Tetrahedron Letters, Vol.31, No.42, pp 5977-5980, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

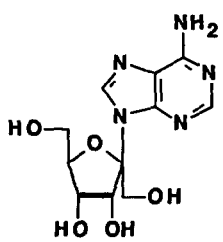
SYNTHESIS OF (±)- PSICOPLANOCIN A.

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

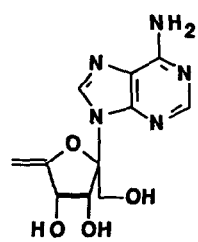
Michael Bodenteich and Victor E. Marquez*
Laboratory of Medicinal Chemistry,
Developmental Therapeutics Program, Division of Cancer Treatment
National Cancer Institute, National Institutes of Health,
Bethesda, Maryland 20892

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

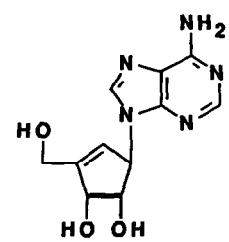
The antibiotic psicofuranine (6-amino-9-ß-D-psicofuranosyl purine, **1**) and the closely related analogue decoynine (**2**) are two interesting nucleosides derived from ketose sugars.[1] Pharmacologically, both compounds are important inhibitors of GMP synthetase and hence cause significant reduction in guanylic acid biosynthesis.[2] 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.[2] 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.[2-4]



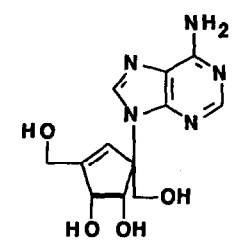
1



2



3



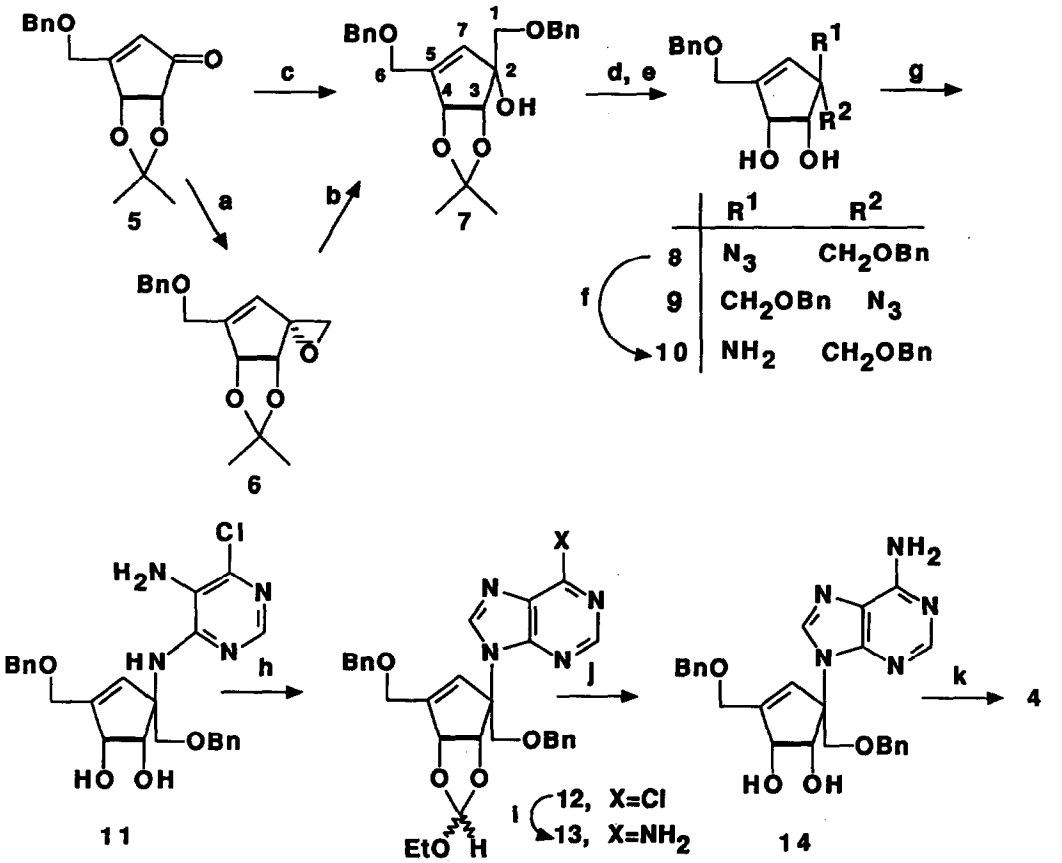
4

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

which also possesses an unsaturated glycon,[9,10] 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.[11]

The protected cyclopentenone derivative (±)-**5**, which was available as reported earlier from D-ribonolactone,[7] was transformed into the tertiary alcohol **7** by two different routes. First, reaction of **5** with dimethyl sulfur methylide in DMSO at low temperature[12,13] produced the desired epoxide **6**, which was then converted to the alcohol **7** by nucleophilic opening of the oxirane ring with sodium benzylate 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°C in THF with benzyloxymethyllithium (readily available by transmetallation of n-$Bu_3SnCH_2OCH_2Ph$ with n-BuLi)[14,15] 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 $CHCl_3$)[16] 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 C_1 methylene protons caused a significant enhancement of the 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.[11,17] 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. NEt_3, n-BuOH in a sealed tube, 145°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 159-60°C; ^{1}H-NMR ($CDCl_3$) δ 3.18(d, J=6.4 Hz, 1H, OH-4'), 3.43(br s, 2H, NH_2), 3.74(d, J_{ab}=9.2 Hz, 1H, H_a-1'), 3.84(d, J_{ab}=9.2 Hz, 1H, H_b-1'), 4.18(dd, J_1=2.3 Hz, J_2=6.4 Hz, 1H, H-3'), 4.24(s, 2H, CH_2-Ph), 4.40(d, J_{ab}=12.0 Hz, 1H, H_a-6'), 4.52-4.63(m, 4H, H_b-6', H-4', CH_2-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** (NH_3/MeOH, sealed tube, 90°C) and sequential treatment of the resulting product **13** with 6 N methanolic HCl and concentrated NH_4OH afforded the partially protected psicoplanocin A derivative **14**. Removal of the two benzyl



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. 2 N 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, 16h, 78%;
i. NH_3/MeOH, 90°C, 20h, 89%;
j. (i) 6N HCl/MeOH, rt, 2h; (ii) conc. NH_4OH, rt, 16 h, 92%;
k. Na/liq. 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 (±)-psicoplanocin A:[18] mp 240 °C; ^{1}H-NMR (DMSO-d_6, D_2O) δ 3.73(d, J_{ab}=11.0 Hz, 1H, H_a-1'), 3.87(d, J_{ab}=11.0 Hz, 1H, H_b-1'), 4.11 (br s, 2H, H-3', H-4'), 4.35(br s, 2H, CH_2-6'), 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^+, 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.

Acknowledgement: We are grateful to Dr. James A. Kelley, Laboratory of Medicinal Chemistry (LMC) for the mass spectral data and to Dr. Joe Barchi (LMC) for the HETCOR and n.O.e. experiments.

References and Notes:

(1) Suhadolnik, R. J. *Nucleoside Antibiotics*; John Wiley-Interscience: New York, 1970; pp105-107.
(2) Nichol, C. A. in *Handb.-Exp. Pharmacol.*, 38 (*Antineoplast. Immunosuppr. Agents, Pt. 2*), 1975; pp 434-457.
(3) Garrett, E. R. J. *J. Am. Chem. Soc.* **1960**, *82,* 827.
(4) York, J. L. *J. Org. Chem.* **1981**, *46,* 2171.
(5) Bodenteich, M.; Marquez, V. E. *Tetrahedron Lett.* **1989**, *30,* 4909.
(6) Tseng, C. K. H.; Marquez, V. E.; Fuller, R. W.; Goldstein, B. M.; Haines, D. R.; McPherson, H.; Parsons, J. L.; Shannon, W. M.; Arnett, G.; Hollingshead, M .; Driscoll, J. S. *J. Med. Chem.* **1989**, *32,* 1442.
(7) Marquez, V. E.; Lim, M.-I.; Tseng, C. K. H.; Markovac, A.; Priest, M. A.; Khan, M. S.; Kaskar, B. *J. Org. Chem.* **1988**, *53,* 5709.
(8) Marquez, V. E.; Lim, M.-I.; Treanor, S. P.; Plowman, J.; Priest, M. A.; Markovac, A.; Khan, M. S.; Kaskar, B.; Driscoll, J. S. *J. Med. Chem.* **1988**, *31,* 1687.
(9) Mitani, T.; Heinze, J. E.; Freese, E. *Biochem. Biophys. Res. Commun.* **1977**, *77,* 1118.
(10) Abedin, Z.-U.; Lopez, J. M.; Freese, E. *Nucleos. Nucleot.* **1983**, *2,* 257.
(11) Marquez, V. E.; Lim, M.-I. *Med. Res. Rev.* **1986**, *6,* 1.
(12) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87,* 1353.
(13) Medich, J. R.; Kunnen, K. B.; Johnson, C. R. *Tetrahedron Lett.* **1987**, *28,* 4143.
(14) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100,* 1481.
(15) Seitz, D. E.; Carroll, J. J.; Cartaya, C. P.; Zapata, S.-H. L. *Synth. Commun.* **1983**, *13,* 129.
(16) Hassner, A.; Fibiger, R.; Andisik, D. *J. Org. Chem.* **1984**, *49,* 4237.
(17) Shealy, Y. F.; Clayton, J. D. *J. Am. Chem. Soc.* **1969**, *91,* 3075.
(18) A sample of this material gave a satisfactory combustion analysis.

(Received in USA 27 June 1990)