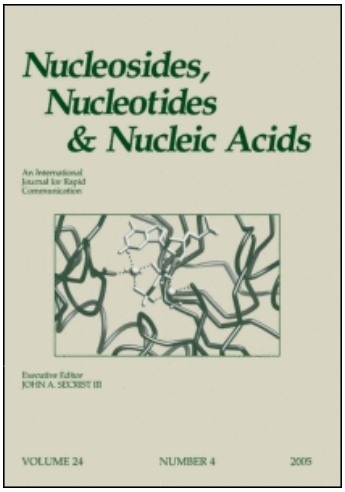

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Psicoplanocin A. A Synthetic Carbocyclic Nucleoside with the Combined Structural Features of Neplanocin A and Psicofuranine

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To cite this Article Marquez, Victor E. and Bodenteich, Michael(1991) 'Psicoplanocin A. A Synthetic Carbocyclic Nucleoside with the Combined Structural Features of Neplanocin A and Psicofuranine', Nucleosides, Nucleotides and Nucleic Acids, 10: 1, 311 — 314
To link to this Article: DOI: 10.1080/07328319108046467
URL: http://dx.doi.org/10.1080/07328319108046467

NUCLEOSIDES & NUCLEOTIDES, 10(1-3), 311-314 (1991)

PSICOPLANOCIN A. A SYNTHETIC CARBOCYCLIC NUCLEOSIDE WITH THE COMBINED STRUCTURAL FEATURES OF NEPLANOCIN A AND PSICOFURANINE

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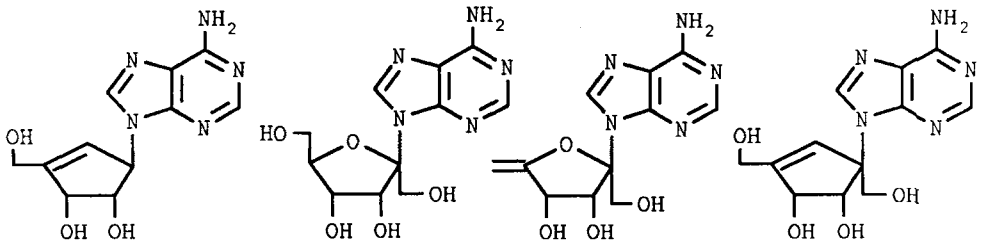
Abstract. Psicoplanocin A represents the first known example of a carbocyclic ketohexose nucleoside. It was synthesized in 8 steps from racemic cyclopentenone **5** which in turn is available from D-ribonolactone.

Of the group of antibiotics that resemble adenosine, neplanocin A (**1**) is a unique compound with an interesting profile of biological activity.[1] In a separate category, the antibiotics psicofuranine (6-amino-9-β-D-psicofuranosyl purine, **2**) and the closely related analogue decoynine (**3**) are two biologically related nucleosides derived from ketose sugars.[2] Pharmacologically, both compounds are important inhibitors of GMP synthetase (XMP aminase) and hence cause significant reduction in guanylic acid biosynthesis.[3] Unlike most bioactive nucleosides, phosphorylation is not necessary for this inhibition.[2,3]



1 2 3 4

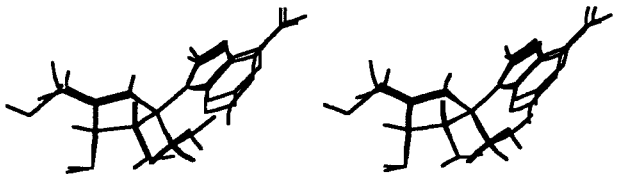
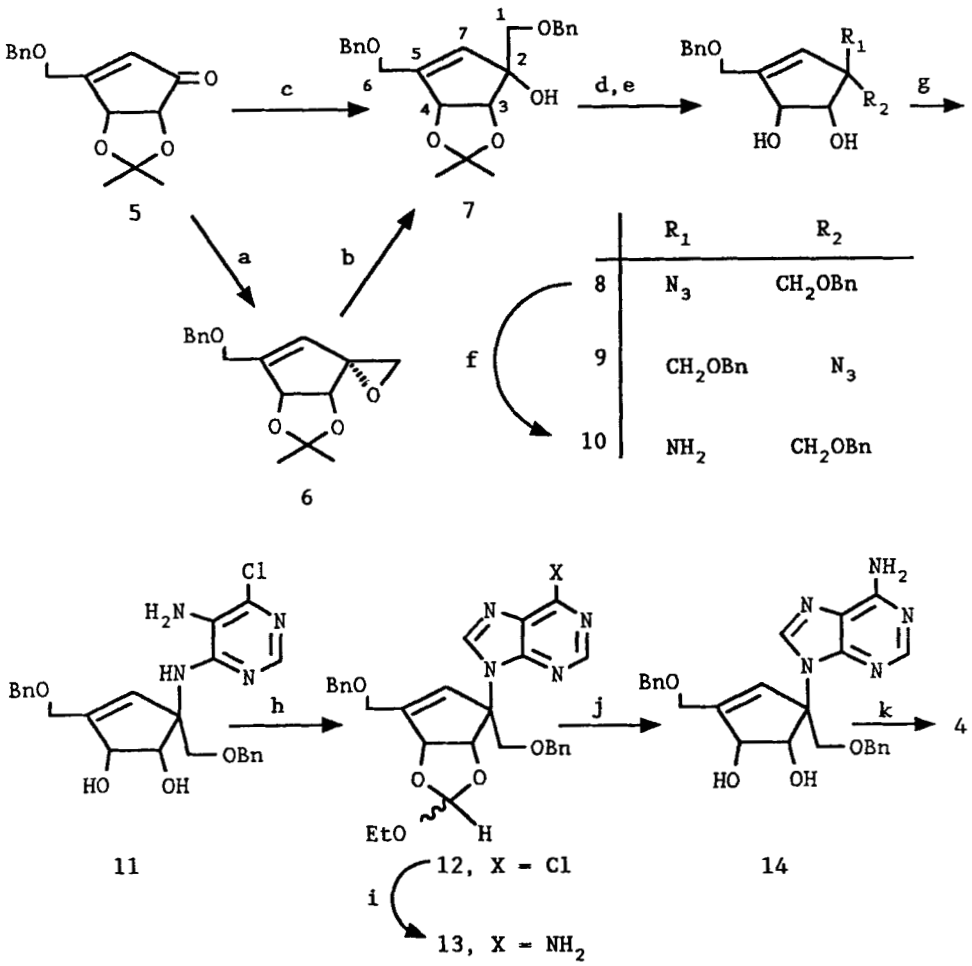


FIGURE 1. Stereo superposition of structures **3** and **4**.

In an attempt to overcome the significant instability of the glycosylic bond of psicofuranine (it undergoes acid-catalyzed hydrolysis 650 times faster than adenosine),[4] the synthesis of psicoplanocin A (**4**) was undertaken. As expected, psicoplanocin A was more conformationally analogous to decoynine (FIG. 1) than psicofuranine. This conformational analogy could be desirable since decoynine has been shown to be more potent than psicofuranine in reducing GTP pools in growing cultures of B. subtilis.[5] This paper describes the synthesis of psicoplanocin A as a chemically stable chemotherapeutic agent structurally resembling both neplanocin A and the ketohexose nucleosides **2** and **3**.

The protected cyclopentenone derivative **5**, which was available from D-ribonolactone,[6] was converted to the tertiary alcohol **7** by two different routes. First, epoxide **6**, obtained by the addition of dimethylsulfur methylide[7,8] to the carbonyl of **5**, underwent nucleophilic ring-opening with sodium benzyloxide to give the desired alcohol **7**. Despite the efficiency of the ring-opening step, the epoxide-forming step gave generally poor yields and this route had to be abandoned. Alternatively, alcohol **7** was generated in one step after treatment of **5** with benzyloxymethyllithium (readily available by transmetallation of n-$Bu_3SnCH_2OCH_2Ph$ with n-Buli).[9,10] The introduction of a nitrogen at the tertiary allylic carbon was achieved by the Lewis acid-catalyzed reaction of **7** with hydrazoic acid (2 N in $CHCl_3$),[11] which produced a good yield of a mixture of epimeric azides (**8** and **9**) with the concomitant loss of the isopropylidene moiety. The desired and less abundant azide **8** (40% of the mixture) was isolated chromatographically (silica gel, toluene/EtOAc 6:1) and characterized by comparative HETCOR and NOE experiments conducted with both isomers. As anticipated, irradiation of the C_1 methylene protons caused a significant enhancement of the C_3 methine proton signal



a. $CH_2=S(CH_3)_2$, DMSO/THF, 5° C, 20-48%;
b. NaOBn, THF, rt, 32 h, 68%;
c. 1.2 eq. n-$Bu_3SnCH_2OCH_2Ph$, BuLi, THF, -78° C, 97%;
d. 2N HN_3 in $CHCl_3$, 0.3 eq. $BF_3.OEt_2$, rt, 16 h, 73%;
e. silica gel chromatography, 29% 8, 44% 9;
f. Lindlar catalyst, MeOH, 1 bar H_2, 2.5 h, 99%;
g. 2 eq. 5-amino-4,6-dichloropyrimidine, NEt_3, n-BuOH, 145° C, 60 h, 42%;
h. $CH(OEt)_3$, cat. HCl, rt, 16 h, 78%;
i. NH_3/MeOH, 90° C, 20 h, 89%;
j. (i) 6N HCl/MeOH, rt, 2 h; (ii) conc. NH_4OH, rt, 16 h, 92%;
k. Na/liquid NH_3, 59%.

only in the case of isomer **9**. The azide **8** was reduced to the carbocyclic amine **10**, from which the construction of the purine ring was performed by classical methods.[1] Due to considerable steric crowding in **10**, forcing conditions were required to achieve the initial condensation between **10** and 5-amino-4,6-dichloropyrimidine. The coupled product **11** was isolated as a crystalline solid which cyclized efficiently to the fully protected purine **12** (endo/exo mixture) in the presence of triethyl orthoformate. Ammonolysis of **12**, and reaction of the resulting adenine analogue with 6 N methanolic HCl, followed by treatment with NH_4OH, afforded the partially protected psicoplanocin A (**14**). Removal of the two benzyl groups by treatment with Na/liquid ammonia and recrystallization of the solid from water, afforded pure (±)-psicoplanocin A, mp 240°C; ^1H NMR (Me_2SO-d_6+D_2O) δ 3.73 (d, 1 H, J = 11.0 Hz, H_a-1′), 3.87 (d, 1 H, J = 11.0 Hz, H_b-1′), 4.11 (br s, 2 H, H-3′, H-4′), 4.35 (br s, 2 H, $H_{a,b}$-6′), 6.46 (s, 1H, H-7′), 8.11 (s, 1 H, H-8), 8.14 (s, 1 H, H-2); high resolution FAB MS, m/z 294.1235 (MH^+, calcd. 294.1202). Anal. Calcd for $C_{12}H_{15}N_5O_4$: C, 49.14; H, 5.16; N, 23.88. Found: C, 49.14; H, 5.19; N, 23.53.

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