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

Michael T. Crimmins,* Bryan W. King, William J. Zuercher, and Allison L. Choy

Venable and Kenan Laboratories of Chemistry, The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599-3290

crimmins@mail.unc.edu

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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. Carbocvir, 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 Shealy4 in 1966, the discovery that the natural carbocyclic nucleosides aristeromycin5,6 and neplanocin7 were selective inhibitors of kinases and polymerases for the causative agent of the pseudosugar ring, and a Trost-type palladium(0)-mediated substitution to assemble the pseudosugar and the aromatic base. Carbocvir, abacavir, and their 2′-methyl derivatives as well as hexenopyranosyl nucleoside analogues have been prepared by this sequence.

Herdwijn 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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Herdwijn 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-
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 aldot 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 aldot metabolism 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 Trost-type allylic substitution of an allylic ester with the purine or pyrimidine base to assemble the nucleoside T (2) ring-closing metathesis (RCM) to form the pseudo sugar ring,15 and (3) asymmetric alkyl addition to control the relative and absolute stereochemistry of the pseudo-sugar17 (Scheme 1). The palladium-catalyzed coupling of the pseudosugar fragment 5 (or its allylic regioisomer) with an aromatic base via an n-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,8b,13d,e,f,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 alkyl 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 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 protocol20 to generate the chlorotitanium enolate of 11 followed by addition of acrolein resulted in diastereoselective syn aldon addition to produce the aldol adduct 11 in 82% yield (98% de, [α]20 D + 50.6 (c = 0.89, CHCl3)). Exposure of 11 to 1 mol % (PCy3)2Cl2Ru=C=PhH in CH2Cl2 at 25°C led to cyclopentenol 12 (97% yield), which was then reduced to diol 13 in 78% yield with LiBH4 (>99.6% ee by chiral HPLC of the bis-(p-toluate) ester).22 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 affect the ring-closing metathesis in this case. Diol 13 was readily converted to the diacetate 14 by exposure to acetic anhydride, triethylamine and 4-(dimethylamino)pyridine. The dicarboxylate 15 was accessed by treatment of the diol with methyl chloroformate in dichloromethane with pyridine as the base.13 Interestingly, if triethylamine was used, the major product was the monoester 15b.23 An attempt to prepare 5-(3-allyloxyphenyl)pyrimidin-4(3H)-one 16 by microwave-assisted reaction of ketone 17 with allyltrimethylsilane resulted in a mixture of 17a and 17b (Scheme 4).24

**Scheme 1**

![Scheme 1](image1)

**Scheme 2**

![Scheme 2](image2)

**References**


used as the base in the methyl chloroformate acylation, cyclic carbonate 16 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. 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 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 disopropylamine 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 Cl2(PCy3)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,24 the use of cyclopropylaminopurine 27 had not been previously investigated. Reaction of diacetate 14 with 2-amino-6-chloropurine in the presence of Pd(PPh3)4 and NaH in 1:1 THF/DMSO at 45 °C yielded an 86:14 mixture of the chloropurine acetate 28a (65% isolated yield of 28a) and its N7 isomer 29a. The analysis of the N7 and N9 coupling products is readily accomplished by 1H 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. 7.85 ppm) is typically upfield of the N7 isomer (ca. 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. They noted that not only...
produced abacavir previously reported. Alternatively, direct hydrolysis of the chloropurine at 45 °C in DMSO resulted in a 95:5 mixture of N9/N7 regioisomers 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 anomerization 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. 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. 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). Locking the system into a northern 2′-exo 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 3′-exo conformation produced poor antiretroviral activity for 5-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.

6-(cyclopropylamino)purine 27 was utilized as the nucleophile in the coupling reaction. Exposure of 27 and diacetate 14 to 10 mol % Pd(PPh3)4 and NaH in DMSO resulted in the 95:5 mixture of N9/N7 regioisomers 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.

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 anomerization 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. 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. 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). Locking the system into a northern 2′-exo 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 3′-exo conformation produced poor antiretroviral activity for 5-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.


(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 conformational analysis, see: Saenger, W. Principles of Nucleic Acid Structure Springer-Verlag: New York, 1984.


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 A₁,2 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: 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 ΔΔG 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 TiCl₄ and 2.5 equiv (−)-sparteine followed by exposure to methacrolein to form the Evans syn aldol adduct 32 in 86% yield (Scheme 8). Alternatively, under slightly different conditions for the aldol addition (2.1 equiv of TiCl₄ and 1.1 equiv of EtN-i-Pr₂), the non-Evans syn aldol adduct 33 was obtained in 81% yield. Reductive removal of the chiral auxiliary in 32 (or 33) was accomplished with LiBH₄ to form diol 34 which was acylated to provide the corresponding diacetate or dicarbonate. Lithium borohydride was utilized since LiBH₄ 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(PPh₃)₄ showed significantly lower yields than in analogous reactions of 14 and 15. Yields were slightly increased by employing Pd₂(dba)₃·CHCl₃/PPPh₃ as the catalyst, but optimized conditions for both 35 and 36 involved Pd₂(dba)₃·CHCl₃/P(Oi-Pr)₃ catalyst system and led to 45% isolated yield of chloropurine acetate 37 and 59% isolated yield of chloropurine carbonate 38. 1H NMR analysis of the crude

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(31) Molecular mechanics calculations were performed with MM2 parameters.
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 pyrimidine 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 α-allyl formation while the purine anion was generated in situ during reactions with allylic carboxylates (such as 15 and 36). Preformation of the purine anion may limit the extent of reversibility of nucleophilic attack on the α-allyl complex, suggesting the N9 isomer is the kinetic product.

Synthesis of α-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 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 α-cyanoacyl 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 and pyridine set the stage for the palladium catalyzed coupling to the purine base. Unfortunately, attempts to couple 2-amino-6-chloropurine 26 and diacetyl 49 in the presence of (Ph3P)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 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 diacetyl 49 in the presence of (Ph3P)4Pd were completely unsuccessful.

With ready access to the dibenzoate 43, the palladium catalyzed coupling with 2-amino-6-chloropurine was again attempted. While use of (Ph3P)4Pd once again failed to produce the nucleoside analogue, use of Pd(0) source resulted in isolation of the coupling product 52 in 79% yield, based on recovered...
starting material. Subsequent exposure of 52 to cyclo-
propylamine in ethanol at reflux followed by basic hydrol-
ysis provided the nucleoside 42 in good yield (Scheme 13).

Conclusion

An efficient, enantioselective synthesis of carboyclic
nucleoside and hex-3-enoxyanisol nucleoside analogues
has been accomplished by exploiting a novel asymmetric
aldol—defin 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 atmosphe-
re of N₂ using oven-dried glassware. Unless otherwise
noted, reagents were obtained from commercial suppliers and
used without further purification. Cl₂(PCy₃)₂Ru=CHPF was
prepared according to a modified procedure of Grubbs and co-
workers.3 Et₂O, THF, and CH₂Cl₂ were purified according to
the method of Grubbs and co-workers.33 Et₃N, EtNİPr₂, DMSO,
and pyridine were distilled from CaH₂. Purification by sil-
ica 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.

4S-Benzyl-3-pent-4-enoylazolidin-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-oxazolidine in 120 mL of THF
was cooled to −78 °C whereupon 63.1 mL (1.01 mmol) of 1.6
M n-butyllithium in hexanes was added slowly. This solu-
tion was stirred for 10 min at −78 °C. The flask containing the
mixed anhydride was cooled to −78 °C, and the lithium-
ated 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
Na₂SO₄, filtered, and concentrated. The residue was purified
by filtration through a pad of silica gel (3:1 hexanes/ethyl
acetate) to give 25.88% (100) of the title compound 10 as a
colorless oil. 1H NMR (250 MHz, CDCl₃) δ: 2.42 (2H, 2H); 2.72
(dd, J = 9.7, 13 Hz, 1H); 3.03 (m, 2H); 3.29 (dd, J = 13, 4 Hz,
4.15 (m, 2H); 4.69 (m, 5H); 6.84 (m, 1H); 7.12–7.37 (5.7 Hz, 5H).
13C NMR (100 MHz, CDCl₃) 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. Found: C, 69.20; H, 6.65; N, 5.33.

[3(2S,3R)-4S]-3-(2-Allyl-3-hydroxypent-4-enyl)-4-ben-
ylazolidin-2-one (11). A solution of the 4S-benzyl-3-pent-
4-enoylazolidin-2-one 10 (4.00 g, 15 mmol) in 70 mL of di-
chloromethane was warmed to 60 °C. Titanium tetraisopropyl-
(1.86 mL, 17 mmol) in 70 mL of dichloromethane was then added
dropwise, resulting in 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. 1H NMR
(250 MHz, CDCl₃) δ: 2.38–2.61 (band, 3H, 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 (5H, 4H); 5.72–
5.96 (m, 2H); 7.12–7.34 (m, 3.5H, CDCl₃) δ: 31.89, 37.87, 47.23,
55.4, 65.88, 73.13, 116.6, 117.1, 127.2, 128.8, 129.3, 131.5, 131.2,
137.2, 153.4, 174.3 IR (film): 3500, 1780 cm⁻¹. [α]D²⁰: +50.6° (c = 0.89,

[3(1R,2R,4S)-4-Benzyl-3-(2-hydroxycyclopentan-3-ene-
carbonyl)azolidin-2-one (12). To a solution of the
[3(2S,3R,4S)-3-(3-hydroxy-2-allyl-1-oxo-4-pentenyl)-4-benzyl-
2-oxazolidinone 11 (767 mg, 2.43 mmol) in 15 mL of di-
chloromethane under argon was added 40 mg of benzylidene(bis-
tricyclohexylphosphine)ruthenium(II) dichloride. The dark
mixture was stirred at 25 °C for 30 min, whereupon TLC showed
no 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 chromato-
graphy to give 0.679 mg (79%) of 12 as a colorless oil. 1H NMR
(250 MHz, CDCl₃) δ: 0.89, 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); 6.84 (m, 1H); 5.09 (m, 1H);
5.74 (m, 1H); 6.02 (m, 1H); 7.15–7.36 (m, 5H). 13C NMR (100
MHz, CDCl₃) 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. [α]D²⁰: −92.5° (c = 0.795, CHCl₃). Anal. Calcld
for C₂₃H₂₂O₅N: C, 68.68; H, 5.96; N, 4.84. Found: C, 68.69;
H, 6.74; N, 4.40.

[1(1R,2R,5S)-5-Hydroxymethyl-2-cyclopenten-1-ol (13). A
solution of [3(1R,2R,4S)-4-benzyl-3-(2-hydroxy-cyclopentan-
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 ob-
served. 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 0.102 mg (78%) of the
diol 13 as a pale yellow oil. 1H NMR (250 MHz, CDCl₃) δ:
2.03–2.49 (band, 3H); 3.33 (br s, 2H); 3.71 (m, 2H); 4.82 (m,
1H); 5.74 (m, 1H); 5.92 (m, 1H). 13C NMR (100 MHz, CDCl₃): δ: 33.54, 42.49, 62.59, 77.61, 132.4, 135.0. IR (film): 3600–3000 (broad) cm⁻¹. [α]D₉ = −125.1° (c = 0.47, CH₂Cl₂). The sample was identical in all respects to an authentic sample. The diol was converted to its bis-p-toluoyl 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 Diacarbonate 15.** To a solution of diol 13 in CH₂Cl₂ at 0 °C under nitrogen was added 2.2 equiv of either triethylamine (for the diacetate and the cyclic carbonate) or pyridine (for the diacarbonate). The acylating agent (3.0 equiv) was then added dropwise followed by a catalytic amount of N,N-dimethylanilinopyridine (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 NaHCO₃ 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 diacarbonate 15 (90% yield).

**Diacetate 14,¹ H NMR (250 MHz, CDCl₃): 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, 6.1, 11.1 Hz, 2H); 5.68–5.75 (m, 1H); 5.79–5.85 (m, 1H); 6.07–6.15 (m, 1H). 13C NMR (100 MHz, CDCl₃): δ: 170.9, 170.5, 134.7, 129.8, 78.04, 63.34, 39.49, 34.61, 21.01, 20.83. 1R: 1740 (broad), 1370, 1235, 1035. [α]D₂ = −178.0° (c = 0.45, CH₂Cl₂).

**Cyclic Carbonate 16.**¹ H NMR (250 MHz, CDCl₃): δ: 2.13–2.48 (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). 13C NMR (100 MHz, CDCl₃): δ: 151.5, 137.5, 128.9, 87.45, 66.2, 35.01, 33.77. 1R: 1750, 1620 cm⁻¹. [α]D₂ = −145.2° (c = 0.44, CH₂Cl₂).

**Diacarbonate 15.**¹ H NMR (250 MHz, CDCl₃): 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); 5.68–5.92 (m, 1H); 6.10–6.15 (m, 1H). 13C NMR (100 MHz, CDCl₃): δ: 155.7, 155.3, 137.7, 129.0, 82.05, 66.61, 54.79, 54.68, 39.39, 34.58. 1R: 1745 (broad), 1440, [α]D₂ = −148.5° (c = 0.46, CH₂Cl₂).

**4S-[(4-Benzyl-2-thioxooxazolidin-3-yl)prop-2-en-1-one** 18. To a cooled solution (−78 °C) of 4-pentenoic acid (2.26 g, 22.6 mmol) and 3.30 mL (237 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-oxazolinidethione in 27 mL of THF was prepared. The reaction mixture was warmed to 0 °C, the reaction mixture was then stirred for 30 min. The reaction mixture was quenched with 5% HCl solution and the layers were separated. The organic layer was washed with saturated NaHCO₃ 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 diacarbonate 15 (90% yield).

**Diacetate 14.**¹ H NMR (250 MHz, CDCl₃): δ: 2.17–2.41 (m, 1H); 2.92–3.20 (m, 1H); 2.64–2.81 (m, 1H); 3.73 (s, 3H); 3.77 (s, 3H); 4.17–4.20 (dd, J = 5.9, 11.0 Hz, 1H); 4.33 (dd, J = 6.9, 11.0 Hz, 1H); 5.68–5.92 (m, 1H); 6.10–6.15 (m, 1H). 13C NMR (100 MHz, CDCl₃): δ: 155.7, 155.3, 137.7, 129.0, 82.05, 66.61, 54.79, 54.68, 39.39, 34.58. 1R: 1745 (broad), 1440, [α]D₂ = −148.5° (c = 0.46, CH₂Cl₂).
Chloropurine Carbonate 28b and Chloropurine Alkaloid 28c. To a solution of 2-aminocarbonylpyrazine (0.378 mmol, 0.064 g) in 1 mL of dimethyl sulfoxide under nitrogen was added tetrakis(triphenylphosphine)palladium(0). Dicarboxylate 15 (0.313 mmol, 0.087 g) or cyclic carbonate 9a was then added in 1 mL of THF. After being stirred for 2 h, the reaction mixture was filtered and purified by flash chromatography to yield 0.027 g (81%) of chloropurine carbonate 28b. 1H NMR (250 MHz, CDCl 3) δ: 1.90–2.03 (m, 1H); 2.74–2.90 (m, 1H); 3.00–3.18 (m, 1H); 3.64–3.70 (m, 1H); 3.92 (m, 1H); 4.28–4.50 (m, 1H); 5.75–5.82 (m, 1H); 6.10–6.19 (m, 1H); 7.89 (s, 1H). 13C NMR (100 MHz, CDCl 3) δ: 58.7, 153.1, 152.1, 118.1, 139.1, 126.9, 125.5, 64.61, 60.66, 47.66, 33.19. IR (film): 3650–3000, 1610 cm −1. \( \alpha_{pk}^D = -88.6^\circ \) (c = 0.43, CH 3 Cl)

Chloropurine Alkaloid 28c. Same procedure as above. Yields range from 61% to 65%. 1H NMR (250 MHz, CDCl 3) δ: 1.90–2.03 (m, 1H); 2.69–2.89 (m, 1H); 3.00–3.18 (m, 1H); 3.64–3.70 (m, 1H); 3.92 (m, 1H); 4.28–4.50 (m, 1H); 5.75–5.82 (m, 1H); 6.10–6.19 (m, 1H); 7.89 (s, 1H). 13C NMR (100 MHz, CDCl 3) δ: 58.7, 153.1, 152.1, 118.1, 139.1, 126.9, 125.5, 64.61, 60.66, 47.66, 33.19. IR (film): 3650–3000, 1610 cm −1. \( \alpha_{pk}^D = -80.0^\circ \) (c = 0.62, CH 3 OH).

(−)-1592U89 20. To a stirred solution of chloropurine acetate 28a (0.177 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, the mixture was filtered and washed with CH 2 Cl 2. The mixture was again refluxed and concentrated. Purification by flash chromatography afforded 0.027 g (81%) of 1592U89 20 identical to that previously reported. 9H 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, 1H); 6.02–6.12 (m, 1H); 7.29 (d, J = 4.2 Hz, 1H); 7.59 (s, 1H). 13C NMR (100 MHz, DMSO-d 6) δ: 159.9, 155.8, 150.9, 137.8, 134.7, 129.9, 119.3, 63.98, 58.01, 47.58, 34.19, 23.76, 63.34. IR (film): 3500–3000 (br), 1590 (br) cm −1. \( \alpha_{pk}^D = -37.5^\circ \) (c = 0.51, CH 3 OH).

(−)-Carbovir 1. 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. 13C NMR (100 MHz, DMSO-d 6) δ: 133.7, 129.6, 118.8, 116.0, 72.8, 53.3, 53.2, 43.1, 41.5, 38.7, 37.9, 37.4, 28.6, 22.1. IR (film): 3500–3000 cm −1. \( \alpha_{pk}^D = -47.0^\circ \) (c = 0.51, CH 3 OH).

Acetate—Cyclopropylaminopurine 30. To a stirred solution of sodium hydride (0.375 mmol, 0.009 g) in 1 mL of dimethyl sulfoxide (1 mL) under nitrogen was added tetrakis(triphenylphosphine) palladium(0) (0.031 mmol, 0.036 g) was added following the addition of diacetate 14 (0.313 mmol, 0.062 g) in 1 mL of THF. The mixture 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 following 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 and concentrated. Purification by flash chromatography provided 0.064 g (62%) of acetate 30. 1H NMR (250 MHz, CDCl 3) δ: 0.55–0.62 (m, 2H); 0.79–0.89 (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). 13C 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. \( \alpha_{pk}^D = -41.0^\circ \) (c = 0.39, CH 3 Cl).
i-Pr2 (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 CH2Cl2 (15 mL). The organic layers were combined, washed with saturated aqueous NaHCO3, dried over Na2SO4, 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%. 1H NMR (200 MHz, CDCl3) (69 mg, 0.44 mmol) in CH2Cl2 (10 mL) at 0 °C were added to a flask fitted with a mechanical stirrer, and the cyclic thionocarbonyl derivative (0.050 g, 0.16 mmol) in 0.5 M NaOH (3 mL) was added. 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 (50 to 100% EtOAc in hexanes) yielded the nudeside analog 38 as a white crystalline solid, 52 mg, 73%. 1H NMR (200 MHz, CDCl3, DMSO-d6): 0.55–0.68 (m, 2) (4.16, s, 3); 1.40–1.73 (m, 1); 2.53–2.66 (m, 2); 2.73–2.84 (m, 2); 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, 1); 7.30 (d, J = 4.4, 1 Hz) (7.59, s, 1). 13C NMR (100 MHz, CDCl3, DMSO-d6): 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 C17H14NaO4 [M]+: calc 301.1777, found 301.1784. [a]β: −62.8 (c 0.58, MeOH).

(−)-1-Methyl 1592U89 40. To a stirring solution of chloroacetate 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% EtOAc in hexanes) affording the diacetate 36 (84 mg, 0.26 mmol) as a white crystalline solid, 80 mg, 73%. 1H NMR (200 MHz, CDCl3, DMSO-d6): 0.55–0.68 (m, 2) (4.16, s, 3); 1.40–1.73 (m, 1); 2.53–2.66 (m, 2); 2.73–2.84 (m, 2); 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, 1); 7.30 (d, J = 4.4, 1 Hz) (7.59, s, 1). 13C NMR (100 MHz, CDCl3, DMSO-d6): 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 C17H14NaO4 [M]+: calc 301.1777, found 301.1784. [a]β: −62.8 (c 0.58, MeOH).

(−)-2-Methylcarbavirin 41. A stirring solution of chloropurin-9-yl)cyclopentene (37). To a solution of hexahexagon NaH (16 mg of a 60% dispersion in mineral oil, 0.40 mmol) in DMSO (1.5 mL) was added 2-amino-6-chloropurin-9-yl)cyclopentene (26) (68 mg, 0.40 mmol). The mixture was heated to 45 °C for 15 min and then cooled to room temperature. Compounds. 6)-3-Allyloxyacetyl-4-benzyloxazolidin-2-one (39). A stirring suspension of PdCl2(dba)2·CHCl3 (21 mg, 0.020 mmol) 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 (EtO-Eloctone) yielded recovered starting diacetate 35 (25 mg) as well as the product 37. 55 mg, 45%. 1H NMR (200 MHz, CDCl3, DMSO-d6): 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); 13C NMR (200 MHz, CDCl3, DMSO-d6): 13.74, 20.98, 34.73, 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 C15H15ClN2O2 [M]+: calc 284.1123, found 284.1125. [a]β: −61.0 (c 0.31, MeOH).
The aqueous layer was extracted with ether, and the combined extracts were washed with brine, dried over Na2SO4, and concentrated in vacuo. Purification by flash chromatography provided 10.0 g (82%) of acyclic oxazolidinone 46. 3H NMR (250 MHz, CDCl3): δ: 7.27 (m, 5H); 5.96 (1H); 5.28 (m, 2H); 4.68 (m, 1H); 4.67 (s, 2H); 4.25 (dd, J = 5.5 Hz, 2H); 3.93 (d, J = 5.7 Hz, 2H); 3.39 (d, J = 5.5 Hz, 1H); 2.79 (dd, J = 9, 5.13 Hz, 1H); 1.98 (brs, 1H); 1.63 (m, 1H); 1.49 (brs, 1H). 13C NMR (CDCl3): δ: 37.96, 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. Calcld for C12H12NO: C, 70.34; H, 7.02. Found: C, 70.28; H, 7.01.

After 5 min, (−)-sparteine (5.67 mL, 25 mmol) in 10 mL of hexane-washed NaH (16 mg of a 60% dispersion in oil, 0.40 mmol) in DMSO (1.5 mL) was added to the yellow precipitate. 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 Pd2(dba)3 (44 mg, 0.07 mmol) and PPh3 (9.7 mg 0.037 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 nucoside analogue 52 as a white crystalline solid 67 mg, 48% (79% based on recovered starting material). 3H NMR (200 MHz, CDCl3): δ: 7.8 (1H); 7.6 (3H); 7.5 (2H); 7.40 (1H); 7.35 (d, J = 10.5 Hz, 1H); 6.90 (dd, J = 10.5, 4.8 Hz, 1H); 5.13 (brs, 2H); 4.13 (m, 1H); 4.02 (dd, J = 12, 3 Hz, A of ABX, 1H); 4.01 (dd, J = 12, 3 Hz, 1H). Anal. Calcld for C24H24N4O2: C, 55.62; H, 6.00; N, 27.80; O, 10.58. Found: C, 55.44; H, 6.20; 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.