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PALLADIUM-ASSISTED ROUTE TO CARBOCYCLIC NUCLEOSIDES: A FORMAL SYNTHESIS OF (±)-ARISTEROMYCIN [1]

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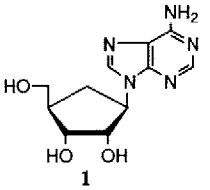
SUMMARY: The carbocyclic nucleoside aristeromycin (1) has been formally synthesized from cyclopentadiene monoepoxide (4) via the sequential generation of cationic (π-allyl)palladium complexes.

Aristeromycin (1) is representative of an intriguing class of naturally occurring compounds known as carbocyclic nucleosides.[2] Structurally speaking, they differ from conventional nucleosides only in the composition of their five-membered ring. Thus, aristeromycin is actually the carbocyclic analogue of the genetic building block adenosine. A significant advantage of this cyclopentane structure is that it does not possess a labile glycosidic bond—a primary site for catabolism in conventional nucleosides. Like the chemically modified nucleoside metabolites they mimic, carbocyclic analogues have the ability to disrupt biological processes at the most basic cellular level.[3] It is this mechanism of action which is most likely responsible for their remarkable antitumor, antibacterial, and antiviral activities. As a consequence, carbocyclic analogues of purine and pyrimidine nucleosides have become prime candidates in the search for new, metabolically stable chemotherapeutic agents.



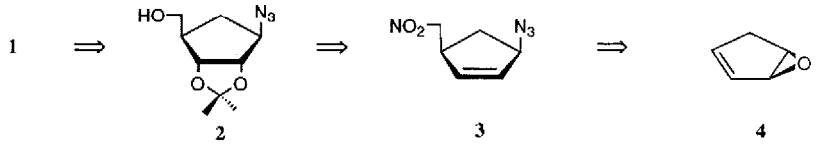
1

Aristeromycin was first synthesized by Shealy and coworkers in 1966.[4] This undertaking has since been repeated by several other groups.[5] At this juncture, we wish to reveal the results from our recent studies and report herein the formal synthesis of (±)-**1** via azido alcohol **2**.

Retrosynthetic dissection (Scheme I) of **1** illustrates our strategic game plan. The enterprise[6] was to introduce the cis-1,4 nitromethyl and azido substituents (**3**) through nucleophilic addition to sequentially-derived cyclopentenyl(π-allyl)palladium complexes—reactions known for their

exceptional regio- and stereochemical control. It was envisioned that the nitromethyl substituent would serve as a chemical progenitor to the hydroxymethyl group on **2**. A recent paper by Tadano[7] has confirmed that retrosynthetic intermediate **2** is indeed a useful precursor to our target nucleoside. Therefore, not only would the preparation of **2** serve to validate the proposed synthetic plan, but it would also constitute a formal synthesis of aristeromycin.

Scheme I



Scheme II outlines the route by which convergent intermediate **2** was prepared.[8] Cyclopentadiene monoepoxide (**4**) was selected as our retrosynthetic starting material since it was known to capture weakly acidic nucleophiles in a cis-1,4 fashion upon exposure to palladium(0)-catalysts.[9,10] Accordingly, treatment of an ice-cooled solution of **4** in nitromethane with 1 mol % $Pd(PPh_3)_4$ cleanly afforded nitromethyl adduct **5** in 87% chromatographed yield (R_f 0.33; 1:1 hexane-ethyl acetate; SiO_2). Interestingly, if the reaction is instead run under the usual conditions—a dilute solution of the nucleophile dissolved in THF—one obtains unacceptable mixtures of **5** and its bis-alkylated counterpart.[11] The reaction most likely proceeds via an intermediate zwitterionic (π-allyl)palladium complex which can abstract a proton from nitromethane (pKa~10) and then undergo backside displacement of its metal by the internally generated nitronate anion. The stereo- and regiochemical assignments on **5** are based upon the characteristic ^1H NMR pattern which arises from the nonequivalent methylene protons in disubstituted *cis*-1,4-cyclopent-2-enes.[12]

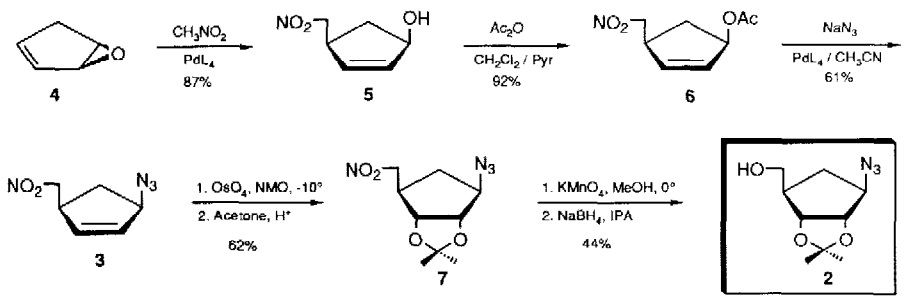
Conversion of allylic alcohol **5** into the corresponding acetate **6**, which was accomplished in near quantitative yield under standard conditions, configured the ring for a second palladium-catalyzed allylic substitution reaction. Model studies[13] on a similarly functionalized, optically active cyclopentenyl acetate had encouraged us that allylic displacement would occur as anticipated at the acetoxy-bearing carbon with retention of configuration. As expected, the palladium-catalyzed reaction[14] between **6** and NaN_3 (2 equiv) in a CH_3CN/H_2O (1:1) solvent system at 45 °C provided the desired cis-azido compound **3** in a 61% chromatographed yield (R_f 0.34; 6:1 hexane-ethyl acetate; SiO_2) together with a 12% yield (R_f 0.43) of the corresponding 1,2-product. It was imperative to quench the reaction immediately after the starting material had been

consumed (TLC assay) since product equilibration leads to an inseparable mixture of cis and trans 1,4-azides.[15]

Stereoselective hydroxylation of the double bond proved tricky. When alkene **3** was exposed to NMO and catalytic OsO_4 (8:1 acetone/H_2O) at ambient temperature, the product immediately ketalized (acetone, 2,2-dimethoxypropane, cat. PTSA), a 2:1 mixture of the trans acetonide **7** and its all-cis diastereomer resulted. Fortunately, it was possible to improve upon this selectivity (4.7:1; 62% yield) by maintaining the temperature at or below -10 °C during the osmylation step. It should be noted that although treatment of **3** with $KMnO_4$ provided the desired trans product exclusively, the yield was an unacceptably low 35%. In this case, apparently, hydroxylation was in direct competition with oxidative cleavage of the carbon-nitro bond (*vide infra*).

Transformation of the nitromethyl moiety into the corresponding hydroxymethyl function was accomplished by a two-step oxidation/reduction sequence. The carbon-nitro bond was oxidatively cleaved with basic $KMnO_4$ in methanol at 0 °C to afford an unstable oil identified as the aldehyde by the distinctive NMR absorption at δ9.6. The formal synthesis of **1** was realized with the reduction of this intermediate by excess $NaBH_4$ in isopropanol which resulted in a two-step 44% yield of (±)-**2** after purification by column chromatography (R_f 0.50; 1:1 hexane-ethyl acetate; SiO_2). Structure proof for the azido alcohol (and its precursors) was ascertained through an exact match of **2** with the authentic spectra kindly provided us by Professor Tadano[7].

Scheme II



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