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Syntheses of carbocyclic aminonucleosides and (−)-*epi*-4′-carbocyclic puromycin: application of palladium(0)/indium iodide-allylations and tethered aminohydroxylations

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ABSTRACT

Carbocyclic aminonucleosides and *epi*-4′-carbocyclic puromycin were prepared from an acylnitroso-derived hetero Diels–Alder cycloadduct. Pd(0)/InI-mediated allylations of a formyl species were used to install the 4′-hydroxymethyl group. A tethered aminohydroxylation strategy was employed to install the *cis*-2′,3′-aminoalcohol moiety with complete regio- and diastereocontrol.

Puromycin is an aminonucleoside natural product that demonstrates broad spectrum antibiotic and antitumor activities (Fig. 1).[1] The 3′-aminoacyl moiety structurally resembles the aminoacyladenyl region of an aminoacyl tRNA[2] and plays a crucial role in terminating protein biosynthesis. Specifically, the α-amino group is transferred to a carboxyl-activated peptidyl-tRNA to form a new peptide bond.[3] However, subsequent aminoacyl-group transfer reactions are precluded due to the presence of an unreactive 3′-amide in the ribosomal acceptor site rather than an activated 3′-ester linkage. As a result, the nascent polypeptide chain is prematurely released from the ribosome.[4]

Although puromycin effectively inhibits transpeptidation, the ribonucleoside is rapidly metabolized in vivo to inactive and toxic components.[5] In order to circumvent enzymatic degradation and toxicity issues, carbocyclic puromycin and related analogs have been prepared and studied extensively.[6] The carbocyclic aminonucleosides have the same mode of action as puromycin and retain antimicrobial activity.[7] Also, carbocyclic nucleosides lack an enzymatically labile glycosidic bond and provide a more metabolically robust scaffold.[8] Structure–activity relationships (SARs) revealed that the 4′-hydroxymethyl group was not required for activity[9] and the 1′,2′,3′,4′-diastereomer lacked biological function. The *cis*-2′,3′-aminoalcohol stereochemistry was essential for activity. Additionally, replacement of the functionalized cyclopentane core with a cyclohexyl ring resulted in decreased inhibition of protein synthesis.[10]

Our research group's continued interest in the syntheses of diverse carbocyclic nucleosides[11] led us to investigate carbocyclic puromycin derivatives. By employing Pd(0)/InI-mediated allylations of a formyl species, 4′-hydroxymethyl groups may be installed in the carbocyclic scaffold with regio- and diastereocontrol.[12] Additionally, a *N*-pentafluorobenzoyloxy carbamate linker may be constructed from the 4′-hydroxymethyl substituent. This substrate may serve as a precursor for a tethered aminohydroxylation[13] to install the *cis*-2′,3′-aminoalcohol moiety. Application of these key synthetic transformations allows complete functionalization of the cyclopentane core and provides aminonucleosides (±)-**1a** and (−)-**1b** and (−)-*epi*-4′-carbocyclic puromycin **2** (Fig. 1).

We have previously reported direct hydroxymethylations at the C-4′ position by using Pd(0)/InI allylation chemistry with carbocyclic platforms (±)-**3a** and (+)-**3b**.[12] Functionalized cyclopentene systems (±)-**3a** and (+)-**3b** serve as key intermediates in the syntheses of diverse carbocyclic nucleosides[14] as well as starting materials in our route to carbocyclic puromycin derivatives.

Treatment of *syn*-1,4 scaffold (±)-**3a** with HCl at 80 °C removed the Boc group (Scheme 1). The crude amine salt was treated with 5-amino-4,6-dichloropyrimidine in refluxing *n*-BuOH for 4 d to afford the S_NAr product (±)-**4a**. Cyclization of compound (±)-**4a** to 6-chloropurine (±)-**5a** was achieved with triethylorthoformate in the presence of catalytic camphor sulfonic acid. The *anti*-1,4 diastereomer (+)-**3b** was subjected to identical reaction conditions to provide chloropurine analog (+)-**5b** (Scheme 2).

We developed a method to key homoallylic alcohols (±)-**5a** and (+)-**5b** and turned our attention in installing the *cis*-2′,3′-aminoalcohol by using a tethered aminohydroxylation reaction.[15,16] *N*-Sulfonyloxy carbamates[17] and *N*-pentafluorobenzoyloxy carbamates[13b] have emerged as reoxidants in tethered aminohydroxylation reactions and avoided the use of chlorinating agents and basic reaction conditions. Although this powerful methodology has already been used in total synthesis,[18] few examples of tethered hydroxyaminations with functionalized homoallylic alcohols have been reported.[13b,16c–e,17]

In order to prepare the appropriate tethered aminohydroxylation precursor, we employed a two-step sequence[19] to *N*-hydroxycarbamate (±)-**7a**. When chloropurine (±)-**5a** was treated with

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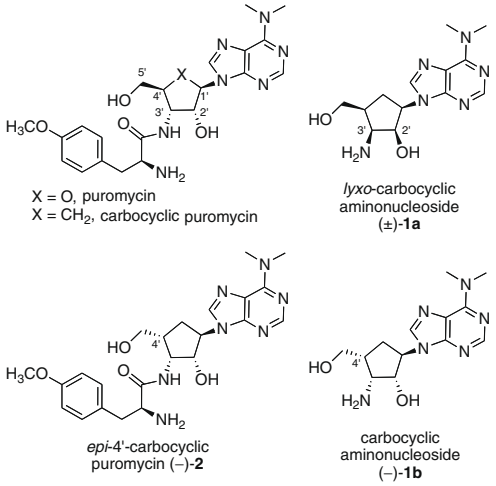
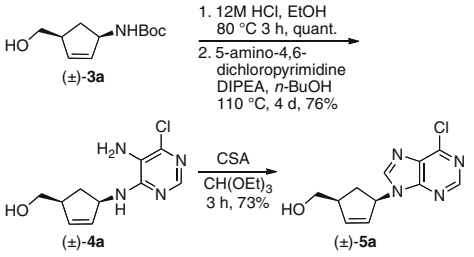


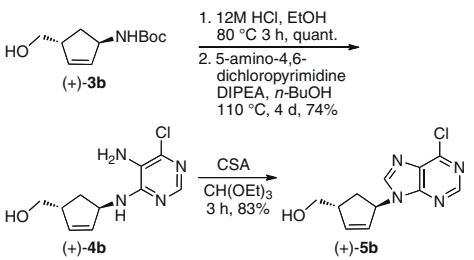
Figure 1. Puromycin and related carbocyclic analogs.



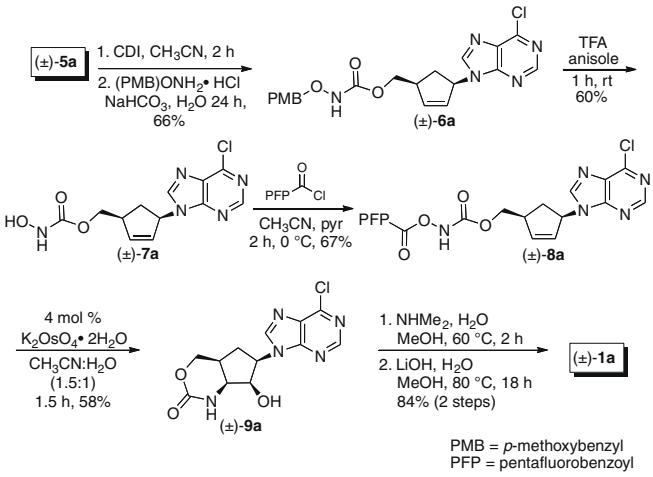
Scheme 1. Preparation of chloropurine (±)-**5a**.

CDI followed by an aqueous solution of *O*-*p*-methoxybenzylhydroxylamine,[20] *N*-benzyloxycarbamate derivative (±)-**6a** was isolated in 66% yield. Removal of the *p*-methoxybenzyl group with neat TFA provided *N*-hydroxycarbamate (±)-**7a** (Scheme 3).

Initial attempts to synthesize *N*-pentafluorobenzoyloxy carbamate (±)-**8a** were thwarted by undesired by-products. When *N*-hydroxycarbamate (±)-**7a** was treated with pentafluorobenzoyl chloride in the presence of Et_3N, the bis-benzoylated product dominated the reaction mixture (ca. 42% by LC–MS). Although bis-benzoylation has not been reported in the syntheses of *N*-pentafluorobenzoyloxy carbamates,[13b] we suspected that deprotonation of the NH with Et_3N readily occurred after mono-benzoylation[21] and the stabilized anion reacted with another equivalent of the acid chloride. In order to minimize the unwanted bis-benzoylation reaction, we exchanged Et_3N for a weaker base. When a CH_3CN solution of *N*-hydroxycarbamate (±)-7**a** was treated with pentafluorobenzoyl chloride in the presence of pyridine, mono-benzoylated derivative (±)-**8a** was isolated as the major product in 67% yield.[22]



Scheme 2. Preparation of chloropurine (±)-**5b**.



Scheme 3. Tethered aminohydroxylation to (±)-**9a** and elaboration to *lyxo*-carbocyclic aminonucleoside (±)-**1a**.

The tethered aminohydroxylation was the key step en route to carbocyclic aminonucleoside core structures. We expected complete regiocontrol and anticipated diastereofacial selectivity to favor the same side where the tether originated. Dihydroxylation of *syn*-1,4-disubstituted cyclopentenes has been studied[23] and the π-facial selection of these reactions was governed by sterics and the Cieplak effect.[24]

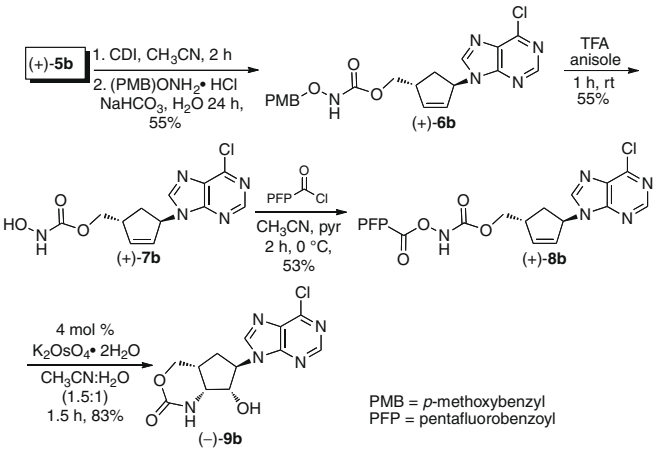
A *t*-BuOH/H_2O (3:1) solution of homoallyl *N*-pentafluorobenzoyloxy carbamate (±)-**8a** was treated with catalytic K_2OsO_4, and hydroxyamination product (±)-**9a** was obtained. However, two competing side reactions contributed to the low conversion to (±)-**9a**. Hydrolysis of *N*-pentafluorobenzoyloxy carbamate (±)-**8a** provided *N*-hydroxycarbamate (±)-**7a**. Additionally, the presence of a homoallyl carbamate[25] suggested that hydrolysis of the imidotrioxoosmium (VII) species[26] was also competitive. When the tethered aminohydroxylation reaction was conducted in *n*-BuOH/H_2O (3:1), the homoallyl carbamate was the dominant product and hydroxyamination product (±)-**9a** was also observed. Although LC–MS and ^1H NMR of the crude product mixtures indicated the formation of an exclusive diastereomer, unwanted by-products precluded the use of these solvent conditions.

Early work on the catalytic asymmetric aminohydroxylation reaction reported the use of CH_3CN/H_2O as an effective solvent system.[27] When a CH_3CN/H_2O (1.5:1) solution of homoallyl *N*-pentafluorobenzoyloxy carbamate (±)-**8a** was treated with catalytic K_2OsO_4, tethered aminohydroxylation product (±)-**9a** was the major component of the reaction mixture (Scheme 3). Cyclic carbamate (±)-**9a** was isolated in 58% yield as the exclusive regio- and diastereoisomer. The relative stereochemistry was determined by NOE correlations in the ROESY spectrum.[28]

Treatment of compound (±)-**9a** with dimethylamine afforded the S_NAr product and the cyclic carbamate was cleaved with LiOH in refluxing MeOH to provide unprecedented *lyxo*-carbocyclic aminonucleoside (±)-**1a**.

We had successfully developed methodology to prepare the *N*-pentafluorobenzoyloxy carbamate linker and identified optimal conditions for the tethered aminohydroxylation reaction by starting with *syn*-1,4-disubstituted cyclopentene diastereomer (±)-**5a**. We applied this optimized route to synthesize carbocyclic aminonucleoside precursor (–)-**9b** (Scheme 4).

Chloropurine analog (+)-**5b** was treated with CDI for 2 h. Then, a solution of *O*-*p*-methoxybenzylhydroxylamine was introduced to provide *N*-(*p*-methoxy)benzyloxycarbamate analog (+)-**6b**.

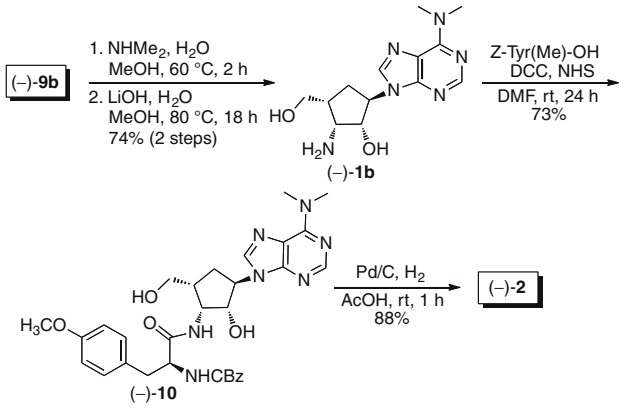


Scheme 4. Tethered aminohydroxylation to (−)-**9b**.

N-Hydroxycarbamate (+)-**7b** was revealed when (+)-**6b** was treated with neat TFA to remove the *p*-methoxybenzyl group. The tethered aminohydroxylation precursor (+)-**8b** was obtained by treatment of substrate (+)-**7b** with a CH_3CN solution of pentafluorobenzoyl chloride in the presence of pyridine. On the first attempt to effect aminohydroxylation, homoallyl *N*-pentafluorobenzoyloxy carbamate (+)-**8b** was treated with catalytic K_2OsO_4 in CH_3CN/H_2O (1.5:1) to afford hydroxyamination product (−)-**9b** in 83% isolated yield. In this case, the 1′-nucleobase is orientated on the opposite side of the tether. The reduced steric bulk may contribute to the increased yield of (−)-**9b** compared to the reaction of diastereomer (±)-**8a**.

Carbocyclic aminonucleoside (−)-**1b** was synthesized by installation of the dimethylamino moiety followed by cleavage of the cyclic carbamate with LiOH (Scheme 5). The carbocyclic derivative (−)-**1b** was coupled to *N*-benzyloxycarbonyl-*p*-methoxyphenyl-L-alanine to provide 3′-derivative (−)-**10**. Hydrogenation in the presence of Pd/C removed the CBz-protecting group and revealed targeted carbonucleoside, *epi*-4′-carbocyclic puromycin (−)-**2**.

In summary, we have synthesized biologically relevant carbocyclic aminonucleosides (±)-**1a** and (−)-**1b** and *epi*-4′-carbocyclic puromycin (−)-**2** from an acylnitroso-derived hetero Diels–Alder cycloadduct. Our route highlighted two key synthetic transformations. Pd(0)/In-mediated allylations were used to install the requisite hydroxymethyl group. A tethered aminohydroxylation was employed to prepare a highly functionalized carbocyclic core with complete diastereo- and regiocontrol.



Scheme 5. Elaboration to carbocyclic aminonucleoside (−)-**1b** and *epi*-4′-carbocyclic puromycin (−)-**2**.

Acknowledgments

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Supplementary data

Supplementary data (general methods, experimental details and characterization for compounds (±)-**1a**, (−)-**1b**, (−)-**2**, (±)-**4a**, (+)-**4b**, (±)-**5a**, (+)-**5b**, (±)-**6a**, (+)-**6b**, (±)-**7a**, (+)-**7b**, (±)-**8a**, (+)-**8b**, (±)-**9a**, (−)-**9b**, and (−)-**10**. Complete proton and carbon assignments of (±)-**9a** and (−)-**9b**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.04.006.

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