Pergamon

Tetrahedron 56 (2000) 4639–4649

TETRAHEDRON

First Synthesis of (−)-Neplanocin C

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Received 13 March 2000; accepted 1 May 2000

Abstract—(−)-Neplanocin C (**4**), a minor component of the neplanocin family of antibiotics and a lead drug for the design of several conformationally constrained nucleosides analogues, was enantioselectively synthesized starting from D-ribono-1,4-lactone via a convergent approach in twelve steps. The proton NMR spectrum of **4** was in agreement with the corresponding natural product. Calculated coupling constants obtained from ab initio molecular modeling studies and from previously published X-ray structure of neplanocin C also corresponded to the spectroscopic data.

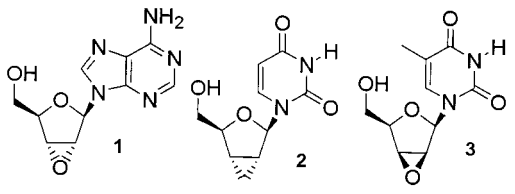
Introduction

The biological properties of nucleosides have been extensively studied, especially as antiviral and antitumor agents.[1] The term carbanucleoside refers to a nucleoside analogue in which a methylene group has replaced the oxygen atom of the furanose ring.[2] These analogues have potent metabolic stability because they are unaffected by phosphorilases and hydrolases that cleave the glycosidic bond of natural nucleosides. Interestingly, they are also recognized by the same enzymes that recognize normal nucleosides displaying, correspondingly, a wide range of biological properties.[3]

On the other hand, the conformation and puckering of the glycon moiety of nucleosides play a critical role in modulating biological activity.[4] It is known that in solution, this ribose unit exits in a rapid dynamic equilibrium between the northern-type (*N*) geometry (2′-*exo*/3′-*endo*) and the facing southern-type (*S*) geometry (2′-*endo*/3′-*exo*) according to the concept of the pseudorotational cycle defined by Altona and Sundaralingman.[5] On the contrary, only one of these conformers is found in the crystalline structure, and the Northern or Southern conformer are solely responsible for molecular recognition of a determined enzyme, such as the activation sequence that leads to active triphosphates, which, in turn, are further recognized by other specific target enzymes. However, as the ribose ring is very flexible and the conformation in solution may be unlike that found in the solid state, any attempt to correlate sugar conformation with a preferred conformation requirement of a specific enzyme for binding, would be flawed unless the crystalline structure and the solution conformation are the same.

It has been reported that a cyclopropane or epoxide ring can confer a remarkable rigidity to the sugar moiety of nucleosides in such a way that the solution conformation is identical to that found in the crystalline structure and, for that reason, the equilibrium $N \Leftrightarrow S$ is unobserved.[6] Compounds **1**, **2** and **3** were the first examples of conformationally rigid nucleosides in which a [3.1.0]-fused hexane system was used as sugar unit. However, the fixed conformations found in each compound with a 2′,3′-epoxy group oriented α and β, respectively, not only differ sharply from those typical for common nucleosides but also present an unusual flat ring puckering (ν_{max}). This effect is more noticeable in the case of compounds **1** or **2** when this ring puckering is practically eliminated with ν_{max} values below 10° (Scheme 1).[6]

On the other hand, neplanocin C (**4**), a naturally occurring carbocyclic nucleoside, is a good prototype of a conformationally locked nucleoside analogue.[7] This compound was isolated from *Ampullariela regularis* and is a minor component of the neplanocin family, which is composed of at least five components: neplanocin C (**4**), A (**5**), B (**6**), D (**7**), and F (**8**) (Scheme 2).[7] Certainly, this nucleoside analogue, also built on a [3.1.0]-bicyclic system, exhibits the typical northern-type (*N*) geometry as determined by the *P* value of the pseudorotational cycle. The calculated *P*



Scheme 1. Chemical structures of representative [3.1.0]-fused nucleosides analogues.

Keywords: carbohydrates; nucleosides; purines; enantiomeric purity.
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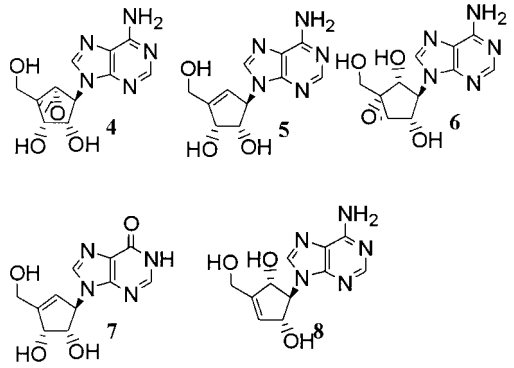
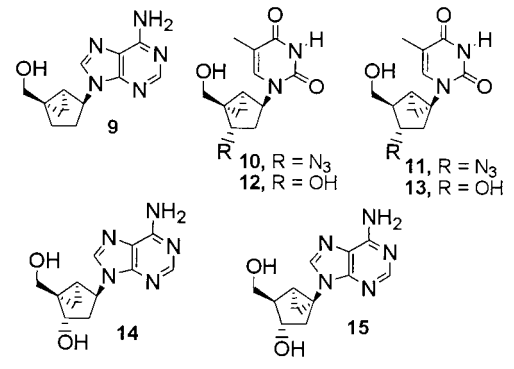
PII: S0040-4020(00)00379-3



Scheme 2. Chemical structures of the neplanocin family of naturally occurring carbanucleosides.

value=338.03° and ν_{max}=21.89° from the solved X-ray structure[8] indicates that this nucleoside analogue is in the predicted northern geometry, specifically, in the $_2E$ conformation that is very close to a pure $^3T_2$ (P=0°) geometry, which is the usual conformation found in normal nucleosides. It has been demonstrated by ab initio molecular orbital calculations that the boat like conformation in an oxabicyclo[3.1.0]hexane system is more stable than the pseudochair conformation.[9]

Several conformationally constrained carbocyclic nucleosides displaying a wide range of biological properties have been prepared taking the chemical structure of neplanocin C as lead drug. For example, adenosine derivative of 2′,3′-dideoxycarbanucleosides locked in the *N* geometry (**9**) is moderately active against HIV;[10a,b] the 5′-triphosphate of conformationally restricted carbocyclic analogues of AZT locked in the Northern conformation (**10**) is exclusively responsible for reverse transcriptase (RT) inhibition,[10c] while the 5′-triphosphate of its isomer rigid in the *S* geometry **11** ((*S*)-methanocarba-AZT) was devoid of activity against RT;[10c] (*N*)-methanocarbathymidine (**12**) is an extremely potent drug against herpes simplex virus 1 and 2 (HSV1 and HSV2) and even more active than well known antiherpetic agents like gancyclovir and acyclovir;[10d,e] (*N*)-methanocarbathymidine and (*S*)-methanocarbathymidine (**13**) present antisense activity, in fact, when **12** replaces thymidine in DNA/RNA heteroduplexes an increment of thermodynamic stability is observed, while **13**, which is locked in the *S* geometry, produces an opposite destabilizing effect;[10f,g] adenosine



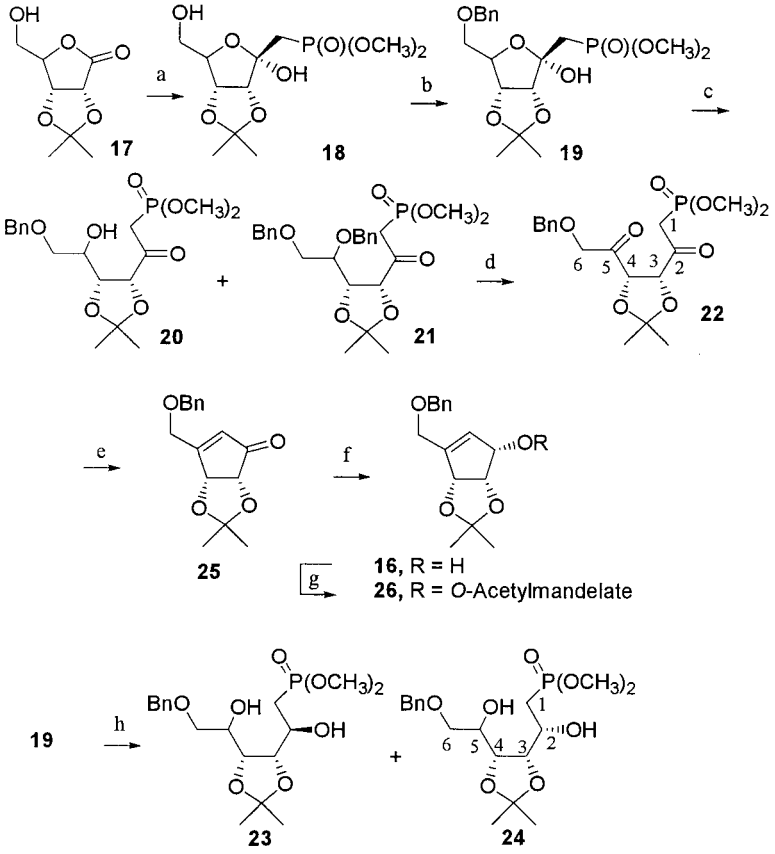
Scheme 3. Chemical structures of biologically active carbanucleosides built on a rigid [3.1.0]hexane system.

derivative (*N*)-methanocarba-2′-desoxyadenosine (**14**) is a substrate of adenosine deaminase (ADA), the enzyme responsible for catalyzing deamination of adenosine to inosine, this compound is deaminated 100 times faster than its antipodal rigid conformer **15**, (*S*)-methanocarba-2′-deoxyadenosine[10h] (Scheme 3). In conclusion, some of the Northern analogues proved to be extremely potent antiviral agents while the Southern derivatives exhibited vanishing inhibitory action.[10]

Although 5′-*nor*-dideoxycarbanucleosides employing an oxabicyclic [3.1.0]hexane system as carbocyclic ring have been prepared,[9] to date the synthesis of neplanocin C has not been accomplished. Bearing in mind the potential usefulness of carbocyclic nucleosides built onto a rigid pseudosugar template, the preparation of this important carbocyclic nucleoside was encouraged.

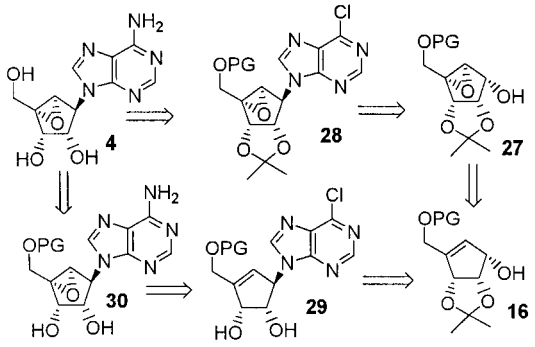
Results and Discussion

The enantioselective preparation of (−)-neplanocin C was successfully carried out using 1,4-ribonolactone as chiral starting material via the known cyclopentenol intermediate **16**.[11] The protection of both secondary hydroxyl groups as an isopropylidene unit to form (−)-2,3-*O*-isopropylidene-D-*ribono*-1,4-lactone (**17**) was conducted according to previously published procedures.[12–14] Several attempts to protect the free primary hydroxyl group of **17** as a benzyl ether were made such as in situ generation of benzyl iodide by treatment with sodium hydride, benzyl bromide and tetrabutyl ammonium iodide in tetrahydrofuran,[15] or silver oxide/benzyl bromide.[16] However, all of these methods failed in terms of the yield without recovering the starting material, probably due to ring opening of the lactone derivative **17**. Therefore, it was decided to change the oxidation state of carbon-1 to avoid ring opening. The lactol group might be resistant to the basic medium required for the introduction of the benzyl moiety. On treatment with lithium dimethyl methylphosphonate, lactone **17** was converted into lactol **18** in very good yield and with high diastereoselectivity, which after reaction with benzyl bromide in the presence of sodium hydride afforded the benzyl ether derivative **19** in excellent yield. The stereochemistry of lactol **18** may be explained by nucleophilic attack from the less hindered β-face of the molecule, modulated by the presence of the isopropylidene group, the presence of its epimer (α-nucleophilic attack) was not detected. ^{1}H and ^{13}C NMR spectra agreed with the presence of a unique diastereomer. Once compound **19** was in hand, a similar synthetic route to that reported for the synthesis of neplanocin A was followed to obtain the cyclopentenol **16**.[11] Thus, hydrolysis of this compound with methanolic potassium hydroxide gave rise to **20**[11] as the main product and **21** as a side product. Compound **20** reacted with Collins reagent to give the diketo derivative **22** in good yield.[11] Although other mild oxidizing agents were employed like oxalylchloride/methyl sulfoxide[17] or tetra-*n*-propyl ammonium perruthenate,[18] they were not able to produce the desired compound, on the contrary, a complex mixture of products was observed in each case. The preparation of **22** was first attempted by another way: reductive ring opening with sodium borohydride[19] of **19** to form the diastereomic



Scheme 4. Reagents and conditions: (a) $(MeO)_2P(O)CH_3$, *n*-BuLi, THF, −78°C→rt, 1 h, 78%; (b) 50% NaH, BnBr, DMF, 0°C, 30 min, 92%; (c) KOH, MeOH, rt, 20 h, 77%; (d) Collins, CH_2Cl_2, rt, overnight, 80%; (e) K_2CO_3, PhH, 18-crown-6, 56°C, 40 min, 35%; (f) $NaBH_4$, $CeCl_3$, MeOH, 0°C, 15 min, 100%; (g) R-*O*-acetylmandelic acid, dicyclohexylcarbodiimide, 4-DMAP, CH_2Cl_2, 0°C, 77%; (h) $NaBH_4$, THF, 0°C, 25% for **23** and 25% for **24**.

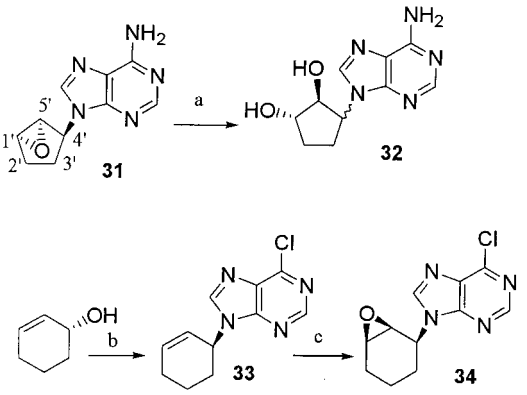
mixture of diols **23** and **24** and successive oxidation of either diol. However, all the oxidation methods employed on each diol (**23** or **24**) failed, giving rise not only to the desired compound **22** but also to partially oxidized product such as **20** and 5-keto derivatives. The cyclization reaction was a critical point for the preparation of the carbocyclic ring. In spite of higher yield having been reported (close to 50%),[11] we were able to obtain the cyclopentenone **25** in only 35% yield on reaction of the diketo derivative **21** with potassium carbonate in benzene in the presence of 18-crown-6 as transfer catalyst. In addition, some other closely related methods for this intramolecular Wittig-type reaction were attempted. For example, the use of sodium hydride as a base in diglyme[19] or in tetrahydrofuran at 65°C did not result in an increase of the yield. Contrarily, several undesired products were formed, and even the starting material could not be recovered. Reduction of the cyclopentenone **25** with sodium borohydride in the presence of cerium chloride afforded the allylic cyclopentenol **16** with high diastereoselectivity.[11] Formation of the diastereomeric β alcohol was not detected (Scheme 4).



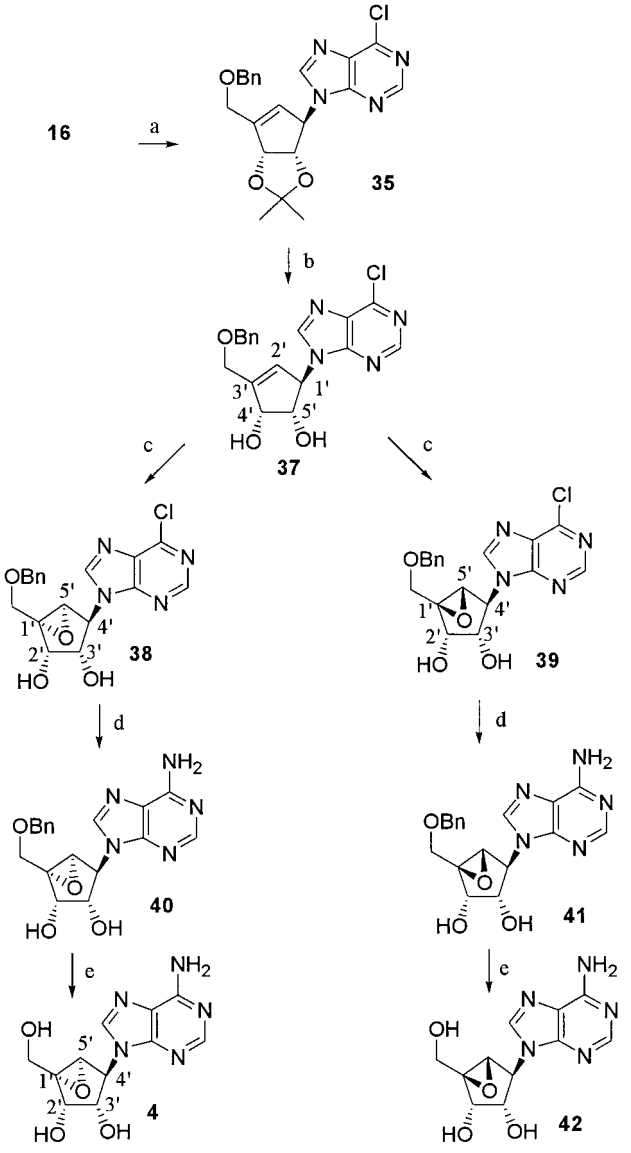
Scheme 5. Retrosynthetic analysis for the preparation of neplanocin C.

It has been demonstrated that compound **22** and other closely related 1,4-diketo-2,3-*O*-isopropylidene derivatives are able to undergo partial racemization.[11,12,20] Then, as the tendency of racemization for **22** under the basic medium of the Wittig-type reaction to form cyclopentenone **25** increases, it was quite important to analyze any loss of optical purity. It was thought that the cyclopentenol **16** could be a suitable substrate to prepare the *O*-acetylmandelate derivatives and, in fact, compound **16** reacted with *O*-acetylmandelic acid in the presence of dicyclohexylcarbodiimide[21] to produce the corresponding ester **26**. From the analysis of the proton NMR spectrum and high performance liquid chromatography of *O*-acetylmandelic ester **26**, the enantiomeric excess of cyclopentenol **16** was found to be 77%.

In order to prepare the target molecule **4**, two synthetic strategies were considered according to the retrosynthetic analysis shown in Scheme 5: (a) diastereoselective epoxidation of the advanced cyclopentenol intermediate (compound **16**) would be directed by the free hydroxyl group to produce



Scheme 6. Reagents and conditions: (a) 60% AcOH, 50°C, 24 h, 92%; (b) 6-chloropurine, Ph_3P, DEAD, THF, rt, 28%; (c) *m*-CPBA, Cl_2CH_2, 0°C→rt, 24 h, 69%.



Scheme 7. Reagents and conditions: (a) 6-chloropurine, PPh_3, DEAD, THF, rt, 1 h; (b) AcOH, 50°C, 24 h, 40% from **16;** (c) *m*-CPBA, CH_2Cl_2, 0°C→rt, 10 days, (d) NH_3/MeOH, 70°C, 5 h, 75% for **40**, 63% for **41**; (e) H_2, 10% Pd/C, MeOH, 3 atm, 88% for **4**, 72% for **42**.

the epoxyalcohol **27** as anticipated by the Hembest rule.[22] Coupling of **27** with 6-chloropurine under Mitsunobu type conditions[23] would lead to the carbanucleoside **28**. Ammonolysis of the chloropurine intermediate followed by cleavage of the isopropylidene and benzyl protective groups would form the desired target molecule. (b) Coupling of the cyclopentenyl alcohol **16** with 6-chloropurine followed by removal of the isopropylidene protective group would give rise to carbocyclic nucleoside precursor **29**. Hydroxyl-directed epoxidation would lead to the carbanucleoside intermediate built on a rigid [3.1.0]oxabicyclic hexane system (compound **30**). Ammonolysis of **30** followed by deprotection of the benzyl ether would produce the desired molecule of neplanocin C. Although the former synthetic approach seems to be very attractive, one critical point was the removal of the isopropylidene group in the presence of a labile epoxy functionality. The use of 60% acetic acid at 50°C is a mild method described[24] for the deprotection of isopropylidene groups. In order to study the stability of the epoxy group under these reaction conditions, carbanucleoside **31** taken as a simple model was employed.[9] This compound, built on an oxabicyclo[3.1.0]-hexane system similar to **28**, underwent ring opening to afford diol **32** in less than one hour when treated with 60% acetic acid, while elimination of the isopropylidene group required 24 h for completion (Scheme 6). Other mild methods for acetonide cleavage were tested like treatment of pyridinium 4-toluenesulfonate in methanol at 65°C[25] or Dowex 50W (H^+) in water at 70°C,[26] however, both of these reaction conditions produced ring opening of the epoxy group. The rest of the known methodologies to carry out this transformation need stronger acid media making them incompatible with the presence of epoxy groups. In the second strategy, epoxidation of the cyclopentenyl pseudosugar in compound **29** could lead to some difficulties due to the propensity of oxidation at the N-1 position.[27] For that reason, the reaction of a simple model (compound **33**) was investigated when this substrate reacted with *m*-chloroperoxybenzoic acid. Surprisingly, no nitrogen of the base underwent oxidation to form the corresponding N-oxides, only the epoxy derivative **34** was isolated.

For the above reasons, it was decided to use the latter synthetic strategy. Therefore, cyclopentenol **16** was coupled with 6-chloropurine under Mitsunobu conditions[23] to give the N-9 alkylated compound (carbanucleoside **35**) as the main product, and a small amount of the undesired N-7 isomer (compound **36**). On treatment with 60% acetic acid at 50°C for 24 h, **35** was converted into diol **37** in 40% overall yield starting from **16** (Scheme 7).

Then, **37** reacted with *m*-chloroperbenzoic acid at room temperature to give a mixture of the precursor of neplanocin C (compound **38**) and the precursor of its diastereomer (compound **39**) in a 1:1 ratio, which was easily purified by column chromatography. The reaction needed ten days for completion. The proton NMR spectrum was quite diagnostic, it unambiguously established the structure of compound **38**. The pseudoanomeric signal corresponding to compound **38** appeared as a singlet centered at 5.06 ppm while the pseudoanomeric signal for **39** was observed as a doublet of doublets centered at 5.02 ppm with coupling constants of 6.6 and 1.1, respectively. These NMR data showed that

Table 1.

Compound	E (kcal/mol)	ΔE	$\phi_{H3'-C3'-C4'-H4'}$	J Calcd	J Obs	$\phi_{H2'-C2'-C3'-H3'}$	J Calcd	J Obs	$\phi_{H4'-C4'-C5'-H5'}$	J Calcd	J Obs
4 (*anti*)	−624884.15	1.58	−90.0	0.0	[a]	−35.6	5.3	7.3	69.5	2.3	[a]
4 (*syn*)	−624885.73		−94.3	0.63	[a]	−34.9	5.4	7.3	73.1	1.9	[a]
37 (*anti*)[b]	−746458.61	−5.9	99.6	0.8	2.2	25.6	6.1	5.1	−50.9	4.2	br s
37 (*syn*)[b]	−746452.74		144.8	5.8	2.2	−18.1	6.8	5.1	−72.1	3.0	br s
42 (*anti*)			155.0	7.9	7.5	−32.8	5.64	m	−54.5	2.69	br s

[a] Not observed.
[b] Neplanocin C numbering was employed for simplicity.

the locked conformations of **38** and **39** perfectly agreed with the published X-ray structure of neplanocin C[8] and the calculated lowest energy conformers for this compound and its diastereomer **39**. Bearing in mind the rigidity of the pseudosugar moiety in this oxabicyclic system, it can be postulated that the dihedral angles of the carbocyclic ring of all synthetic intermediates that lead to the target molecule should be almost identical providing quite similar proton NMR spectra. Therefore, the optimized energy conformer of **38** (base in the *anti* position) presented torsion angles $\phi_{H3'-C3'-C4'-H4'}=-90°$, $\phi_{H2'-C2'-C3'-H3'}=-35.6°$ and $\phi_{H4'-C4'-C5'-H5'}=69.45°$ and calculated coupling constants of 0.0, 5.3, and 2.3 Hz, respectively. The calculated torsion angles for **39** (base in the *anti* position) were $\phi_{H3'-C3'-C4'-H4'}=155°$, $\phi_{H2'-C2'-C3'-H3'}=-33°$ and $\phi_{H4'-C4'-C5'-H5'}=-55°$ with estimated coupling constants of 7.9, 5.6 and 2.7 Hz, respectively. These data were quite in agreement with the observed NMR spectra (see Table 1). Moreover, the unusual stereochemical course of the epoxidation reaction can be explained bearing in mind that the base in the *anti* position in **37** is almost 6 kcal/mol more stable that the *syn* conformer. Then, the electrophilic epoxidizing agent can also coordinate with the N-3 rather than exclusively with the hydroxyl groups affording equal amounts of **38** and **39**.

Treatment of **38** with methanolic ammonia gave the purine derivative **40** in good yield, which after catalytic hydrogenation gave rise to (−)-neplanocin C. The remarkable stability of the epoxy functionality under methanolic ammonia at high temperature had already been described by us.[9] The proton NMR spectrum of the synthetic product was identical to that previously described.[7f] In a similar way, compound **39** was transformed into **41**, which was additionally converted into carbanucleoside **42** in a comparable overall yield.

The ab initio energy calculations of optimized conformers were performed with the program GAUSSIAN 98W employing a HF/6-31Gdp basis set.[28] All geometries were initially pre-optimized by the molecular mechanics method (MM^+), and also by semiempirical methods such as PM3 or AM1 employing the HyperChem program. The initial semiempirical calculations were not acceptable due to some divergences with the experimental data.

Compound **42** was devoid of activity against Herpes Simplex virus type 1 (HSV-1) strain F, Human Cytomegalovirus (HCMV) strain Davis Polio virus type 3, Vesicular Stomatitis virus (VSV) and Junin virus strain IV.

In summary, the first synthesis of neplanocin C was achieved providing a general methodology for the preparation of this important class of conformationally rigid nucleoside analogues built on a oxabicyclo[3.1.0]hexane system as pseudosugar moiety.

Experimental

The glassware used in air and/or moisture sensitive reactions was flame-dried and reactions were carried out under a dry argon atmosphere. Unless otherwise noted, chemicals were commercially available and used without further purification. Solvents were distilled before use. Benzene and tetrahydrofuran were 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). Positive ion fast atom bombardment mass spectra (FABMS) were obtained on a VG ZAB BEqQ spectrometer at an accelerating voltage of 8 kV and a resolution of 500. Thioglycerol was used as the sample matrix, and ionization was effected by a beam of cesium atoms. Accurate mass analysis for the final products was conducted at a resolution of 2850 (10% valley) in the molecular ion region using charge-exchanged xenon atoms and glycerol as a matrix. The glycerol peaks at m/z 277 (Gly_3H^+) and 369 (Gly_4H^+) were used as reference ions and the VG-7070-EHF mass spectrometer was voltage scanned under computer control. The standard VG peak centroiding software of the 11/250 data system was used to assign and calculate masses for the reference and sample ions, respectively. High resolution FAB mass spectrometry for the rest of the compound was performed with a JEOL

SX102 spectrometer using 6 kV Xe atoms following desorption from a glycerol matrix.

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.

(−)-1-Deoxy-1-(dimethylphosphono)-3,4-*O*-isopropylidene-D-*ribo*-hexofuranose (18). To a solution of dimethyl methylphosphonate (15.0 mL, 136 mmol) in anhydrous tetrahydrofuran (150 mL) cooled at −78°C under a nitrogen atmosphere was added *n*-butyllithium (82 mL, 119 mmol, 1.5 M solution in hexane) dropwise over a 10 min period. Then, a solution of **17** (6.1 g, 32 mmol) in anhydrous tetrahydrofuran (30 mL) was added dropwise to the resulting mixture. After the addition was completed, the reaction mixture was allowed to warm to room temperature and the mixture was stirred for an additional hour. The reaction mixture was neutralized by addition of glacial acetic acid, and partitioned between brine (150 mL) and methylene chloride (100 mL). The organic layer was dried (Na_2SO_4), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) employing hexane–EtOAc (3:2) as eluant to give 7.91 g (78% yield) of pure **18** as a white solid: mp 98–99°C; $[\alpha]_D^{24}=-7.0°$ (*c* 1.0, $CHCl_3$); IR (film, KBr) 3398, 2998, 2956, 2851, 1653, 1471, 1280, 1212, 1037, 876, 834; ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 2.34 (m, 2H, H-1), 3.73 (m, 2H, H-$6_{a,b}$), 3.76 (d, *J*=11.3, Hz, 3H, P(OCH_3)$_a$), 3.83 (d, *J*=11.1 Hz, 3H, P(OCH_3)$_b$), 4.35 (t, *J*=6.0 Hz, 1H, H-4), 4.53 (d, *J*=5.8 Hz, 1H, H-5), 4.94 (d, *J*=5.8 Hz, 1H, H-3), 6.51 (br s, 1H, –O*H*); ^{13}C NMR ($CDCl_3$) δ 24.7 (*C*H_3), 26.3 (*C*H_3), 31.2 (d, J_{C-P}=137 Hz, C-1), 53.5 (d, J_{C-P}=6.8 Hz, P(O*C*H_3)$_a$), 54.0 (d, J_{C-P}=6.8 Hz, P(O*C*H_3)$_b$), 63.9 (C-6), 81.9 (C-5), 86.9 (C-4), 87.5 (C-3), 105.0 (d, J_{C-P}=7 Hz, C-2), 112.5 (*C*(CH$_3$)$_2$).

(−)-6-*O*-Benzyl-1-deoxy-1-(dimethylphosphono)-3,4-*O*-isopropylidene-D-*ribo*-hexofuranose (19). A solution of compound **18** (5.8 g, 18.5 mmol) in anhydrous *N*,*N*-dimethylformamide (15 mL) cooled at 0°C was treated with benzyl bromide (2.64 mL, 22.2 mmol). Then, a 50% sodium hydride dispersion (2.00 g, 40.7 mmol) was added portionwise over 15 min while the temperature was maintained at 0°C. The reaction mixture was stirred at 0°C for 30 min. The reaction was quenched by addition of a saturated aqueous solution of ammonium chloride (100 mL). The mixture was extracted with methylene chloride (2×50 mL), and the combined organic layers were washed with brine (5×50 mL), dried (Na_2SO_4), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) using hexane–EtOAc (4:1) as eluant to give 6.80 g of pure **19** (92% yield) as a yellow pale oil: $[\alpha]_D^{24}=-12.8°$ (*c* 1.5, $CHCl_3$), lit.[11] $[\alpha]_D^{24}=-14.0°$ (*c* 0.93, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 2.40 (m, 2H, H-1), 3.65 (m, 2H, H-6), 3.73 (d, *J*=11.0 Hz, 3H, P(OCH_3)$_a$), 3.83 (d, *J*=11.0 Hz, 3H, P(OCH_3)$_b$), 4.30 (t, *J*=5.9 Hz, 1H, H-4), 4.51 (d, *J*=5.8 Hz, 1H, H-5), 4.57 (m, 2H, OCH_2Ph), 4.78 (d, *J*=5.9 Hz, 1H, H-3), 7.32 (m, 5H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 25.1 (*C*H_3), 26.5 (*C*H_3), 31.3 (d, J_{C-P}=6.8 Hz, C-1), 51.9 (d, J_{C-P}=6.7 Hz, P(O*C*H_3)$_a$), 53.4 (d, J_{C-P}=6.7 Hz, P(O*C*H_3)$_b$), 71.3 (C-6), 73.4 (O*C*H_2Ph), 82.8 (C-5), 84.8 (C-4), 86.5 (d, J_{C-P}=8.3 Hz, C-3), 105.3 (d, J_{C-P}=6.8 Hz, C-2), 112.7 (*C*(CH$_3$)$_2$), 127.7 (Ph), 128.4 (Ph), 137.5 (Ph); MS (*m*/*z*, relative intensity) 403 (2), 295 (2), 241 (8), 219 (2), 213 (2), 151 (3), 91 (100).

(−)-6-*O*-Benzyl-1-deoxy-1-(dimethylphosphono)-3,4-*O*-isopropylidene-D-ribo-hexulose (20); (−)-5,6-*O*-dibenzyl-1-deoxy-1-(dimethylphosphono)-3,4-*O*-isopropylidene-D-*ribo*-hexulose (21). To a solution of **19** (6.40 g, 16.0 mmol) in methanol (50 mL) was added potassium hydroxide (1.80 g, 32.0 mmol). The reaction mixture was stirred at room temperature for 20 h. The mixture was neutralized with an aqueous saturated solution of ammonium chloride and was extracted with methylene chloride (3×50 mL). The combined organic phases were washed with brine (2×70 mL), dried (Na_2SO_4), and the solvent was evaporated. The product was purified by column chromatography (silica gel) using hexane–EtOAc (1:1) as eluant to afford 4.91 g of pure compound **20** (77% yield) as a yellow syrup and 0.79 g (12% yield) of compound **21** as a yellow syrup. Compound **20**: $[\alpha]_D^{24}=-8.3°$ (*c* 1.05, $CHCl_3$), lit.[11] $[\alpha]_D^{24}=-8.2°$ (*c* 1.02, $CHCl_3$); IR (film, cm^{-1}) 3350, 2959, 2924, 2852, 2360, 2339, 1733, 1348, 1041, 870, 742, 706; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.37 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 3.33 (dd, *J*=22.3, 14.3 Hz, 1H, H-1_a), 3.46 (dd, *J*=22.3, 14.3 Hz, 1H, H-1_b), 3.56 (dd, *J*=9.8, 6.2 Hz, 1H, H-6_a), 3.70 (dd, *J*=9.8, 3.2 Hz, 1H, H-6_b), 3.69 (d, *J*=11.4 Hz, 3H, P(OCH_3)$_a$), 3.70 (d, *J*=11.4 Hz, 3H, P(OCH_3)$_b$), 3.90 (m, 1H, H-5), 4.24 (t, *J*=6.4 Hz, 1H, H-4), 4.57 (m*AB*, 2H, OCH_2Ph), 4.62 (d, *J*=6.2 Hz, 1H, H-3), 7.33 (m, 5H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 26.0 (*C*H_3), 26.9 (*C*H_3), 37.2 (d, J_{C-P}=131.0 Hz, C-1), 53.1 (d, J_{C-P}=6.8 Hz, P(O*C*H_3)$_2$), 70.9 (C-6), 71.6 (C-5), 73.5 (O*C*H_2Ph), 77.5 (C-4), 82.7 (C-3), 111.3 (*C*(CH$_3$)$_2$), 127.7 (Ph), 128.4 (Ph), 137.9 (Ph), 199.5 (C-2); MS (*m*/*z*, relative intensity) 403(4), 345 (5), 327 (7), 223 (17), 151 (31), 124 (37), 91 (100). Compound **21**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 3.23 (dd, *J*=22.1, 14.4 Hz, 1H, H-1_a), 3.41 (dd, *J*=22.3, 14.4 Hz, 1H, H-1_b), 3.60 (dd, *J*=10.3, 5.6 Hz, 1H, H-6_a), 3.73 (d, *J*=11.2 Hz, 3H, P(OCH_3)$_a$), 3.74 (d, *J*=11.4 Hz, 3H, P(OCH_3)$_a$), 3.84 (m, 1H, H-5), 4.40 (t, *J*=5.8 Hz, 1H, H-4), 4.53 (m*AB*, 2H, OCH_2Ph), 4.62 (d, *J*=6.4 Hz, 1H, H-3), 4.70 (d, *J*=11.6 Hz, 1H, OCH_aPh), 4.77 (d, *J*=11.6 Hz, 1H, OCH_bPh), 7.27–7.35 (m, 10H, aromatic protons); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.8 (*C*H_3), 26.7 (*C*H_3), 36.7 (d, J_{C-P}=131.6 Hz, C-1), 52.7 (d, J_{C-P}=6.8 Hz, P(O*C*H_3)$_2$), 69.6 (C-6), 72.9 (O*C*H_2Ph), 73.2 (O*C*H_2Ph), 77.3 (C-5), 78.0 (C-4), 81.7 (d, J_{C-P}=2.7 Hz, C-2), 110.9 (*C*(CH$_3$)$_2$), 127.5 (Ph), 127.7 (Ph), 128.1 (Ph), 137.9 (Ph), 138.0 (Ph), 201.3 (C-2).

(−)-6-*O*-Benzyl-1-deoxy-1-(dimethylphosphono)-3,4-*O*-isopropylidene-D-*erythro*-2,5-hexodiulose (22). To a magnetically stirred solution of pyridine (6.8 mL, 83.6 mmol) in anhydrous methylene chloride (100 mL) cooled at 0°C was added powdered chromium trioxide (4.18 g, 41.8 mmol) under argon atmosphere. Then, a solution of the hydroxy ketone **20** (2.8 g, 7.0 mmol) in

anhydrous methylene chloride (10 mL) was added and the reaction mixture was allowed to warm to room temperature and was stirred overnight. The mixture was then filtered through a silica gel pad eluting with EtOAc–acetone (2:1) and the solvent was evaporated to afford 2.14 g (80% yield) of the diketone **22** as a yellow pale oil that was used in the next step without further purification: $[\alpha]_D^{24}=-13.4°$ (*c* 1.2, $CHCl_3$), lit.[11] $[\alpha]_D^{24}=-14.1°$ (*c* 1.0, $CHCl_3$); IR (film, cm^{-1}) 3451, 1733, 1640, 1262, 1041; ^1H NMR (500 MHz, $CDCl_3$) δ 1.40 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 3.25 (dd, *J*=22.8, 14.1 Hz, 1H, H-1_a), 3.49 (dd, *J*=22.5, 14.1 Hz, 1H, H-1_b), 3.78 (d, *J*=11.2 Hz, 3H, P(OCH_3)$_a$), 3.80 (d, *J*=11.2 Hz, 3H, P(OCH_3)$_b$), 4.39 (d, *J*=18.2 Hz, 1H, H-6_a), 4.48 (d, *J*=18.5 Hz, 1H, H-6_b), 4.62 (s, 2H, OCH_2Ph), 4.79 (d, *J*=5.7 Hz, 1H, H-3), 4.82 (d, *J*=5.9 Hz, 1H, H-4), 7.35 (m, 5H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 25.9 (*C*H_3), 26.1 (*C*H_3), 37.0 (d, J_{C-P}=130.3 Hz, C-1), 53.1 (d, J_{C-P}=4.5 Hz, P(O*C*H_3)$_2$), 72.6 (C-6), 73.4 (O*C*H_2Ph), 79.4 (C-4), 81.5 (d, J_{C-P}=2.5 Hz, C-3), 113.0 (*C*(CH_3)$_2$), 127.7 (Ph), 128.0 (Ph), 128.5 (Ph), 136.9 (Ph), 199.6 (d, J_{C-P}=7.5 Hz, C-2), 204.7 (C-5).

6-*O*-Benzyl-1-deoxy-1-dimethylphosphono-3,4-*O*-isopropylidene-D-allose (23); 6-*O*-benzyl 1-deoxy-3,4-*O*-isopropylidene-D-altrose (24). A solution of lactol **19** (780 mg, 1.95 mmol) in tetrahydrofuran (20 mL) was treated with sodium borohydride (265 mg, 7.0 mmol) at 0°C. The reaction mixture was stirred at room temperature for 2 h, then an aqueous saturated solution of ammonium chloride (100 mL) was added. The mixture was extracted with ether (3×50 mL). The combined organic layers were washed with brine (3×50 mL), dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) eluting with hexane–EtOAc (2:3) to afford 198 mg (25% yield) of compound **23** as a white solid and 210 mg (25% yield) of compound **24** as a white solid: Compound **23**: ^1H NMR ($CDCl_3$) δ 1.31 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.81–2.01 (m, 2H, H-1), 3.59 (dd, *J*=9.9, 6.3 Hz, 1H, H-6_a), 3.77 (d, *J*=10.9 Hz, 6H, P(OCH_3)$_2$), 4.61 (m*AB*, 2H, OCH_2Ph), 7.34 (m, 5H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 25.4 (*C*H_3), 27.9 (*C*H_3), 29.4 (d, J_{C-P}=140.3 Hz, C-1), 65.3 (d, J_{C-P}=5.7 Hz, C-3), 68.6 (C-5), 71.7 (C-6), 73.5 (O*C*H_2Ph), 77.3 (C-4), 80.3 (d, J_{C-P}=16.0 Hz, C-2), 108.8 (*C*(CH_3)$_2$), 127.7 (Ph), 128.4 (Ph), 138.1 (Ph). Compound **24**: ^1H NMR ($CDCl_3$) δ 1.34 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 2.17 (dd, *J*=18.3, 6.3 Hz, 2H, H-1), 3.24 (s, 1H, –O*H*), 3.56 (dd, *J*=9.8, 5.7 Hz, 1H, H-6_a), 3.74 (d, *J*=10.9 Hz, 3H, P(OCH_3)$_a$), 3.75 (d, *J*=11.0 Hz, 3H, P(OCH_3)$_b$), 4.06–4.15 (m, 3H), 4.43 (m, 1H), 4.57 (m*AB*, 2H, OCH_2Ph) 7.33 (m, 5H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 25.5 (*C*H_3), 27.5 (*C*H_3), 30.5 (d, J_{C-P}=140.1 Hz, C-1), 52.6 (d, J_{C-P}=7.4 Hz, P(O*C*H_3)$_2$), 65.0 (d, J_{C-P}=4.0 Hz, C-3), 68.6 (C-5), 72.1 (C-6), 73.7 (O*C*H_2Ph), 77.9 (C-4), 80.1 (d, J_{C-P}=16.1 Hz, C-2), 108.9 (*C*(CH_3)$_2$), 128.0 (Ph), 128.7 (Ph), 138.3 (Ph).

(4*R*,5*R*)-(−)-3-[(Benzyloxy)methyl]-4,5-*O*-isopropylidene-2-cyclopentenone (25). A solution of diketone **22** (1.00 g, 2.5 mmol), previously azeotroped with benzene (2×10 mL), dissolved in anhydrous benzene (5 mL), was added to a stirred suspension of powered potassium carbonate (415 mg, 3.00 mmol) and 18-crown-6 ether (463 mg, 1.75 mmol) in anhydrous benzene (20 mL) at 56°C under argon atmosphere. The reaction mixture was stirred at this temperature for 40 min. Then, the mixture was allowed to cool to room temperature, was filtered and the filtrate was poured into ethyl ether (30 mL). The resulting mixture was washed with brine (3×15 mL), dried (Na_2SO_4) and the solvent was evaporated. The product was purified by column chromatography (silica gel) employing hexane–EtOAc (9:1) as eluant to afford 240 mg (35% yield) of pure **25** as a colorless oil: $[\alpha]_D^{24}=-7.9°$ (*c* 0.6, $CHCl_3$), lit.[11] $[\alpha]_D^{24}=-7.2°$ (*c* 1.02, $CHCl_3$); IR (film, cm^{-1}) 2986, 2939, 2852, 1730, 1629, 1382, 1215, 1148, 1082, 868, 741, 701; ^1H NMR ($CDCl_3$) δ 1.39 (s, 6H, C(CH_3)$_2$), 4.33 (dd, *J*=17.3, 1.1 Hz, 1H, H-6_a), 4.49 (d, *J*=5.6 Hz, 1H, H-4), 4.49 (dd, *J*=17.3, 1.6 Hz, 1H, H-6_b), 4.64 (s, 2H, OCH_2Ph), 5.08 (d, *J*=5.6 Hz, 1H, H-5), 5.20 (t, *J*=1.7 Hz, 1H, H-2), 7.29 (m, 5H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 26.1 (*C*H_3), 27.3 (*C*H_3), 67.4 (C-6), 73.3 (O*C*H_2Ph), 77.6 (C-4)*, 77.9 (C-5)*, 115.4 (*C*(CH_3)$_2$), 127.6 (Ph), 128.3 (C-2), 128.4 (Ph), 137.2 (Ph), 173.6 (C-3), 201.5 (C-1); MS (*m*/*z*, relative intensity) 259 (1), 168 (25), 110 (40), 91 (100). *Signal assignment may be interchanged.

(1*S*,4*R*,5*S*)-(+)-3-[(Benzyloxy)methyl]-4,5-*O*-isopropylidene-2-cyclopenten-1-ol (16). To a solution of **25** (729 mg, 2.66 mmol) and cerium(III) chloride heptahydrate (834 mg, 2.24 mmol) in methanol (20 mL) cooled at 0°C, sodium borohydride (156 mg, 4.12 mmol) was added portionwise while the temperature was maintained between 0 and 5°C. After 15 min the pH was adjusted to 7 with acetic acid. Water (10 mL) was added and the mixture was extracted with ethyl ether (3×20 mL). The organic phase was washed with brine (3×30 mL), dried (Na_2SO_4), and the solvent was evaporated to give 734 mg (100%) of the desired alcohol **16** as a colorless oil: $[\alpha]_D^{24}=+25.1°$ (*c* 1.12, $CHCl_3$), lit.[29] $[\alpha]_D^{24}=+41.6$ (no solvent informed); ^1H NMR (500 MHz, $CDCl_3$) δ 1.40 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 2.70 (d, *J*=9.8 Hz, 1H, H-1), 4.16 (m, 2H, H-6), 4.56 (s, 2H, –OCH_2Ph), 4.76 (t, *J*=5.5 Hz, 1H, H-5), 5.80 (m, 1H, H-2), 7.29 (m, 5H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 26.6 (*C*H_3), 27.6 (*C*H_3), 66.3 (C-6), 72.9 (O*C*H_2Ph), 73.3 (C-1), 77.8 (C-5), 83.0 (C-4), 112.6 (*C*(CH_3)$_2$), 127.6 (Ph), 128.4 (Ph), 131.4 (C-2), 138.0 (Ph), 143.6 (C-3).

(1*S*,4*R*,5*S*)-(−)-3-[(Benzyloxy)methyl]-4,5-*O*-isopropylidene-2-cyclopenten-1-yl (*R*)-*O*-acetylmandelate (26). A solution of dicyclohexylcarbodiimide (52 mg, 0.25 mmol) in anhydrous methylene chloride (2 mL) was added dropwise to a stirred solution of (*R*)-(−)-*O*-acetylmandelic acid (44 mg, 0.23 mmol), alcohol **16** (62 mg, 0.23 mmol) and 4-(dimethylamino)pyridine (10 mg) in anhydrous methylene chloride (5 mL) at 0°C. A white precipitate of dicyclohexylurea was observed in the reaction medium before the addition was completed. The reaction mixture was stirred at room temperature for an additional 24 h. The dicyclohexylurea was removed by filtration, and the resulting filtrate was washed successively with an aqueous 0.5 M solution of HCl (3×5 mL), an aqueous 1 M solution of Na_2CO_3 (2×10 mL) and brine (3×10 mL). The organic layer was dried (Na_2SO_4), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) eluting with hexane–EtOAc (9:1) to afford 76 mg (77% yield) of

ester **26** (diastereomeric mixture) as a white solid: de 77% (corresponds to ee 77% for **16**) determinated by HPLC (Alltech Ultrasphere ODS-2 5 μm, 250×10 mm column; 4.0 mL/min; MeOH–H_2O 85:15; λ=270 nm) t_{r1}= 9.12 min, t_{r2}=9.97 min; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.17 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 2.19 (s, 3H, CH_3CO), 4.10 (d, J=13.9 Hz, 1H, H-6_a), 4.16 (d, J=13.9 Hz, 1H, H-6_b), 4.55 (s, 2H, OCH_2Ph), 4.80–5.00 (m, 1H, H-1), 4.88 (s, 1H, AcOC*H*), 5.23 (br s, 1H, H-5), 5.35 (br s, 1H, H-4), 6.07 (d, 1H, J=10.3 Hz, H-2), 7.30–7.60 (m, 10H, aromatic protons); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.6 (CO*C*H$_3$), 20.8 (CO*C*H$_3$), 26.9 (*C*H$_3$), 27.2 (*C*H$_3$), 27.3 (*C*H$_3$), 66.4 (C-6), 73.0 (O*C*H$_2$Ph), 74.2 (AcO*C*H), 75.3 (C-5), 76.5 (C-1), 76.9 (C-1), 83.0 (C-4), 112.9 (*C*(CH$_3$)$_2$), 125.7 (Ph), 127.7 (Ph), 127.8 (Ph), 128.4 (Ph), 128.5 (Ph), 128.7 (Ph), 129.2 (Ph), 133.3 (C-2), 133.5 (C-2), 137.9 (Ph), 146.1 (C-3), 167.3 (*C*O), 167.9 (*C*O), 170.1 (*C*OCH$_3$).

(±)-6-Amino-9-[(2,3-dihydroxycyclopentan-1-yl]-purine (32). A solution of **31** (50 mg; 0.23 mmol) in 60% acetic acid (5 mL) was stirred for 1 h at 50°C. The solvent was evaporated to give 51 mg (92% yield) of **32** as a colorless oil: ^{1}H NMR (500 MHz, CD_3OD) δ 2.24 (m, 2H, H-5′), 2.58 (m, 2H, H-4′), 4.62 (m, 1H, H-1′), 4.96 (m, 2H, H-2′, H-3′), 8.17 (s, 1H, H-8), 8.45 (s, 1H, H-2); ^{13}C NMR (125 MHz, CD_3OD) δ 32.5 (C-5′), 33.8 (C-4′), 62.5 (C-1′), 65.3 (C-3′), 75.8 (C-2′), 118.5 (C-5), 139.0 (C-4), 140.4 (C-8), 145.0 (C-2), 158.8 (C-6).

(±)-9-(2-Cyclohexen-1-yl)-6-chloropurine (33). A suspension of 6-chloropurine (1.90 g, 12.0 mmol) and triphenylphosphine (4.00 mg, 15.0 mmol) in anhydrous tetrahydrofuran (30 mL) was treated with diethylazodicarboxylate (2.67 g, 15.0 mmol) under argon atmosphere. The resulting mixture was vigorously stirred for 10 min. Then, a solution of (±)-2-cyclohexen-1-ol (982 mg, 10.0 mmol) in tetrahydrofuran (5 mL) was added in one portion. The reaction mixture was stirred at room temperature for 2 h. The solvent was evaporated and the residue was adsorbed on silica gel and purified by column chromatography using hexane–EtOAc (4:1) as eluant to afford 641 mg (28% yield) of pure compound **33** as a white solid: mp 134°C; ^{1}H NMR ($CDCl_3$) δ 1.60–2.40 (m, 6H, H-4′, H-5′, H-6′), 5.33 (m, 1H, H-1′), 5.82 (m, 1H, H-2′), 6.28 (s, 1H, H-3′), 8.18 (s, 1H, H-8), 8.73 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$) δ 18.8 (C-5′), 24.5 (C-6′), 29.6 (C-4′), 50.3 (C-1′), 123.4 (C-3′), 131.9 (C-5),134.9 (C-2′), 144.1 (C-8), 150.7 (C-4), 151.31 (C-6), 151.5 (C-2).

(±)-2-(6-Chloropurin-9-yl-7-oxabicyclo[4.1.0]heptane (34). To a solution of compound **33** (200 mg, 0.85 mmol) in methylene chloride (6 mL) was added dropwise a solution of 80% *m*-chloroperbenzoic acid (588 mg, 1.70 mmol) in methylene chloride (5 mL) at 0°C. The reaction mixture was stirred at room temperature for 24 h. The solvent was evaporated and the residue was purified by column chromatography using hexane–EtOAc (1:1) as eluant to afford 137 mg (69% yield) of pure epoxide **34** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.40–2.20 (m, 6H, H-4′, H-5′, H-6′), 3.45 (m, 2H, H-2′, H-3′), 5.13 (m, 1H, H-1′), 8.41 (s, 1H, H-8), 8.73 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$) δ 20.2 (C-5′), 22.2 (C-6′), 26.4 (C-4′), 52.3 (C-1′), 53.2 (C-2′)*, 54.7 (C-3′)*, 144.1 (C-8), 151.7 (C-2). * Signal assignment may be interchanged.

(−)-9-[(Benzyloxy)methyl-4,5-*O*-isopropylidene-2-cyclopenten-1-yl]-6-chloropurine (35); (−)-7-[(Benzyloxy)-methyl-4,5-*O*-isopropylidene-2-cyclopenten-1-yl]-6-chloropurine (36). A suspension of 6-chloropurine (214 mg, 1.39 mmol) and triphenylphosphine (455 mg, 1.73 mmol) in anhydrous tetrahydrofuran (3 mL) was treated with diethylazodicarboxylate (303 mg, 1.73 mmol) under argon atmosphere. The resulting mixture was vigorously stirred for 10 min, then after a solution of alcohol **16** (319 mg, 1.16 mmol) in tetrahydrofuran (5 mL) was added in one portion. The reaction mixture was stirred at room temperature for 1 h. The solvent was evaporated and the residue was adsorbed on silica gel and purified by column chromatography using hexane–EtOAc as eluant to afford 487 mg of compound **35** and 90 mg of the N-7 derivative (compound **36**). Compound **35**: ^{1}H NMR ($CDCl_3$) δ 1.37 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 4.25 (m, 2H, H-6′$_{a,b}$), 4.63 (s, 2H, OCH_2Ph), 4.75 (d, J=5.5 Hz, 1H, H-5′), 5.42 (d, J=5.5 Hz, 1H, H-4′), 5.66 (s, 1H, H-1′), 5.84 (s, 1H, H-2′), 7.34 (m, 5H, aromatic protons), 8.03 (s, 1H, H-8), 8.75 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$) δ 25.6 (*C*H$_3$), 27.1 (*C*H$_3$), 66.2 (C-1′)*, 66.3 (C-6′)*, 72.8 (O*C*H$_2$Ph), 83.8 (C-4′)*, 83.9 (C-5′)*, 112.9 (*C*(CH$_3$)$_2$), 121.9 (C-2′), 127.4 (Ph), 127.5 (Ph), 128.2 (Ph), 137.5 (Ph), 143.7 (C-8), 149.8 (C-3′), 151.7 (C-2); MS (*m*/*z*, relative intensity) 414 (1), 412 (1), 357 (2), 355 (6), 327 (3), 325 (10), 250 (10), 248 (34), 201 (32), 157 (11), 155 (23), 91 (100). Compound **36**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 4.30 (m, 2H, H-6′), 4.64 (d, J=5.7 Hz, 1H, H-5′), 4.66 (s, 2H, OCH_2Ph), 5.24 (d, J=5.5 Hz, 1H, H-4′), 5.96 (s, 1H, H-1′), 6.04 (s, 1H, H-2′), 7.34 (m, 5H, aromatic protons), 8.11 (s, 1H, H-8), 8.90 (s, 1H, H-2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.0 (*C*H$_3$), 27.1 (*C*H$_3$), 66.2 (C-1′), 66.6 (C-6′), 72.1 (O*C*H$_2$Ph), 83.0 (C-4′)*, 83.5 (C-5′)*, 112.6 (*C*(CH$_3$)$_2$), 121.2 (C-2′), 127.4 (Ph), 127.6 (Ph), 128.1 (Ph), 137.3 (Ph), 146.1 (C-8), 151.2 (C-3′), 152.2 (C-2). *Signals assignment may be interchanged.

(−)-9-[(1*R*,4*R*,5*S*)-3-(Benzyloxy)methyl-4,5-dihydroxy-cyclopent-2-en-1-yl]-6-chloropurine (37). A solution of **35** (400 mg) in 60% acetic acid (5 mL) was stirred for 24 h at 50°C. The solvent was evaporated under vacuum and the residue was purified by column chromatography using hexane–ethyl acetate (1:4) as eluant to yield 173 mg of **37** (40% yield, two steps from **16**) as a colorless oil: $[\alpha]_D^{24}$=−32.6° (*c* 0.68, $CHCl_3$); UV (MeOH) λ_{max}=266 nm; ^{1}H NMR ($CDCl_3$) δ 3.21 (br s, 1H, −O*H*), 4.32 (m, 3H, H-5′, H-6′$_{a,b}$), 4.63 (s, 2H, OCH_2Ph), 4.83 (d, J=5.1 Hz, 1H, H-4′), 5.56 (distorted t, J=2.2, 1.5 Hz 1H, H-1′), 6.06 (d, J=1.5 Hz, 1H, H-2′), 7.36 (m, 5H, Ph), 8.10 (s, 1H, H-8), 8.74 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$) δ 66.8 (C-1′), 67.4 (C-6′), 73.4 (O*C*H$_2$Ph), 73.7 (C-4′), 77.4 (C-5′), 124.6 (C-2′), 127.9 (Ph), 128.1 (Ph), 128.6 (Ph), 143.4 (C-8), 147.8 (C-3′), 151.8 (C-2); FAB MS (*m*/*z*, relative intensity) 373 ([M+H]$^+$, 100), 339 (17), 245 (16), 201 (14), 155 (94); HRMS (FAB) Calcd for $C_{18}H_{18}ClN_4O_3$ 373.1067, found 373.1073.

(1*R*,2*S*,3*S*,4*S*,5*R*)-(−)-1-Benzyloxymethyl-4-(6-chloropurin-9-yl)-6-oxa-bicyclo[3.1.0]hexane-2,3-diol (38);

(1*S*,2*S*,3*S*,4*S*,5*S*)-(−)-1-benzyloxymethyl-4-(6-chloropurin-9-yl)-6-oxa-bicyclo[3.1.0]hexane-2,3-diol (39). To a solution of compound **37** (167 mg, 0.45 mmol) in methylene chloride (6 mL) was added dropwise a solution of 80% *m*-chloroperbenzoic acid (116 mg, 0.54 mmol) in methylene chloride (5 mL) at 0°C. The reaction mixture was stirred at room temperature for 10 days. The solvent was evaporated and the residue was purified by column chromatography (silica gel) eluting with hexane–EtOAc (2:3) to produce 57 mg of pure epoxy alcohol **38** as a white solid and 60 mg of pure epoxy alcohol **39** as a white solid (69% overall yield). Compound **38**: mp 53–54°C, $[\alpha]_D^{24}=-25.6°$ (*c* 0.89, $CHCl_3$); UV (MeOH); $\lambda_{max}=266$ nm; IR (KBr, cm^{-1}) 3270, 2952, 2867, 2367, 2339, 1719, 1605, 1569, 1412, 1341, 1113, 949, 849; ^1H NMR (500 MHz, $CDCl_3$) δ 3.76 (s, 1H, H-5′), 4.02 (m*AB*, 2H, BnOCH_2), 4.15 (d, *J*=6.8 Hz, 1H, H-3′), 4.65 (m*AB*, 2H, PhCH_2O), 4.95 (d, *J*=7.0 Hz, 1H, H-2′), 5.06 (s, 1H, H-4′), 7.33 (m, 5H, Ph), 8.20 (s, 1H, H-8), 8.65 (s, 1H, H-2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 59.2 (C-5′), 62.0 (C-4′), 66.9 (BnO*C*H_2), 69.9 (C-1′), 71.4 (C-2′), 73.9 (Ph*C*H_2O), 75.8 (C-3′), 127.0 (Ph), 128.2 (Ph), 128.6 (Ph), 129.8 (C-5), 137.2 (Ph), 144.2 (C-8), 151.2 (C-6), 151.8 (C-4), 152.1 (C-2); FAB MS (*m/z*, relative intensity) 389 ($[M+H]^+$, 100), 355 (18), 155 (30). Compound **39**: mp 63–64°C, $[\alpha]_D^{24}=-26.9°$ (*c* 1.19, $CHCl_3$); UV (MeOH) $\lambda_{max}=266$ nm; IR (KBr, cm^{-1}) 3259, 2924, 2852, 2368, 2353, 1754, 1598, 1555, 1405, 1341, 1120, 963, 707; ^1H NMR (500 MHz, $CDCl_3$) δ ^1H NMR (500 MHz, $CDCl_3$) δ 3.80 (d, *J*=11.6 Hz, 1H, BnOCH_aH), 3.95 (br s, 1H, H-5′), 4.18 (t, *J*=5.9 Hz, 1H, H-3′), 4.21 (d, *J*=11.6 Hz, 1H, BnOCHH_b), 4.50 (d, *J*=5.0 Hz, 1H, H-2′), 4.63 (d, *J*=11.8 Hz, 1H, OCH_aHPh), 4.67 (d, *J*=11.8 Hz, 1H, OC$H$$H_b$Ph), 5.02 (dd, *J*=6.6, 1.1 Hz, 1H, H-4′), 7.36 (m, 5H, aromatic protons), 8.42 (s, 1H, H-8), 8.75 (s, 1H, H-2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 58.8 (C-5′), 62.3 (C-4′), 65.9 (C-1′), 66.2 (BnO*C*H_2), 69.3 (C-2′), 73.8 (O*C*H_2Ph), 75.1 (C-3′), 127.9 (Ph), 128.1 (Ph), 128.6 (Ph), 130.0 (C-5), 137.3 (Ph), 143.4 (C-8), 151.0 (C-2); HRMS (FAB) Calcd for $C_{18}H_{18}ClN_4O_4$ 389.1017, found 389.1008.

(1*R*,2*S*,3*S*,4*S*,5*R*)-(−)-4-(6-Amino-purin-9-yl)-1-benzyloxymethyl-6-oxa-bicyclo[3.1.0]hexane-2,3-diol (40). Compound **38** (50 mg, 0.13 mmol) was treated with methanolic ammonia (2 mL, saturated at −78°C) and heated in 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 CH_2Cl_2–methanol (9:1) as eluant to afford 22 mg (75% yield) of pure **40** as a white solid: mp 77–78°C; $[\alpha]_D^{24}=-29.9°$ (*c* 0.69, CH_3OH); UV (MeOH) $\lambda_{max}=260$ nm; ^1H NMR (500 MHz, CD_3OD) δ 3.74 (s, 1H, H-5′), 3.82 (d, *J*=11.7 Hz, 1H, BnOCH_aH), 4.11 (d, *J*=11.7 Hz, 1H, BnOCHH_b), 4.14 (d, *J*=6.9 Hz, 1H, H-3′), 4.63 (m*AB*, 2H, PhCH_2O), 4.85 (d, *J*=7.3 Hz, 1H, H-2′), 4.93 (s, 1H, H-4′), 7.27 (m, 5H, Ph), 8.09 (s, 1H, H-8), 8.13 (s, 1H, H-2); ^{13}C NMR (125 MHz, CD_3OD) δ 60.6 (C-5′), 62.9 (C-4′), 67.7 (BnO*C*H_2), 70.5 (C-1′), 72.0 (C-2′), 74.6 (O*C*H_2Ph), 76.7 (C-3′), 120.3 (C-5), 128.8 (Ph), 128.8 (Ph), 129.4 (Ph), 139.4 (Ph), 141.3 (C-8), 150.6 (C-4), 157.3 (C-6); HRMS (FAB) Calcd for $C_{18}H_{20}N_5O_4$ 370.1515, found 370.1513.

(1*S*,2*S*,3*S*,4*S*,5*S*)-(−)-4-(6-Amino-purin-9-yl)-1-benzyloxymethyl-6-oxa-bicyclo[3.1.0]hexane-2,3-diol (41). Compound **39** (50 mg, 0.13 mmol) was treated with methanolic ammonia (2 mL, saturated at −78°C) and heated in sealed tube at 70°C for 2 h. The mixture was cooled to room temperature and the solvent was evaporated. The residue was purified by column chromatography (silica gel) using methylene chloride: methanol (95:5) as eluant to afford 30 mg (63% yield) of pure **41** as a white solid: mp 177–178°C; $[\alpha]_D^{24}=-54.3°$ (*c* 0.19, CH_3OH); UV (MeOH) $\lambda_{max}=260$ nm; ^1H NMR (500 MHz, CD_3OD) δ 3.57 (d, *J*=11.8 Hz, 1H, BnOCH_aH), 3.83 (br s, 1H, H-5′), 4.23 (dd, *J*=7.7, 5.4, Hz 1H, H-3′), 4.32 (d, *J*=11.8 Hz, 1H, BnOCHH_b), 4.35 (d, *J*=5.1 Hz, 1H, H-2′), 4.78 (m*AB*, 2H, PhCH_2O), 5.00 (d, *J*=7.6 Hz, 1H, H-4′), 7.33 (m, 5H, aromatic protons), 8.21 (s, 1H, H-8), 8.27 (s, 1H, H-2); ^{13}C NMR (125 MHz, CD_3OD) δ 60.5 (C-5′), 61.7 (C-4′), 66.8 (C-1′), 67.6 (BnO*C*H_2), 70.0 (C-2′), 74.5 (O*C*H_2Ph), 75.8 (C-3′), 120.0 (C-5), 128.8 (Ph), 128.9 (Ph), 129.2 (Ph), 139.4 (Ph), 140.6 (C-8), 151.5 (C-4), 153.9 (C-2), 157.4 (C-6); HRMS (FAB) Calcd for $C_{18}H_{20}N_5O_4$ 370.1515, found 370.1513.

(1*R*,2*S*,3*S*,4*S*,5*R*)-(−)-4-(6-Amino-purin-9-yl)-1-hydroxymethyl-6-oxa-bicyclo[3.1.0]hexane-2,3-diol (Neplanocin C, 4). A solution of **40** (22 mg, 0.06 mmol) in methanol (5 mL) in the presence of 5% palladium on charcoal (5 mg) was treated with hydrogen at 3 atm. The reaction was stirred at room temperature for 4 h. The mixture was filtered off and the solvent was evaporated. The residue was purified by column chromatography (silica gel) employing CH_2Cl_2–MeOH (4:1) as eluant to produce 14 mg (88% yield) of pure **4** as a white solid: mp>270°C (lit.[7e] mp 222–226°C, decomp.); $[\alpha]_D^{24}=-41.5°$ (*c* 0.21, water), lit.[7e] $[\alpha]_D^{24}=-43.6$ (*c* 0.6, water); UV (MeOH) $\lambda_{max}=262$ nm; ^1H NMR (500 MHz, DMSO-d_6) δ 3.60 (d, *J*=12.5 Hz, 1H, HOCH_aH–), 3.62 (s, 1H, H-5′), 3.96–4.00 (m, 2H, HOCHH_b, H-3′), 4.64 (d, *J*=7.3 Hz, 1H, H-2′), 4.83 (s, 1H, H-4′), 7.23 (s, 2H, NH_2), 8.09 (s, 1H, H-8), 8.14 (s, 1H, H-2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 57.5 (C-4′), 58.6 (HO*C*H_2–), 60.3 (C-5′), 69.3 (C-2′), 70.5 (C-1′), 75.0 (C-3′), 118.8 (C-5), 139.1 (C-8), 149.1 (C-4), 152.5 (C-2), 156.0 (C-6); HRMS (FAB) Calcd for $C_{11}H_{14}N_5O_4$ (MH^+) 280.1046, found 280.1057.

(1*S*,2*S*,3*S*,4*S*,5*S*)-(−)-4-(6-Aminopurin-9-yl)-1-hydroxymethyl-6-oxa-bicyclo[3.1.0]hexane-2,3-diol (42). A solution of **41** (22 mg, 0.06 mmol) in methanol (5 mL) in the presence of 5% palladium on charcoal (5 mg) was treated with hydrogen at 3 atm. The reaction was stirred at room temperature for 4 h. The mixture was filtered off and the solvent was evaporated. The residue was purified by column chromatography (silica gel) employing CH_2Cl_2–MeOH (4:1) as eluant to give 12 mg (72% yield) of pure **42** as a white solid: mp>270°C, $[\alpha]_D^{24}=-88.0°$ (*c* 0.13, water); UV (MeOH) $\lambda_{max}=262$ nm; ^1H NMR (500 MHz, DMSO-d_6) δ 3.16 (d, *J*=5.2 Hz, 2H, HOCH_2),3.48 (dd, 1H, *J*=12.6, 5.5 Hz, –O*H*), 3.77 (br s, 1H, H-5′), 4.10–4.20 (m, 2H, H-3′, H-2′), 4.83 (d, *J*=7.5 Hz, 1H, H-4′), 5.08 (d, *J*=7.6 Hz, 1H, –O*H*), 5.34 (d, *J*=5.2 Hz, 1H, –O*H*), 7.21 (s, 2H, –NH_2), 8.15 (s, 1H, H-8), 8.16 (s, 1H, H-2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 57.3 (C-4′), 59.2 (HO*C*H_2), 59.5 (C-5′), 66.7 (C-1′), 67.9 (C-2′), 73.1

(C-3′), 119.0 (C-5), 138.5 (C-8), 150.1 (C-4), 152.5 (C-2), 156.0 (C-6); HRMS (FAB) Calcd for $C_{11}H_{14}N_5O_4$ (MH^+) 280.1046, found 280.1065.

Acknowledgements

Thanks are owed to the Fundación Antorchas, the Agencia Nacional de Promoción Científica y Tecnológica (PICT 06-00000-00579), the National Research Council of Argentina (CONICET) and the Universidad de Buenos Aires for financial support. We also thank Dr James A. Kelley, Laboratory of Medicinal Chemistry, NCI, NIH for accurate mass determination, and Dr Carlos A. Pujol for antiviral assays.

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