Pergamon

TETRAHEDRON

Tetrahedron 58 (2002) 3129–3136

Enantioselective synthesis of (+)-neplanocin F

María J. Comin, Julieta Leitofuter and Juan B. Rodríguez*

Departamento de Química Orgánica, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Pabellón 2, Ciudad Universitaria, 1428 Buenos Aires, Argentina

Received 8 January 2002; accepted 11 March 2002

Abstract—(+)-Neplanocin F ((+)-**5**), a minor component of the neplanocin family of antibiotics was enantioselectively synthesized starting from D-ribono-1,4-lactone via a convergent approach in 14 steps. This synthetic approach employed a regioselective protection of a secondary allylic hydroxyl group over a homoallylic one as key step. © 2002 Elsevier Science Ltd. All rights reserved.

---

1. Introduction

The term carbanucleoside refers to a nucleoside analogue in which a methylene group has replaced the oxygen atom of the furanose ring.[1–4] Due to this surrogate, these analogues have potent metabolic stability because they are unaffected by phosphorylases and hydrolases that cleave the glycosidic bond of natural nucleosides. Remarkably, they are recognized by the same enzymes that recognize normal nucleosides displaying, correspondingly, a wide range of pharmacological responses mainly as antiviral and antitumor agents.[5,6] The neplanocin family is an important class of natural carbocyclic nucleosides isolated from *Ampullariella regularis* as fermentation products.[7] Of the neplanocins, that include at least five components, such as neplanocin C ((−)-**1**), neplanocin A ((−)-**2**), neplanocin B ((−)-**3**), neplanocin D ((−)-**4**), and neplanocin F ((−)-**5**), only **1** and **2** have received extensive consideration (Fig. 1). Neplanocin C is a notable model of conformationally locked nucleoside analogue that led to the development of several carbocyclic nucleosides either in the Northern or Southern hemisphere. All of them were designed either as building block for the synthesis of oligonucleotides[8] or as antiviral agents.[9] Neplanocin A has received much attention due to its interesting biological properties. In fact, a significant number of syntheses of neplanocin A[10,11] as well as of its analogues have been reported.[12] On the other hand, neplanocin F is a minor member of the neplanocin family, and presently, only one synthetic approach for the total synthesis of (±)-**5** has been reported.[13] Although neplanocin F is devoid of antiviral activity, it would be very important to have a general enantioselective method to make this compound and other closely related carbanucleosides available bearing in mind that small structural variations either at the base or at the pseudosugar moiety could result in biological activity.

2. Results and discussion

A straightforward synthesis of the unnatural isomer of neplanocin F was enantioselectively achieved from D-ribono-1,4-lactone through the known cyclopentenol **6** in 14 steps.[11e,14–16] We recently described an improved procedure for the synthesis of this important advanced

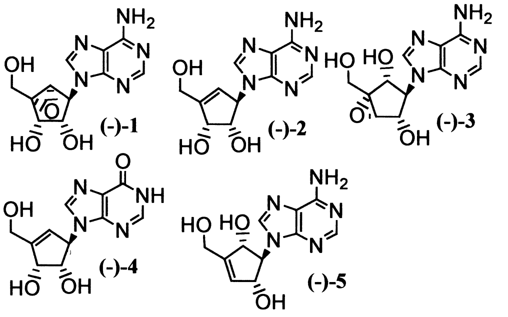
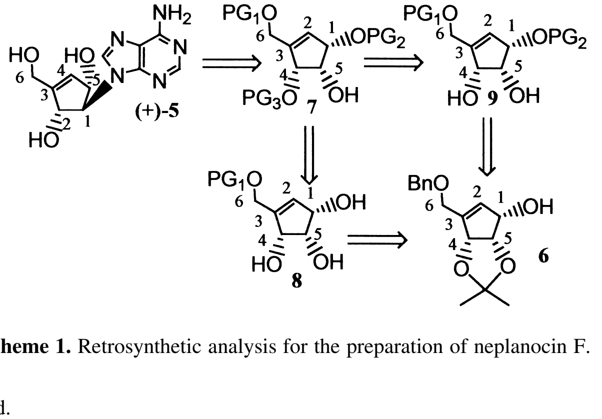


Figure 1. Chemical structures of the neplanocin family of naturally occurring carbanucleosides.

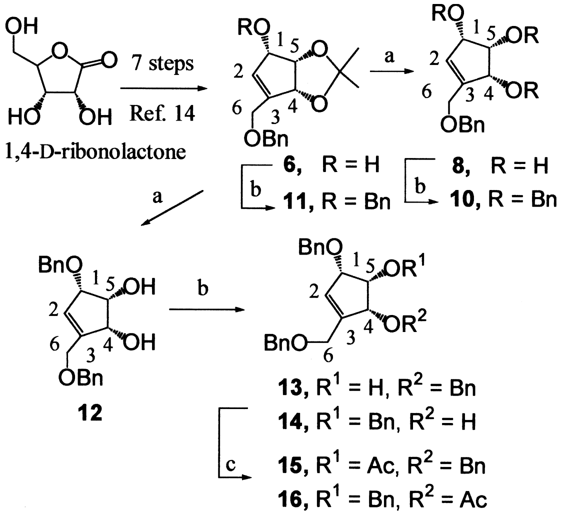


Scheme 1. Retrosynthetic analysis for the preparation of neplanocin F.

Keywords: neplanocin; *Ampullariella regularis*; nucleoside; carbocyclic.

[*] Corresponding author. Tel.: +54-11-4-576-3346; fax: +54-11-4-804-1692; e-mail: jbr@qo.fcen.uba.ar

PII: S0040-4020(02)00287-9



Scheme 2. *Reagents and conditions*: (a) 60% AcOH, 50°C, 24 h, 96% for **8**, 100% for **12**; (b) BnBr, 50% NaH, DMF, 0°C, 63% for **10**, 85% for **11**, 30% for **13**, 33% for **14**; (c) Ac$_2$O, py, room temperature, 24 h, 80% for **15**, 80% for **16**.

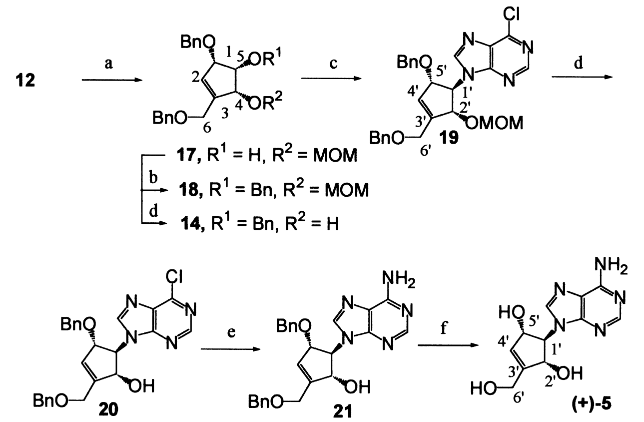
synthetic intermediate with an accurate determination of the enatiomeric excess (77% from the ^{1}H NMR analysis of the Mosher's ester of **6**).[14] The loss of optical purity when employed an intramolecular Wittig-type reaction as key step for the synthesis of **6** and other closely related carbocyclic rings has been noticed by us and other authors.[11e,15–17] The general approach for the synthesis of neplanocin F is outlined in the retrosynthetic analysis presented in Scheme 1. Compound numbering for all carbocyclic rings was kept for clarity as illustrated for the cyclopentenyl alcohol **6**. The same consideration must be considered once the heterocyclic base was introduced (compounds (+)-**5**, **19**, **20** and **21**). A critical step for obtaining optically pure neplanocin F was the coupling of the heterocyclic base via a Mitsunobu-type reaction with the corresponding glycon **7**, in which the hydroxyl group at C-5 was not protected, while the rest of the hydroxyl groups (C-1, C-4 and C-6) remained protected. The selective monoprotection of polyhydroxylated compounds has been subject of research for many years because of its importance in organic synthesis.[18] In order to obtain the carbocyclic ring with this C-5 position free, there were two ways to follow starting from **6**: (a) selective protection of both allylic hydroxyl groups on triol **8** over the homoallylic position, which would be less favoured to carry out a S$_N$2 reaction due to electronic effect and also to the resultant steric effects produced once each protecting groups are being incorporated in either allylic sites, C-1 and C-4, respectively; (b) sequential protection, first blocking the free alcohol at C-1, followed by cleavage of the isopropylidene group, and finally selective protection of the allylic hydroxyl position of the resulting diol **9** with an appropriate protecting group. Once the required synthetic intermediate **7** were at hand, a convergent approach would lead to the target molecule by introducing the base via a Mitsunobu-type reaction and further removal of the corresponding protecting groups.

The former route was primarily attempted taking advantage of the reactivity of the allylic alcohols, but the treatment of **8** with 2 equiv. of benzyl bromide under different conditions led to the tetra-*O*-benzyl derivative **10** and to the recovered unreacted starting material in all cases (Scheme 2).

A straightforward synthesis of (+)-neplanocin F was performed employing the second approach. Therefore, cyclopentenol **6** reacted with benzyl bromide in *N*,*N*-dimethylformamide at 0°C[19] to afford the corresponding benzyl ether **11** in good yield, which after treatment with acetic acid at 60°C[20] gave rise to compound **12** in almost theoretical yield.

The selective monoprotection of the resulting diol would be the key step for the synthesis of the target molecule. This strategy, although simpler than the former one, was challenging and not trivial at the beginning. In fact, both secondary hydroxyl groups of the glycol unit exhibited minor different electronic and steric environment. This approach was first attempted by treatment of **12** with 1 equiv. of benzyl bromide. Unfortunately, no regioselectivity was observed, on the contrary, a 2:3 mixture of 4-*O*-benzyl and 5-*O*-benzyl ethers were isolated (compounds **13** and **14**, respectively). Each compound was unambiguously characterized from the analysis of the proton NMR spectra of compounds **13** and **14** and the changing of indicative chemical shifts of their respective acetyl derivatives **15** and **16**, respectively. The H-5 signal of **13** was quite diagnostic to differentiate both regioisomers. This signal was observed as a triplet centred at 4.33 ppm with a coupling constant of 5.2 Hz after deuterium oxide exchange employing methyl sulfoxide-d_6 as a solvent. The multiplicity shown by H-5 can be justified by the presence of the two vicinal hydrogen atoms with similar coupling constant values. The complete assignment of ^{1}H and ^{13}C NMR spectra was conducted employing homonuclear and heteronuclear correlated spectroscopy. The H-5 of the acetylated product **15** shifted downfield 1.2 ppm compared to the same signal of **13** indicating that the C-4 position had been benzylated. On the other hand, the monobenzylation at the C-5 position of compound **12** to give **14** was also determined by NMR spectroscopy. The ^{1}H NMR spectrum corresponding to this compound was thoroughly assigned by 2D NMR techniques as well. The typical signals for this compound were a triplet centred at 4.01 ppm with a coupling constant of 5.3 Hz, a double of doublets centred at 4.39 ppm and coupling constants of 5.0 and 1.8 Hz corresponding to H-5 and H-1, respectively, and a doublet peak at 4.36 ppm with a coupling constant of 6.2 Hz from the unprotected hydroxyl group at H-4. This signal shifted downfield to 5.63 ppm keeping a similar coupling constant (5.7 Hz) when **14** was acetylated to afford **16**.

As the benzylation reaction favoured the undesired product **14**, it was decided to replace the benzyl functionality by other protecting group that could be introduced discriminating between these two positions. Regioselective introduction of the methoxymethyl (MOM) protecting group seemed to be appropriate to differentiate between allylic and homoallylic secondary alcohols. Actually, Friesen and Vanderwal have reported a high regioselective method for introducing a MOM moiety onto the less sterically hindered hydroxyl group of a glycol.[21] This approach is based on the formation of an orthoester intermediate prepared from the



Scheme 3. *Reagents and conditions*: (a) (i) trimethyl orthoformate, CH_2Cl_2, CAN, room temperature, 2 h, (ii) DIBAL, −78°C 1 h →0°C 10 min, 66%; (b) BnBr, 50% NaH, DMF, 0°C, 90%; (c) 6-chloropurine, DEAD, PPh_3, THF, room temperature, 16 h, 57%; (d) CF_3COOH, CH_2Cl_2, room temperature, 16 h, 70% for 14, 76% for 20; (e) MeOH/NH_3, 70°C, 5 h, 77%; (f) (i) BCl_3, CH_2Cl_2, −78°C, (ii) MeOH, −78°C, 85%.

corresponding diol on reaction with trimethyl orthoformate followed by in situ reductive cleavage by treatment with DIBAL in methylene chloride at low temperature. Contrary to these findings, Yamamoto had previously described a similar method to protect a secondary alcohol with MOM groups in the presence of a primary alcohol.[22] The regioselectivity of this one pot reaction is strongly modulated by the electronegativity and steric bulk of the substituents in the vicinity of the glycol group. Therefore, it was decided to explore its scope in our specific problem. Therefore, glycol **12** was treated with trimethyl orthoformate in the presence of ceric ammonium nitrate as catalyst. The resulting orthoester was treated in situ with DIBAL-H at −78°C to give rise to the monoprotected MOM derivative at the allylic position exclusively (compound **17**) in good yields. Surprisingly, when the commonly described camphorsulfonic acid[21,22] was used as catalyst instead of ceric ammonium nitrate, simply unreacted starting material was isolated. In order to confirm the formation of the desired product, compound **17** was treated with benzyl bromide followed by MOM cleavage by reaction with trifluoroacetic acid in methylene chloride to produce the above described *O*-benzyl derivative **14** exclusively. The regioselectivity observed in the introduction of a single protecting group at the allylic hydroxyl group in **12** was very encouraging. This approach allowed us to have an advanced synthetic intermediate with the alcohol free at the required position with the appropriate absolute stereochemistry. The oxidant ceric ammonium nitrate constitutes a novel catalyst in this MOM-monoprotection methodology. Further studies on this matter are currently being pursued in our laboratory (Scheme 3).

Therefore, the heterocyclic base (6-chloropurine) was coupled with **17** via a Mitsunobu-type reaction to produce solely the *N*-9 alkylated product (compound **19**).[23] The presence of the undesired *N*-7 isomer was not detected. On treatment with trifluoroacetic acid,[24] **19** was converted into **20**, which after reaction with methanolic ammonia gave the purine derivative **21** in good yield. Removal of the remaining two benzyl ethers by treatment with boron trichloride[25] in methylene chloride at −78°C on this substrate gave rise to the target molecule (+)-neplanocin F (Scheme 3). The *N*-9 alkylated position was unambiguously established by UV spectroscopy of the target molecule (+)-**5** showing a maximum peak at 260 nm, typical of this pattern.[9a,b] In addition, the ^{1}H NMR spectrum perfectly agreed with that previously described for the synthetic racemic product.[13] Moreover, the melting point matched the described for the natural product, while the optical rotation presented almost the same absolute value with the opposite sign.[26]

In conclusion, the first enantioselective synthesis of (+)-neplanocin F was achieved providing a general methodology for the preparation of closely related carbocyclic nucleosides, which belong to the neplanocin family of antibiotics. This synthetic approach was more efficient than the previously reported racemic preparation in 17 synthetic steps from the same starting material.

3. Experimental

3.1. General

The glassware used in air and/or moisture sensitive reactions were flame-dried and carried out under a dry argon atmosphere. Unless otherwise noted, chemicals were commercially available and used without further purification. Solvents were distilled before use. Tetrahydrofuran was distilled from sodium/benzophenone ketyl, methylene chloride was distilled from phosphorus pentoxide and stored over freshly activated 4 Å molecular sieves. Anhydrous *N*,*N*-dimethylformamide was used as supplied from Aldrich.

Nuclear magnetic resonance spectra were recorded using a Bruker AC-200 MHz or a Bruker AM-500 MHz spectrometers. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane. The ^{1}H NMR spectra are referenced with respect to the residual $CHCl_3$ proton of the solvent $CDCl_3$ at 7.26 ppm. Coupling constants are reported in Hertz. ^{13}C NMR spectra were fully decoupled and are referenced to the middle peak of the solvent $CDCl_3$ at 77.0 ppm. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet.

Melting points were determined using a Fisher–Johns apparatus and are uncorrected. IR spectra were recorded using a Nicolet Magna 550 spectrometer.

Low-resolution mass spectra were obtained on a VG TRIO 2 instrument at 70 eV (direct inlet). Accurate mass analysis for the final product was conducted at a resolution of 2700 (10% valley) in the molecular ion region. Glycerol was used as a FAB matrix and ionization was effected by an atom beam generated from charge-exchanged xenon ions. The glycerol peaks at *m*/*z* 185 (Gly_2H^+) and 277 (Gly_3H^+) were used as reference ions and the VG-7070-EHF mass spectrometer was voltage scanned under control of a Maspec-II data system. Standard data system software was used to assign and calculate masses of the reference and sample ions, respectively.

Column chromatography was performed with E. Merck silica gel (Kieselgel 60, 230–400 mesh). Analytical thin layer chromatography was performed employing 0.2 mm coated commercial silica gel plates (E. Merck, DC-Aluminum sheets, Kieselgel 60 F_{254}) and was visualized by 254 nm UV or by immersion into an ethanolic solution of 5% H_2SO_4.

Elemental analyses were conducted by Atlantic Microlab Inc., Norcross, Georgia. The results were within ±0.4% of the theoretical values except where otherwise stated.

3.1.1. (1*S*,4*R*,5*S*)-3-(Benzyloxy)methyl-cyclopent-2-ene-1,4,5-triol (8). Compound **6** (100 mg; 0.36 mmol) was dissolved in 60% acetic acid (5 mL) and the mixture was stirred at 50°C for 24 h. The solvent was evaporated and the residue was purified by column chromatography (silica gel) using a mixture of hexane–EtOAc (1:4) as eluant to afford 82 mg (96% yield) of pure compound **8** as a colorless oil: R_f 0.22 (hexane–EtOAc, 3:7); ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.07 (t, J=5.5 Hz, 1H, H-5), 4.18 (m, 2H, CH_2OBn), 4.36–4.42 (m, 2H, H-1, H-4), 4.53 (m, 2H, OCH_2Ph), 5.94 (d, J=1.1 Hz, 1H, H-2), 7.32 (m, 5H, Ph); ^{13}C NMR (50 MHz, $CDCl_3$) δ 66.9 (C-6), 71.4 (C-5), 72.8 (O$C\mathrm{H_2}$Ph), 73.2 (C-1)*, 73.6 (C-4)*, 127.7 (Ph), 128.3 (Ph), 130.2 (C-2), 137.8 (Ph), 145.5 (C-3). *Signal assignment may be interchanged.

3.1.2. (1*S*,4*R*,5*S*)-1,4,5-Tribenzyloxy-3-(benzyloxy)-methyl-2-cyclopentene (10). A solution of alcohol **8** (18 mg; 0.008 mmol) in anhydrous *N*,*N*-dimethylformamide (1 mL) cooled at 0°C was treated with benzyl bromide (20 μL, 0.016 mmol). Then, a 50% sodium hydride dispersion (4 mg, 0.016 mmol) was added while the temperature was maintained at 0°C. The reaction mixture was stirred at 0°C for 40 min. The reaction was quenched by addition of a saturated aqueous solution of ammonium chloride (1 mL). The mixture was extracted with methylene chloride (3×2 mL), and the combined organic layers were washed with brine (2×2 mL), dried (Na_2SO_4), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) using hexane–EtOAc (19:1) as eluant to give 19.6 g of pure **10** (63% yield) as the main product: R_f 0.45 (hexane–EtOAc, 4:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.12 (t, J=5.7 Hz, 1H, H-5), 4.13 (m, 2H, CH_2OBn), 4.41 (m, 1H, H-4), 4.45 (d, J=11.8 Hz, 1H, OCH_aHPh), 4.50 (d, J=12.1 Hz, 1H, OCHH_bPh), 4.66–4.79 (m, 6H, 3-OCH_2Ph), 6.02 (s, 1H, H-2), 7.24–7.28 (m, 15H, Ph); ^{13}C NMR (50 MHz, $CDCl_3$) δ 67.0 (C-6), 71.1 (O$C\mathrm{H_2}$Ph), 71.6 (O$C\mathrm{H_2}$Ph), 72.1 (O$C\mathrm{H_2}$Ph), 72.9 (O$C\mathrm{H_2}$Ph), 78.7 (C-5)*, 78.7 (C-1)*, 78.9 (C-4)*, 127.3 (Ph), 127.4 (Ph), 127.5 (Ph), 127.6 (Ph), 127.7 (Ph), 127.9 (Ph), 127.9 (Ph), 128.0 (Ph), 128.2 (Ph), 128.2 (Ph), 128.3 (Ph), 128.4 (Ph), 128.8 (C-2), 138.1 (Ph), 138.6 (Ph), 139.0 (Ph), 139.1 (Ph), 144.3 (C-3). *Signal assignment may be interchanged.

3.1.3. (1*S*,4*R*,5*S*)-1-Benzyloxy-3-[(benzyloxy)methyl]-4,5-(isopropylidenedioxy)-2-cyclopentene (11). A solution of alcohol **6** (966 mg; 3.5 mmol) in anhydrous *N*,*N*-dimethylformamide (7 mL) cooled at 0°C was treated with benzyl bromide (0.46 mL, 3.9 mmol). Then, a 50% sodium hydride dispersion (185 mg, 3.9 mmol) was added portionwise over 15 min while the temperature was maintained at 0°C. The reaction mixture was stirred at 0°C for 40 min. The reaction was quenched by addition of an aqueous saturated solution of ammonium chloride (20 mL). The mixture was extracted with methylene chloride (3×30 mL), and the combined organic layers were washed with brine (2×10 mL), dried (Na_2SO_4), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) using hexane–EtOAc (19:1) as eluant to give 1.120 g (85% yield) of pure **11** as a yellow pale oil: R_f 0.46 (hexane–EtOAc, 4:1); $[\alpha]_\mathrm{D}^{24}=-3.8°$ (c 1.21, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.40 (s, 3H, CH_3), 1.45 (s, 3H CH_3), 4.17 (m, 2H, H-6), 4.39 (dq, J=5.0, 2.0 Hz, 1H, H-1), 4.55 (dAB, J=20.1 Hz, 2H, OCH_2Ph), 4.61 (d, J=12.1 Hz, 1H, OCH_aHPh), 4.80 (t, J=5.5 Hz, 1H, H-5), 4.81 (d, J=12.1 Hz, 1H, OCHH_bPh), 4.91 (d, J=5.7 Hz, 1H, H-4), 5.80 (d, J=0.7 Hz, 1H, H-2), 7.32 (m, 10H, Ph); ^{13}C NMR (50 MHz, $CDCl_3$) δ 26.8 ($C\mathrm{H_3}$), 27.6 ($C\mathrm{H_3}$), 66.4 (C-6), 71.8 (O$C\mathrm{H_2}$Ph), 72.9 (O$C\mathrm{H_2}$Ph), 78.0 (C-5), 79.8 (C-1), 82.9 (C-4), 112.5 ($C\mathrm{(CH_3)_2}$), 127.6 (Ph), 127.6 (Ph), 128.0 (Ph), 128.3 (Ph), 128.4 (Ph), 128.8 (C-2), 138.1 (Ph), 138.4 (Ph), 143.1 (C-3).

3.1.4. (1*S*,4*S*,5*R*)-1-Benzyloxy-3-[(benzyloxy)methyl]-2-cyclopentene-4,5-diol (12). Compound **11** (1.00 g, 2.38 mmol) was dissolved in 60% acetic acid (10 mL) and the mixture was stirred at 50°C for 24 h. The solvent was evaporated under vacuum to give 775 mg of nearly pure compound **12** (100% yield) as a white solid, which was used as such in the next step. An analytical sample was purified by column chromatography (silica gel) using a mixture of hexane–EtOAc (7:3) as eluant: R_f 0.26 (hexane–EtOAc, 3:2); mp 57–58°C; $[\alpha]_\mathrm{D}^{24}=+15.3°$ (c 1.7, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.20 (m, 2H, H-6), 4.21–4.40 (m, 3H, H-1, H-4, H-5), 4.55 (mAB, 2H, OCH_2Ph), 4.63 (d, J=11.7 Hz, 1H, OCH_aHPh), 4.71 (d, J=11.7 Hz, 1H, OCHH_bPh), 5.89 (s, 1H, H-2), 7.34 (m, 10H, Ph); ^{13}C NMR (50 MHz, $CDCl_3$) δ 66.8 (C-6), 70.6 (C-5), 72.1 (O$C\mathrm{H_2}$Ph), 72.9 (O$C\mathrm{H_2}$Ph), 74.2 (C-4), 79.9 (C-1), 126.7 (C-2), 127.6 (Ph), 127.8 (Ph), 127.9 (Ph), 128.3 (Ph), 128.5 (Ph), 137.6 (Ph), 137.9 (Ph), 146.9 (C-3). Anal. calcd for $C_{20}H_{22}O_4$: C 73.60, H 6.79. Found: C 73.65, H 6.76.

3.1.5. (1*S*,4*R*,5*S*)-1,4-Di(benzyloxy)-3-[(benzyloxy)methyl]-cyclopent-3-en-5-ol (13) and (1*S*,4*R*,5*S*)-1,5-di(benzyloxy)-3-[(benzyloxy)methyl]-cyclopent-3-en-4-ol (14). *Method a*. To a solution of diol **12** (52 mg, 0.159 mmol) in anhydrous *N*,*N*-dimethylformamide (2 mL) was cooled at 0°C were added benzyl bromide (21 μL; 0.175 mmol) and a 50% sodium hydride dispersion (10 mg, 0.19 mmol). The mixture was stirred at 0°C for 30 min. The reaction was quenched by addition of a saturated aqueous solution of ammonium chloride (2 mL). The mixture was extracted with methylene chloride (3×10 mL), and the combined organic layers were washed with brine (2×5 mL), dried (Na_2SO_4), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) using hexane–EtOAc (9:1) as eluant to give 20 mg of **13** and 28 mg of the regioisomer **14** (73% overall yield) as colorless oils. Compound **13**: R_f 0.58 (hexane–EtOAc, 7:3); ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.06 (m, 2H, CH_2OBn), 4.17 (d, J=4.8 Hz, 1H, H-4), 4.21 (d, J=5.0 Hz, 1H, H-1), 4.33 (t, J=5.2 Hz, 1H, H-5), 4.43 (d, J=12.1 Hz, 1H, OCH_aHPh), 4.47 (d, J=12.3 Hz, 1H, OCHH_bPh), 4.50 (d, J=12.3 Hz, 1H, OCH_aHPh), 4.53 (d, J=12.1 Hz, 1H, OCH_aHPh), 4.68 (d, J=12.1 Hz, 1H, OCHH_bPh), 4.72 (d, J=11.9 Hz, 1H, OCHH_bPh), 5.84 (s, 1H, H-2), 7.26–7.34 (m, 15H, Ph); ^{13}C NMR (50.3 MHz, CDCl$_3$) δ 66.9 (C-6), 71.2 (C-5), 72.0 (O*C*H$_2$Ph), 72.8 (O*C*H$_2$Ph), 73.0 (O*C*H$_2$Ph), 79.8 (C-1), 80.1 (C-4), 127.7 (Ph), 127.8 (Ph), 128.0 (Ph), 128.4 (C-2), 128.6 (Ph), 138.1 (Ph), 138.3 (Ph), 144.8 (C-3). Compound **14**: R_f 0.48 (hexane–EtOAc, 7:3); ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.01 (t, J=5.3 Hz, 1H, H-5), 4.13 (m*AB*, 2H, CH_2OBn), 4.36 (d, J=6.2 Hz, 1H, H-4), 4.39 (dd, J=5.0, 1.8 Hz, 1H, H-1), 4.49 (m*AB*, 2H, OCH_2Ph), 4.54–4.56 (m, 3H, OCH_2Ph, OH), 4.62 (d, J=11.6 Hz, 1H, OCH_aHPh), 4.73 (d, J=11.6 Hz, 1H, OCHH_bPh), 5.84 (s, 1H, H-2), 7.25–7.32 (m, 15H, Ph); ^{13}C NMR (50 MHz, CDCl$_3$) δ 67.1 (C-6), 71.8 (O*C*H$_2$Ph), 72.4 (O*C*H$_2$Ph), 72.7 (C-4), 72.9 (O*C*H$_2$Ph), 78.7 (C-5), 79.7 (C-1), 127.5 (C-2), 127.6 (Ph), 127.7 (Ph), 127.8 (Ph), 128.0 (Ph), 128.3 (Ph), 128.4 (Ph), 138.0 (Ph), 138.1 (Ph), 138.6 (Ph), 147.6 (C-3).

Method b (MOM cleavage from compound **18**). To a solution of compound **18** (13 mg, 0.03 mmol) in methylene chloride (2 mL) was added trifluoroacetic acid (200 μL). The reaction mixture was stirred at room temperature overnight. The mixture was treated with an aqueous saturated solution of sodium bicarbonate (2 mL) and was extracted with CH$_2$Cl$_2$ (3×3 mL). The organic phase was dried (MgSO$_4$) and the solvent was evaporated. The residue was purified by column chromatography (silica gel) to afford 9 mg (70% yield) of compound **14** as a colorless oil.

3.1.6. (1*S*,4*R*,5*S*)-1,4-Di(benzyloxy)-3-[(benzyloxy)-methyl]-5-(acetyloxy)-2-cyclopentene (15). A solution of compound **13** (10 mg; 0.028 mmol) in pyridine (1 mL) was treated with acetic anhydride (0.5 mL). The solution was stirred at room temperature for 24 h. Then the mixture was quenched with 5% hydrochloric acid (0.5 mL) and stirred for additional 30 min. The mixture was extracted with methylene chloride (3×2 mL). The combined organic phases were washed with a saturated aqueous solution of sodium bicarbonate (2×1 mL), brine (2 mL), and dried (Na$_2$SO$_4$). The solvent was removed by distillation under reduced pressure and the residue was purified by preparative TLC (silica gel) employing hexane–EtOAc (4:1) as eluant to afford 10 mg (80% yield) of pure compound **15** as a colorless oil: R_f 0.38 (hexane–EtOAc, 4:1); ^{1}H NMR (500 MHz, CDCl$_3$) δ 2.07 (s, 3H, CH_3), 4.13 (s, 2H, CH_2OBn), 4.43 (m, 2H, H-1, H-4), 4.47 (d, J=11.9 Hz, 1H, OCH_aHPh), 4.51 (d, J=11.9 Hz, 1H, OCHH_bPh), 4.52 (d, J=11.9 Hz, 1H, OCH_aHPh), 4.55 (d, J=12.1 Hz, 1H, OCH_aHPh), 4.62 (d, J=12.1 Hz, 1H, OCHH_bPh), 4.63 (d, J=11.9 Hz, 1H, OCHH_bPh), 5.52 (t, J=5.5 Hz, 1H, H-5), 5.93 (s, 1H, H-2), 7.31 (m, 15H, Ph); ^{13}C NMR (50.3 MHz, CDCl$_3$) δ 21.0 (CH$_3$), 66.5 (C-6), 71.8 (O*C*H$_2$Ph), 72.5 (O*C*H$_2$Ph), 72.6 (O*C*H$_2$Ph), 72.9 (C-5), 79.0 (C-4)*, 79.4 (C-1)*, 127.6 (C-2), 127.7 (Ph), 127.7 (Ph), 127.7 (Ph), 127.9 (Ph), 128.3 (Ph), 128.3 (Ph), 128.4 (Ph), 128.4 (Ph), 138.0 (Ph), 138.3 (Ph), 138.4 (Ph), 143.7 (C-3), 171.0 (*C*OCH$_3$).

3.1.7. (1*S*,4*R*,5*S*)-1,5-Bis(benzyloxy)-3-[(benzyloxy)-methyl]-4-(acetyloxy)-2-cyclopentene (16). To a solution of compound **14** (9 mg; 0.022 mmol) in pyridine (1 mL) was added acetic anhydride (0.5 mL). The solution was stirred at room temperature for 24 h. The reaction was worked up as depicted for **15**. The residue was purified by preparative TLC (silica gel) employing hexane–EtOAc (4:1) as eluant to afford 8 mg (80% yield) of pure compound **16** as a colorless oil: R_f 0.36 (hexane–EtOAc, 4:1); ^{1}H NMR (500 MHz, CDCl$_3$) δ 2.05 (s, 3H, CH_3), 4.10 (s, 3H, CH_2OBn, H-5), 4.39 (dd, J=5.5, 1.3 Hz, 1H, H-1), 4.48 (d, J=11.8 Hz, 1H, OCH_aHPh), 4.53 (d, J=12.1 Hz, 1H, OCHH_bPh), 4.64 (d, J=11.8 Hz, 1H, OCH_aHPh), 4.65 (d, J=11.9 Hz, 1H, OCH_aHPh), 4.67 (d, J=12.1 Hz, 1H, OCHH_bPh), 4.71 (d, J=12.1 Hz, 1H, OCHH_bPh), 5.63 (d, J=5.7 Hz, 1H, H-4), 6.01 (d, J=0.7 Hz, H-2), 7.31 (m, 15H, Ph); ^{13}C NMR (125 MHz, CDCl$_3$) δ 21.1 (*C*H$_3$), 66.7 (C-6), 71.3 (O*C*H$_2$Ph), 72.8 (O*C*H$_2$Ph), 72.9 (O*C*H$_2$Ph), 73.3 (C-5), 77.9 (C-4), 78.8 (C-1), 127.5 (Ph), 127.6 (Ph), 127.7 (Ph), 127.7 (Ph), 127.7 (Ph), 127.9 (Ph), 128.3 (Ph), 128.3 (Ph), 128.4 (Ph), 130.7 (C-2), 137.9 (Ph), 138.3 (Ph), 138.8 (Ph), 142.6 (C-3), 170.9 (*C*OCH$_3$).

3.1.8. (1*S*,4*R*,5*S*)-1-Benzyloxy-3-[(benzyloxy)methyl]-4-[(methoxy)methoxy]-cyclopent-3-en-5-ol (17). A solution of diol **12** (178 mg; 0.54 mmol) in anhydrous methylene chloride (10 mL) was treated with trimethyl orthoformate (120 μL, 1.08 mmol) in the presence of ceric ammonium nitrate CAN (20 mg) as catalyst under argon atmosphere. The reaction mixture was stirred at room temperature for 2 h. The solution was cooled at −78°C, and neat DIBAL-H (1.0 mL, 5.40 mmol) was added. The mixture was stirred at this temperature for 1 h and then placed in an ice bath. After 10 min, an aqueous 1.0N solution of hydrochloric acid (2 mL) and an aqueous saturated solution of sodium and potassium tartrate (10 mL) were added and the mixture was extracted with methylene chloride (3×15 mL). The combined organic layers were washed with brine (2×50 mL), dried (Na$_2$SO$_4$), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) using a mixture of hexane–EtOAc (17:3) as eluant to give 131 mg (66% yield) of pure compound **17** as a colorless oil: R_f 0.41 (hexane–EtOAc, 3:2); $[\alpha]_D^{24}$= +31.4° (c 1.8, CHCl$_3$); IR (film, cm^{-1}) 3277, 2930, 2862, 1746, 1257, 1108; ^{1}H NMR (200 MHz, CDCl$_3$) δ 3.39 (s, 3H, OCH_3), 4.17 (m, 2H, H-6), 4.20–4.27 (m, 2H, H-1, H-4), 4.37 (m, 1H, H-5), 4.52 (m, 2H, OCH_2Ph), 4.65 (d, J=12.1 Hz, 1H, OCH_aHPh), 4.69 (d, J=6.9 Hz, 1H, CH_aHOCH$_3$), 4.75 (d, J=12.4 Hz, 1H, OCHH_bPh), 4.82 (d, J=6.6 Hz, 1H, CHH_bOCH$_3$), 5.96 (s, 1H, H-2), 7.32 (m, 10H, Ph); ^{13}C NMR (50 MHz, CDCl$_3$) δ 55.8 (O*C*H$_3$), 66.9 (C-6), 71.3 (C-5), 72.2 (O*C*H$_2$Ph), 72.8 (O*C*H$_2$Ph), 78.7 (C-4), 79.6 (C-1), 96.7 (*C*H$_2$OCH$_3$), 127.7 (C-2, Ph), 127.8 (Ph), 127.9 (Ph), 128.4 (Ph), 128.8 (Ph), 138.0 (Ph), 138.2 (Ph), 144.9 (C-3). Anal. calcd for C$_{22}$H$_{26}$O$_5$: C 71.33, H 7.07. Found: C 71.29, H 6.98.

3.1.9. (1*S*,4*R*,5*S*)-1,5-Dibenzyloxy-3-[(benzyloxy)methyl]-4-[(methoxy)methoxy]-cyclopent-3-en-5-ol (18). A solution of alcohol **17** (62 mg; 0.17 mmol) in anhydrous *N*,*N*-dimethylformamide (2 mL) cooled at 0°C was treated with benzyl bromide (24 μL, 0.20 mmol) under argon atmosphere. Then, a 50% sodium hydride dispersion (10 mg; 0.20 mmol) was added while the temperature was maintained at 0°C. The reaction mixture was stirred at 0°C for 1 h. The reaction was quenched by addition of an aqueous saturated solution of ammonium chloride (2 mL). The mixture was extracted with methylene chloride (3×3 mL), and the combined organic layers were washed with brine (2×3 mL), dried (Na_2SO_4), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) using hexane–EtOAc (17:3) as eluant to afford 68 mg (90% yield) of pure compound **18** as a colorless oil: R_f 0.62 (hexane–EtOAc, 7:3); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.35 (s, 3H, OCH_3), 3.98 (t, J=5.6 Hz, 1H, H-5); 4.19 (m, 2H, H-6), 4.35 (d, J=4.3 Hz, 1H, H-1), 4.47 (d, J=5.7 Hz, 1H, H-4), 4.50 (d, J=11.9 Hz, 1H, OCH_aHPh), 4.53 (d, J=11.9 Hz, 1H, OCHH_bPh); 4.65 (d, J=12.1 Hz, 1H, OCH_aHPh), 4.66 (d, J=12.1 Hz, 1H, OCH_aHPh), 4.70 (d, J=12.3 Hz, 1H, OCHH_bPh), 4.75 (d, J=6.4 Hz, 1H, OCH_aHOCH$_3$), 4.76 (d, J=11.4 Hz, 1H, OCHH_bPh), 4.85 (d, J=6.8 Hz, 1H, OCHH_bCH$_3$), 6.00 (s, 1H, H-2), 7.31 (m, 15H, Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.6 (OCH$_3$), 67.0 (C-6), 70.9 (OCH$_2$Ph), 71.9 (OCH$_2$Ph), 72.8 (OCH$_2$Ph), 76.8 (C-5), 78.2 (C-4)*, 78.4 (C-1)*, 96.4 (OCH$_2$O), 127.4 (Ph), 127.5 (Ph), 127.7 (C-2), 127.7 (Ph), 127.7 (Ph), 128.0 (Ph), 128.2 (Ph), 128.3 (Ph), 128.8 (Ph), 138.0 (Ph), 138.5 (Ph), 138.9 (Ph), 144.8 (C-3). *Signal attributions may be interchanged.

3.1.10. (+)-9-[(1*R*,2*R*,5*S*)-5-Benzyloxy-3-(benzyloxy)methyl-2-(methoxy)methoy-cyclopent-3-en-1-yl]-6-chloropurine (19). A suspension of 6-chloropurine (88 mg, 0.56 mmol) and triphenylphosphine (399 mg, 1.52 mmol) in anhydrous tetrahydrofuran (5 mL) was treated with diethylazodicarboxylate (206 mg, 0.56 mmol) under argon atmosphere. The resulting mixture was vigorously stirred for 10 min, then a solution of alcohol **17** (100 mg, 0.27 mmol) in tetrahydrofuran (2 mL) was added in one portion. The reaction mixture was stirred at room temperature overnight. The solvent was evaporated and the residue was adsorbed on silica gel and purified by column chromatography (silica gel) using hexane–EtOAc (4:1) as eluant to afford 80 mg (57% yield) of compound **19** as a colorless oil: R_f 0.36 (hexane–EtOAc, 3:2); $[\alpha]_D^{24}$=+12.8° (c 0.8, $CHCl_3$); IR (film, cm^{-1}) 3067, 3036, 2936, 2862, 1740, 1560, 1040; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.06 (s, 3H, OCH_3), 4.17 (d, J=13.4 Hz, 1H, H-6$'_a$), 4.21 (d, J=13.9 Hz, 1H, H-6$'_b$), 4.36 (d, J=12.1 Hz, 1H, OCH_aHPh), 4.44 (mAB, 2H, OCH_2Ph), 4.54 (d, J=11.8 Hz, 1H, CH_aHOCH$_3$), 4.56 (d, J=11.4 Hz, 1H, OCHH_bPh), 4.61 (d, J=11.8 Hz, 1H, CHH_bOCH$_3$), 4.72 (t, J=6.0 Hz, 1H, H-1$'$), 5.01 (m, 1H, H-5$'$), 5.12 (d, J=5.9 Hz, 1H, H-2$'$), 6.10 (s, 1H, H-4$'$), 7.02 (m, 2H, Ph), 7.11 (m, 3H, Ph), 7.34 (m, 5H, Ph), 7.95 (s, 1H, H-8), 8.61 (s, 1H, H-2). ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.5 (OCH$_3$), 65.9 (C-6$'$), 71.2 (C-1$'$), 72.0 (OCH$_2$Ph), 72.8 (OCH$_2$Ph), 81.6 (C-5$'$), 82.5 (C-2$'$), 97.0 (OCH$_2$OCH$_3$), 127.6 (C-4$'$, Ph), 127.7 (Ph), 127.8 (Ph), 127.9 (Ph), 128.0 (Ph), 128.2 (Ph), 128.4 (Ph), 128.9 (Ph), 132.3 (C-5), 137.3 (Ph), 137.8 (Ph), 143.0 (C-3$'$), 145.8 (C-8), 151.1 (C-4), 151.3 (C-6), 151.4 (C-2); MS (m/z, relative intensity) 506 ($[M+1]^+$, 1), 429 (2), 338 (4), 247 (3), 171 (16), 157 (18), 105 (25), 91 (100).

3.1.11. (+)-9-[(1*R*,2*R*,5*S*)-5-Benzyloxy-3-(benzyloxy)methyl-2-hydroxy-cyclopent-3-en-1-yl]-6-chloropurine (20). To a solution of compound **19** (72 mg; 0.14 mmol) in methylene chloride (3 mL) was added trifluoroacetic acid (200 μL). The reaction mixture was stirred at room temperature 48 h. The mixture was extracted with an aqueous saturated solution of sodium bicarbonate (2 mL) and was extracted with CH_2Cl_2 (3×3 mL). The organic phase was dried ($MgSO_4$) and the solvent was evaporated. The residue was purified by column chromatography (silica gel) to afford 50 mg (76% yield) of compound **20** as a colorless oil: R_f 0.18 (hexane–EtOAc, 3:2); $[\alpha]_D^{24}$= +32.4° (c 0.9, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.20–4.35 (m, 3H, H-6$'$, H-1$'$), 4.41 (d, J=12.3 Hz, 1H, OCH_aHPh), 4.50–4.63 (m, 3H, OCH_2Ph, H-2$'$), 4.66 (d, J=11.8 Hz, 1H, OCHH_bPh), 5.06 (dt, J=6.5, 1.5 Hz, 1H, H-5$'$), 5.09 (m, 1H, H-2$'$), 6.08 (s, 1H, H-4$'$), 7.18 (m, 5H, Ph), 7.34 (m, 5H, Ph), 7.99 (s, 1H, H-8), 8.61 (s, 1H, H-2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 66.6 (C-6$'$), 71.7 (C-1$'$), 72.4 (OCH$_2$Ph), 73.2 (OCH$_2$Ph), 76.4 (C-2$'$), 80.8 (C-5$'$), 126.5 (C-4$'$) 127.8 (Ph), 127.9 (Ph), 128.1 (Ph), 128.4 (Ph), 128.5 (Ph), 137.1 (Ph), 137.6 (Ph), 143.6 (C-3$'$, 145.3 (C-8), 151.3 (C-2); MS (m/z, relative intensity) 463 ($[M+1]^+$, 1), 271 (3), 354 (8), 155 (13), 91 (100)

3.1.12. (+)-9-[(1*R*,2*R*,5*S*)-5-Benzyloxy-3-(benzyloxy)methyl-2-hydroxy-cyclopent-3-en-1-yl]-6-aminopurine (21). Compound **20** (30 mg, 0.06 mmol) was treated with methanolic ammonia (1 mL, saturated at −78°C) and heated in a sealed tube at 70°C for 5 h. The mixture was cooled to room temperature and the solvent was evaporated. The residue was purified by column chromatography (silica gel) using ethyl acetate as eluant to afford 22 mg (77% yield) of pure **21** as a white solid: R_f 0.25 (EtOAc); mp 157–158°C; $[\alpha]_D^{24}$=+42.2° (c 0.8, $CHCl_3$); ^{1}H NMR (500 MHz, CD_3OD) δ 4.18 (dq, J=13.9, 0.9 Hz, 1H, H-6$'_a$), 4.23 (dt, J=16.1, 2.3 Hz, 1H, H-6$'_b$), 4.41 (d, J=12.3 Hz, 1H, OCH_aHPh), 4.54 (d, J=12.3 Hz, 1H, OCHH_bPh), 4.56 (d, J=11.7 Hz, 1H, OCH_aHPh), 4.60 (t, J=6.3 Hz, 1H, H-1), 4.61 J=11.9 Hz, 1H, OCHH_bPh), 5.03 (dt, J=6.2, 1.5 Hz, 1H, H-1$'$), 5.09 (d, J=6.5 Hz, 1H, H-2$'$), 6.02 (p, J=1.4 Hz, 1H, H-4$'$), 7.05 (m, 5H, Ph), 7.34 (m, 5H, Ph), 8.06 (s, 1H, H-8), 8.07 (s, 1H, H-2); ^{13}C NMR (125 MHz, CD_3OD) δ 67.2 (C-6$'$), 72.6 (OCH$_2$Ph), 73.5 (C-1$'$), 73.7 (OCH$_2$Ph), 77.3 (C-2$'$), 82.6 (C-5$'$), 120.9 (C-5), 128.0 (C-4$'$), 128.7 (Ph), 128.7 (Ph), 128.8 (Ph), 129.0 (Ph), 129.1 (Ph), 129.4 (Ph), 139.2 (Ph), 139.6 (Ph), 142.7 (C-8), 145.8 (C-3$'$), 150.8 (C-4), 153.3 (C-2), 157.3 (C-6). Anal. calcd for $C_{25}H_{25}N_5O_3\cdot 1.35$EtOAc: C 64.92, H 6.42, N 12.45. Found: C 65.32; H, 6.50; N, 12.08.

3.1.13. (+)-9-[(1*R*,2*R*,5*S*)-2,5-Dihydroxy-3-(hydroxy)methyl-cyclopent-3-en-1-yl]-6-aminopurine (5), (+)-neplanocin F. A solution of compound **21** (22 mg; 0.05 mmol) in anhydrous methylene chloride (4 mL), cooled at −78°C, was treated with a 1.0 M solution of boron trichloride in methylene chloride 400 μL) under argon atmosphere. The reaction mixture was stirred at −78°C for 5 h, and then for 1 h at −45°C. The mixture was cooled again to −78°C then methanol (1.0 mL) was added, and the mixture was stirred at −78°C for an additional 1 h. The reaction mixture was allowed to warm up to room temperature and the solvent was evaporated. Methanol (6×5 mL) was added and evaporated after each addition. The residue was purified by reverse phase column chromatography using a cartridge (C-18 octadecyl) and eluting with water to afford after lyophylisation 11 mg (85%) of pure neplanocin F as a white solid: R_f 0.05 (EtOAc–MeOH, 9:1); mp 220°C (d), lit.[26] 223°C for the natural isomer; $[\alpha]_D^{24}=+6.3°$ (c 0.53, H_2O), lit.[26] $[\alpha]_D^{24}=-6.6°$ (c 0.8, H_2O) for the natural isomer; UV (H_2O) λ_{max} 260 nm; ^1H NMR (500 MHz, DMSO-d_6) δ 3.88 (d, J=15.6 Hz, 1H, H-6$'_a$), 3.99 (d, J=15.6 Hz, 1H, H6$'_b$), 4.29 (t, J=6.7 Hz, 1H, H-1$'$), 4.79–4.81 (m, 2H, H-5$'$, H-2$'$), 5.54 (s, 1H, H-4$'$), 8.20 (s, 1H, H-8), 8.37 (s, 1H, H-2); ^{13}C NMR (125 MHz, D_2O) δ 58.7 (CH_2OH), 74.0 (C-1$'$), 76.3 (C-2$'$), 77.3 (C-5$'$), 119.8 (C-5), 128.3 (C-4$'$), 144.8 (C-8), 145.7 (C-3$'$), 146.5 (C-2), 149.8 (C-4), 151.3 (C-6); HRMS (FAB) Calcd for $C_{11}H_{14}N_5O_3$ (MH^+) 264.1097, found 264.1096.

Acknowledgements

Thanks are owed to the National Research Council of Argentina (Grant PIP 635/98) and the Universidad de Buenos Aires (Grant X-080) for partial financial support. We also thank Dr James A. Kelley, Laboratory of Medicinal Chemistry, National Cancer Institute, NIH for accurate mass determination.

References

1. Crimmins, M. T. *Tetrahedron* **1998**, *54*, 9229–9272.
2. Borthwick, A. D.; Biggadike, K. *Tetrahedron* **1992**, *48*, 571–623.
3. Agrofolio, L.; Suhas, E.; Farese, A.; Condom, R.; Challand, S. R.; Earl, R. A.; Guedj, R. *Tetrahedron* **1994**, *50*, 10611–10670.
4. Zhu, X. F. *Nucleosides Nucleotides Nucl. Acids* **2000**, *19*, 651–690.
5. Marquez, V. E.; Lim, M.-I. *Med. Res. Rev.* **1986**, *6*, 1–40.
6. Marquez, V. E. *Advances in Antiviral Drug Design*; De Clercq, E., Ed.; JAI: Greenwich, CT, 1996; Vol. 2, pp 89–146.
7. (a) Yaginuma, S.; Muto, N.; Tsujino, M.; Sudate, Y.; Hayashi, M.; Otani, M. *J. Antibiot.* **1981**, *34*, 359–366. (b) Isono, K. *J. Antibiot.* **1988**, *41*, 1711–1739. (c) De Clercq, E. *Antimicrob. Agents Chemother.* **1985**, *28*, 84–89. (d) De Clercq, E.; Bernaerts, R.; Bregstrom, D. E.; Robins, M. J.; Montgomery, J. A.; Holy, A. *Antimicrob. Agents Chemother.* **1986**, *29*, 482–487. (e) Hayashi, M.; Yaginuma, S.; Muto, N.; Tsujino, M. *Nucl. Acids Res. Symp. Ser.* **1980**, *8*, s65–s67. (f) Otani, M.; Yaginuma, S.; Tsujino, M.; Muto, N.; Tagata, S. Ger. Pat. 1979, 29,17,000; CA, 92, 109108.
8. (a) Marquez, V. E.; Siddiqui, M. A.; Ezzitouni, A.; Russ, P.; Wang, J.; Wagner, R. W.; Mateucci, M. D. *J. Med. Chem.* **1996**, *39*, 3739–3747. (b) Altmann, K.-H.; Kesselring, R.; Francotte, E.; Rihs, G. *Tetrahedron Lett.* **1994**, *35*, 2331–2334. (c) Altmann, K.-H.; Imwinkelried, R.; Kesselring, R.; Rihs, G. *Tetrahedron Lett.* **1994**, *35*, 7265–7268.
9. (a) Rodriguez, J. B.; Marquez, V. E.; Nicklaus, M. C.; Barchi Jr., J. J. *Tetrahedron Lett.* **1993**, *34*, 6233–6236. (b) Rodriguez, J. B.; Marquez, V. E.; Nicklaus, M. C.; Mitsuya, H.; Barchi Jr., J. J. *J. Med. Chem.* **1994**, *37*, 3389–3399. (c) Marquez, V. E.; Ezzitouni, A.; Russ, P.; Siddiqui, M. A.; Ford, Jr., H.; Feldman, R. J.; Mitsuya, H.; George, C.; Barchi Jr., J. J. *J. Am. Chem. Soc.* **1998**, *120*, 2780–2789. (d) Siddiqui, M. A.; Ford Jr., H.; George, C.; Marquez, V. E. *Nucleosides Nucleotides* **1996**, *15*, 235–250. (e) Marquez, V. E.; Russ, P.; Alonso, R.; Siddiqui, M. A.; Shin, K.-J.; George, C.; Nicklaus, M. C.; Dai, F.; Ford, Jr., H. *Nucleosides Nucleotides* **1999**, *18*, 521–530. (f) Jeong, L. S.; Marquez, V. E.; Yuan, C.-S.; Borchardt, R. T. *Heterocycles* **1995**, *41*, 2651–2656. (g) Ezzitouni, A.; Marquez, V. E. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1073–1078. (h) Ezzitouni, A.; Russ, P.; Marquez, V. E. *J. Org. Chem.* **1997**, *62*, 4870–4873. (i) Ezzitouni, A.; Barchi, Jr., J. J.; Marquez, V. E. *J. Chem. Soc., Chem Commun.* **1995**, 1345–1346.
10. (a) Hegedus, L. S.; Geisler, L. *J. Org. Chem.* **2000**, *65*, 4200–4203. (b) Shin, D. H.; Lee, H. W.; Park, S. S.; Kim, J. H.; Jeong, L. S.; Chun, M. W. *Arch. Pharm. Res.* **2000**, *23*, 302–309. (c) Yoshida, N.; Kamikubo, T.; Ogasawara, K. *Tetrahedron Lett.* **1998**, *39*, 4677–4678. (d) Ohira, S.; Sawamoto, T.; Yamato, M. *Tetrahedron Lett.* **1995**, *36*, 1537–1538.
11. (a) Marquez, V. E.; Lim, M.; Tseng, C. K.-H.; Markovac, A.; Priest, M. A.; Khan, M. S.; Kaskar, B. *J. Org. Chem.* **1988**, *53*, 5709–5714. (b) Bestmann, H. J.; Roth, D. *Angew. Chem., Int. Ed. Eng.* **1990**, *29*, 99–100. (c) Trost, B. M.; Madsen, R.; Guile, S. D. *Tetrahedron Lett.* **1997**, *38*, 1707–1710.
12. (a) Shuto, S.; Niizuma, S.; Matsuda, A. *J. Org. Chem.* **1998**, *63*, 4489–4493. (b) Niizuma, S.; Shuto, S.; Matsuda, A. *Tetrahedron* **1997**, *53*, 13621–13632. (c) Obara, T.; Shuto, S.; Saito, Y.; Snoeck, R.; Andrei, G.; Balzarini, J.; De Clercq, E.; Matsuda, A. *J. Med. Chem.* **1996**, *39*, 3847–3852. (d) Shuto, S.; Obara, T.; Saito, Y.; Yamashita, K.; Tanaka, M.; Sasaki, T.; Andrei, G.; Snoeck, R.; Neyts, J.; Padalko, E.; Balzarini, J.; De Clercq, E.; Matsuda, A. *Chem. Pharm. Bull.* **1997**, *45*, 1163–1168. (e) Shuto, S.; Obara, T.; Saito, Y.; Andrei, G.; Snoeck, R.; De Clercq, E.; Matsuda, A. *J. Med. Chem.* **1996**, *39*, 2392–2399. (f) Wolfe, M. S.; Lee, Y.; Bartlett, W. J.; Borcherding, D. R.; Borchardt, R. T. *J. Med. Chem.* **1992**, *35*, 1782–1791.
13. (a) Bodenteich, M.; Marquez, V. E. *Tetrahedron Lett.* **1989**, *30*, 4909–4912. (b) Bodenteich, M.; Marquez, V. E.; Hallows, W. H.; Goldstein, B. M. *J. Org. Chem.* **1991**, *57*, 2071–2076.
14. Comin, M. J.; Rodríguez, J. B. *Tetrahedron* **2000**, *56*, 4639–4649.
15. Hill, J. M.; Hutchinson, E. J.; Le Grand, D. M.; Roberts, S. M.; Thorpe, A. J.; Turner, N. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1483–1487.
16. Shiozaki, M.; Arai, M.; Kobayashi, Y.; Kasuya, A.; Miyamoto, S.; Furukawa, Y.; Takayama, T.; Haruyama, H. *J. Org. Chem.* **1994**, *59*, 4450–4460.
17. Rodríguez, J. B. *Tetrahedron* **1999**, *55*, 2157–2170.
18. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; 3rd ed; Wiley: New York, 1999; pp 17–200.
19. Fukuzawa, A.; Sato, H.; Masamune, T. *Tetrahedron Lett.* **1987**, *28*, 4303–4306.
20. Lewbart, M. L.; Schneider, J. J. *J. Org. Chem.* **1969**, *34*, 3505–3512.
21. Friesen, R. W.; Vanderwal, C. *J. Org. Chem.* **1996**, *61*, 9103–9110.
22. Takasu, M.; Naruse, Y.; Yamamoto, H. *Tetrahedron Lett.* **1988**, *29*, 1947–1950.
23. (a) Mitsunobu, O. *Synthesis* **1981**, 1–28. (b) Jenny, T. F.; Previsani, N.; Brenner, S. A. *Tetrahedron Lett.* **1991**, *32*, 7029–7032. (c) Jenny, T. F.; Horlacher, J.; Previsani, N.; Brenner, S. A. *Helv. Chim. Acta* **1992**, *75*, 1944–1954.
24. Woodward, R. B.; Logush, E.; Nambiar, K. P.; Sakan, K.; Ward, D. E.; Au-Yeung, B.-W.; Balaram, P.; Browne, L. J.; Card, P. J.; Chen, C. H.; Chênevert, R. B.; Fliri, A.; Frobel, K.; Gais, H.-J.; Garrat, D. G.; Hayakawa, K.; Heggie, W.; Hesson,

D. P.; Hoppe, D.; Hoppe, I.; Hyatt, J. A.; Ikeda, D.; Jacobi, P. A.; Kim, K. S.; Kobuke, Y.; Kojima, K.; Krowicki, K.; Lee, V. J.; Leutert, T.; Malchenko, S.; Martens, J.; Mattheus, R. S.; Ong, B. S.; Press, J. B.; Rajan Babu, T. V.; Rousseau, G.; Sauter, H. M.; Suzuki, M.; Tatsuta, K.; Tolbert, L. M.; Truesdale, E. A.; Uchida, I.; Ueda, Y.; Uyehara, T.; Vasella, A. T.; Vladuchick, W. C.; Wade, P. A.; Williams, R. M.; Wong, H. N.-C. *J. Am. Chem. Soc.* **1981**, *103*, 3120–3123.

25. Williams, D. R.; Brown, D. L.; Benbow, J. W. *J. Am. Chem. Soc.* **1989**, *111*, 1923–1925.
26. Yaginuma, S.; Tsujino, M.; Muto, N.; Otani, M.; Hayashi, M.; Ishimura, F.; Fujii, T.; Watanabe, S.; Matsuda, T.; Watanabe, T.; Abe, J. *Current Chemotherapy and Infectious Disease*; Nelson, J. D., Grassi, C., Eds.; American Society for Microbiology: Washington, DC, 1979; Vol. 2, pp 1558–1559.