Synthesis of Carbocyclic Analogues of 1-β-D-Psicofuranosyl Nucleosides. *psico*-Cyclopentenyladenosine (Psicoplanocin A) and *psico*-Cyclopentenylcytosine

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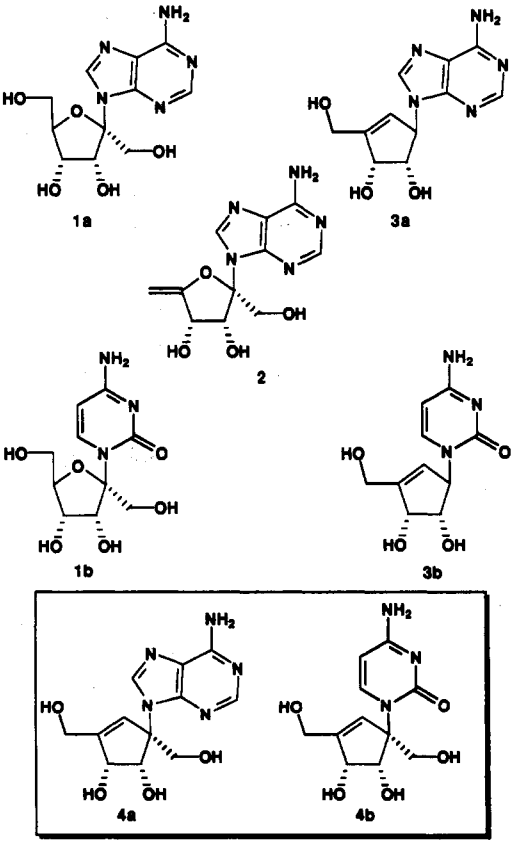
Psicoplanocin A (**4a**) and *psico*-cyclopentenylcytosine (**4b**) represent the first two known examples of carbocyclic ketohexose nucleosides. These two stable compounds combine structural features of two known classes of natural products: neplanocin A and the ketohexose nucleosides psicofuranine (**1a**) and decoynine (**2**). Both compounds were synthesized in racemic form from (±)-cyclopentenone **5**, which in turn was available from D-ribonolactone. Construction of the surrogate glycon moiety commenced with the attachment of a protected hydroxymethyl fragment onto the ketone carbonyl of **5** via nucleophilic addition of [(benzoyloxy)methyl]lithium to give intermediate **7**. Introduction of the requisite nitrogen at the tertiary allylic carbon of **7** was achieved by the BF_3·OEt_2-catalyzed addition of hydrazoic acid to a generated transitional allylic cation. This method produced the epimeric azides **8a** and **8b**, and following conversion of the β-azide (**8a**) to the corresponding carbocyclic amine, the purine and pyrimidine rings of psicoplanocin A and *psico*-cyclopentenylcytosine were constructed by conventional methods. An X-ray crystallographic analysis corroborated the structure of psicoplanocin A determined from NOE experiments on the epimeric azides. Both psicoplanocin A and *psico*-cyclopentenylcytosine were found to be devoid of cell cytotoxicity and in vitro antiviral activity.

Psicofuranine (**1a**) and decoynine (**2**) are two unique ketonucleoside antibiotics[1] that function as inhibitors of the biosynthesis of guanylic acid from inosinic acid.[2] These nucleosides appear to bind unaltered to a regulatory site of the enzyme, and therefore, their activity is not subject to metabolic conversion to the corresponding nucleotides.[2] Psicofuranine, in particular, has been recognized to have important antitumor and antibacterial properties,[3] but its instability to both acidic and basic conditions constitutes a significant drawback.[4] In fact, psicofuranine undergoes acid-catalyzed cleavage of its glycosylic bond 650 times faster than adenosine.[5] In an attempt to circumvent such hydrolytic instability, the corresponding carbocyclic nucleoside with a cyclopentene structure was conceived as a target (psicoplanocin A, **4a**). The selection of the cyclopentene structure, which is a structural motif characteristic of the antitumor antibiotic neplanocin A (**3a**),[6,7] was based on the fact that in the structure of the more potent congener of psicofuranine, decoynine (**2**), the presence of the double bond flattens the ribose ring to a conformation that is mimicked very nicely by the cyclopentene ring of neplanocin. The three-dimensional analogy between decoynine and the chosen target, psicoplanocin A (**4a**), was evident from a simple molecular modeling comparison.[8]



Cyclopentenylcytosine (CPE-C, **3b**) was independently synthesized in our laboratory and by Ohno in Japan some

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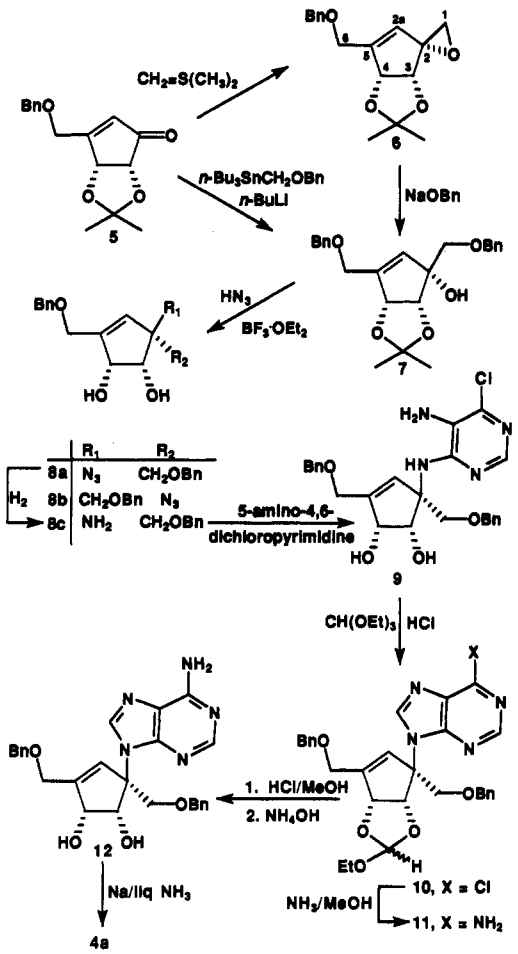
Scheme I



years ago.[9-12] This compound was selected from our carbocyclic nucleoside program based on its excellent antitumor and antiviral properties.[12] CPE-C is currently being evaluated as an antitumor drug in Phase I clinical trials sponsored by the NCI. On the basis of these considerations, the synthesis of *psico*-cyclopentenycytosine (**4b**) was undertaken. *psico*-Cyclopentenylcytosine is structurally related to the known 1-(β-D-psicofuranosyl)-cytosine (**1b**).[13] According to the published X-ray structure of **1b**, the extra hydroxymethyl appendage appears to have little influence on the overall conformation of the molecule relative to cytidine.[14] Therefore, it was considered of interest to investigate how a comparable modification of CPE-C would modulate the biological activity of such a potent antimetabolite.

Results and Discussion

The pivotal cyclopentenone derivative (±)-**5** (Scheme I), obtained as reported earlier from D-ribonolactone,[15,16] was used as the starting material. Although we have also synthesized this lactone in pure enantiomeric form [(−)-**5**],[15,16] we decided, for economic reasons, to utilize the racemate first. In addition, as we shall see later, there is one step in the synthetic sequence that would have inevitably caused racemization of the product had we started with the pure enantiomeric cyclopentenone. The synthesis of psicoplanocin A has already been reported in preliminary form.[8,17] As shown in Scheme I, reaction of **5** with dimethyl sulfur methylide in DMSO at low temperature[18,19] produced epoxide **6** which was easily converted to the tertiary alcohol **7** by nucleophilic opening of the oxirane ring with sodium benzylate. Although this conversion was very efficient, this route was later abandoned due to the generally poor yields of epoxide **6**. Alternatively, **7** was generated directly and in excellent yield after treatment of **5** with [(benzyloxy)methyl]lithium which was readily available by transmetalation of *n*-$Bu_3SnCH_2OCH_2Ph$ with *n*-BuLi.[20,21] The stereochemistry of **7** is presumed to be as shown due to the extremely hindered concave face of the bicyclic [3.3.0] system present in **5** which will direct nucleophilic attack from the β-side. Indeed, we have previously reported the exclusive formation of the corresponding α-alcohol following borohydride reduction of **5**.[15] The introduction of the nitrogen at the tertiary allylic carbon was achieved by the BF_3·Et_2O-catalyzed reaction of **7** with hydrazoic acid[22] which gave a mixture of epimeric azides **8a** and **8b**. Among several Lewis acid catalysts tried, BF_3·Et_2O was the only one that worked. This reaction occurred with the simultaneous partial loss of the isopropylidene moiety, and additional treatment with trifluoroacetic acid was required to remove this group completely. At this stage, the epimeric azides were easily separated by column chromatography. The desired azide (**8a**) with the β-configuration was separated from its more polar epimer, but unfortunately it constituted the minor isomer (40%) of the mixture. As alluded to earlier, even if we had started with an enantiomerically pure precursor, racemization would have occurred at this stage due to the symmetry of the allylic cationic intermediate (Figure 1).

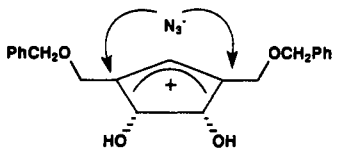


Figure 1. Transitional symmetric allylic cation-showing azide ion attack from either termini.

Determination of the structures of the epimeric azides (**8a**/**8b**) by NMR was performed on the protected compounds **13a** and **13b**. The bicyclic nature of the O3′–O4′ isopropylidene intermediates offered a more rigid backbone for the establishment of nuclear Overhauser enhancements (NOE) of the ring protons. Equilibrium, 1-D NOE difference experiments performed with **13b** in degassed $CDCl_3$ and acetone-d_6 showed a characteristic

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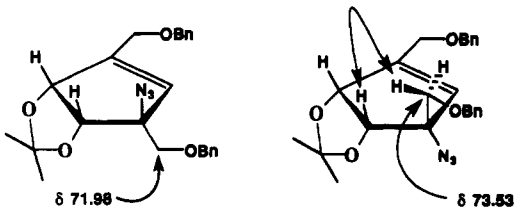


Figure 2. NMR data for epimeric azides **13a** and **13b**. NOE interactions are marked by a double arrow.

enhancement of the C3′ proton signal when the C1′ protons were irradiated. Such an enhancement was not observed for compound **13a**. Assignment of the ^{13}C signals from heteronuclear multiple quantum coherence (HMQC) spectra at 125 MHz revealed an upfield shift in the C1′ carbon of **13b** as compared with **13a** due to *endo* face van der Waals shielding.[23] This is illustrated in Figure 2. These data provided sound evidence that **13a** embodied the desired stereochemistry at C2′ for processing to **4b**. This was later corroborated by the X-ray analysis of synthetic psicoplanocin A (*vide infra*).

Reduction of the azide function of **8a** occurred uneventfully in the presence of Lindlar catalyst, and construction of the adenine ring from carbocyclic amine **8c** was performed by an adaptation of the classical sequence.[24,25] Due to considerable steric crowding in **8c**, forcing conditions were required to achieve its condensation with 5-amino-4,6-dichloropyrimidine. Compound **9** was isolated as a crystalline solid, and ring closure to an *endo*/*exo* mixture of the protected chloropurine intermediate **10** was easily achieved. Ammonolysis of **10** and sequential treatment of the resulting product **11** with HCl, followed by neutralization with ammonia, afforded the partially protected psicoplanocin A precursor **12**. Removal of the two benzyl moieties with sodium in liquid ammonia gave pure (±)-psicoplanocin A (**4a**).

For the synthesis of *psico*-cyclopentenylcytosine (**4b**), the azide **8b** was again reprotected with the isopropylidene group to give **13a** (Scheme II). Reduction of this compound to the amine **13b** was followed by its condensation with 3-ethoxypropenoyl isocyanate to give the urea intermediate **14**. Attempts to cyclize this intermediate under basic conditions (DMF/aqueous ammonia), as performed earlier,[12] failed to give the desired uracil derivative **15a**. Cyclization was successfully achieved in the presence of H_2SO_4/ethanol, and reprotection of the resulting diol as the isopropylidene acetal gave the uracil precursor **15a**. Complete ddeprotection of this material with BCl_3 produced the carbocyclic *psico*-cyclopentenyluracil (**16**). Transformation of uracil **15a** to the corresponding cytidine analogue was accomplished by standard methodology[11] consisting of converting **15a** to the thiouracil derivative **15b** with Lawesson's reagent, followed by ammonolysis to the fully protected carbocyclic **17**. Deprotection of **17** with BCl_3 gave the desired target, *psico*-cyclopentenylcytosine (**4b**).

Biological evaluation of psicoplanocin A (**4a**) and *psico*-cyclopentenylcytosine (**4b**) indicated that neither compound was cytoxic to Molt 4 cells in vitro and that only psicoplanocin A showed marginal antiviral activity against the arenaviruses Junin and Tacaribe.

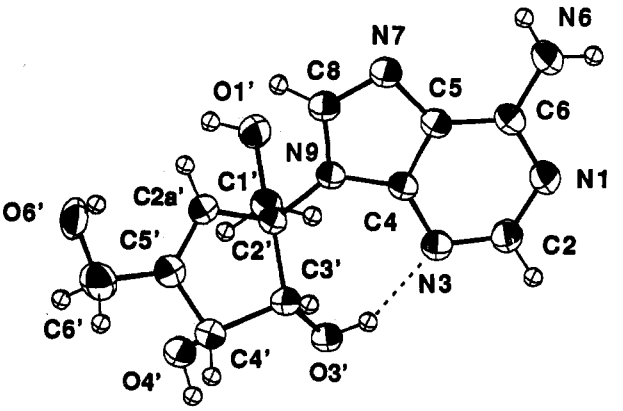
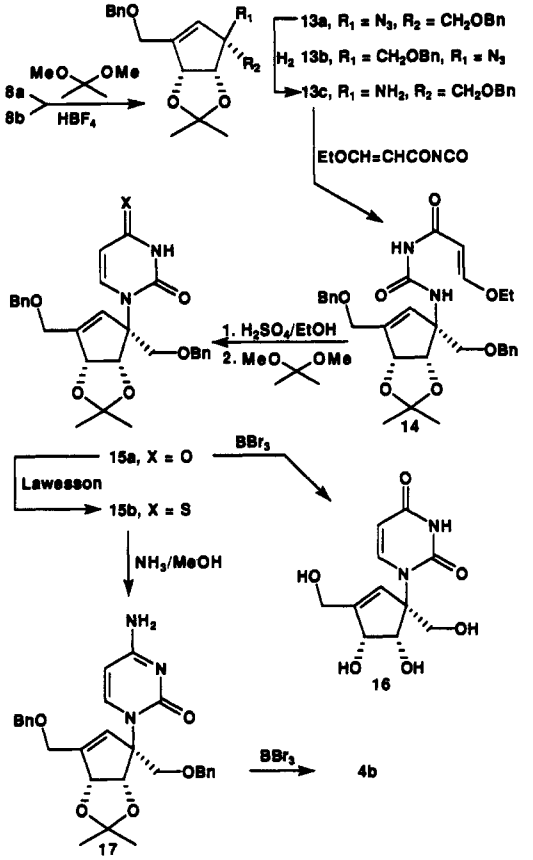


Figure 3. Molecular structure of psicoplanocin A. Non-hydrogen atoms are represented by thermal ellipsoids at the 50% probability level. O6′ is disordered and is shown in its highest occupancy orientation. The dashed line indicates intermolecular hydrogen bond between O3′and N3.

Scheme II



X-ray Crystallography. The molecular structure of psicoplanocin A is shown in Figure 3. The adenine moiety is planar within ±0.03 Å. The amine nitrogen deviates from the adenine plane by 0.118(2) Å. Bond lengths and angles for the base are comparable to those found in adenosine,[26] neplanocin A,[27] and neplanocin F.[28] The glycosylic bond length in psicoplanocin A is 1.481(4) Å, slightly longer than the value of 1.476 Å seen in neplanocin A,[27] but reasonable for a purine nucleoside (e.g., adenosine: 1.479 Å).[26] The glycosylic torsion angle χ, C4–N9–

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C2′–C2a′, is 159.4(2)° placing it in the *anti* range. This general conformation is also observed in neplanocin A,[27] neplanocin F,[28] and 3-deazaneplanocin A,[29] although the angles vary considerably within this family of molecules.

The cyclopentene ring in psicoplanocin A is similar to that in neplanocin A[27] and 3-deazaneplanocin A.[29] The ring double bond, base linkage, and disposition of hydroxyl and CH_2OH substituents are the same as in neplanocin A, the only difference being the addition of the CH_2OH substituent at C2′ in psicoplanocin A. The C2′, C2a′, C5′, and C4′ atoms deviate no more than 0.003(2) Å from their least-squares plane. The cyclopentene ring assumes an envelope conformation, C3′ lying 0.511(2) Å above the C2′–C2a′–C5′–C4′ plane. If the pseudorotation concept is applied to the cyclopentene ring,[30] the phase angle *P* is 163°. This defines the pucker as C3′-endo, if C2a′ is taken to be analogous to the furanose O4′. Using the labeling scheme shown in Figure 3, a C3′-exo/C4′-endo pucker is seen in the solid state of neplanocin A,[27] a C3′-endo conformation is seen in 3-deazaneplanocin A,[29] and a C2′-exo pucker is seen in neplanocin F.[28] The amplitude of the puckering in psicoplanocin A is 32.7°, equivalent to the dihedral angle between the C2′–C2a′–C5′–C4′ and C2′–C3′–C4′ planes. This is comparable to the 29.5° value observed in 3-deazaneplanocin A,[29] and it is indicative of the limited flexibility of the cyclopentene ring in both structures.

The interplanar angle between the mean plane of all cyclopentane carbons and all adenine heavy atoms is 24.4°, which is smaller than the analogous angles observed in other members of this family of molecules (neplanocin A, 81.5°; neplanocin F, 87.7°; 3-deazaneplanocin A, 66.2°). The presence of the CH_2OH substituent at C2′ in psicoplanocin A may, in part, account for this conformation by sterically preventing an interplanar angle closer to 90°, which otherwise appears to be preferred for this class of compounds. The conformation about the glycosylic bond in psicoplanocin A is further stabilized by an intramolecular hydrogen bond between N3 of the adenine ring and HO3′ of the cyclopentene ring. Note however, that neplanocin A, which lacks the extra CH_2OH substituent, does not show this intramolecular hydrogen bond.[27] The CH_2OH substituent at C5′ is disordered (for a description of modeling, see X-ray experimental procedures in the supplementary material). The 66% occupancy CH_2OH substituent at C5′ lies approximately in the C2′–C2a′–C5′–C4′ plane. The torsion angle O6′–C6′–C5′–C2a′ is 348.3(3)°, reflecting the *cis* orientation of the C6′–O6′ bond with respect to the C2a′–C5′ double bond. This is analogous to the structures of 3-deazaneplanocin A,[29] neplanocin F,[28] and neplanocin A,[27] in which the CH_2OH substituents are similarly oriented relative to the carbocyclic double bond. O6′ accepts a hydrogen bond from the HO1′ of a neighboring psicoplanocin A molecule. The 33% occupancy CH_2OH at C5′ lies out of the plane of the carbocyclic double bond, with the torsion angle O6″–C6′–C5′–C2a′ equal to 218.6(4)°. HO6″ is involved in intermolecular hydrogen bonding to the O1′ of a neighboring psicoplanocin A molecule, which accounts for the disorder of the CH_2OH substituent at C5′. Adenine rings in the crystal structure are partially stacked, with an extensive intermolecular hydrogen bonding network among the waters of crystallization and neighboring psicoplanocin A molecules. This creates a water channel parallel to the axis of the unit cell. A table listing all hydrogen bonding interactions is deposited with the Cambridge Crystallographic Data Centre. It can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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Experimental Section

General. All chemical reagents were commercially available. Melting points were determined on a Mel-Temp II apparatus, Laboratory Devices, USA, and are uncorrected. Column chromatography was performed on silica gel 60, 230–400 mesh (E. Merck), and analytical TLC was performed on Merck silica gel 60 F_{254} aluminum sheets. Infrared spectra were recorded on a Perkin-Elmer 1600 Series FTIR. Proton and carbon NMR spectra were recorded in $CDCl_3$ unless otherwise indicated at 200 and 50 MHz, respectively, on a Varian XL-200 instrument. Chemical shifts are expressed as δ values with reference to Me_4Si. In the carbon spectra the signs + and − refer to the peaks above or below the base line in the fully decoupled attached proton test (APT). One-dimensional NOE experiments were performed at rt on a Varian XL-200 with a relaxation delay of 10 s and low power decoupling gated off during acquisition. HMQC and HMBC experiments were performed at 125 MHz using standard pulse sequences on a Varian VXR500 spectrometer at 25 °C. Positive-ion fast-atom bombardment mass spectra (FABMS) were obtained at an accelerating voltage of 6 kV and a resolution of 2000. Glycerol was used as the sample matrix and ionization was effected by a beam of xenon atoms. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, GA, or by Galbraith Laboratories, Inc. Knoxville, TN.

(±)-6-*O*-Benzyl-3,4-*O*-isopropylidene-1,2-anhydro-2a,5-didehydro-2a-carba-α-psicofuranose (6). A suspension of NaH (0.180 g, 80%, 6.0 mmol) was thoroughly washed with petroleum ether and dried under vacuum to remove the mineral oil. Under a nitrogen atmosphere, DMSO (2 mL) was introduced via syringe, and the mixture was heated to 65 °C for 45 min. After the addition of dry THF (4.5 mL) and cooling to a temperature of 0–5 °C, a solution of trimethylsulfonium iodide (1.224 g, 6 mmol) in DMSO (5 mL) was added dropwise during the course of 3 min. After 1 min, and at the same low temperature, a solution of **5** (1.227 g, 4.47 mmol) in anhydrous THF (3 mL) was added at a rapid rate, and stirring was continued for 10 min. The reaction was quenched by the addition of ice-water (50 mL), and the mixture was extracted repeatedly with ether. The combined organic extract was dried (Na_2SO_4) and reduced to dryness, and the oily residue was purified by silica gel column chromatography using petroleum ether/ethyl acetate (3:1) as eluant. The product-containing fractions were combined and evaporated to give **6** (0.620 g, 48%) as a colorless oil: ^1H NMR δ 1.39 (s, 3 H, CH_3), 1.48 (s, 3 H, CH_3), 3.04 (d, J_{AB} = 5.0 Hz, 1 H, H-1$_a$), 3.22 (d, J_{AB} = 5.0 Hz, 1 H, H-1$_b$), 4.23 (unresolved AB system, 2 H, H-6$_{a,b}$), 4.59 (s, 2 H, OCH_2Ph), 4.61 (d, J = 5.7 Hz, 1 H, H-3), 5.11 (d, J = 5.7 Hz, 1 H, H-4), 5.51 (s, 1 H, H-2a), 7.34 (br s, 5 H, Ph); ^{13}C NMR δ 26.50 (−, CH_3), 27.57 (−, CH_3), 52.85 (+, C-1), 65.38 (+, C-2), 66.58 (+, C-6), 72.98 (+, OCH_2Ph), 78.64 (−, C-3), 82.56 (−, C-4), 113.07 (+, CMe_2), 127.58 (−, Ph), 127.67 (−, Ph), 127.90 (−, Ph), 128.34 (−, Ph, C-2a), 137.75 (+, Ph), 147.45 (+, C-5). Anal. Calcd for $C_{17}H_{20}O_4 \cdot 0.25H_2O$: C, 69.72; H, 7.06. Found: C, 69.51; H, 6.97.

(±)-1,6-Di-*O*-benzyl-3,4-*O*-isopropylidene-2a,5-didehydro-2a-carba-α-psicofuranose (7). From Epoxide 6. A stirred suspension of sodium hydride (0.090 g, 80%, 3.0 mmol) in anhydrous THF (10 mL) under argon was cooled to 0 °C. Benzyl alcohol (0.400 g, 3.7 mmol) was added dropwise, and the mixture was allowed to warm to rt. After continued stirring for 30 min, a solution of **6** (0.282 g, 0.978 mmol) in dry THF (2 mL) was added, and stirring was continued for 32 h. The reaction was quenched by the cautious addition of water (30 mL), and the mixture was extracted twice with ether (2 × 50 mL). The organic extract was dried (Na_2SO_4) and concentrated under vacuum. Silica gel column chromatography using toluene/ethyl acetate (3:1) afforded 0.228 g (59%) of **7** as an oil. A second chromatography

of the less pure fractions using petroleum ether/ethyl acetate (3:1) provided an additional 0.036 g (9%) of **7** plus unreactive **6** (0.014 g).

From Ketone 5. A stirred solution of *n*-Bu_3SnCH_2OBn (9.312 g, 22.6 mmol) in anhydrous THF (150 mL) was cooled to −78 °C under argon. A solution of *n*-BuLi in hexane (12.98 mL, 1.6 N, 22.6 mmol) was added over a period of 2 min while the temperature was maintained below −65 °C. Stirring continued for 3 min, and a solution of **5** (5.177 g, 18.87 mmol) in dry THF (5 mL) was added at a rapid rate. The mixture was allowed to react for another 10 min and quenched by the addition of saturated aqueous NH_4Cl solution (50 mL). The resulting mixture was extracted with ether (3 × 100 mL), and the organic extracts were combined, dried (Na_2SO_4), and evaporated under vacuum. The obtained oily residue was purified by silica gel colum chromatography using petroleum ether/ethyl acetate (6:1) to give 7.27 g (97%) of **7** as a colorless oil: ^1H NMR δ 1.37 (s, 3 H, CH_3), 1.42 (s, 3 H, CH_3), 3.16 (s, 1 H, OH), 3.44 (d, J_{AB} = 9.5 Hz, 1 H, H-1_a), 3.58 (d, J_{AB} =9.5 Hz, 1 H, H-1_b), 4.15 (s, 2 H, H-$6_{a,b}$), 4.53–4.57 (m, 5 H, 2 × CH_2Ph, H-3), 4.98 (d, J = 5.6 Hz, 1 H, H-4), 5.67 (s, 1 H, H-2a), 7.25–7.39 (m, 10 H, 2 × Ph); ^{13}C NMR δ 26.56 (−, CH_3), 27.61 (−, CH_3), 66.15 (+, C-1), 72.48, 73.53, 74.00 (+, C-6, 2 × CH_2Ph), 80.72 (+, C-2), 80.88 (−, C-3), 83.08 (−, C-4), 112.62 (+, CMe_2), 127.55 (−, Ph), 128.29 (−, Ph), 131.59 (−, C-2a), 137.94 (+, Ph), 137.99 (+, Ph), 143.47 (+, C-5). Anal. Calcd for $C_{24}H_{28}O_5$: C, 72.71; H, 7.12. Found: C, 72.61; H, 7.15.

(±)-1,6-Di-*O*-benzyl-2a,5-didehydro-2a-carba-β-psicofuranosyl Azide (8a). A solution of **7** (2.154 g, 5.83 mmol) in 50 mL of 2 N HN_3 chloroform solution (caution: use inside the hood) was treated dropwise with $BF_3{\cdot}Et_2O$ (0.4 mL) and stirred at rt for 16 h. The excess acid was neutralized with aqueous saturated $NaHCO_3$ (30 mL), and the organic layer was separated and combined with the chloroform extracts (2 × 40 mL) of the aqueous layer. The combined organic extract was dried (Na_2SO_4), concentrated, and column chromatographed over silica gel using toluene/ethyl acetate (6:1) as eluant. Collection of the appropriate fractions afforded 0.353 g of an inseparable mixture of isopropylidene-protected azides **13a** and **13b**, followed by 0.529 g of **8a** and 0.732 g of its more polar isomer **8b**. The mixture of protected azides was then treated with 50% aqueous trifluoroacetic acid at room temperature for 1.5 h and partitioned between water and chloroform and the organic layer separated, dried, and subjected to the same chromatographic separation as described above. This operation afforded a combined yield of 0.606 g (29%) of **8a** and 0.904 g (43%) of **8b** as colorless oils.

8a: IR (film) 2090 cm^{-1} (N_3); ^1H NMR δ 2.83 (d, J = 8.4 Hz, 1 H, OH), 2.99 (d, J = 10.7 Hz, 1 H, OH), 3.43 (d, J_{AB} = 9.0 Hz, 1 H, H-1_a), 3.73 (d, J_{AB} = 9.0 Hz, 1 H, H-1_b), 4.11–4.19 (m, 3 H, H-$6_{a,b}$, H-3), 4.38 (dd, J = 10.7, 5.9 Hz, 1 H, H-4), 4.54 (m, 4 H, 2 × CH_2Ph), 5.75 (s, 1 H, H-2a), 7.25–7.35 (m, 10 H, 2 × Ph); ^{13}C NMR δ 66.71 (+, C-1), 68.98 (+, C-6), 72.78 (+, CH_2Ph), 73.27 (−, C-4), 73.88 (+, CH_2Ph), 74.80 (+, C-2), 76.54 (−, C-3), 127.66, 127.77, 128.00, 128.13, 128.33, 128.40, 128.65, 128.94 (−, Ph, C-2a), 136.22 (+, Ph), 137.61 (+, Ph), 147.20 (+, C-5). Anal. Calcd for $C_{21}H_{23}N_3O_4$: C, 66.13; H, 6.08; N, 11.02. Found: C, 66.04; H, 6.11; N, 10.96.

8b: IR (film) 2090 cm^{-1} (N_3); ^1H NMR δ 2.57 (d, J = 5.7 Hz, 1 H, OH), 2.93 (d, J = 7.6 Hz, 1 H, OH), 3.47 (d, J_{AB} = 9.6 Hz, 1 H, H-1_a), 3.57 (d, J_{AB} = 9.6 Hz, 1 H, H-1_b), 4.04 (dd, J = 7.5, 5.7 Hz, 1 H, H-3), 4.21 (s, 2 H, H-$6_{a,b}$), 4.48 (t, J = 5.7 Hz, 1 H, H-4), 4.55 (s, 4 H, 2 × CH_2Ph), 5.93 (s, 1 H, H-2a), 7.28–7.37 (m, 10 H, 2 × Ph); ^{13}C NMR δ 66.92 (+, C-1), 72.80 (+, CH_2Ph), 73.56 (+, CH_2Ph), 73.62 (−, C-4), 73.88 (−, C-3), 73.94 (+, C-2), 127.60, 127.79, 128.15, 128.41, (−, Ph, C-2a), 137.42 (+, Ph), 137.54 (+, Ph), 147.38 (+, C-5). **8b** was not further characterized.

(±)-2-*N*-(5-Amino-6-chloropyrimidin-4-yl)-1,6-di-*O*-benzyl-2a,5-didehydro-2a-carba-β-psicofuranosylamine (9). Lindlar catalyst (0.30 g) was suspended in a solution of **8a** (0.606 g, 1.589 mmol) in methanol and hydrogenated at atmospheric pressure. After 2 h, TLC analysis (silica gel, $CHCl_3$/MeOH (9:1)) indicated that a quantitative conversion had taken place. The suspension was filtered through Celite, and after removal of the solvent and drying under high vacuum (2 h), compound **8c** (0.559 g, 99%) was obtained as a highly viscous oil. A solution of this oil (0.546 g, 1.536 mmol) in n-BuOH (10 mL) containing Et_3N (1 mL) and 5-amino-4,6-dichloropyrimidine (0.521 g, 3.179 mmol) was stirred and heated at 145 °C (bath temperature) in a sealed vessel for 60 h. Removal of the solvent produced a residue that was purified by silica gel column chromatography, first using toluene/ethyl acetate (3:1) as eluant to remove excess of 5-amino-4,6-dichloropyrimidine followed by ethyl acetate. Concentration of the appropriate fractions afforded crystalline **9** (0.312 g, 42%) after cooling: mp 159–60 °C; ^1H NMR δ 3.18 (d, J = 6.4 Hz, 1 H, OH), 3.43 (br s, 2 H, NH_2), 3.74 (d, J_{AB} = 9.2 Hz, 1 H, H-$1'_a$), 3.84 (d, J_{AB} = 9.2 Hz, 1 H, H-$1'_b$), 4.18 (dd, J = 6.4, 2.3 Hz, 1 H, H-3'), 4.24 (s, 2 H, CH_2Ph), 4.40 (d, J_{AB} = 12.0 Hz, 1 H, H-$6'_a$), 4.52–4.63 (m, 4 H, H-$6'_b$, H-4', CH_2Ph), 5.31 (s, 1 H, NH), 5.96 (s, 2 H, H-2a', OH), 7.23–7.37 (m, 10 H, 2 × Ph), 7.98 (s, 1 H, H-2); ^{13}C NMR δ 67.10 (+, C-2'), 69.61 (+, C-1'), 70.54 (+, C-6'), 72.93 (+, CH_2Ph) , 73.54 (+, CH_2Ph), 73.95 (−, C-3'), 77.70 (−, C-4'), 123.10 (+, C-5), 127.71, 127.89, 127.98, 128.37 (−, Ph), 129.85 (−, C2a'), 137.07, 137.7 (+, Ph), 142.56 (+, C-6), 145.26 (+, C-5'), 147.7 (−, C-2), 153.38 (+, C-4). Anal. Calcd for $C_{25}H_{27}ClN_4O_4$: C, 62.17; H, 5.63; N, 11.60. Found: C, 62.06; H, 5.67; N, 11.55.

(±)-9-[1,6-Di-*O*-benzyl-3,4-*O*-(ethoxymethylene)-2a,5-didehydro-2a-carba-β-psicofuranosyl]-6-chloropurine (10). A suspension of **9** (0.888 g, 1.838 mmol) in triethyl orthoformate (15 mL) was treated with five drops of concentrated HCl, and the resulting clear solution was stirred at room temperature overnight. The reaction was terminated by the addition of triethylamine (2 mL). The solvent was removed under vacuum, and the resulting oily residue was purified by silica gel column chromatography using petroleum ether/ethyl acetate (2:1) as eluant. Combination of the appropriate fractions gave 0.195 g of uncyclized material plus 0.787 g (78%) of **10** as an exo/endo mixture of the ethoxymethylene acetals: ^1H NMR δ 1.10–1.25 (2t, 3 H, CH_2CH_3), 3.45–3.65 (2q, 2 H, CH_2CH_3), 3.81 (d, J_{AB} = 10.1 Hz, 1 H, H-$1'_a$), 3.97 (d, J_{AB} = 10.1 Hz, 1 H, H-$1'_b$), 4.24–4.33 (m, 2 H, H-$6'_{a,b}$), 4.41–4.73 (m, 2 H, CH_2Ph), 4.62 (s, 2 H, CH_2Ph), 5.27–5.35 (m, 2 H, H-3', H-4'), 5.92 and 5.94 (singlets, 1 H, EtOCH), 6.27 and 6.35 (singlets, 1 H, H-2a'), 6.90–7.38 (m, 10 H, Ph), 8.09 and 8.11 (singlets, 1 H, H-8), 8.59 and 8.60 (singlets, 1 H, H-2). This compound was contaminated with traces of $Et_3N{\cdot}Cl$ and was used directly in the following step.

(±)-9-[1,6-Di-*O*-benzyl-3,4-*O*-(ethoxymethylene)-2a,5-didehydro-2a-carba-β-psicofuranosyl]adenine (11). A solution of **10** (0.787 g, 1.433 mmol) in saturated methanolic ammonia (8 mL) was heated in a pressure vessel at 90–95 °C for 20 h. After cooling, the solvent was evaporated and the crude product was purified by silica gel column chromatography with $CHCl_3$/MeOH (19:1) as eluant to give 0.677 g (89%) of **11** as a white foam: ^1H NMR δ 1.05–1.25 (2t, 3 H, CH_2CH_3), 3.40–3.65 (2q, 2 H, CH_2CH_3), 3.82 (d, J_{AB} = 10.4 Hz, 1 H, H-$1'_a$), 3.94 (d, J_{AB} = 10.4 Hz, 1 H, H-$1'_b$), 4.20–4.65 (m, 6 H, H-$6'_{a,b}$, 2 × CH_2Ph), 5.32 and 5.35 (singlets, 2 H, H-3', H-4'), 5.91 (m, 3 H, EtOCH, NH_2), 6.29 and 6.35 (singlets, 1 H, H-2a'), 6.90–7.40 (m, 10 H, Ph), 7.79 and 7.81 (singlets, 1 H, H-8), 8.26 and 8.28 (singlets, 1 H, H-2). Anal. Calcd for $C_{29}H_{31}N_5O_5$: C, 65.77; H, 5.90; N, 13.22. Found: C, 65.85; H, 5.84; N, 13.17.

(±)-9-[1,6-Di-*O*-Benzyl-2a,5-didehydro-2a-carba-β-psicofuranosyl]adenine (12). A solution of **11** (0.677 g, 1.278 mmol) in 6 N methanolic HCl (30 mL) was stirred at room temperature, and after 30 min the corresponding hydrochloride began to precipitate. The reaction was allowed to proceed for 1.5 h more. The solvent was removed under reduced pressure, and the residue was suspended and stirred in concentrated NH_4OH (50 mL) for 18 h. After filtration, the solid obtained was recrystallized from ethanol to give pure **12** as fine crystals, mp 192–194 °C: ^1H NMR ($CDCl_3$/MeOH-d_4) δ 3.87 (d, J_{AB} = 9.7 Hz, 1 H, H-$1'_a$), 3.98 (d, J_{AB} = 9.7 Hz, 1 H, H-$1'_b$), 4.30–4.34 (m, 3 H, H-$6'_{a,b}$, H-3'), 4.47–4.68 (m, 5 H, H-4', 2 × CH_2Ph), 6.59 (s, 1 H, H-2a'), 7.00–7.37 (m, 10 H, Ph), 8.06 (s, 1 H, H-8), 8.18 (s, 1 H, H-2); ^{13}C NMR ($CDCl_3$/MeOH-d_4) δ 66.36 (+, C-2'), 71.63 (+, C-1'), 72.05 (−, C-3'), 72.57 (+, C-6'), 72.75 and 73.65 (+, 2 × CH_2Ph), 76.93 (−, C-4'), 118.72 (+, C-5), 126.26 (−, C-2a'), 127.04, 127.19, 127.31, 127.40, 127.60, 127.70, 127.87 (−, Ph), 136.60 and 137.22 (+, Ph), 139.42 (−, C-8), 146.77 (+, C-5'), 148.46 (+, C-4), 151.34 (−, C-2), 155.39 (+, C-6). Anal. Calcd for $C_{26}H_{27}N_5O_4$: C, 65.95; H, 5.75; N, 14.79. Found: C, 65.89; H, 5.75; N, 14.74.

(±)-9-[2a,5-Didehydro-2a-carba-β-psicofuranosyl]adenine [4a, (±)-psicoplanocin A]. A solution of **12** (0.097 g, 0.244 mmol) in liquid ammonia (ca. 25 mL) at −78 °C was stirred under

argon and reacted with small portions of sodium metal until the blue color persisted. After such time, the solution was stirrred for 3 min. The reaction was quenched by the addition of solid NH_4Cl (25 mg), and the ammonia was allowed to evaporate. The solid residue obtained was dissolved in hot water (10 mL), filtered to remove traces of the insoluble starting material, and stored overnight at 4 °C. The crystalline solid was collected. An additional crop was obtained from the alkaline mother liquor after it was neutralized with acetic acid and reduced in volume (5 mL) to give a combined yield of 0.042 g (59%) of psicoplanocin A as colorless fine crystals, mp 240–245 °C dec: ^{1}H NMR (Me_2SO-d_6 + D_2O) δ 3.73 (d, J_{AB} = 11.0 Hz, 1 H, H-1′$_a$), 3.87 (d, J_{AB} = 11.0 Hz, 1 H, H-1′$_b$), 4.11 (br s, 2 H, H-3′, H-4′), 4.35 (br s, 2 H, H-6′$_{a,b}$), 6.46 (s, 1 H, H-2a′), 8.11 (s, 1 H, H-8), 8.14 (s, 1 H, H-2); ^{13}C NMR (Me_2SO-d_6 + D_2O) δ 58.31 (+, C-2′), 63.46 (+, C-1′), 71.69 (+, C-6′), 74.35 (–, C-3′), 77.17 (–, C-4′), 119.13 (+, C-5), 124.53 (–, C-2a′), 139.81 (–, C-8), 149.00 (+, C-5′), 149.88 (+, C-4), 151.48 (–, C-2), 155.88 (+, C-6); 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.

(±)-1,6-Di-*O*-benzyl-3,4-*O*-isopropylidene-2a,5-didehydro-2a-carba-β-psicofuranosylazide (13a). A solution of the azidodiol **8a** (1.22 g, 3.19 mmol) in CH_2Cl_2 (75 mL) was treated with 2,2-dimethoxypropane (3 mL) and five drops of HBF_4 (54% solution in ether). The reaction mixture was stirred for 1 min and then immediately quenched by the addition of Et_3N (1 mL). The solvent was removed under reduced pressure, and the oily residue was purified by silica gel column chromatography with petroleum ether/ethyl acetate (19:1) as eluant to give 1.07 g (80%) of **13a** as a clear oil: ^{1}H NMR δ 1.32 (s, 6 H, 2 × CH_3), 3.69 (d, J_{AB} = 10.0 Hz, 1 H, H-1$_a$), 3.77 (d, J_{AB} = 10.0 Hz, 1 H, H-1$_b$), 4.17 (s, 2 H, H-6$_{a,b}$), 4.49 (d, J = 5.0 Hz, 1 H, H-3), 4.57 (s, 2 H, CH_2Ph), 4.62 (s, 2 H, CH_2Ph), 5.18 (d, J = 5.0 Hz, 1 H, H-4), 5.92 (s, 1 H, H-2a), 7.27–7.39 (m, 10 H, Ph); ^{13}C NMR δ 26.23 (–, CH_3), 27.30 (–, CH_3), 66.11 (+, C-2), 71.98, 72.75, 73.62 and 75.58 (+, 4 × CH_2), 83.85 and 84.08 (–, C-3 and C-4), 112.54 (+, CMe_2), 125.36 (–, C-2a), 127.54, 127.66, 128.33, and 128.41 (–, Ph), 137.82 and 137.9 (+, Ph), 147.35 (C-5). Anal. Calcd for $C_{24}H_{27}N_3O_4$: C, 68.93; H, 6.46; N, 9.97. Found: C, 68.69; H, 6.43; N, 9.87.

(±)-1,6-Di-*O*-benzyl-3,4-*O*-isopropylidene-2a,5-didehydro-2a-carba-α-psicofuranosyl Azide (13b). In the same manner as described for 13a, this compound was obtained as a clear oil: ^{1}H NMR δ 1.41 (s, 3 H, CH_3), 1.55 (s, 3 H, CH_3), 3.40 (d, J_{AB} = 11.0 Hz, 1 H, H-1$_a$), 3.44 (d, J_{AB} = 11.0 Hz, 1 H, H-1$_b$), 4.22 (s, 2 H, H-6$_{a,b}$), 4.57 (s, 2 H, CH_2Ph), 4.62 (s, 2 H, CH_2Ph), 4.65 (d, J = 5.0 Hz, 1 H, H-3), 5.05 (d, J = 5.0 Hz, 1 H, H-4), 5.80 (s, 1 H, H-2a), 7.27–7.39 (m, 10 H, Ph); ^{13}C NMR δ 26.21 (–, CH_3), 27.00 (–, CH_3), 66.00 (+, C-2), 72.51, 73.02, 73.53 and 73.88 (+, 4 × CH_2), 82.80 and 83.10 (–, C-3 and C-4), 112.50 (+, CMe_2), 126.50, 126.51, 127.60, 127.73, 128.12 (–, C-2a, Ph), 137.80 and 138.10 (+, Ph), 147.00 (C-5).

(±)-2-*N*-[(3-Ethoxy-2-propenamido)carbonyl]-1,6-di-*O*-benzyl-3,4-*O*-isopropylidene-2a,5-didehydro-2a-carba-β-psicofuranosylamine (14). A solution of 3-ethoxypropenoyl chloride (0.429 g, 3.19 mmol) in benzene (1 mL) was added dropwise to a vigorously stirred suspension of silver cyanate (1.2 g, 8.0 mmol) in anhydrous benzene (10 mL) that was maintained at 10 °C during the addition. The reaction mixture was stirred for 30 min more before it was filtered through a pad of Celite. The Celite cake was washed with benzene (2 × 3 mL), and the combined filtrate containing 3-ethoxypropenoyl isocyanate was used immediately. Separately, carbocyclic amine **13c** was prepared from the reduction of azide **13a** (1.068 g, 2.53 mmol) in ethanol (50 mL) over Lindlar's catalyst (0.530 g) at atmospheric pressure in a similar manner as described for **8c**. A benzene solution of **13c** (20 mL) was cooled to 10 °C and treated dropwise with the solution of 3-ethoxy-propenoyl isocyanate. The mixture was stirred further at that temperature for 30 min before the reaction was terminated by the addition of MeOH (1 mL). The solvents were evaporated under reduced pressure, and the residue was dissolved in ether (3 mL). After the addition of a few drops of petroleum ether, the solution was kept at 5 °C overnight. The precipitated solid that formed was collected and dried to give the desired pyrimidine precursor **14** (1.103 g, 82%), mp 107–110 °C. An analytical sample was obtained by recrystallization from the same solvent system to give a white crystalline solid, mp 113–115 °C: ^{1}H NMR δ 1.28–1.37 (m, 9 H, CH_3CH_2O, 2 × CH_3), 3.58 (d, J_{AB} = 10.0 Hz, 1 H, H-1′$_a$), 3.89–3.92 (m, 3 H, CH_3CH_2O, H-1′$_b$), 4.17 (AB multiplet, 2 H, H-6′$_{a,b}$), 4.51 (AB multiplet, 2 H, CH_2-Ph), 4.64 (s, 2 H, CH_2Ph), 4.91 (d, J = 6.0 Hz, 1 H, H-3′), 5.23 (d, J = 12 Hz, 1 H, CH=CH-OEt), 5.35 (d, J = 6.0 Hz, 1 H, H-4′), 5.71 (s, 1 H, H-2a′), 7.26–7.43 (m, 10 H, Ph), 7.63 (d, J = 12.0 Hz, 1 H, CH=CH-OEt), 9.05 (s, 1 H, NH), 9.36 (s, 1 H, NH); ^{13}C NMR δ 14.57 (–, CH_2CH_3), 26.11 and 27.24 (–, 2 × CH_3), 66.25, 67.46, 67.88, 71.00, 72.25 and 73.53 (+, C-1′, C-2′, C-6′, CH_2CH_3, 2 × CH_2Ph), 84.58 and 85.16 (–, C-3′, C-4′), 97.85 (–, CH=CH-OEt), 111.98 (+, CMe_2), 127.43, 127.55, 127.63, 127.74 and 128.19 (–, C-2a′, Ph), 138.34 (+, Ph), 144.24 (+, C-5′), 154.32 (+, CO), 162.51 (–, CH=CH-OEt), 167.92 (+, CO). Anal. Calcd for $C_{30}H_{36}N_2O_7$: C, 67.15; H, 6.76; N, 5.22. Found: C, 67.26; H, 6.83; N, 5.29.

(±)-1-[1,6-Di-*O*-benzyl-3,4-*O*-isopropylidene-2a,5-didehydro-2a-carba-β-psico-furanosyl]uracil (15a). A solution of **14** (0.179 g, 0.333 mmol) in EtOH (20 mL) was treated with 2 N H_2SO_4 (20 mL), and the resulting mixture was heated to reflux until the initially formed precipitate was dissolved (2.5 h). The solvent was removed under reduced pressure, and the residue was extracted with CH_2Cl_2 (2 × 20 mL). The organic solution was treated with excess 2,2-dimethoxypropane (1.5 mL) and HBF_4 (54% in ether, 4 drops) and stirred at room temperature for 2 min. After the reaction was quenched with Et_3N (0.5 mL), the solvent was evaporated and the residue obtained was purified by silica gel preparative TLC with $CHCl_3$/MeOH (19:1) as eluant. The isolated semisolid **15a** (0.089 g, 54%) was used in the next steps without further purification: ^{1}H NMR δ 1.34 (s, 3 H, CH_3), 1.40 (s, 3 H, CH_3), 3.58 (d, J = 10.0 Hz, 1 H, H-3′), 4.21 (s, 2 H, CH_2Ph), 4.42 (d, J_{AB} = 12.0 Hz, 1 H, H-1′$_{a,b}$), 4.50 (d, J_{AB} = 12.0 Hz, 1 H, H-1′$_b$), 4.52 (d, J = 10.0 Hz, 1 H, H-4′), 4.60 (s, 2 H, CH_2Ph), 5.03 (d, J_{AB} = 6.0 Hz, 1 H, H-6′$_a$), 5.08 (d, J_{AB} = 6.0 Hz, 1 H, H-6′$_b$), 5.60 (dd, J = 8.0, 3.0 Hz, 1 H, H-5), 6.06 (s, 1 H, H-2a′), 7.16–7.40 (m, 11 H, H-6, Ph), 8.37 (br s, 1 H, NH); ^{13}C NMR δ 25.55 (–, CH_3), 26.94 (–, CH_3), 66.55, 69.59, 73.32, 74.41, and 77.23 (+, C-1′, C-2′, C-6′, 2 × CH_2Ph), 83.30 and 83.75 (–, C-3′ and C-4′), 100.69 (–, C-5), 112.83 (+, CMe_2), 125.13 (–, C-2a′), 127.48, 127.67, 127.76, 127.90, 128.31 and 128.44 (–, Ph), 137.51 and 137.72 (+, Ph), 143.36 (–, C-6), 148.23 (+, C-5′), 150.24 (+, C-2), and 163.06 (C-4).

(±)-1-[2a,5-Didehydro-2a-carba-β-psicofuranosyl]-uracil (16). A solution of BBr_3 (1 M in CH_2Cl_2, 0.73 mL) was added to a cold (–78 °C) solution of **15a** (0.089 g, 0.181 mmol) in CH_2Cl_2 (6 mL). The reaction mixture was stirred at that temperature for 2.5 h and quenched by the addition of MeOH (1 mL). After the reaction was allowed to reach room temperature, the solvent was evaporated and the residue was coevaporated three times with MeOH. The residue was dissolved in a 3:1 mixture of $CHCl_3$/MeOH (1 mL) and chromatographed on a small column (silica gel, 3 g) using the same solvent mixture. Fractions containing the product were combined, evaporated, and rechromatographed under the same conditions. The resulting glassy product was dissolved in water (4 mL) and lyophilized to give **16** (0.025 g, 51%) as an amorphous powder: ^{1}H NMR (MeOH-d_4) δ 3.78 (d, J_{AB} = 11.0 Hz, 1 H, H-1′$_a$), 4.13 (d, J_{AB} = 11.0 Hz, 1 H, H-1′$_b$), 4.28 (br s, 2 H, H-6′$_{a,b}$), 4.40 (d, J = 6.0 Hz, 1 H, H-3′), 4.55 (d, J = 6.0 Hz, 1 H, H-4′), 5.63 (d, J = 8.3 Hz, 1 H, H-5), 6.36 (s, 1 H, H-2a′), 7.77 (d, J = 8.3 Hz, 1 H, H-6); ^{13}C NMR (MeOH-d_4) δ 60.13 (+, C-1′), 63.13 (+, C-6′), 73.97 (–, C-3′), 78.10 (–, C-4′), 79.63 (+, C-2′), 101.73 (–, C-5), 125.84 (–, C-2a′), 145.63 (–, C-6), 151.91 (+, C-5′), 153.70 (+, C-2), 166.46 (+, C-4); FAB MS *m/z* (relative intensity) 363 (MH^+, glycerol, 27), 271 (MH^+, 61), 113 (b + 2H, 100); high-resolution FAB MS *m/z* 271.0958 (MH^+, calcd 271.0930). This compound did not give a satisfactory elemental analysis. Anal. Calcd for $C_{11}H_{14}N_2O_6$: C, 48.89; H, 5.22; N, 10.37. Found: C, 44.09; H, 5.08; N, 9.01. The differences observed would indicate a ca. 10% contamination with inert material, possibly silica gel from the chromatography.

(±)-1-[2a,5-Didehydro-2a-carba-β-psicofuranosyl]cytosine (4b). A solution of **15a** (0.339 g, 0.691 mmol) in HMPT (10 mL) was treated with Lawesson's reagent (0.204 g, 0.504 mmol) and heated with stirring for 3 h at 100 °C. After being cooled to rt, the reaction mixture was partitioned between ethyl acetate and saturated $NaHCO_3$ (40 mL each). The organic layer was

washed with brine (15 mL), dried (Na_2SO_4), and evaporated to give a residue that was purified by silica gel column chromatography with $CHCl_3$/acetone (9:1) as eluant. The thiouracil intermediate **15b** was obtained as a yellow oil (0.146 g, 42%). When the column was futher eluted with $CHCl_3$/MeOH (9:1), unreacted **15a** contaminated with HMPT was isolated. This crude material was dissolved in toluene (20 mL) and heated to reflux in the presence of an excess of Lawesson's reagent for 1 h. The toluene was removed by distillation under vacuum, and the residue was purified, as before, to give an additional 0.082 g of **15b** (combined yield 65%): ^{1}H NMR δ 1.33 (s, 3 H, CH_3), 1.39 (s, 3 H, CH_3), 3.58 (d, J = 10.0 Hz, 1 H, H-3′), 4.21 (s, 2 H, CH_2Ph), 4.42 (d, J_{AB} =12.0 Hz, 1 H, H-1′$_a$), 4.50 (d, J_{AB} = 12.0 Hz, 1 H, H-1′$_b$), 4.45 (d, J = 10.0 Hz, 1 H, H-4′), 4.61 (s, 2 H, CH_2Ph), 4.99 (d, J_{AB} = 6.0 Hz, 1 H, H-6′$_a$), 5.08 (d, J_{AB} = 6.0 Hz, 1 H, H-6′$_b$), 6.05 (s, 1 H, H-2a′), 6.28 (dd, J = 8.0, 3.0 Hz, 1 H, H-5), 7.05 (d, J = 8.0 Hz, 1 H, H-6), 7.16–7.35 (m, 10 H, Ph), 9.45 (br s, 1 H, NH); ^{13}C NMR δ 25.40 (–, CH_3), 26.78 (–, CH_3), 66.50, 69.10, 73.25, 73.39, and 77.92 (+, C-1′, C-2′, C-6′, 2 × CH_2Ph), 83.24 and 83.38 (–, C-3′ and C-4′), 111.91 (–, C-5), 112.96 (+, CMe_2), 124.60 (–, C-2a′), 127.60, 127.80, 127.93, 128.01, and 128.40 (–, Ph), 137.55 (+, Ph), 138.35 (–, C-6), 147.67 (+, C-5′), 148.75 (+, C-2), and 189.30 (C-4).

The oily thiopyrimidine (0.228 g, 0.450 mmol) was dissolved in saturated methanolic ammonia (14 mL) and heated in a pressure vessel at 75 °C for 18 h. The solvent was then removed, and the residue was purified by silica gel column chromatography with $CHCl_3$/MeOH (9:1) as eluant to give intermediate **17** (0.176 g, 80%) as a colorless foam. This penultimate intermediate was used directly for the final deprotection step: ^{1}H NMR δ 1.31 (s, 3 H, CH_3), 1.37 (s, 3 H, CH_3), 3.62 (d, J = 10.0 Hz, 1 H, H-3′), 4.20 (s, 2 H, CH_2Ph), 4.42 (s, 2 H, H-1′$_{a,b}$), 4.59 (s, 2 H, CH_2Ph), 4.70 (d, J = 10.0 Hz, 1 H, H-4′), 5.02 (d, J_{AB} = 6.0 Hz, 1 H, H-6′$_a$), 5.13 (d, J_{AB} = 6.0 Hz, 1 H, H-6′$_b$), 5.65 (d, J = 7.0, 1 H, H-5), 6.08 (s, 1 H, H-2a′), 7.15–7.36 (m, 11 H, H-6, Ph); ^{13}C NMR δ 25.61 (–, CH_3), 27.02 (–, CH_3), 66.68, 70.11, 73.33, and 77.06 (+, C-1′, C-2′, C-6′, 2 × CH_2Ph), 83.31 and 83.93 (–, C-3′ and C-4′), 93.67 (–, C-5), 112.29 (+, CMe_2), 126.44 (–, C-2a′), 127.32, 127.75, 127.80, and 128.40 (–, Ph), 137.68 and 138.25 (+, Ph), 144.15 (–, C-6), 147.00 (+, C-5′), 156.15 (+, C-2), and 165.57 (C-4).

The final deprotection step consisted of treating a cold (–78 °C) solution of **17** (0.176 g, 0.359 mmol) in CH_2Cl_2 (15 mL) with a 1 M solution of BBr_3 in CH_2Cl_2 (1.44 mL) which was added dropwise to prevent a rise in temperature. The reaction mixture was stirred for 2.5 h at –78 °C, warmed to 0 °C, and quenched by the addition of MeOH (1 mL). The solvent was removed under reduced pressure and the residue dissolved in MeOH (10 mL) and evaporated again. This addition–evaporation process was repeated three times. The residue was partitioned between water (7 mL) and ether (5 mL), and the aqueous layer was applied to a Dowex-AG 50 X-8 (H^+) ion-exchange resin (5 mL) which was washed with water (20 mL) and eluted with 2 N NH_4OH. Fractions containing the product were pooled and lyophilized to give 0.046 g (48%) of a light-brown powder. The compound was decolorized by passing it through a short reversed-phase C-18 cartridge which was eluted with water to give **4b** as an amorphous lyophilized solid: ^{1}H NMR (D_2O) δ 3.59 (d, J_{AB} = 12.0 Hz, 1 H, H-1′$_a$), 4.06 (d, J_{AB} = 11.0 Hz, 1 H, H-1′$_b$), 4.16 (br s, 2 H, H-6′$_{a,b}$), 4.23 (d, J = 6.0 Hz, 1 H, H-3′), 4.49 (d, J = 6.0 Hz, 1 H, H-4′), 5.74 (d, J = 8.0 Hz, 1 H, H-5), 6.10 (s, 1 H, H-2a′), 7.49 (d, J = 8.0 Hz, 1 H, H-6); ^{13}C NMR δ 58.49 (+, C-1′), 62.13 (+, C-6′), 72.76 (–, C-3′), 76.70 (–, C-4′), 78.34 (+, C-2′), 95.17 (–, C-5), 125.41 (–, C-2a′), 144.59 (–, C-6), 149.26 (+, C-5′), 158.83 (+, C-2), 165.76 (+, C-4); FAB MS m/z (relative intensity) 362 (MH^+ glycerol, 18), 270 (MH^+, 76), 112 (b + 2H, 100). Anal. Calcd for $C_{11}H_{15}N_3O_5 \cdot H_2O$: C, 45.99; H, 5.96; N, 14.63. Found: C, 45.76; H, 5.85; N, 14.51.

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Supplementary Material Available: Details of X-ray analysis (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.