gratefully acknowledged. We also thank the National Science Foundation (CHE-8905894) and Biotechnology Research and Development Corporation for financial support. Additional support for J.B.G. in the form of an Alfred P. Sloan Fellowship and an NIH Research Career Development Award (K04 CA01571) is gratefully acknowledged. Financial support for J.A.L. from a University of Iowa Biocatalysis Predoctoral Fellowship is also appreciated.

Supplementary Material Available: ^1H NMR spectra for sulpinines A and C and secopenitrem B and a ^{13}C NMR spectrum of sulpinine B (4 pages). Ordering information is given on any current masthead page.

Synthesis and Structural Determination of (±)-Neplanocin F

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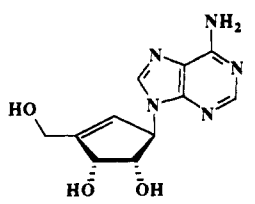
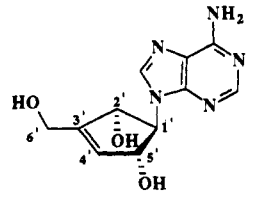
Neplanocin F (**2**), a minor constituent of the family of neplanocin antibiotics, was synthesized as a racemate in 12 steps from cyclopentenone **3**/**4**, which in turn was available from D-ribonolactone. The carbocyclic ring of neplanocin F corresponds to the allylic rearranged isomer of the biologically active agent neplanocin A. Regiospecific reduction of the racemic cyclopentenone **3**/**4** and protection of the resulting α-alcohol as a benzyl ether **6** produced, after removal of the isopropylidene moiety, a compound (**7**) having allylic and homoallylic secondary alcohol functionalities. Differences in the reactivity of these two secondary alcohols were successfully manipulated to prepare the homoallylic substituted azide **14**, which was then reduced and converted to the desired adenine ring by conventional methods. The spectral properties of the synthesized material [(±)-neplanocin F] were identical to those of the natural product, except for its lack of optical rotation. X-ray crystallographic analysis helped corroborate the structure. In contrast to its bioactive isomer, neoplanocin A, neplanocin F was devoid of cytotoxicity and in vitro antiviral activity.

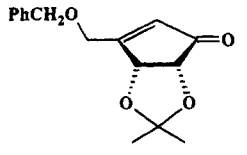
Synthetic modifications of the naturally occurring carbocyclic nucleoside neplanocin A (**1**) have, in some instances, resulted in analogues with superior antitumor and antiviral activities relative to the parent compound.[1-3] Of the various neplanocin analogues isolated from *ampullariella regularis* A11079,[4] neplanocin A has received wide attention because of its interesting biological properties.[5-7] In contrast, the other minor metabolites of the neplanocin family have received less attention, perhaps due to the lack of adequate amounts for testing. Based on this premise, we embarked on a project aimed at providing a suitable synthetic route to one of these minor metabolites, neplanocin F (**2**), which is an allylic rearranged isomer of neplanocin A.[8] Some of these results have been briefly reported in a previous communication from this laboratory,[9] and in the present paper we present a detailed account of this work. In addition, we provide additional crystallographic evidence for the correct structure of neplanocin F in order to resolve a discrepancy that exists between two published communications[8,10] and the patent literature[11] regarding the stereochemistry of the 2′-hydroxyl group.



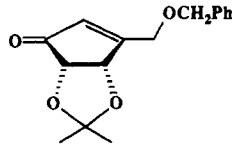
1 (Neplanocin A)



2 (Neplanocin F)



3



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Results and Discussion

During the scale-up synthesis of (−)-neplanocin A, the desired cyclopentenone enantiomer **3** was efficiently separated from smaller quantities of the racemate which consists of a mixture of **3** and **4**.[12] As this process was repeated several times for the syntheses of other cyclopentenyl nucleosides, significant quantities of the racemate were accumulated. For the synthesis of natural neplanocin F, the mirror image enantiomer **4** appeared to be a most suitable starting material since the double bond would appear moved to the desired rearranged position after appropriate addition of the base to the carbocyclic moiety

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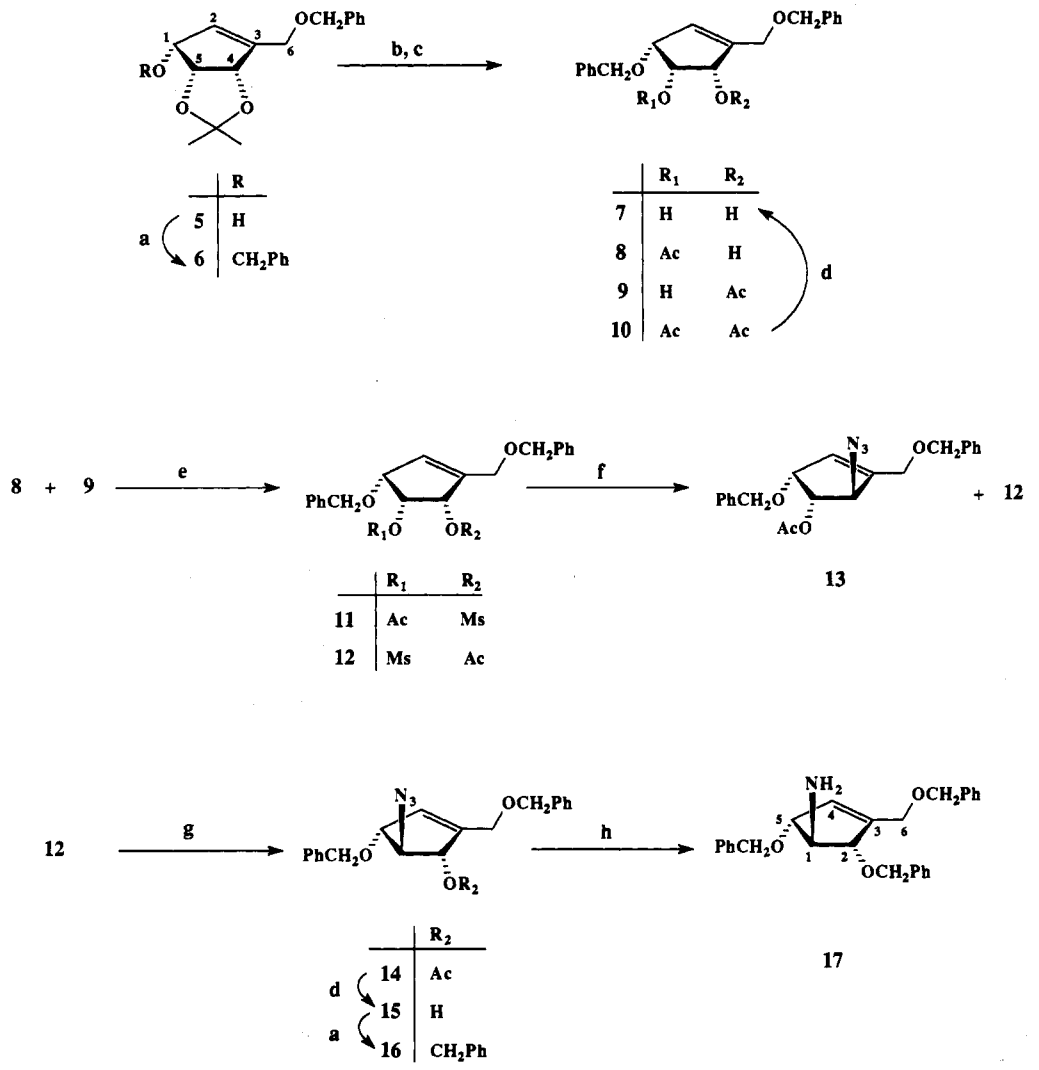
Scheme I[a]



[a] (a) NaH/DMF, $PhCH_2Br$; (b) 40% TFA; (c) Ac_2O/Et_3N/DMAP; (d) NaOMe/MeOH; (e) $MeSO_2Cl/Et_3N$; (f) LiN_3/DMSO/rt; (g) LiN_3/DMSO/110 °C; (h) $[H_2]$/Lindlar catalyst/MeOH, rt.

(vide infra). However, it was reasoned that, initially, it was more expedient to begin the synthesis with the racemate (3/4) despite the fact that this approach would only lead to (±)-neplanocin F, with separation of the desired (−)-enantiomer to be performed later if warranted by its biological activity.

Using chemistry reported earlier for compound 3,[12] the racemate (3/4) was reduced regioselectively and stereoselectively to the α-allylic alcohol 5 (only the desired enantiomer is shown in Scheme I). Protection of the newly formed alcohol as a benzyl ether, followed by the acid-catalyzed removal of the isopropylidene moiety, gave the diol intermediate 7. Treatment of this diol with 1.2 equiv of acetic anhydride gave a quantitative yield of a mixture of three compounds (8–10) from which the diacetate 10 (40%) was easily separated by column chromatography. The remaining monoacetates (60%) could not be separated, but under equilibrium conditions, the ratio of 9 to 8 was in favor of the allylic monoacetate 9 (75% of the mixture) as determined by proton NMR. This reactivity difference was later exploited in the separation of isomers by reacting the mixture of monoacetates with methanesulfonyl chloride and treating the resulting mixture of mesylates (11 and 12) with lithium azide at room temperature. Under these conditions it was anticipated that only the allylic mesylate, derived from 8, would react. Indeed, after 30 min, the reaction mixture consisted of azide 13 and the unreacted mesylate 12. Chromatographic removal of 13 from this mixture afforded pure mesylate 12, which when reacted under more forcing conditions gave the desired azide 14 with the expected inversion of configuration. In preparation for the harsh conditions required the formation of the purine ring, the acetate group in 14 was removed and replaced with the more robust benzyl moiety to give compound 16. Hydrogenation of azide 16 over Lindlar catalyst gave the carbocylic amine 17 in which the disposition of the hydroxyl groups and double bond were those demanded by the structure of neplanocin F.

Formation of the purine ring (Scheme II), was performed by the classical sequence involving condensation of 17 with 5-amino-4,6-dichloropyrimidine followed by ring closure of the resulting intermediate 18 with triethyl orthoformate

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(10) Yaginuma, S.; Tsujino, M.; Muto, N.; Otani, M.; Hayashi, M., Ishimura, F.; Fujii, T.; Watanabe, S.; Matsuda, T.; Watanabe, T.; Abe, J. *Current Chemotherapy of Infectious Diseases, Proc. 11th Intl. Congress Chemother.* **1979**, *2*, 1558.
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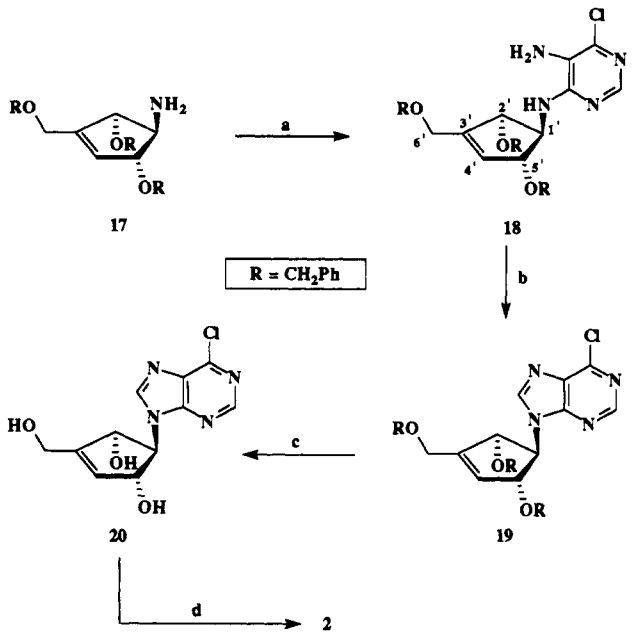
Scheme II[a]



[a] (a) 5-Amino-4,6-dichloropyrimidine/Et_3N/*n*-BuOH/145 °C; (b) $(EtO)_3CH$/HCl/rt; (c) BCl_3/CH_2Cl_2/−78 °C; (d) NH_3/MeOH/110 °C.

to give the protected carbocyclic chloropurine **19**.[13,14] Removal of the three benzyl protective groups with boron trichloride afforded the chloropurine carbocyclic nucleoside **20** which was converted to the desired (±)-neplanocin F (**2**) by treatment with methanolic ammonia under pressure. Recrystallization of the crude material from water produced (±)-neplanocin F as colorless crystals. The proton NMR spectrum of synthetic racemic neplanocin F was identical to the spectrum obtained from a sample of natural (−)-neplanocin F kindly provided by Dr. Satoshi Yaginuma, from the Toyo Jozo Co., in Japan. In addition, the following crystal-structure determination on our synthetic product illustrates the correct disposition of the hydroxyl groups and compares the structure of this carbocyclic nucleoside with that of its likely biological progenitor neplanocin A.

X-ray Crystallography. The X-ray-derived molecular structure of neplanocin F is shown in Figure 1. The adenine moiety is planar within ±0.02 Å. The amine nitrogen deviates from the adenine plane by 0.046 (1) Å. Bond lengths and angles for the base are comparable to those found in both adenosine[15] and neplanocin A.[16] The glycosidic bond length in neplanocin F is 1.465 (7) Å, close to the value of 1.476 Å seen in neplanocin A[16] and in the range seen in purine nucleosides.[15] The glycosidic torsion angle χ, C4–N9–C1′–C2′, is −114.0 (1)°, placing it in the anti range. This conformation is also observed in both neplanocin A[16] and 3-deazaneplanocin A.[2]

The cyclopentene ring in neplanocin F differs in several respects from that in neplanocin A and 3-deazaneplanocin A. The data confirm that the double bond is between C3′ and C4′ instead of between C2′ and C3′. The two hydroxyl groups are attached to C2′ and C5′ instead of C4′ and C5′, both hydroxyls lying "below" the cyclopentene ring relative

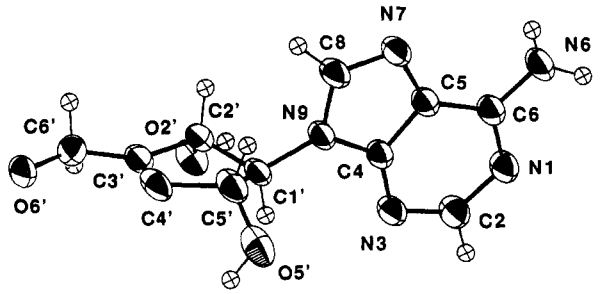


Figure 1. Molecular structure of neplanocin F. Only one enantiomorph is illustrated. Thermal ellipsoids of non-hydrogen atoms are drawn at the 50% probability level. Due to disorder, hydrogens on C4′ and O6′ were not observed (see the Experimental Section).

to the base. The C2′, C3′, C4′, and C5′ atoms deviate by no more than 0.001 (2) Å from their least-squares plane. The cyclopentene ring assumes an envelope conformation, C1′ lying 0.370 (2) Å below the C2′–C3′–C4′–C5′ plane. If the pseudorotation concept is applied to the cyclopentene ring,[17] the phase angle *P* is 126°. This defines the pucker as C1′-exo, if C2′ is taken to be analogous to the furanose O4′. Using the same numbering system as in Figure 1, a C5′-exo–C4′-endo pucker is seen in the solid state structure of neplanocin A[16] while a C5′-endo conformation is seen in 3-deazaneplanocin A.[2] The amplitude of puckering is 23.6° in neplanocin F, equivalent to the dihedral angle between the C2′–C3′–C4′–C5′ and C2′–C1′–C5′ planes. This is comparable to the 29.5° value observed in 3-deazaneplanocin A and is indicative of the limited flexibility of the cyclopentene ring in both structures.[2,17]

The CH_2OH substituent lies approximately in the C2′–C3′–C4′–C5′ plane. The torsion angle O6′–C6′–C3′–C4′ is −2.8 (4)°, reflecting the cis orientation of the C6′–O6′ bond with respect to the C3′–C4′ double bond. In the stuctures of 3-deazaneplanocin A and neplanocin A, the CH_2OH substituents are similarly oriented relative to the carbocycle C2′–C3′ double bond. Thus, the hydroxyl group in these structures points in the opposite direction from that observed here, resulting in O6′–C6′–C3′–C4′ torsion angles closer to 180°.[2,16]

Biological Evaluation. In contrast to neplanocin A, neplanocin F was not cytotoxic to L-1210 cells in vitro at micromolar concentrations. At higher concentrations (1 mM) it produced only weak (43%) inhibition of cell growth. Likewise, the compound was devoid of antiviral activity against Herpes Simplex Virus type-1 (E-377) cultured in Vero cells and Human Influenza Virus type A_0/PR/8/34 in MDCK cells.

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. Silica gel 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. Eluant mixture compositions in volume is as follows: A = petroleum ether/ethyl acetate, 9:1; B = petroleum ether/ethyl acetate, 7:3; C = petroleum ether/ethyl acetate, 3:1; D = chloroform/methanol, 19:1; E = chloroform/methanol, 9:1. 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, in 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

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base line in the fully decoupled attached proton test (APT). Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, GA, or by Galbraith Laboratories, Inc., Knoxville, TN.

(1α,4α,5α)-1-(Benzyloxy)-3-[(benzyloxy)methyl]-4,5-(isopropylidenedioxy)-2-cyclopentene (6). A solution of (±)-cyclopentenol (**5**; 6.94 g, 25.2 mmol)[12] in DMF (30 mL) was added dropwise to a stirred suspension of NaH [0.980 g (80%), 32.6 mmol] in DMF (20 mL) during a period of 10 min. After hydrogen evolution ceased (40 min), the mixture was cooled to 10 °C and benzyl bromide (5.58 g, 3.88 mL, 32.6 mmol) in DMF (10 mL) was added slowly. The mixture was allowed to reach room temperature, stirred for 40 min more, quenched with MeOH (5 mL), diluted with water, and extracted with ether (3 × 70 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography on silica gel (solvent system A) affored 7.36 g (80%) of **6** as a colorless oil which was used directly without any further purification in the next step: ^{1}H NMR δ 1.43 (s, 3 H, CH_3), 1.48 (s, 3 H, CH_3), 4.18 (s, 2 H, H-$6_{a,b}$), 4.40 (m, 1 H, H-1), 4.56 (s, 2 H, CH_2Ph), 4.63 (d, J = 12 Hz, 1 H, CHHPh), 4.82 (t, J = 5.4 Hz, 1 H, H-5), 4.84 (d, J = 12 Hz, 1 H, CHHPh), 4.94 (d, J = 5.7 Hz, 1 H, H-4), 5.82 (s, 1 H, H-2), 7.25–7.50 (m, 10 H, Ph); ^{13}C NMR δ 26.70 (–), 27.58 (–), 66.32 (+), 71.68 (+), 72.76 (+), 77.89 (–), 79.66 (–), 82.81 (–), 112.38 (+), 127.56 (–), 127.94 (–), 128.29 (–), 128.75 (–), 138.01 (+), 138.28 (+), 143.03 (+).

(1α,4α,5α)-1-(Benzyloxy)-3-[(benzyloxy)methyl]-2-cyclopentene-4,5-diol (7). A mixture of **6** (6.93 g, 18.9 mmol) and 40% trifluoroacetic acid was vigorously stirred for 25 min at room temperature. The solvent was removed under vacuum, and the oily residue obtained was redissolved in CH_2Cl_2 (100 mL), washed successively with water (20 mL) and saturated $NaHCO_3$ solution (20 mL), and dried (Na_2SO_4). Following removal of the solvent, the residue was taken up in warm ether (30 mL), and after seeding, it gave 5.07 g (82%) of **7** as colorless needles: mp 54–55 °C; ^{1}H NMR δ 2.80 (d, J = 8.4 Hz, 1 H, OH), 3.11 (d, J = 6.2 Hz, 1 H, OH), 4.20 (s, 2 H, H-$6_{a,b}$), 4.24–4.68 (m, 7 H, 2 CH_2Ph, H-1, H-4, H-5), 5.89 (s, 1 H, H-2), 7.30–7.38 (m, 10 H, Ph); ^{13}C NMR δ 66.81 (+), 70.54 (–), 72.15 (+), 72.99 (+), 74.15 (–), 79.95 (–), 126.75 (–), 127.72 (–), 127.93 (–), 128.02 (–), 128.42 (–), 128.54 (–), 137.60 (+), 137.95 (+), 146.96 (+). Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found: C, 74.10; H, 6.79.

(1α,4α,5α)-1-(Benzyloxy)-3-[(benzyloxy)methyl]-5-(acetyloxy)-2-cyclopenten-4-ol (8), (1α,4α,5α)-1-(Benzyloxy)-3-[(benzyloxy)methyl]-4-(acetyloxy)-2-cyclopenten-5-ol (9), and (1α,4α,5α)-1-(Benzyloxy)-3-[(benzyloxy)methyl]-4,5-bis(acetyloxy)-2-cyclopentene (10). The diol **7** (4.95 g, 15.2 mmol) was dissolved in 100 mL of CH_2Cl_2 containing 3 mL of Et_3N and catalytic amounts of DMAP. This solution was treated with Ac_2O (1.86 g, 18.2 mmol) and stirred for 45 min at room temperature. The reaction mixture was then extracted successively with water and 10% H_2SO_4 (30 mL each), dried (Na_2SO_4), and evaporated to dryness. The semisolid residue obtained was purified by flash column chromatography (solvent B) to give compounds **8** and **9** (3.36 g, 60%) as a semisolid mixture consisting of a 3/1 raio of **9**/**8** as estimated by ^{1}H NMR. This mixture was used as such in the following step. Compound **10** (2.44 g, 39%) was isolated as a clear oil: ^{1}H NMR δ 2.00 (s, 6 H, 2 CH_3), 4.03 (s, 2 H, H-$6_{a,b}$), 4.46–4.67 (m, 5 H, 2 CH_2Ph, H-1), 5.40 (t, J = 5.0 Hz, 1 H, H-5), 5.60 (d, J = 6.6 Hz, 1 H, H-4), 6.01 (s, 1 H, H-2), 7.27–7.38 (m, 10 H, Ph); ^{13}C NMR δ 20.68 (–), 66.17 (+), 71.57 (–), 72.18 (+), 72.80 (+), 73.22 (–), 78.75 (–), 127.70 (–), 128.34 (–), 128.40 (–), 130.51 (–), 137.81 (+), 138.19 (+), 141.88 (+), 170.23 (+).

Recycling of Diacetate 10 to Diol 7. A freshly prepared solution of NaOMe (30 mg of NaH in 10 mL of MeOH) was added to a solution of **10** in MeOH (40 mL). After the mixture was stirred for 45 min, the solvent was removed under reduced pressure and the residue was recrystallized from ether to give 1.66 g (85.7%) of diol **7**.

(1α,4β,5α)-1-(Benzyloxy)-3-[(benzyloxy)methyl]-4-azido-5-(acetyloxy)-2-cyclopentene (13) and (1α,4α,5β)-1-(Benzyloxy)-3-[(benzyloxy)methyl]-4-(acetyloxy)-5-azido-2-cyclopentene (14). A solution of a mixture of **8** and **9** (3.36 g, 9.12 mmol) in CH_2Cl_2 (60 mL) containing Et_3N (2 mL) was treated with MsCl (1.36 g, 0.92 mL, 11.86 mmol) and stirred for 30 min at room temperature. The reaction mixture was extracted with 2 N H_2SO_4 (15 mL), and the organic layer was separated, dried (Na_2SO_4), and evaporated under vacuum to give an oily mixture of the crude mesylates. This mixture was dissolved in DMSO (50 mL), treated with anhydrous LiN_3 (0.350 g, 7.15 mmol), and stirred under an argon atmosphere at room temperature for 30 min. Removal of the solvent in vacuo (0.05 mbar, maximum bath temperature 35 °C) afforded a semisolid residue which was partitioned between water and ether. The ether layer was separated, dried (Na_2SO_4), and evaporated to dryness to yield a mixture of **13** and the unreacted mesylate **12**. This mixture was separated by flash chromatography on silica gel (eluant C), and the fractions containing the less polar compound were combined to give 0.907 g (25%) of **13** as a colorless oil: IR (neat) 2200 cm^{-1}; ^{1}H NMR δ 2.04 (s, 3 H, CH_3), 4.02 (m, 2 H, H-$6_{a,b}$), 4.50 (s, 2 H, CH_2Ph), 4.55 (s, 2 H, CH_2Ph), 4.58–4.74 (m, 2 H, H-1, H-4), 5.02 (t, J =5.7 Hz, 1 H, H-5), 5.86 (m, 1 H, H-2), 7.25–7.43 (m, 10 H, Ph); ^{13}C NMR δ 20.78 (–), 66.25 (+), 68.61 (–), 72.22 (+), 72.81 (+), 78.11 (–), 78.23 (–), 127.66 (–), 127.72 (–), 128.01 (–), 128.42 (–), 137.63 (+), 138.00 (+), 143.10 (+), 170.52 (+). The fractions containing the more polar unreacted mesylate **12** were combined, and the solvent was evaporated. The oily residue obtained was dissolved in DMSO (40 mL) and treated with LiN_3 (0.650 g, 13 mmol), and the mixture was stirred under argon at 110 °C for 48 h. Afterwards the DMSO was evaporated in vacuo, and the resulting crude azide was purified by flash column chromatography as before to give **14** (1.542 g, 43%) as a colorless oil: IR (neat) 2200 cm^{-1}; ^{1}H NMR δ 2.05 (s, 3 H, CH_3), 4.00 (t, J = 4.4 Hz, 1 H, H-5), 4.02 (br s, 2 H, H-$6_{a,b}$), 4.35 (m, 1 H, H-1), 4.50 (m, 2 H, CH_2Ph), 4.65 (m, 2 H, CH_2Ph), 5.61 (d, J = 4.4 Hz, 1 H, H-4), 5.98 (s, 1 H, H-2), 7.29–7.41 (m, 10 H, Ph); ^{13}C δ 20.78 (–), 65.90 (+), 71.87 (+), 72.80 (+), 72.94 (–), 79.30 (–), 84.48 (–), 127.69 (–), 127.83 (–), 127.94 (–), 128.42 (–), 128.50 (–), 129.53 (–), 137.56 (+), 137.71 (+), 141.35 (+), 170.30 (+). Anal. Calcd for $C_{22}H_{23}N_3O_4$: C, 67.16; H, 6.02; N, 10.68. Found: C, 67.06; H, 5.93; N, 11.00.

(1α,4α,5β)-1-(Benzyloxy)-3-[(benzyloxy)methyl]-4-hydroxy-5-azido-2-cyclopentene (15). A solution of **14** (0.901 g, 2.29 mmol) in MeOH was stirred at room temperature for 30 min in the presence of NaOMe (0.030 g). After neutralizing the solution with 3 drops of glacial AcOH, the solvent was removed under vacuum. The remaining crude product was purified by short column chromatography (silica gel, eluant C) to yield the title compound as a syrupy oil (0.792 g, 98%): ^{1}H NMR δ 3.26 (d, J = 6.0 Hz, 1 H, OH), 3.90 (t, J = 5.1 Hz, 1 H, H-5), 4.14 (m, 2 H, H-$6_{a,b}$), 4.30 (m, 1 H, H-4), 4.50 (m, 3 H, CH_2Ph, H-1), 4.65 (m, 2 H, CH_2Ph), 5.82 (br s, 1 H, H-2), 7.26–7.45 (m, 10 H, Ph); ^{13}C NMR δ 66.35 (+), 71.60 (+), 72.76 (+), 75.38 (–), 78.47 (–), 83.63 (–), 127.36 (–), 127.71 (–), 127.81 (–), 128.39 (–), 137.41 (+), 137.55 (+), 143.38 (+). Anal. Calcd for $C_{20}H_{21}N_3O_3$: C, 68.36; H, 6.02; N, 11.96. Found: C, 68.22; H, 6.13; N, 11.96.

(1α,4α,5β)-1,4-Bis(benzyloxy)-3-[(benzyloxy)methyl]-5-azido-2-cyclopentene (16). A stirred solution of **15** (0.708 g, 2.02 mmol) in DMF (20 mL) was treated under an argon atmosphere with an oil suspension of NaH (80%, 0.120 g, 4.0 mmol), and stirring was continued until hydrogen evolution ceased (30 min). To the resulting brown mixture was added benzyl bromide (0.530 g, 0.37 mL, 3.1 mmol) dropwise, and stirring was continued for an additional 30 min. The reaction was quenched by careful addition of water and further diluted with additional water (60 mL). The mixture was extracted three times with ethyl ether (3 × 30 mL), and the organic layers were combined, dried (Na_2SO_4), and reduced to dryness. Flash chromatography over silica gel (eluant A) afforded 0.766 g (86%) of the tribenzyl compound **16** as a colorless oil which was used directly in the next step: ^{1}H NMR δ 3.98 (t, J = 5.0 Hz, 1 H, H-5), 4.10 (s, 2 H, H-$6_{a,b}$), 4.32 (m, 2 H, H-1, H-4), 4.50 (m, 2 H, CH_2Ph), 4.55–4.74 (m, 4 H, 2 CH_2Ph), 5.87 (br s, 1 H, H-2), 7.27–7.45 (m, 15 H, Ph); ^{13}C NMR δ 66.09 (+), 71.48 (+), 72.26 (+), 72.78 (+), 74.12 (–), 84.20 (–), 84.60 (–), 127.49 (–), 127.67 (–), 127.76 (–), 128.37 (–), 137.72 (+), 143.25 (+).

(1β,2α,5α)-1-Amino-2,5-bis(benzyloxy)-3-[(benzyloxy)-methyl]-3-cyclopentene (17). A stirred suspension of Lindlar catalyst (0.600 g) in 100 mL of a methanolic solution of **16** (0.766 g, 1.74 mmol) was hydrogenated at atmospheric pressure until TLC analysis (eluant D) indicated that all starting material had been consumed. Removal of the catalyst by filtration over a pad of Celite and evaporation of the solvent under vacuum afforded

a crude oil which was subjected to flash chromatography over silica gel (eluant D). The product-containing fractions were pooled and combined with the aid of CH_2Cl_2 to yield after evaporation of the solvent 0.623 g (86%) of **17** as a colorless oil: ^{1}H NMR δ 1.22 (br s, 2 H, NH_2), 3.43 (t, J = 4.6 Hz, 1 H, H-1), 4.00–4.20 (m, 4 H, H-5, H-2, H-6$'_{a,b}$), 4.45–4.70 (m, 6 H, 3 CH_2Ph), 5.91 (br s, 1 H, H-4), 7.20–7.40 (m, 15 H, Ph); ^{13}C NMR (Me_3SO-d_6) δ 66.06 (–), 66.13 (+), 70.09 (+), 70.67 (+), 71.63 (+), 88.28 (–), 88.50 (–), 127.26 (–), 127.42 (–), 128.00 (–), 138.29 (+), 138.97 (+), 143.39 (+). Anal. Calcd for $C_{27}H_{29}NO_3$ + 5% CH_2Cl_2: C, 77.40; H, 6.99; N, 3.41. Found: C, 77.14; H, 6.93; N, 3.32.

(1β,2α,5α)-1-*N*-(5-Amino-6-chloropyrimidin-4-yl)-2,5-bis(benzyloxy)-3-[(benzyloxy)methyl]-3-cyclopentenylamine (18). A solution of the carbocyclic amine **17** (0.538 g, 1.29 mmol), 5-amino-4,6-dichloropyrimidine (0.425 g, 2.59 mmol), and Et_3N (2 mL) in 1-butanol (10 mL) was heated to reflux under argon (bath temperature 145 °C) for 2 days. The solvent was removed under high vacuum to leave a semicrystalline residue which after trituration with 10 mL of a 3:1 mixture of petroleum ether/ethyl acetate produced a precipitate consisting of excess 5-amino-4,6-dichloropyrimidine. The filtrate was applied to a silica gel column and eluted with eluant C to yield two major fractions consisting of unreacted amine **17** (0.211 g, 39%) and the desired product **18** (0.358 g, 51%) which was isolated as an oil: ^{1}H NMR δ 3.33 (br s, 2 H, NH_2), 4.20 (m, 2 H, H-6$'_{a,b}$), 4.47–4.65 (m, 9 H, H-1′, H-2′, H-5′, 3 CH_2Ph), 5.23 (d, J = 7.3 Hz, 1 H, NH), 5.97 (s, 1 H, H-4′), 7.20–7.40 (m, 15 H, Ph), 8.00 (s, 1 H, H-2); ^{13}C NMR δ 64.54 (–), 66.43 (+), 71.11 (+), 71.89 (+), 72.70 (+), 84.12 (–), 122.02 (+), 125.20 (–), 127.54 (–), 127.75 (–), 127.85 (–), 128.14 (–), 128.23 (–), 128.35 (–), 129.94 (–), 137.84 (+), 138.20 (+), 138.28 (+), 142.74 (+), 144.25 (+), 148.94 (–), 153.79 (+). Anal. Calcd for $C_{31}H_{31}ClN_4O_3$: C, 68.56; H, 5.75; N, 10.32; Cl, 6.53. Found: C, 67.44; H, 6.06; N, 10.24; Cl, 6.20.

9-[(1β,2α,5α)-2,5-Bis(benzyloxy)-3-[(benzyloxy)methyl]-3-cyclopenten-1-yl]-6-chloropurine (19). A solution of **18** (0.350 g, 0.64 mmol) in 10 mL of triethyl orthoformate was treated with four drops of concentrated HCl and stirred at room temperature overnight. After termination of the reaction by addition of 0.5 mL of Et_3N, the solvent was evaporated under reduced pressure and the residue was purified by preparative TLC (eluant E) to give 0.296 g (83%) of **19** as a highly viscous syrup: ^{1}H NMR δ 4.23–4.39 (m, 4 H, H-6$'_{a,b}$, CH_2Ph), 4.47–4.63 (m, 5 H, H-1′, 2 CH_2Ph), 4.90 (d, J = 6.9 Hz, 1 H, H-5′), 5.02 (d, J = 6.9 Hz, 1 H, H-2′), 6.05 (s, 1 H, H-4′), 6.70–7.15 (m, 10 H, Ph), 7.20–7.40 (m, 5 H, Ph), 7.73 (s, 1 H, H-8), 8.46 (s, 1 H, H-2); ^{13}C NMR δ 65.99 (+), 70.98 (–), 71.93 (+), 72.71 (+), 72.89 (+), 80.30 (–), 80.46 (–), 127.52 (–), 127.75 (–), 127.90 (–), 128.10 (–), 128.43 (–), 132.18 (+), 137.05 (+), 137.22 (+), 137.72 (+), 143.61 (+), 145.35 (+), 150.76 (+), 150.86 (+). Anal. Calcd for $C_{32}H_{29}ClN_4O_3$ + 5% CH_2Cl_2: C, 69.07; H, 5.26; N, 10.05. Found: C, 68.90; H, 5.50; N. 9.87.

9-[(1β,2α,5α)-2,5-Dihydroxy-3-(hydroxymethyl)-3-cyclopenten-1-yl]-6-chloropurine (20). A cooled solution (–78 °C) of **19** (0.274 g, 0.49 mmol) in 50 mL of CH_2Cl_2 was treated with 3.5 mL of 1 M BCl_3 and maintained at that temperature with stirring for 2.5 h. The reaction was quenched by addition of 0.6 mL of methanol and then allowed to warm up to room temperature. During the warming up period a precipitate was formed. After further addition of methanol (10 mL) the suspension was concentrated under vacuum to a volume of ca. 10 mL, and a crystalline product (0.092g, 77%), corresponding to compound **20**, was obtained by filtration; mp >225 °C; ^{1}H NMR (Me_2SO-d_6, C_2D_6CO, D_2O) δ 4.10–4.34 (br AB, 2 H, H-6$'_{a,b}$), 4.64 (t, J = 7.2 Hz, 1 H, H-1′), 5.14–5.27 (m, 2 H, H-5′, H-2′), 5.82 (distorted t, 1 H, H-4′), 8.68 (s, 1 H, H-8), 8.71 (s, 1 H, H-2). Anal. Calcd for $C_{11}H_{10}ClN_4O_3$·0.05H_2O: C, 46.76; H, 3.96; N, 19.83. Found: C, 46.76; H, 4.03, N, 19.46.

(±)-Neplanocin F (2). Compound **20** (0.086 g, 0.30 mmol) was suspended in 10 mL of MeOH. The suspension was transferred to a cooled (–78 °C) stainless steel bomb, and 10 mL of anhydrous ammonia was condensed into the vessel. After sealing the bomb, it was heated to 110 °C for 3 days. The solution was evaporated to dryness, and the residue was redissolved in 6 mL of hot water and applied to a small (6 mL) column of Dowex AG 50-W8 (H^+ form) resin. After washing the column with water (25 mL) the product was eluted with 2 N NH_4OH. The combined fractions containing neplanocin F were pooled and reduced to dryness to leave a crystalline residue which was further purified by reversed-phase chromatography over a short C-18 column using water as eluant. Concentration of the product-containing fractions to a volume of ca. 5 mL caused precipitation of neplanocin F (32.3 mg, mp 256–257 °C, 39%) after cooling overnight in the refrigerator (5 °C). The mother liquors were again subjected to reversed-phase chromatography to afford after lyophilization additional neplanocin F (42 mg, 50%) as a white powder: ^{1}H NMR (Me_2SO-d_6) δ 3.92–4.19 (m, 2 H, H-6$'_{a,b}$, converts to an AB quartet after D_2O exchanged), 4.30 (t, J = 6.5 Hz, 1 H, H-1′), 4.82 (t, J = 5.5 Hz, 1 H, CH_2OH), 4.91–5.04 (m, 2 H, H-2′, H-5′), 5.40–5.50 (2 d, 2 H, OH), 5.65 (s, 1 H, H-4′), 7.21 (br s, 2 H, NH_2), 8.09 (s, 1 H, H-8), 8.18 (s, 1 H, H-2); FAB MS m/z (relative intensity) 264 (MH^+, 73), 136 (b + 2H, 100); high-resolution FAB MS m/z 264.1097 (MH^+, calcd 264.1099). Anal. Calcd for $C_{11}H_{13}N_5O_3$·H_2O: C, 48.53; H, 5.18; N, 25.72. Found: C, 48.66; H, 5.18; N, 25.54.

Antiviral Evaluation. Antiviral evaluations were carried out under NIH purchase order 263-MD-610174 at Southern Research Institute, Birmingham, AL, under the direction of Dr. William Shannon and Ms. Gussie Arnett.

Single-Crystal X-ray Analysis of Neplanocin F. Crystals of the racemic free base $C_{11}H_{13}N_5O_3$·H_2O were obtained from slow evaporation from a 10:1 water/ethanol mixture at room temperature. Cell dimension and intensity data were collected from a transparent, pale yellow plate of approximate dimensions 0.05 × 0.32 × 0.38 mm^3 by Analytical Diffraction Services, Inc., Notre Dame, IN. All measurements were made at 294 ± 1 K employing an Enraf-Nonius CAD4 diffractometer with graphite-monochromated Cu Kα radiation. Lattice constants were obtained by least-squares refinement of the angular settings of 25 reflections in the range 86.4° < 2θ < 90.2°. These indicated a triclinic cell with dimensions a = 7.555 (1), b = 7.958 (1), and c = 11.862 (a) Å; α = 92.84 (1), β = 103.38 (1), and γ = 116.14 (1)°. There were no systematic absences. The space group was determined to be $P\bar{1}$ from this fact plus considerations of the chirality of the molecule at C1′. Other crystal data are Z = 2, fw = 281.27, V = 613.5 (2) Å^3, and ρ_{calc} = 1.53 g/cm^3.

The data collection range was 3–156° in 2θ. The scan type used was ω – 2θ, with a variable scan width $\Delta\omega$ = (0.90 + 0.142 tan θ)°. The scan rate was 4.12 deg/min in ω. A total of 5089 reflections were collected, of which 4579 had $\mathbf{I} > 1.5\sigma(I)$. These were averaged to give 2551 unique reflections. Three standard reflections measured after every 150 scans showed no decline in intensity. Data were corrected for Lorentz and polarizations effects. An absorption correction was made via the empirical psi scan method.[18]

The structure was solved by direct methods by employing MULTAN78.[19] An E map calculated from the set of phases with the highest combined figure of merit yielded all non-hydrogen atoms. Subsequent least-squares refinements and difference Fourier maps indicated an apparent disorder of the CH_2OH substituent between the C3′ and C4′ positions. This effect is produced by equal but disordered occupancy of each molecular site by enantiomorphs, resulting in an approximate mirror plane in the plane of the base. The positions of most hydrogen atoms were obtained from difference Fourier maps employing only low-angle data [(sin θ)/λ < 0.4 Å^{-1}]. Hydrogens on the disordered carbons were placed in stereochemically reasonable positions and subsequently refined. Hydrogens on the disordered hydroxyl groups were not located. One water molecule per molecule of neplanocin F was found in the crystal structure, acting as a hydrogen bonding donor to N5 of one neplanocin F molecule and as an acceptor from HO2′ on a neighboring molecule.

The structure was refined by using full-matrix least-squares techniques. The function minimized was $\sum w(\Delta F)^2$, where ΔF = $|F_o| - |F_c|$. Weights $w = 1/\sigma_{new}^2$ were used, where $\sigma_{new}^2 = \sigma^2 + 0.5A|F_o|^2 + 0.5B[(\sin\theta)/\lambda]^2$ and $\sigma = \sigma(F_o^2)/2|F_o|$. Values of A and B were obtained by a least-squares minimization of the function of $|DF|^2 - \sigma_{new}^2$ for 20 separate segments in $|F_o|$ and (sin

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$\theta)/\lambda$. Non-hydrogen atoms were refined anisotropically. Positional parameters of all hydrogen atoms were refined with isotropic temperature factors. Occupancies of the two disordered CH_2OH substituents were fixed at 0.5 each, but no additional constraints were imposed.

Final refinements converged to the values of $R = \sum|\Delta F|/\sum|F_o| = 0.056$ and $R_w = [\sum w(DF)^2/\sum w|F_o|^2]^{1/2} = 0.070$ for all 2551 observations m and 260 variables n. The discrepancy factor $S = [\sum w(\Delta F)^2/(m-n)]^{1/2} = 0.86$. The largest final parameter shift observed was 0.01σ, and the largest peak on the final difference map was 0.4 e/Å^3. Atomic scattering factors for the non-hydrogen atoms were from ref 20. Scattering factors for the hydrogen atoms were those of Stewart et al.[21] The DNA system of programs was used throughout.[22] Final fractional atomic coordinates and thermal parameters are available as supplementary material.

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Supplementary Material Available: Tables of fractional atomic coordinates, thermal parameters, and bond lengths and angles (5 pages). This material is contained in many 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.

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Synthesis of α-(1→2)-, α-(1→3)-, α-(1→4)-, and α-(1→5)-C-Linked Disaccharides through 2,3,4,6-Tetra-*O*-acetylglucopyranosyl Radical Additions to 3-Methylidene-7-oxabicyclo[2.2.1]heptan-2-one Derivatives[1]

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The "naked sugar" (+)-1 (1*R*,2*S*,4*R*)-2-cyano-7-oxabicyclo[2.2.1]hept-5-en-2-yl (1*S'*)-camphanate) has been converted into (+)-(1*R*,4*R*,5*R*,6*R*)-3-methylidene-5-*exo*,6-*exo*-(isopropylidenedioxy)-7-oxabicyclo[2.2.1]heptan-2-one ((+)-**3**) and (−)-(1*S*,4*R*,5*R*,6*R*)-5-*exo*-(benzeneselenyl)-6-*endo*-chloro-3-methylidene-7-oxabicyclo[2.2.1]heptan-2-one ((−)-**26**). Reductive addition of 2,3,4,6-tetra-*O*-acetylglucopyranosyl radical onto (+)-**3** and (−)-**26** were highly stereoselective giving exclusively 3-*endo*-(glucosylmethyl)-7-oxabicyclo[2.2.1]heptan-2-one derivatives. The anomeric selectivity (α-*C*-glucoside vs β-*C*-glucoside) was 5.5:1 with (+)-**3** and 8:1 with (−)-**26**. The *C*-glucosides so-obtained were transformed into α-(1→2)-, α-(1→3)-, α-(1→4)-, and α-(1→5)-C-linked disaccharide derivatives which combine α-D-glucopyranose with L-*altro*-hexonolactone, L-*manno*-hexonolactone, L-mannose, and L-(*talo*-hexofuranosid)uronic acid, respectively.

Introduction

The replacement of the interglycosidic oxygen atom in disaccharides by a methylene group generates a class of interesting analogues of disaccharides, namely the *C*-disaccharides, which constitute potential inhibitors of glycosidases[2a] and disaccharidases.[2b] Inhibitors of α-amylases and other mammalian intestinal carbohydrate-splitting enzymes have aroused medical interest in the treatment of metabolic diseases such as diabetes.[2b,3] Inhibitors of sucrose as well as maltase may bring about a reduction in food consumption and weight gain.[4] A large number of cellular recognition events are thought to involve the specific binding of particular classes of oligosaccharides on one cell surface to "receptor" glycoproteins on the surface of another cell.[5,6] The immense number of structures that can be made from a relatively small number of saccharide units and the multiplicity and specificity of the enzymes which assemble them suggest that intercellular communication is encoded in oligosaccharides.[5,7] Thus, specific glycosidase inhibitors may find applications as antiviral,[8] antitumor,[9] or fertility control agents.[10] Since

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