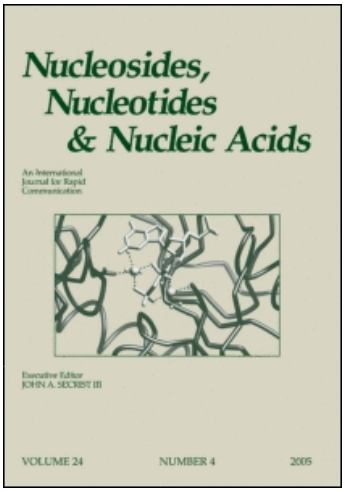


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# Synthesis of 6β-Hydroxyaristeromycin - A Novel Type of Carbocyclic Nucleoside Analogue

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# SYNTHESIS OF 6'β-HYDROXYARISTEROMYCIN - A NOVEL TYPE OF CARBOCYCLIC NUCLEOSIDE ANALOGUE

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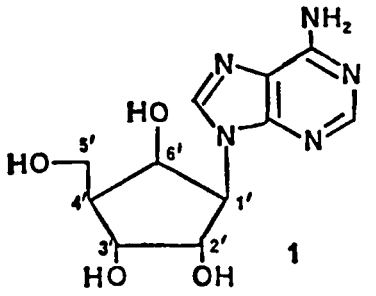
Abstract: The synthesis of racemic 6'β-hydroxyaristeromycin (1) is described.



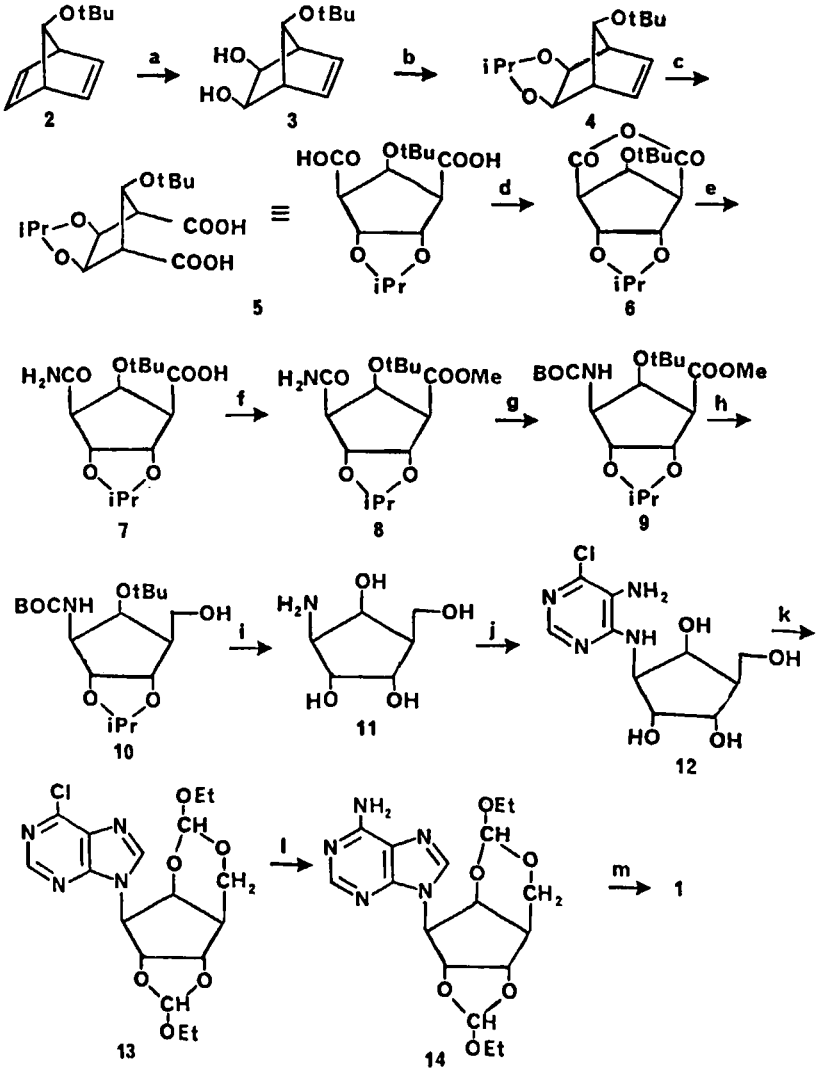
Since the first synthesis[1] and isolation[2] of the antibiotic aristeromycin, carbocyclic analogues of nucleosides have been the subject of many investigations[3]. More recently, the discovery of another group of antibiotics[4], neplanocins A, B, C, D and F, have added a potent stimulus to an already active area of research. Neplanocin B, C and E are the first carbocyclic nucleosides carrying a heteroatom (oxygen) at the C-6' of the cyclopentane ring. It was, therefore, of interest to synthesize analogues functionalized of C-6', e.g., both epimers of 6'-hydroxyaristeromycin. The synthesis of 6'β-epimer 1 is described herein. While our work was in progress, the 6'α-epimer was obtained by an entirely different approach[5].




1

The overall strategy for synthesis of 6'β-hydroxyaristeromycin (1) follows that employed in the first synthesis of aristeromycin[1]. Nevertheless, significant changes in synthetic approach were necessary in order to cope with a higher degree of functionality in the molecule of 1.

Our sequence (Scheme 1) commenced with cis-hydroxylation of readily available[6] 7-tert.-butoxynorbornadiene (2) to give the expected exo-diol



Scheme 1 - reagents: a. $KMnO_4$, 18-crown-6, $Me_2CO$, -70° or $OsO_4$ (catalytic), $Me_3N$-O, aq. $Me_2CO$. b. $Me_2CO$, $CuSO_4$. c. aq. $KMnO_4$. d. DCC, pyridine. e. $NH_3$, THF. f. $CH_2N_2$, ether. g. $Pb(OAc)_4$, tert.-BuOH,Δ. h. $Ca(BH_4)_2$, THF. i. 2 M HCl, MeOH. j. 5-Amino-4,6-dichloropyrimidine, $NEt_3$, BuOH,Δ. k. $CH(OEt)_3$, TsOH. l. $NH_3$, MeOH,Δ. m. 6 M HCl, MeOH. Abbreviations: DCC, dicyclohexylcarbodiimide; THF, tetrahydrofuran; TsOH, p-toluenesulfonic acid; iPr, isopropylidene; BOC, tert.-butoxycarbonyl.

3 at the least hindered double bond of 2. This reaction was effected either with $KMnO_4$ and 18-crown-6 in acetone at -70° (40%) or, more conveniently, with $OsO_4$ and $Me_3N$-O in aqueous acetone at room temperature (40%). Diol 3 was smoothly transformed into the corresponding 2,3-O-isopropylidene derivative 4 by using acetone and $CuSO_4$ (70%). The acid-labile tert.-butoxy function is completely stable under these conditions. Oxidation of 4 with aqueous $KMnO_4$ at 0 - 25° gave the dicarboxylic acid 5 (80 - 90%). The latter was converted by reaction with DCC in pyridine to the corresponding cyclic anhydride (6) which was transformed *in situ* to the monoamide 7 by treatment with $NH_3$ in THF (80%). Esterification of 7 with $CH_2N_2$ afforded ester amide 8 (71%). Hofmann rearrangement of 8, induced by $Pb(OAc)_4$ in refluxing tert.-BuOH[7], gave the BOC-amino ester 9 (98%). This reaction, which is a modification of a "classical" Hofmann rearrangement, proceeds also with retention of configuration. Reduction of 9 with $Ca(BH_4)_2$ in THF then led to the corresponding protected alcohol 10 (81%). The latter was totally deprotected with 2 M HCl in methanol to give the amino tetrol salt 11 (83%). The adenine ring was constructed by a conventional approach[1,8]: Compound 11 was transformed with 5-amino-4,6-dichloropyrimidine and $NEt_3$ in BuOH to intermediate 12 (92%). Imidazole ring closure was effected with $CH(OEt)_3$ - TsOH reagent which also blocked both cis-oriented diols in the form of a bis-orthoformate 13 (80%). Ammonolysis of 13 with $NH_3$ in methanol (pressure bomb, 100°) afforded the respective adenine derivative 14 (83%). Deprotection with 6 M HCl in methanol led to the desired analogue 1 which was isolated by chromatography on Dowex 50 (elution with dilute $NH_4OH$, 68%).

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