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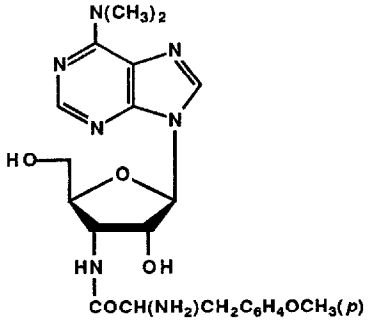
HIGH-YIELD SYNTHESIS OF 3'-AMINO-3'-DEOXYNUCLEOSIDES. CONVERSION OF ADENOSINE TO 3'-AMINO-3'-DEOXYADENOSINE [1]

Mirna C. Samano and Morris J. Robins*

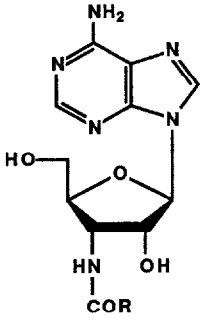
Department of Chemistry, Brigham Young University, Provo, UT 84602, U.S.A.*
and Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada

Summary : A 5'-*O*-silylated-2',3'-anhydroadenosine derivative underwent epoxide opening smoothly with dimethylboron bromide. The *N*-benzyl carbamate derived from the trans bromohydrin was ring-closed with sodium hydride. Deprotection (fluoride, hydroxide, and hydrogenolysis) gave 3'-amino-3'-deoxyadenosine (**6**) in 66% yield from adenosine (9 steps).

Porter *et al.*[2] reported isolation of puromycin (**A**) from *Streptomyces alboniger* in 1952, the year after announcement of the first nucleoside antibiotic, cordycepin[3] (3'-deoxyadenosine). Puromycin was the initially recognized member of the 3'-amino-3'-deoxyadenosine family of antibiotics and has been employed extensively in studies on protein biosynthesis.[4] Its 3'-*N*-(*p*-methoxy-L-phenylalanyl)amino substituent mimics the charged 3'-terminus of aminoacylated transfer ribonucleic acid (tRNA) and functions as an alternative acceptor of the growing peptide chain at the peptidyl tRNA site of ribosomes. The isolation of 3'-acetamido-3'-deoxyadenosine (**B**, **R** = CH_3), "homocitrullylaminoadenosine" (**B**, **R** = $COCH(NH_2)(CH_2)_4NHCONH_2$), "lysylaminoadenosine" (**B**, **R** = $COCH(NH_2)(CH_2)_4NH_2$), and 3'-amino-3'-deoxyadenosine (**6**) from microbiological cultures was reported subsequently.[4]



A



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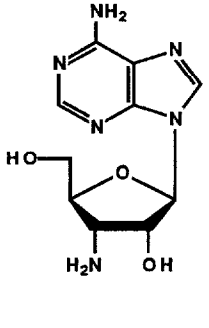


6

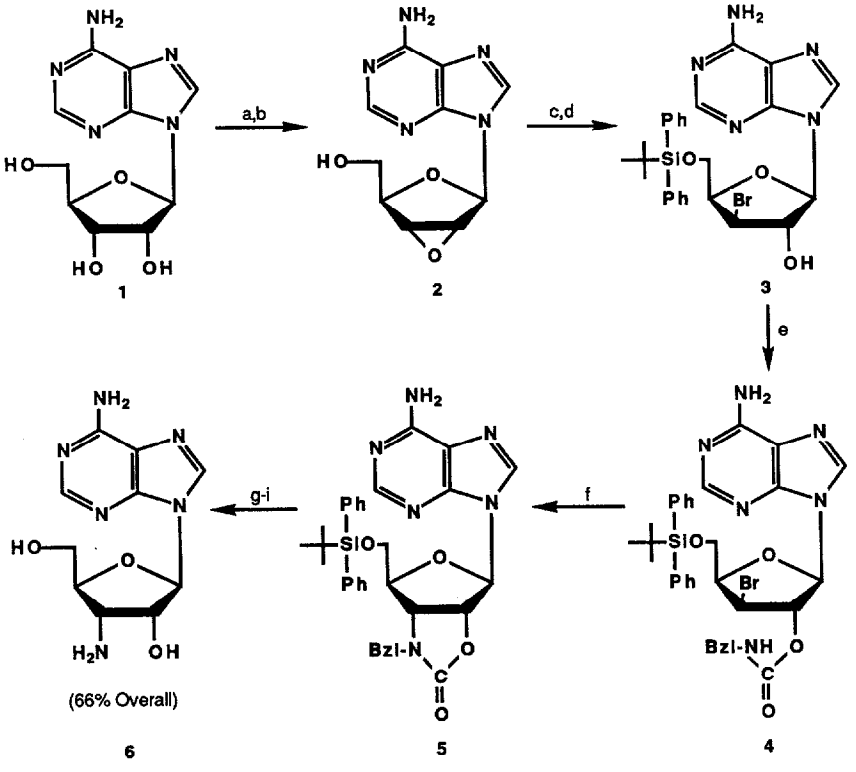
Several syntheses[4] of 3'-amino-3'-deoxyadenosine (**6**) and related aminosugar nucleosides have been reported. The initial synthesis by Baker and co-workers (overall yield <2%) involved preparation of a derivative of 3-amino-3-deoxyribose (12 steps from xylose) and its coupling with a chloromercury salt derivative of adenine.[5] Subsequent synthetic efforts have produced 3-amino-3-deoxyribose derivatives from glucose or xylose in overall yields of ≤36%.[6] Coupling with a purine base followed by conversion to the antibiotic requires further steps and yield losses. Transformation of adenosine to 3'-amino-3'-deoxyadenosine has been reported, but the overall yield again was low (<5%).[7a,b] We now describe a 9-stage synthesis of the parent 3'-amino-3'-deoxyadenosine antibiotic with an overall yield of 66%. This convenient and highly efficient sequence employs reactions that proceed at or below ambient temperature with actual yields of ≥90% for each of the individual steps (and average yields of >95%).

Treatment of adenosine (**1**) with α-acetoxyisobutyryl bromide in "moist" acetonitrile[8] followed by direct treatment of the mixture of *trans*-3'(2')-bromo-2'(3')-acetates[9] with Dowex 1X2(OH^-) resin in methanol gave 2',3'-anhydroadenosine (**2**, 92%).[8] Selective protection of the primary alcohol group of **2** with *tert*-butyldiphenylsilyl chloride/pyridine to give 2',3'-anhydro-5'-*O*-*tert*-butyldiphenylsilyladenosine[10] proceeded quantitatively. Use of the previously noted[7c] HBr/DMF reagent for epoxide ring opening resulted in mixed glycosyl bond cleavage and recovery of starting material, or more extensive glycosyl cleavage if treatment was continued until starting material was completely consumed. However, the use of dimethylboron bromide[11] circumvented this acidic side-reaction and gave clean and quantitative formation of 9-(3-bromo-5-*O*-*tert*-butyldiphenylsilyl-3-deoxy-β-**D**-xylofuranosyl)adenine (**3**).

The protected bromohydrin (**3**) reacted readily with acylisocyanates and the resulting acylcarbamate derivatives underwent intramolecular nucleophilic ring closure to the desired oxazolidinones.[12] However, treatment of the 3'-*N*-acyloxazolidinones with base gave deacylated oxazolidinone derivatives that were resistant to further cleavage under conditions that preserved the nucleoside skeleton.[12] Baker, Goodman, and co-workers had used phenylisothiocyanate in an analogous sequence to prepare a 2-*N*-phenylamino-2-deoxymannopyranoside derivative.[13] We anticipated that a 3'-*N*-benzyloxazolidinone analogue would undergo decarbonylation under mild basic conditions since anionization of the oxazolidinone ring would be precluded.

Treatment of **3** with benzylisocyanate/triethylamine gave 9-(2-*O*-benzylcarbamoyl-3-bromo-5-*O*-*tert*-butyldiphenylsilyl-3-deoxy-β-**D**-xylofuranosyl)adenine (**4**). Ring closure to give 3'-*N*-benzylamino-5'-*O*-*tert*-butyldiphenylsilyl-3'-*N*,2'-*O*-carbonyl-3'-deoxyadenosine (**5**) proceeded smoothly when purified crystalline **4** was treated overnight at -20°C with sodium hydride in tetrahydrofuran. However, variable yields of **5** were obtained by treatment of **4** after

the usual work-up. Removal of the silyl group from **5** with tetrabutylammonium fluoride gave 3'-*N*-benzylamino-3'-*N*,2'-*O*-carbonyl-3'-deoxyadenosine. This 3'-*N*-benzylated oxazolidinone derivative underwent the anticipated decarbonylation in aqueous 0.5 *N* sodium hydroxide at ambient temperature to give 3'-*N*-benzylamino-3'-deoxyadenosine. Hydrogenolysis of the *N*-benzyl group occurred readily at ambient pressure and temperature in the presence of palladium on carbon, or by transfer hydrogenolysis with palladium on polyethylenimine beads in formic acid/methanol/water to give the target antibiotic 3'-amino-3'-deoxyadenosine (**6**).



(a) $Me_2C(OAc)COBr/MeCN/H_2O$(trace). (b) Dowex 1X2 (OH^-)/MeOH (a-b, 92%). (c) *t*-BuSi(Ph)$_2$Cl/C_5H_5N (98%). (d) $Me_2BBr/Et_3N/CH_2Cl_2$/-78°C (98%). (e) $PhCH_2NCO/Et_3N$/THF/MeCN (91%). (f) NaH/THF/-20°C. (g) Bu_4NF/THF (f-g, 93%). (h) 0.5 *N* NaOH/H_2O (90%). (i) H_2/Pd/C/EtOH or Pd/polyethylenimine/HCO_2H/MeOH/H_2O(7:14:29) (98%).

This work also constitutes syntheses of the 3'-*N*-acylamino-3'-deoxyadenosine (**B**) series of antibiotics that have been prepared from **6**.[6d] Our route is applicable to nucleoside antibiotics related to adenosine for which base-aminosugar coupling procedures are more problematical. Synthetic details, spectroscopic data, and other applications will be reported.

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