An Efficient Asymmetric Approach to Carbocyclic Nucleosides: Asymmetric Synthesis of 1592U89, a Potent Inhibitor of HIV Reverse Transcriptase

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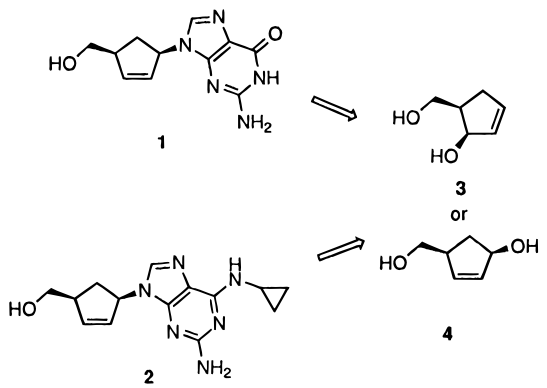
Carbocyclic nucleosides have been the focus of much recent attention in the development of new antitumor and antiviral therapeutic agents.[1] The search for antiviral agents, particularly for the treatment of human immunodeficiency virus (HIV) and hepatitis B virus (HBV), resulted in the discovery of carbovir (**1**), which has been shown to possess significant *in vitro* activity as an inhibitor of HIV reverse transcriptase (Scheme 1).[2,3] More recently, a new reverse transcriptase inhibitor 1592U89 (**2**), which is currently in phase II clinical trials, has been discovered and reported to hold remarkable promise for the treatment of HIV.[4] Reduction of viral load of greater than 99% as well as significant improvements in CD4 counts for HIV-infected patients have been observed after dosing for 12 weeks with 1592U89 (**2**).[5] Continuous improvement in the enantioselective syntheses of carbocyclic nucleosides is required due to their therapeutic significance. An efficient and general approach to the asymmetric synthesis of carbocyclic nucleosides such as carbovir (**1**) and 1592U89 (**2**) is described here.

An attractive convergent approach for the enantioselective synthesis of carbocyclic nucleosides involves Trost's[6] palladium-catalyzed coupling of purine or pyrimidine bases with carbocyclic allylic carbonates or acetates.[7] This strategy requires ready access to enantiomerically pure 5-(hydroxymethyl)-2-cyclopenten-1-ol (**3**) or the isomeric

Scheme 1



4-(hydroxymethyl)-2-cyclopenten-1-ol (**4**), each of which gives access to the same π-allyl palladium intermediate for coupling to the nucleoside base. Our approach to the synthesis of **3** relies on the realization that combination of an asymmetric aldol condensation[8] with a ring closure metathesis reaction[9] can provide rapid entry into functionalized, enantiomerically pure carbocycles. Condensation of the lithiated (*S*)-4-benzyl-2-oxazolidinone with the pentenoic pivalic mixed anhydride **5** provided the pentenoyloxazolidinone **6**[10] in near-quantitative yield (Scheme 2). Use of the Evans' dialkylboron triflate protocol[8a] for diastereoselective *syn* aldol condensation with acrolein produced the aldol product **7**[10] in 82% yield [(>99% de $[\alpha]^{24}_D$ +50.6° (c = 0.89, $CHCl_3$)]. The critical ring closure metathesis was accomplished in 97% yield by exposure of a dichloromethane solution of diene **7** to 1% of the Grubbs[9a] catalyst for 30 min to form the cyclopentenol **8**[10] [$[\alpha]^{24}_D$ −92.5° (c = 0.795, $CHCl_3$)]. The chiral auxiliary was reductively removed with lithium borohydride[11] to provide the required diol **3** in 78% yield [$[\alpha]^{24}_D$ −125.1° (c = 0.47, $CHCl_3$), >99.6% ee by chiral HPLC of the di-*p*-toluate].

Diol **3** was converted to cyclic carbonate **9** (52%),[3b] dicarbonate **10** (90%),[3a,f,k] and diacetate **11**[10] (90%) for evaluation of the palladium-catalyzed coupling with 2-amino-6-chloropurine (**12**) and 2-amino-6-(cyclopropylamino)purine (**13**). Reaction of diacetate **11** with 2-amino-6-chloropurine (**12**) in the presence of tetrakis(triphenylphosphine)palladium(0) and sodium hydride gave an 86:14 mixture of the carbocyclic nucleoside **14a**[10] and the corresponding N7 coupling product **15a** (65% yield of **14a** after chromatography) (Scheme 3).[12] The problem of N9−N7 regioselectivity is a common problem in classic Vorbruggen coupling of purines with sugars,[13] but has

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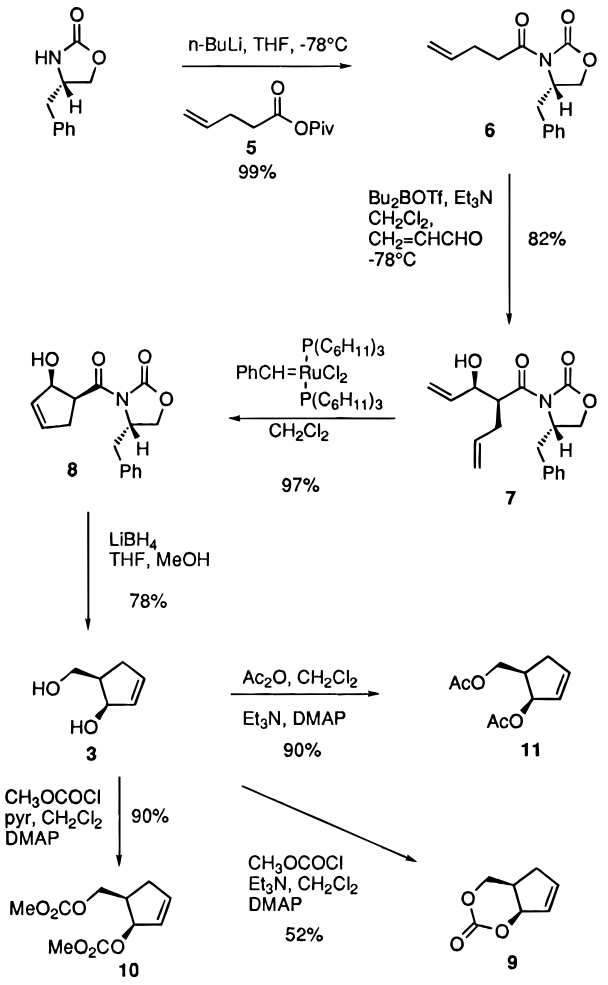
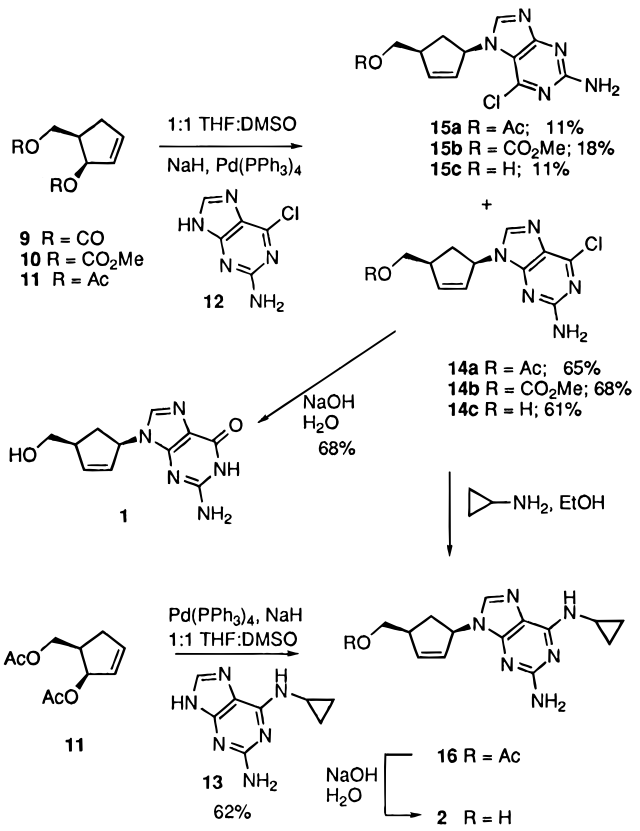
Scheme 2



only recently been recognized in palladium-catalyzed coupling in carbocyclic nucleoside synthesis.[12] Use of the cyclic carbonate in the coupling reaction with 2-amino-6-chloropurine (**12**) gave a similar result (71% of an 85:15 mixture of N9:N7 isomers **14c:15c**), but the dicarbonate gave only a 74:26 mixture of **14b:15b** (68% of **14b** after purification). Treatment of the chloropurine **14a** with cyclopropylamine in ethanol followed by hydrolysis of the acetate (NaOH, H_2O) produced 1592U89 (**2**) in 81% overall yield. Alternatively, direct hydrolysis of **14a** with sodium hydroxide produced carbovir (**1**) in 68% yield.[3]

The N9:N7 regioselectivity improved significantly when the 2-amino-6-(cyclopropylamino)purine (**13**) was utilized as the nucleophile in the palladium-catalyzed coupling. Exposure of diacetate **11** and 2-amino-6-(cyclopropylamino)purine (**13**) with 10 mol % of tetrakis(triphenylphosphine)palladium(0) and sodium hydride in DMSO resulted in a 95:5 mixture of the N9:N7 regiosiomers. The

Scheme 3



N9 isomer **16** was obtained in 62% yield after chromatography and was readily hydrolyzed to 1592U89 with aqueous sodium hydroxide.

The approach described here provides rapid and efficient access to carbocyclic nucleosides in high enantiomeric purity.[14] The other enantiomeric series of carbocyclic nucleosides would be equally available by starting with the (*R*)-4-benzyl-2-oxazolidinone or a comparable auxiliary. The strategy of combining a ring closure metathesis with reactions that provide control of absolute acyclic stereochemistry should find wide application in the synthesis of enantiomerically enriched carbocycles and heterocycles. Additional work in this area is in progress.

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Supporting Information Available: Experimental procedures and compound characterization data for compounds **1**−**3**, **6**−**11**, **14a**−**c**, and **16** (6 pages).

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(14) U.S. patent applied for.