

## SYNTHESIS OF ( $\pm$ )- PSICOPLANOCIN A.

A CARBOCYCLIC NUCLEOSIDE COMBINING THE STRUCTURAL FEATURES OF PSICOFURANINE AND NEPLANOCIN A.

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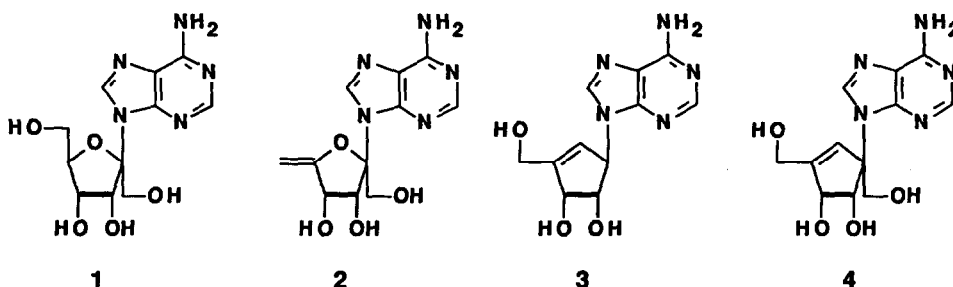
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**Abstract:** ( $\pm$ )-Psicoplanocin A (**4**) was synthesized in 8 steps from racemic cyclopentenone **5**, which is available from D-ribonolactone.

The antibiotic psicofuranine (6-amino-9- $\beta$ -D-psicofuranosyl purine, **1**) and the closely related analogue decoynine (**2**) are two interesting nucleosides derived from ketose sugars.<sup>1</sup> Pharmacologically, both compounds are important inhibitors of GMP synthetase and hence cause significant reduction in guanylic acid biosynthesis.<sup>2</sup> Unlike most bioactive nucleosides, their activity does not depend on metabolic conversion to the corresponding nucleotides, and experimental evidence suggests that they bind to the enzyme at a regulatory site as free nucleosides.<sup>2</sup> Psicofuranine, in particular, has been reported to have important antitumor and antibacterial properties but its instability to both acidic and basic conditions constitute a significant drawback.<sup>2-4</sup>

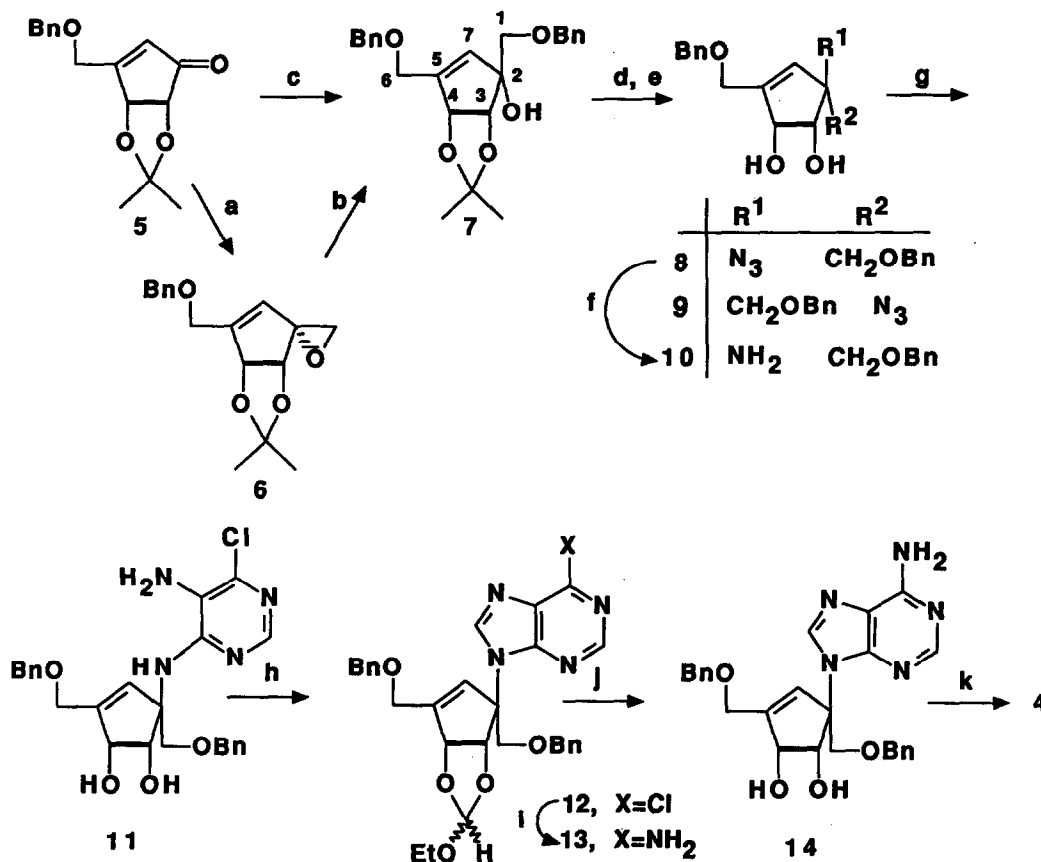


As part of our ongoing search for bioactive carbocyclic nucleosides possessing the characteristic cyclopentenyl moiety of neplanocin A (**3**),<sup>5-8</sup> the synthesis of psicoplanocin A (**4**) was undertaken. In addition, the recognized superior biological potency of decoynine

which also possesses an unsaturated glycon,<sup>9,10</sup> provided an additional incentive for the synthesis of **4**. Of further interest was also the expected stability of the new compound by virtue of its carbocyclic structure.<sup>11</sup>

The protected cyclopentenone derivative ( $\pm$ )-**5**, which was available as reported earlier from D-ribonolactone,<sup>7</sup> was transformed into the tertiary alcohol **7** by two different routes. First, reaction of **5** with dimethyl sulfur methylide in DMSO at low temperature<sup>12,13</sup> produced the desired epoxide **6**, which was then converted to the alcohol **7** by nucleophilic opening of the oxirane ring with sodium benzyolate in THF. Although the conversion of **6** into **7** was very efficient, this route had to be abandoned due to the erratic and generally poor yields that were obtained of the epoxide **6**. This was probably due to the efficient formation of the enolate form of the starting ketone **5** under the reaction conditions. To overcome this problem a direct approach to the alcohol **7** was explored. Treatment of **5** at  $-78^{\circ}\text{C}$  in THF with benzyloxymethyl lithium (readily available by transmetalation of  $n\text{-Bu}_3\text{SnCH}_2\text{OCH}_2\text{Ph}$  with  $n\text{-BuLi}$ )<sup>14,15</sup> produced the desired alcohol **7** in nearly quantitative yield. 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  $\text{CHCl}_3$ )<sup>16</sup> to give a mixture of the pivotal intermediate azide **8** along with its epimer **9**. Although the overall yield was good, the ratio of **8/9** (2/3) was in favor of the undesired epimer. The structures of **8** and **9** were assigned on the basis of HETCOR and n.O.e experiments. As anticipated, irradiation of the  $\text{C}_1$  methylene protons caused a significant enhancement of the  $\text{C}_3$  methine proton signal only in the case of isomer **9**. These isomers were separated by silica gel chromatography (toluene/ethyl acetate 6/1) and the less polar isomer **8** was isolated and reduced to **10**. Construction of the adenine base from this carbocyclic amine was performed by an adaption of the classical sequence.<sup>11,17</sup> Because of the considerable steric crowding in **10**, forcing conditions were required to achieve the condensation of 5-amino-4,6-dichloropyrimidine to produce **11** (2 eq. of the pyrimidine base, 2eq.  $\text{NEt}_3$ ,  $n\text{-BuOH}$  in a sealed tube,  $145^{\circ}\text{C}$ , 3 days). Removal of the solvents and purification by silica gel chromatography (toluene/ethyl acetate 3/1 followed by ethyl acetate) produced intermediate **11** as a crystalline solid: mp  $159\text{-}60^{\circ}\text{C}$ ;  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  3.18(d,  $J=6.4$  Hz, 1H, OH-4'), 3.43(br s, 2H,  $\text{NH}_2$ ), 3.74(d,  $J_{ab}=9.2$  Hz, 1H,  $\text{H}_a\text{-}1'$ ), 3.84(d,  $J_{ab}=9.2$  Hz, 1H,  $\text{H}_b\text{-}1'$ ), 4.18(dd,  $J_1=2.3$  Hz,  $J_2=6.4$  Hz, 1H, H-3'), 4.24(s, 2H,  $\text{CH}_2\text{-Ph}$ ), 4.40(d,  $J_{ab}=12.0$  Hz, 1H,  $\text{H}_a\text{-}6'$ ), 4.52-4.63(m, 4H,  $\text{H}_b\text{-}6'$ , H-4',  $\text{CH}_2\text{-Ph}$ ), 5.31(s, 1H, NH), 5.96(s, 2H, H-7', OH-3'), 7.23-7.37(m,

10 H, 2xPh), 7.98(s, 1H, H-2). Ring closure of **11** was accomplished with triethyl orthoformate in the presence of HCl to give the protected chloropurinyl derivative **12** as an endo/exo mixture. Ammonolysis of **12** ( $\text{NH}_3/\text{MeOH}$ , sealed tube,  $90^\circ\text{C}$ ) and sequential treatment of the resulting product **13** with 6 N methanolic HCl and concentrated  $\text{NH}_4\text{OH}$  afforded the partially protected psicoplanocin A derivative **14**. Removal of the two benzyl



- a.  $\text{CH}_2=\text{S}(\text{CH}_3)_2$ , DMSO/THF,  $5^\circ\text{C}$ , 20 - 48%;  
 b. NaOBn, THF, rt, 32 h, 68%;  
 c. 1.2 eq.  $n\text{-Bu}_3\text{SnCH}_2\text{OCH}_2\text{Ph}$ , BuLi, THF,  $-78^\circ\text{C}$ , 97%;  
 d. 2 N  $\text{HN}_3$  in  $\text{CHCl}_3$ , 0.3 eq.  $\text{BF}_3\cdot\text{OEt}_2$ , rt, 16 h, 73%;  
 e. silica gel chromatography, 29% **8**, 44% **9**;  
 f. Lindlar catalyst, MeOH, 1 bar  $\text{H}_2$ , 2.5 h, 99%;  
 g. 2 eq. 5-amino-4,6-dichloropyrimidine,  $\text{NEt}_3$ ,  $n\text{-BuOH}$ ,  $145^\circ\text{C}$ , 60 h, 42%;  
 h.  $\text{CH}(\text{OEt})_3$ , cat. HCl, rt, 16h, 78%;  
 i.  $\text{NH}_3/\text{MeOH}$ ,  $90^\circ\text{C}$ , 20h, 89%;  
 j. (i) 6N HCl/MeOH, rt, 2h; (ii) conc.  $\text{NH}_4\text{OH}$ , rt, 16 h, 92%;  
 k. Na/liq.  $\text{NH}_3$ , 59%.

groups was performed with sodium in liquid ammonia to give crude racemic **4**, which was purified by recrystallisation from water to give pure ( $\pm$ )-psicoplanocin A:<sup>18</sup> mp 240 °C; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, D<sub>2</sub>O)  $\delta$  3.73(d, J<sub>ab</sub>=11.0 Hz, 1H, H<sub>a</sub>-1'), 3.87(d, J<sub>ab</sub>=11.0 Hz, 1H, H<sub>b</sub>-1'), 4.11 (br s, 2H, H-3', H-4'), 4.35(br s, 2H, CH<sub>2</sub>-6'), 6.46(s,1H, H-7'), 8.11(s, 1H, H-8), 8.14(s, 1H, H-2); high resolution FAB MS, m/z 294.1235 (MH<sup>+</sup>, calcd. 294.1202).

This synthesis provides the first example of a carbocyclic analogue of a ketohexose nucleoside. Further synthetic studies in this field are currently in progress in this laboratory.

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