtN-*i*-Pr_2 (0.91 mL, 5.24 mmol). After 20 min, the reaction mixture was cooled to −78 °C, and freshly distilled methacrolein (0.43 mL, 5.24 mmol) was added. After being stirred for 1 h at −78 °C and an additional 1 h at 0 °C, the reaction was quenched by the addition of half-saturated NH_4Cl and was extracted with CH_2Cl_2. The organic fractions were dried over $MgSO_4$, concentrated under vacuum, and purified by silica gel chromatography (5−10% EtOAc in hexanes elution) to yield **33** as a white crystalline solid, 1.20 g, 74%. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.82 (s, 3); 2.32−2.60 (m, 2); 2.66 (d, 1, J = 3.2 Hz); 2.72 (dd, 1, J = 13.4, 10.0 Hz); 3.26 (dd, 1, J = 13.4, 3.5 Hz); 4.17−4.33 (m, 2); 4.58 (br s, 1); 4.83−5.08 (m, 4); 5.15 (br s, 1); 5.33 (dt, 1, J = 9.6, 4.8); 5.73−5.93 (m, 1); 7.18−7.36 (m, 5). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.52, 31.04, 37.72, 44.79, 60.19, 70.34, 73.98, 112.56, 117.00, 127.45, 129.01, 129.37, 135.11, 135.48, 143.99, 176.28, 185.39. IR (film): 3500, 1790 cm^{-1}. HRMS for $C_{19}H_{23}NNaO_3S$ $[MNa]^+$: calcd 368.1296, found 368.1277. $[\alpha]_D$: +81.4 (c 0.76, CH_2Cl_2).

(3*S*,4*R*)-4-Hydroxymethyl-2-methyl-1,6-heptadien-3-ol (34). To a stirring solution of aldol adduct **32** (1.65 g, 4.78 mmol) and MeOH (0.25 mL, 6.21 mmol) in Et_2O (50 mL, 0.1 M) at 0 °C was added $LiBH_4$ (3.10 mL of a 2.0 M solution in THF, 6.21 mmol) dropwise. The reaction was stirred 1.5 h and then quenched by the slow addition of 15% NaOH. The resulting solution was extracted with Et_2O until no diol was observed by TLC in the aqueous layer. The organic fractions were combined, dried over $MgSO_4$, concentrated under vacuum, and purified by silica gel chromatography (30% EtOAc in hexanes elution) to yield diol **34** as a clear, colorless oil, 0.694 g, 93%. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.66 (s, 3); 1.69−1.79 (m, 1); 1.96−2.12 (m, 2); 3.08 (br s, 2); 3.68 (d, 2, J = 4.8 Hz); 4.25 (d, 1, J = 3.4 Hz); 4.89−5.07 (m, 4); 5.65−5.86 (m, 1). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.21, 28.77, 41.87, 63.64, 76.73, 111.12, 116.25, 137.18, 145.65. IR (film): 3600−3100 cm^{-1}. $[\alpha]_D$: −4.3 (c 0.53, CH_2Cl_2).

(3*S*,4*R*)-3-Acetoxy-4-acetoxymethyl-2-methylcyclopentene (35). To a stirring solution of diol **34** (56 mg, 0.36 mmol) in CH_2Cl_2 at 25 °C were added Ac_2O (0.10 mL, 1.1 mmol), EtN-

i-Pr_2 (0.16 mL, 0.90 mmol), and DMAP (4.4 mg, 0.036 mmol). After 1 h, the reaction was quenched with 5% HCl (10 mL) and extracted with CH_2Cl_2 (15 mL). The organic layers were combined, washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated. The resulting yellow oil was purified by silica gel chromatography (10 to 25% EtOAc in hexanes), affording the diacetate as a clear, colorless oil, 72 mg, 95%. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.70 (s, 3); 2.02 (s, 3); 2.05 (s, 3); 1.94−2.15 (m, 2); 2.21−2.31 (m, 1); 3.95 (d, 2, J = 6.0 Hz); 4.90−5.06 (m, 4); 5.23 (d, 1, J = 5.4 Hz); 5.62−5.83 (m, 1). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 18.58, 20.82, 20.98, 30.90, 38.68, 63.23, 76.23, 113.76, 117.06, 135.62, 141.14, 170.00, 170.93. IR (film): 1740, 1640 cm^{-1}. $[\alpha]_D$: −4.2 (*c* 0.44, CH_2Cl_2). Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 65.13; H, 8.47. To a solution of the diacetate from above (0.280 g, 1.16 mmol) in CH_2Cl_2 (80 mL) at reflux was added $Cl_2(PCy_3)_2Ru{=}CHPh$ (0.045 g, 0.055 mmol). The reaction was allowed to proceed overnight. The solvent was removed under vacuum, and the residue was purified by silica gel chromatography (10 to 15% EtOAc in hexanes) to yield the product as a clear, colorless oil, 239 mg, 97%. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.65 (s, 3); 1.98 (s, 3); 2.01 (s, 3); 2.02−2.17 (m, 1); 2.31−2.46 (m, 1); 2.62−2.81 (m, 1); 3.96−4.14 (m, 2); 5.59 (s, 1); 5.69 (d, 1, J = 7.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.94, 20.81, 20.89, 33.92, 39.90, 63.42, 79.87, 129.67, 138.12, 170.77, 170.94. IR (film): 1740 cm^{-1}. $[\alpha]_D$: −50.9 (*c* 0.49, CH_2Cl_2). Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.15; H, 7.59.

(3*S*,4*R*)-4-Hydroxymethyl-2-methyl-1,6-heptadien-3-ol Bis(methyl carbonate). To a stirring solution of diol **34** (69 mg, 0.44 mmol) in CH_2Cl_2 (10 mL) at 0 °C were added $ClCO_2Me$ (0.17 mL, 2.2 mmol), pyridine (0.18 mL, 2.2 mmol), and DMAP (11 mg, 0.088 mmol). The reaction mixture was allowed to warm to room temperature and was then stirred 4 h. The reaction was quenched with 5% HCl and extracted with CH_2Cl_2. The organic layers were combined, washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated. The resulting yellow oil was purified by silica gel chromatography (10−25% EtOAc in hexanes), affording the biscarbonate as a clear, colorless oil, 103 mg, 86%. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.72 (s, 3); 2.01−2.16 (m, 2); 2.27−2.37 (m, 1); 3.74 (s, 3); 3.75 (s, 3); 4.06 (d, 2, J = 5.2 Hz); 4.97−5.02 (m, 3); 5.06−5.09 (m, 2); 5.62−5.83 (m, 1). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 18.33, 30.43, 38.99, 54.81, 66.43, 80.23, 114.56, 117.51, 135.18, 140.65, 155.03, 155.59. IR (film): 1750, 1640 cm^{-1}. HRMS for $C_{13}H_{20}NaO_6$ $[MNa]^+$: calcd 295.1158, found 295.1145. $[\alpha]_D$: −4.8 (*c* 0.63, CH_2Cl_2).

(3*S*,4*R*)-3-Methoxycarbonyloxy-4-methoxycarbonyloxymethyl-2-methylcyclopentene (36). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.69 (s, 3); 2.07−2.22 (m, 1); 2.33−2.47 (m, 1); 2.69−2.87 (m, 1); 3.75 (s, 3); 3.78 (s, 3); 4.05−4.27 (m, 2); 5.53−5.60 (m, 2). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.87, 33.76, 40.04, 54.64, 54.70, 66.93, 84.37, 130.15, 137.48, 155.54, 155.71. IR (film): 1750 cm^{-1}. HRMS for $C_{11}H_{16}NaO_6$ $[MNa]^+$: calcd 267.0845, found 267.0831. $[\alpha]_D$: −53.8 (*c* 0.44, CH_2Cl_2).

(3*S*,5*R*)-Acetoxymethyl-1-methyl-5-(2-amino-6-chloropurin-9-yl)cyclopentene (37). To a solution of hexane-washed NaH (16 mg of a 60% dispersion in mineral oil, 0.40 mmol) in DMSO (1.5 mL) was added 2-amino-6-chloropurine **26** (68 mg, 0.40 mmol). The mixture was heated to 45 °C for 15 min and then cooled to room temperature. Concurrently, P(O-*i*-Pr)$_3$ (0.039 mL, 0.16 mmol) was added to a stirring suspension of $Pd_2(dba)_3{\cdot}CHCl_3$ (21 mg, 2.0 μmol) in THF (1.0 mL) and stirred for 15 min, at which time the solution was homogeneous and green-yellow in color. The THF solution was transferred via cannula to the DMSO solution, and the cyclic diacetate **35** (81 mg, 0.38 mmol) was added in THF (0.5 mL). The reaction mixture was heated at 45 °C overnight and then was quenched with water. The resulting mixture was extracted with EtOAc. The organic layers were combined, washed with water, and concentrated. Purification by silica gel chromatography (Et_2O elution) yielded recovered starting diacetate **35** (25 mg) as well as the product **37**: 55 mg, 45%. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.57 (s, 3); 1.71−1.84 (m, 1); 2.07 (s, 3); 2.73−2.89 (m, 1); 3.06−3.14 (m, 1); 4.17 (d, J = 5.6, 2 Hz); 5.11 (br s, 1); 5.32−5.40 (m, 1); 5.69−5.73 (m, 1); 7.76 (s, 1). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.74, 20.98, 34.74, 43.04, 62.18, 66.65, 125.54, 131.61, 138.54, 140.91, 151.25, 153.63, 158.92, 171.10. IR (film): 3500−3100, 1730, 1620 cm^{-1}; HRMS for $C_{14}H_{16}ClN_5NaO_2$ $[MNa]^+$: calcd 344.0890, found 344.0894. $[\alpha]_D$: −29.7 (*c* 0.39, CH_2Cl_2).

(3*S*,5*R*)-Methoxycarbonyloxymethyl-1-methyl-5-(2-amino-6-chloropurin-9-yl)cyclopentene (38). To a stirring suspension of $Pd_2(dba)_3{\cdot}CHCl_3$ (32 mg, 0.031 mmol) in THF (1.5 mL) was added P(O-*i*-Pr)$_3$ (0.060 mL, 0.24 mmol). The reaction was stirred for 20 min before being transferred via cannula to a stirring solution of cyclic dicarbonate **36** (149 mg, 0.61 mmol) and 2-amino-6-chloropurine (103 mg, 0.61 mmol) in DMSO (1.5 mL). The reaction mixture was heated to 45 °C overnight and then was quenched with water. The resulting mixture was extracted with EtOAc. The organic layers were combined, washed with water, and concentrated. Purification by silica gel chromatography (50 to 100% EtOAc in hexanes) yielded the nucleoside analogue **38** as a white crystalline solid, 122 mg, 59%. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.56 (s, 3); 1.78−1.91 (m, 1); 2.74−2.90 (m, 1); 3.06−3.18 (m, 1); 3.78 (s, 3); 4.18−4.34 (m, 2); 5.09 (br s, 2); 5.32−5.42 (m, 1); 5.68−5.71 (m, 1); 7.84 (s, 1). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.67, 34.23, 43.17, 54.95, 62.13, 69.79, 125.45, 130.90, 139.04, 141.25, 151.21, 153.67, 155.85, 158.90. IR (film): 3500−3100, 1750, 1610 cm^{-1}. HRMS for $C_{14}H_{16}ClN_5NaO_3$ $[MNa]^+$ calcd 360.0839, found 360.0818. $[\alpha]_D$: −41.1 (*c* 0.36, CH_2Cl_2).

(−)-2′-Methyl 1592U89 40. To a stirring solution of chloropurine carbonate **38** (84 mg, 0.26 mmol) was added cyclopropylamine (0.090 mL, 1.3 mmol). The reaction was heated to reflux for 15 min, at which time TLC showed clean conversion to a more polar intermediate (R_f 0.08, EtOAc). After the mixture was cooled to room temperature, 0.5 M NaOH (4 mL) was added, and the reaction mixture was heated to reflux for 2 h. The solvent was removed under vacuum, and the residue was purified by silica gel chromatography to yield the product **40** as a white crystalline solid, 54 mg, 73%. ^{1}H NMR (200 MHz, DMSO-d_6) δ: 0.55−0.68 (m, 4); 1.46 (s, 3); 1.58−1.73 (m, 1); 2.53−2.66 (m, 1); 2.73−2.84 (m, 1); 2.96−3.07 (m, 1); 3.41−3.46 (m, 1); 4.70−4.76 (m, 1); 5.19−5.27 (m, 1); 5.68 (s, 1); 5.81 (s, 2); 7.30 (d, J = 4.4, 1 Hz); 7.59 (s, 1). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 6.40, 13.51, 23.81, 34.66, 46.26, 60.49, 64.42, 113.42, 131.85, 135.20, 138.02, 151.28, 155.88, 160.8. IR (film): 3600−3000 (br), 1590 (br) cm^{-1}. HRMS for $C_{15}H_{21}N_6O$ $[MH]^+$: calcd 301.1777, found 301.1784. $[\alpha]_D$: −62.8 (*c* 0.58, MeOH).

(−)-2′-Methylcarbovir 41. A stirring solution of chloropurine acetate **37** (0.050 g, 0.16 mmol) in 0.5 M NaOH (3 mL) was heated to reflux for 6 h. The solution was cooled to room temperature, and solvent was removed under vacuum. The residue was purified by silica gel chromatography (5−10% MeOH in CH_2Cl_2) to yield the product **41** as a white crystalline solid, 24 mg, 60%. ^{1}H NMR (200 MHz, DMSO-d_6) δ: 1.46 (s, 3); 1.56−1.70 (m, 1); 2.53−2.65 (m, 1); 2.72−2.81 (m, 1); 3.42 (t, 2, J = 5.4 Hz); 4.68 (t, 1, J = 5.1 Hz); 5.13−5.22 (m, 1); 5.68−5.70 (m, 1); 6.41 (br s, 2); 7.58 (s, 1); 10.54 (s, 1). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 13.48, 34.71, 46.28, 60.84, 64.31, 116.41, 132.18, 135.39, 137.68, 151.14, 153.49, 156.82. IR (film): 3400−3200, 1693, 1637 cm^{-1}. HRMS for $C_{12}H_{14}N_5NaO_2$ $[MNa]^+$: calcd 284.1123, found 284.1135. $[\alpha]_D$: −61.0 (*c* 0.31, MeOH).

(3*R*)-3-Allyloxyacetyl-4-benzyloxazolidin-2-one (46). A solution of the allyloxyacetic acid (5.48 g, 42.1 mmol) and triethylamine (6.2 mL, 44.2 mmol) in 350 mL of ether was added to a flask fitted with a mechanical stirrer, and the mixture was cooled to −78 °C. Pivaloyl chloride (5.44 mL, 44.2 mmol) was added slowly over 15 min, and the resultant mixture was stirred for 5 min at −78 °C and then warmed to 0 °C for 1 h. In a separate flask, (*S*)-4-benzyl-2-oxazolidinone (7.46 g, 42.1 mmol) in 50 mL of THF was cooled to −78 °C, and *n*-BuLi (26.0 mL, 42.5 mmol) was added dropwise. After addition was complete, the mixture was stirred at −78 °C for 10 min. The solution of mixed anhydride was recooled to −78 °C, and the lithiated oxazolidinone was then transferred via cannula into the mixed anhydride. After being stirred for 15

min at −78 °C, the mixture was warmed to 0 °C for 30 min. The reaction was quenched with water and warmed to 25 °C. The aqueous layer was extracted with ether, and the combined extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography provided 10.0 g (82%) of acyloxazolidinone **46**. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.27 (m, 5H); 5.96 (m, 1H); 5.28 (m, 2H); 4.68 (m, 1H); 4.67 (s, 2H); 4.23 (m, 2H); 4.16 (d, J = 5.7 Hz, 2H); 3.32 (dd, J = 3, 8, 9.5 Hz, 1H); 2.79 (dd, J = 9, 5, 13 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ: 37.69, 54.73, 67.22, 69.53, 72.48, 118.2, 127.4, 129.0, 129.4, 133.7, 134.9, 153.3, 170.2. IR (neat): 1780 cm^{-1}. Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.40; H, 6.11; N, 5.22.

[3(2*S*,3*R*),4*R*]-3-(2-Allyloxy-3-hydroxyhex-4-enoyl)-4-benzyloxazolidin-2-one 44. A solution of the allyloxyacetyl oxazolidinone **46** (2.75 g, 10 mmol) in 50 mL of dichloromethane was cooled to 0 °C. Titanium tetrachloride (1.2 mL, 11 mmol) was added dropwise, producing a yellow precipitate. After 5 min, (−)-sparteine (5.67 mL, 25 mmol) in 10 mL of dichloromethane was added dropwise, resulting in a red-black solution. The solution was stirred at 0 °C for 20 min and then cooled to −78 °C. Freshly distilled crotonaldehyde (1.24 mL, 1.05 g, 15 mmol) in 2 mL of dichloromethane was then added dropwise. When addition was complete, the mixture was warmed to 0 °C for 30 min, whereupon half-saturated ammonium chloride was added. The mixture was filtered through Celite and the layers were separated. The aqueous layer was extracted twice with 50 mL of dichloromethane. The combined organic extracts were dried over sodium sulfate and concentrated. Purification of the residue by flash chromatography afforded 3.00 g (87%) of **44** as a viscous, colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.27 (m, 5H); 5.91 (m, 1H); 5.74 (q, J = 5.2 Hz, 1H); 5.59 (m, 1H); 5.28 (m, 2H); 5.18 (d, J = 4.9 Hz); 4.67 (m, 1H); 4.32(brs, 1H); 4.14 (m, 3H); 3.35 (dd, J = 3, 11 Hz, 1H); 2.79 (dd, J = 7.8, 11 Hz, 1H); 1.70 (d, J = 5.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 17.67, 37.70, 55.60, 66.81, 72.27, 73.61, 79.81, 118.54, 127.43, 128.96, 129.30, 129.38, 133.91, 134.99, 153.31, 170.70. IR (neat): 3490, 1760, 1710 cm^{-1}. HRMS for $C_{19}H_{23}NO_5Na$ $[M^+ + Na]^+$: calcd 368.1474, found 368.1468.

(2*R*,3*R*)-2-Allyloxy-hept-4-ene-1,3-diol (50). To a stirring solution of aldol adduct **44** (1.30 g, 3.76 mmol) and methanol (0.20 mL, 4.88 mmol) in diethyl ether (30 mL, 0.1 M) at 0 °C was added $LiBH_4$ (2.44 mL of a 2.0 M solution in THF, 4.88 mmol) dropwise. The reaction was stirred for 1.5 h and then quenched by the slow addition of 15% NaOH (30 mL). The resulting solution was extracted with diethyl ether until no diol was observed by TLC in the aqueous layer. The organic fractions were combined, dried over $MgSO_4$, concentrated under vacuum, and purified by silica gel chromatography (30% EtOAc in hexanes elution) to yield diol **50** as a clear, colorless oil, 0.569 g, 88%. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 5.91 (m, 1H); 5.77 (q, J = 6.4 Hz, 1H); 5.50 (m, 1H); 5.26 (m, 2H); 4.17 (m, 2H); 3.68 (m, 2H); 3.32 (m, 1H); 2.8 (d, J = 3.7 Hz, 1H); 2.51 (brt, J = 4.8 Hz, 1H); 1.73 (d, J = 6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 17.77, 61.20, 71.86, 72.64, 81.96, 117.48, 129.37, 129.60, 134.49. IR (film): 3600−3100 cm^{-1}. Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.85; H, 9.46.

(2*R*,3*R*)-2-Allyloxyhept-4-ene-1,3-diol Dibenzoate 51. To a stirring solution of diol **50** (569 mg, 3.31 mmol) in 30 mL of CH_2Cl_2 at 25 °C was added benzoyl chloride (0.961 mL, 1.16 g, 8.28 mmol), Et_3N (1.4 mL, 9.9 mmol), and DMAP (12 mg, 0.1 mmol). After 12 h, the reaction was quenched with 5% HCl (10 mL) and extracted with CH_2Cl_2. The organic layers were combined and washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated. The resulting yellow oil was purified by silica gel chromatography (10−25% EtOAc in hexanes), affording the dibenzoate **51** (1.068 g, 85%) as a clear, colorless oil that was used directly in the metathesis reaction. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.08 (m, 4H); 7.54 (m, 2H); 7.41 (m, 4H); 5.58−6.10 (m, 4H); 5.21−5.42 (m, 2H); 4.57 (dd, J = 4, 11.5 Hz, A of ABX, 1H); 4.41 (dd, J = 6, 11.5 Hz, B of ABX, 1H); 4.23 (dq, J = 5, 1.5 Hz, 1H); 3.95 (ddd, J = 4, 5, 9.5 Hz, 1H); 1.72 (dd, J = 6, 2 Hz, 3H). IR (neat): 1720, 1603, 1264 cm^{-1}.

2-Hydroxymethyl-3,6-dihydro-2*H*-pyran-3-ol (Dibenzoate) 43. To a solution of the dibenzoate **51** (977 mg. 2.57 mmol) in 100 mL of dichloromethane under argon was added 42 mg of benzylidine(bis-tricyclohexylphosphine)ruthenium(II) dichloride. The dark mixture was stirred at 25 °C for 2 h, whereupon TLC showed complete reaction. Air was bubbled through the mixture for 3 h to oxidize the remaining catalyst. Concentration followed by purification of the residue by flash chromatography gave 826 mg (95%) of **43** as a colorless oil, 95%. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.03 (m, 4H); 7.53 (m, 2H); 7.41 (m, 4H); 6.15 (d, J = 3 Hz, 2H); 5.42 (brs, 1H); 4.62 (dd, J = 13, 6.5 Hz, A of ABX, 1H); 4.48 (d, J = 13, 5.8 Hz, B of ABX, 1H); 4.41 (dd, J = 17.6, 1 Hz, A of ABX, 1H); 4.26 (dd, J = 17.6, 2 Hz, B of ABX, 1H); 4.12 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 63.8, 65.0, 65.8, 74.0, 122.2, 128.4, 128.5, 129.7, 129.8, 129.9, 132.6, 133.1, 133.2, 180.2, 182.4. IR (neat): 1720 cm^{-1}. $[\alpha]^{24}_D$: −233.3° (c = 0.47, CH_2Cl_2). HRMS for $C_{20}H_{18}NO_5Na$ $[M^+ + Na]^+$: calcd 361.1052, found 361.1039.

[2*S*,5*S*]-[5-(2-Amino-6-cyclopropylaminopurin-9-yl)-5,6-dihydro-2*H*-pyran-2-yl]methylbenzoate (49). To a solution of hexane-washed NaH (16 mg of a 60% dispersion in mineral oil, 0.40 mmol) in DMSO (1.5 mL) was added 2-amino-6-chloropurine **26** (62 mg, 0.37 mmol). The mixture was heated to 45 °C for 15 min and then cooled to room temperature. Dibenzoate **43** (124 mg, 0.37 mmol) in 2 mL of THF was added followed by $Pd_2(dba)_3$·$CHCl_3$ (38 mg, 0.037 mmol) and PPh_3 (9.7 mg 0.37 mmol). The reaction mixture was heated to 45 °C overnight and then was quenched with water. The resulting mixture was extracted with EtOAc. The organic layers were combined, washed with water, and concentrated. Purification by silica gel chromatography (50 to 100% EtOAc in hexanes) yielded the dibenzoate 50 mg (40%) plus the nucleoside analogue **52** as a white crystalline solid 67 mg, 48% (79% based on recovered starting material). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.05 (m, 2H); 8.00 (s, 1H); 7.53 (m, 3H); 6.26 (d, J = 10.5 Hz, 1H); 6.09 (dd, J = 10.5, 4.8 Hz, 1H); 5.13 (brs, 2H); 5.13 (brs, 2H); 4.92 (m, 1H); 4.54 (m, 3H); 4.12 (d, J = 12 Hz, A of ABX, 1H); 4.01 (dd, J = 12, 3 Hz, 1H). Anal. Calcd for $C_{23}H_{24}N_5$: C, 72.61; H, 6.36; O, 21.03. Found: C, 72.33; H, 6.22; N, 20.81.

[2*S*,5*S*]-[5-(2-Amino-6-cyclopropylamino-purin-9-yl)-5,6-dihydro-2*H*-pyran-2-yl]methanol 42. To a stirring solution of chloropurine benzoate **52** (54 mg, 0.14 mmol) in 1 mL of absolute ethanol was added cyclopropylamine (0.10 mL, 1.4 mmol). The reaction was heated to reflux for 5 h, at which time TLC showed complete conversion to a more polar intermediate. After the mixture was cooled to room temperature, 0.5 M NaOH (4 mL) was added, and the reaction mixture was heated to reflux for 2 h. The solvent was removed under vacuum, and the residue was purified by silica gel chromatography to yield the product **42** as a white crystalline solid, 17 mg, 40%. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.70 (s, 1H); 6.15 (d, J = 11 Hz, 1H); 6.12 (brs, 1H); 6.03 (dd, J = 11, 5 Hz, 1H); 4.82 (s, 1H); 4.78 (m, 1H); 4.38 (brs, 1H); 4.02 (dd, J = 12, 3 Hz, A of ABX, 1H); 3.94 (dd, J = 12, 3 Hz, B of ABX, 1H); 3.83 (m, 1H); 3.70 (dd, J = 12.5, 4.8 Hz, B of BABX, 1H); 2.90 (brs, 1H); 0.78 (m, 2H); 0.51 (m, 2H). Anal. Calcd for $C_{14}H_{18}N_6O_2$: C, 55.62; H, 6.00; N, 27.80; O, 10.58. Found: C, 55.44; H, 6.020; N, 27.99.

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Supporting Information Available: NMR spectra for obtained compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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