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Enantioselective Syntheses of Carbanucleosides from the Pauson-Khand Adduct of Trimethylsilylacetylene and Norbornadiene

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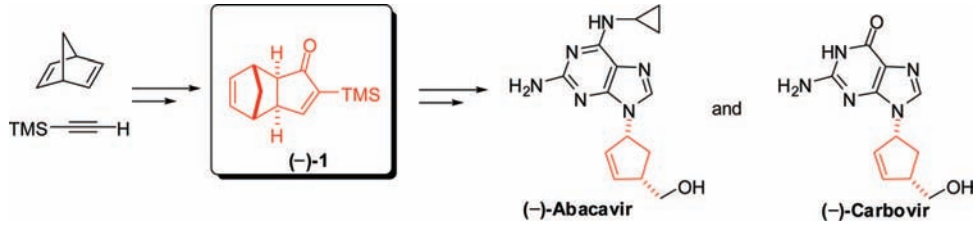
ABSTRACT



A new enantioselective approach to carbanucleosides from Pauson-Khand (PK) adduct 1 is disclosed. The chiral cyclopentenone 1 is readily accessible in enantiomerically pure form via PK reaction of trimethylsilylacetylene and norbornadiene using *N*-benzyl-*N*-diphenylphosphino-*tert*-butyl-sulfinamide as a chiral P,S ligand. (−)-Carbavir and (−)-Abacavir were enantioselectively synthesized starting from (−)-1. The key steps of the sequence are a photochemical conjugate addition of a hydroxymethyl radical, a retro-Diels−Alder reaction, and a palladium catalyzed allylic substitution to introduce the nucleobase.

Nucleoside analogs have attracted a great deal of attention due to their important pharmacological activity, mainly as antiviral and antitumor drugs.[1] AZT (Zidovudin), antiviral against HIV, and Acyclovir (Zovirax), antiviral against Herpex simplex, are well-known marketed drugs.[2] Carbanucleosides constitute an important class of nucleoside analogs.[3] Aristeromycin and Neplanocin are naturally occurring carbocyclic nucleosides with antitumor and antiviral activity that show greater metabolic stability to phosphorylases than their glycosidic relatives. Both have shown broad-spectrum antiviral properties as a consequence of inhibiting S-adenosyl-L-homocysteine hydrolase (SAH), although their clinical application has been limited because of their significant cytotoxicity.[4]

Carbovir and Abacavir (Ziagen) are synthetic five membered-ring carbanucleosides. They also have shown major antiviral and anticancer activities. Due to its toxicity, Carbovir was not developed beyond the preclinical phase, but Abacavir was approved and launched for the treatment of HIV.

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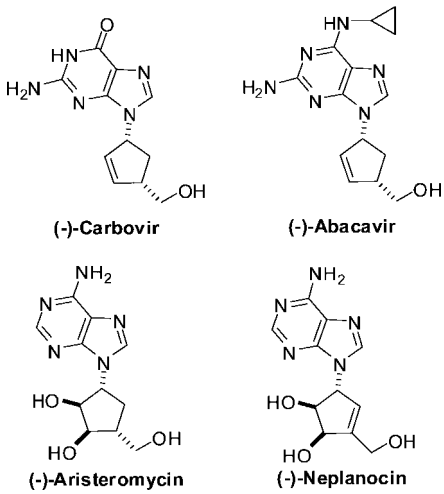


Figure 1. Structures of some pharmacologically important carbanucleosides.

Due to their biological properties, these compounds have been synthesized by various routes, primarily via enzymatic resolution, kinetic resolution, or stereospecific synthesis from sugars.[5,6] However, to date few general approaches based on asymmetric synthesis have been reported.[7] Some years ago, Schmalz and co-workers[8] disclosed a new approach to carbocyclic nucleosides based on an intramolecular Pauson-Khand reaction,[9] although the synthesis of enantiopure compounds required kinetic resolution with the Corey's CBS reagent. We have recently described several practical enantioselective versions of the intermolecular Pauson-Khand reaction, that have led to the cycloadduct **1** in high yield and optical purity.[10] We envisaged that this compound could be a convenient starting material for many carbanucleosides. Herein we describe an enantioselective synthesis of (−)-Carbovir and (−)-Abacavir as examples of a new general approach to carbanucleosides based on asymmetric intermolecular PK reactions.

Our approach is based on the retrosynthetic analysis shown in Figure 2. Several pharmacologically important carbanucleosides would be accessible from cyclopentenone **2** by stereoselective reduction of the enone followed by allylic substitution and protecting group manipulation. We envisioned cyclopentenone **2** could be prepared by retro-Diels−Alder reaction of a norbornadiene derivative. In seeking smooth deprotection conditions, high stability to Lewis acids, and bulkiness to direct the enone reduction, we chose a triisopropylsilyl ether as a protecting group. Therefore, the key step of this synthetic approach would be the stereoselective introduction of a d^1-synthon into cyclopentenone **1**, readily accessible by intermolecular PKR.[11]

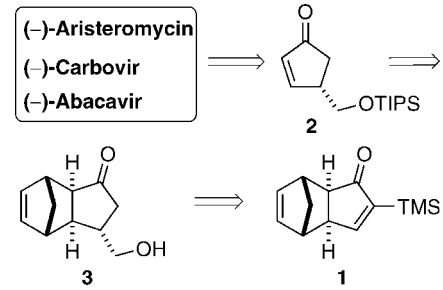
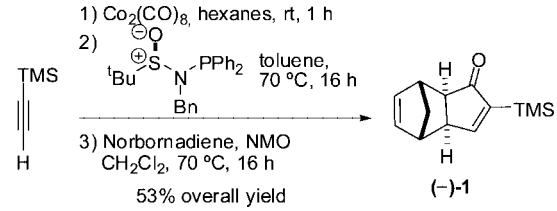


Figure 2. Retrosynthetic analysis of carbanucleosides.

Scheme 1. Preparation of Optically Pure (−)-**1**[10a]



Multigram quantities of both racemic and optically active PK adduct **1** were prepared from trimethylsilylacetylene and norbornadiene following our reported procedures (Scheme 1).[10] The enantiomeric excess of **1** was determined to be >99% by GC (beta-DEX).

The conjugate addition of a d^1 synthon to the enone was next explored. Additions of either *tert*-butoxymethyl

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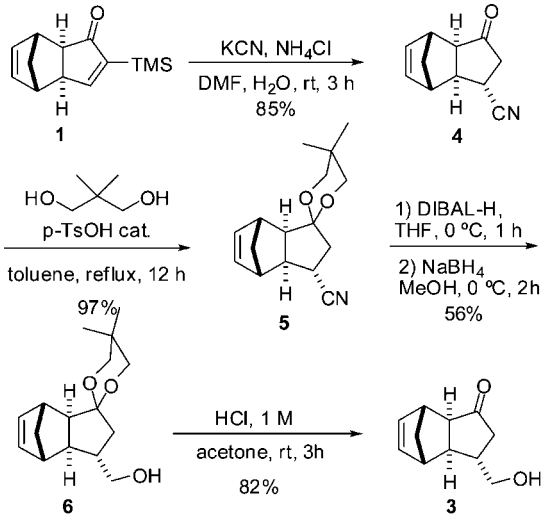
lithium[12] or (methoxymethoxy)methyl lithium ($MOMOCH_2Li$)[13] catalyzed by copper were unsuccessful. However, the Michael addition of cyanide took place smoothly with concomitant deprotection of the TMS group and complete stereoselectivity. Thus, treatment of **1** with potassium cyanide in DMF/H_2O in the presence of ammonium chloride afforded **4** in 85% yield (Scheme 2).

Scheme 2. Introduction of a Hydroxymethyl Group via Cyanide Conjugate Addition



Although the conjugate addition/deprotection reaction was very efficient, the conversion of the nitrile to a hydroxymethyl group required protection of the ketone, which implied lengthening of the sequence. Gratifyingly, we were able to introduce the hydroxymethyl group in one step using the photochemical addition of hydroxymethyl radical. This methodology, largely overlooked, was developed by Fraser-Reid and co-workers.[14]Using benzophenone as a triplet sensitizer, a solution of **1** in methanol was irradiated at 365 nm to afford **7** with complete stereospecificity and in excellent yield. As previously described,[15] direct irradiation without benzophenone affords 1-TMS-tricyclo[5.2.1.$0^{2,6}$]deca-3,8-dien-10-one in good yield. The formation of this rearranged product could be avoided using at least 70% mol of triplet sensitizer. The TMS group was then easily deprotected with TBAF treatment of the crude to afford the desired alcohol **3** in 78% overall yield (Scheme 3). The hydroxyl group was protected as triisopropylsilyl ether under standard conditions to give **8** in 89% yield.

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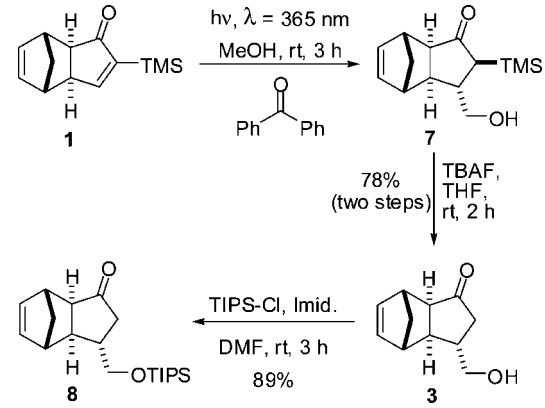
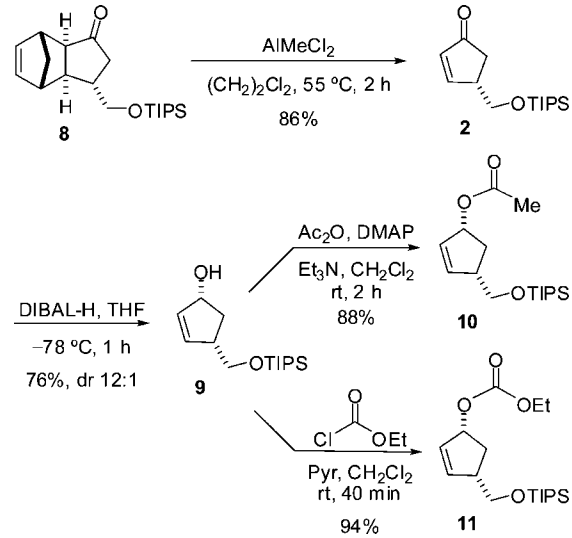
Scheme 3. Photochemical Addition of a Hydroxymethyl Group



We then submitted the protected hydroxymethyl cyclopentanone **8** to the retro-Diels−Alder conditions developed by Grieco[16] using $AlMeCl_2$ as a Lewis acid and maleic anhydride as a cyclopentadiene scavenger. This provided cyclopentenone **2** in 86% yield (Scheme 3). To introduce the nucleic bases by palladium catalyzed allylic substitution, we had to prepare an allyl derivative. To this end, cyclopentenone **2** was reduced with DIBAL-H at low temperature to give allyl alcohol **9** in good yield. As expected, the bulky TIPS group directed the reduction to the opposite face of the enone, giving a 12:1 diastereomeric ratio of *cis/trans* products (as determined by NMR) easily separable by chromatography. To explore the allyl substitution, **9** was derivatized without complication to the corresponding acetate **10** and carbonate **11** (Scheme 4).

Scheme 4. Preparation of Hydroxycyclopentenone Derivatives



Under the standard conditions[17] (treatment with 2-chloroaminopurine in the presence of $Pd(PPh_3)_4$ in DMF),

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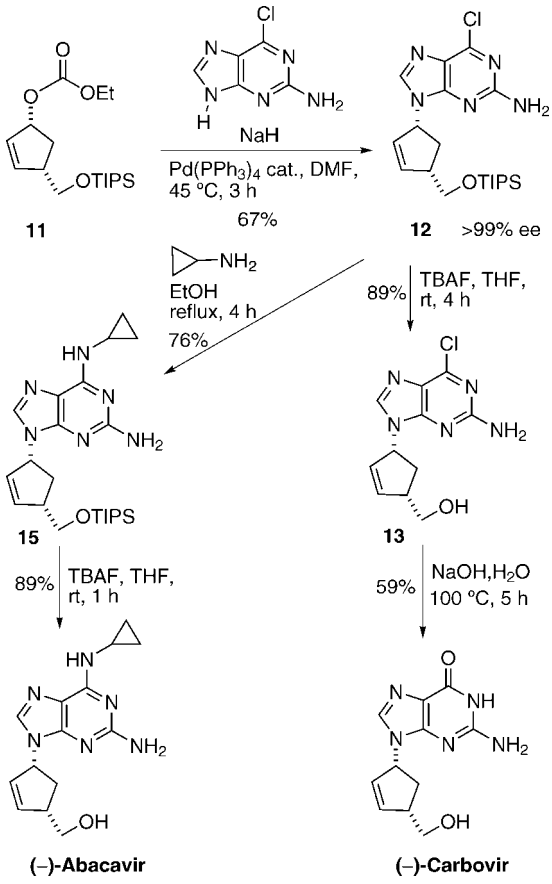
Scheme 5. Final Steps of the Syntheses



carbonate **11** afforded a nearly 1:1 mixture of regioisomers (N7 and N9) in moderate yield. Starting from acetate **10** and using sodium hydride as base improved the regioselectivity to 5:1, but the yield was still low (50% yield). Gratifiyingly, reaction of carbonate **11** using sodium hydride as a base afforded the key nucleoside in 84% yield with a 4:1 dr of N9/N7 regioisomers. The desired regioisomer at N9 (**12**) was obtained in 67% yield after chromatographic purification. Its optical purity was checked by chiral HPLC (Chiralpak IA) and determined to be >99% ee, as expected (Scheme 5).

Finally, the key intermediate **12** was transformed into the final products. Deprotection of the silyl ether followed by basic hydrolysis with NaOH afforded Carbovir in excellent yield. On the other hand, introduction of a cyclopropylamine (CPA) fragment followed by deprotection of the silyl ether by TBAF gave Abacavir in excellent yield and optical purity (Scheme 5).

In summary, we have developed a new enantioselective approach to the synthesis of carbanucleosides starting from the Pauson-Khand cycloadduct of trimethylsilylacetylene and norbornadiene **1** showing its usefulness as a cyclopentenone synthon. This PK adduct is readily available in enantiomerically pure form using *N*-benzyl-*N*-diphenylphosphino-*tert*-butyl-sulfinamide as a chiral P,S ligand. Starting from PK adduct **1**, the hydroxymethyl group was efficiently added via photochemical conjugate addition. Protection as a triisopropylsilyl ether followed by retro-Diels−Alder reaction afforded the protected hydroxymethyl cylopentenone **2**. Diastereoselective reduction to the corresponding allyl alcohol and palladium catalyzed substitution afforded an advanced intermediate **12** that was converted into enantiomerically pure (−)-Carbovir and (−)-Abacavir.

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Supporting Information Available: Experimental procedures and characterization of compounds **2**−**15**. ^{1}H and ^{13}C NMR spectra of compounds **1**−**12** and **15**. This material is available free of charge via the Internet http://pubs.acs.org.

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