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NEW EFFICIENT METHOD FOR THE SYNTHESIS OF THE ANTIVIRAL AGENT CARBOVIR

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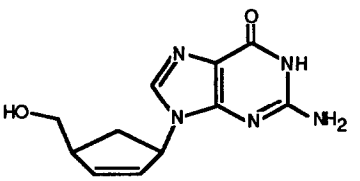
Summary: An efficient synthesis of (±)-carbovir **1** and simple des(hydroxymethyl) analogues, e.g., **5**, is reported which uses a new approach for attaching nucleoside bases to cycloalkene systems.

Carbocyclic nucleosides, i.e., carbocyclic analogues of normal purine or pyrimidine nucleosides (which have a methylene group in place of the ring oxygen atom), are of great interest as potential antiviral and antitumor agents.[2] The recent discovery that carbovir **1**, the carbocyclic analogue of 2',3'-didehydro-2',3'-dideoxyguanosine, is a selective inhibitor of human immunodeficiency virus (HIV-1) in vitro[3] has increased interest in this compound and its close structural analogues. Indeed its hydrolytic stability and ability to inhibit the infectivity and replication of HIV in T-cells at concentrations well below toxic levels make carbovir **1** an excellent candidate for development as an antiretroviral agent in treating AIDS.[4] Because of this important biological activity, the development of new general methods for the synthesis of carbovir and its analogues has been a recent area of strong interest, with several total and formal syntheses having been reported.[4,5] We report here a new, general approach to cycloalkenyl nucleosides which permits a short synthesis of carbovir **1**.



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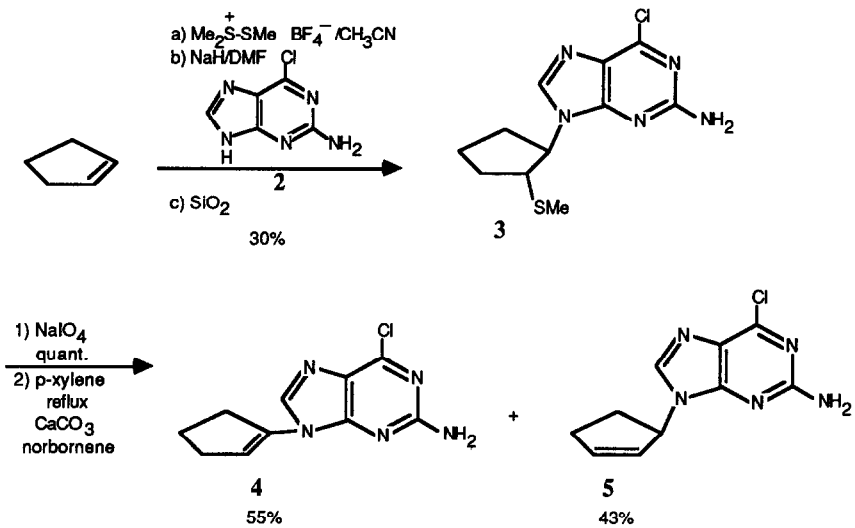
We reasoned that one route to these compounds would be the anti aminothioalkylation (azasulfenylation) of a cyclic alkene (via an episulfonium salt) to give a trans 1-amino-2-thioalkylcycloalkane, the thioalkyl group of which would be subsequently oxidized to the sulfoxide and subjected to thermal elimination of a sulfenic acid to produce the desired allylic nucleoside. A simpler version of this chemistry, namely azasulfenylation of an alkene, had been described by the groups of Trost and Caserio in 1982.[6] They showed that treatment of alkenes with the readily

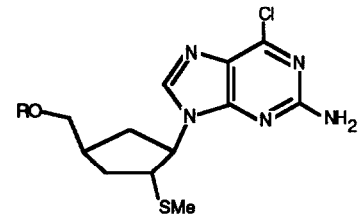
prepared dimethyl(methylthio)sulfonium fluoroborate, DMTSF (Me_2SSMe^+ BF_4^-), followed by addition of a nitrogen nucleophile (generally an amine or azide ion) afforded good yields of the trans 1-amino-2-methylthiocycloalkanes. We decided to use a variation of this process for preparing the desired carbovir analogues. Thus treatment of cyclopentene with DMTSF in acetonitrile, followed by evaporation of the solvent, addition of dimethylformamide (DMF), and then addition of the anion of 6-amino-4-chloropurine (prepared in situ from **2** and sodium hydride) in DMF furnished the desired trans 2-methylthio nucleoside analogue **3** in 30% yield after column chromatographic purification. Oxidation with periodate gave in quantitative yield the sulfoxide which was eliminated in refluxing *p*-xylene in the presence of norbornene and calcium carbonate[7] to afford the desired 3-cyclopentenyl nucleoside **5** in 43% yield. This compound was accompanied by the other possible elimination product, namely the 1-cyclopentenyl nucleoside **4** in 55% yield.



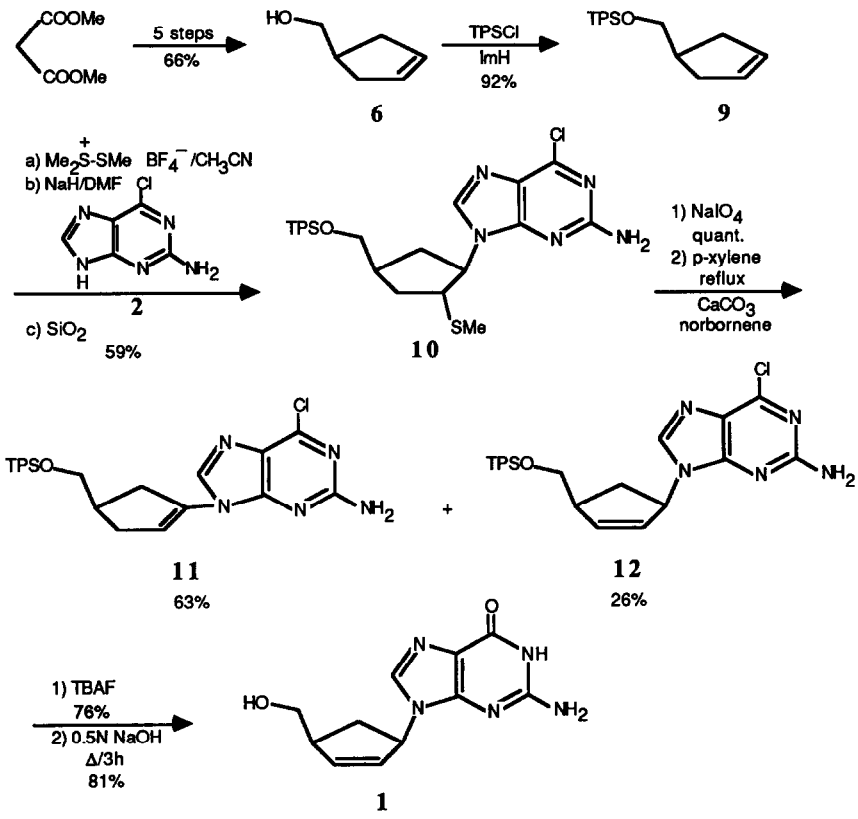
That the major product was due to the elimination toward the heteroatom was surprising (since, in general, eliminations of this type afford mainly the allylic products resulting from loss of the proton away from the heteroatom[8]) and is presumably due to the fact that the proton α to the purine ring is more acidic than the other proton since the nitrogen lone pair is tied up in the aromatic imidazole ring.[9]

Having shown that this aminothioalkylation process could be extended to the sodium anions of purine nucleosides as nucleophiles, we then decided to carry out a short synthesis of carbovir **1**. The 4-(hydroxymethyl)cyclopentene **6** was prepared in 5 steps from dimethyl malonate in 66% overall yield by known chemistry.[10] Treatment of **6** directly with DMTSF and then the anion of the chloropurine **2** gave the desired product **7** but in only 26% yield, implying that the free hydroxyl group was detrimental to the yield. The primary hydroxyl was protected as the *t*-butyldimethylsilyl ether (TBS ether) and then subjected to the aminothioalkylation reaction as before to afford two products, the alcohol **7** in 45% yield and the silyl ether **8** in 14% yield, indicating that the silyl ether was not stable to the reaction

conditions. Therefore the alcohol **6** was protected as the *t*-butyldiphenylsilyl (TPS) ether **9** and subjected to the aminothioalkylation conditions to give the desired product **10** in 59% yield. It is important to point out that in all of these reactions only one diastereomer is isolated, namely the one in which the alkylthio group added initially anti to the large alkoxymethyl group, presumably due to steric hindrance. Oxidation with periodate to the sulfoxide and thermal elimination as before furnished a mixture of the undesired 9-(1-cyclopentenyl)purine **11** and the desired 9-(3-cyclopentenyl)purine **12** in yield of 63% and 26% respectively. Conversion of **12** into carbovir **1** was straightforward. Removal of the silyl protecting group with TBAF (76 % yield) and replacement of the chloride with hydroxide (81% yield) afforded (±)-carbovir **1**, thereby ending a short (6 step) synthesis of **1** from the known alcohol **6**. Further research in this area of carbocyclic nucleoside synthesis is currently underway in our laboratory.



7 R = H
8 R = TBS



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9) Treatment of cyclohexene with DMTSF in acetonitrile followed by evaporation of the solvent, addition of DMF, and then addition of the anion of adenine (prepared by treatment of adenine with sodium hydride) in DMF afforded the trans 9-[(2-methylthio)cyclohexyl]adenine in 34% yield. Oxidation and thermal elimination as above gave the desired 9-(3-cyclohexen-1-yl)adenine in 33% yield and the undesired 9-(1-cyclohexenyl)adenine in 52% yield, thus implying that elimination toward the nitrogen is a general process in these systems.

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