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A short and novel synthesis of carbocyclic nucleosides and 4′-*epi*-carbocyclic nucleosides from 2-cyclopenten-1-ones☆

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Abstract—Carbocyclic nucleoside analogues remain interesting target molecules having the potential to combine biological activity with greater metabolic stability than their sugar counterparts. This paper describes a rapid and versatile synthetic approach to such compounds based on commercial cyclopentenones (e.g., **1**) that has been developed in our laboratory. Carbocyclic nucleosides like 2′-methyl-aristeromycin **6** were synthesized in racemic form in 5 steps via key intermediate **4**. The procedure was also adapted to the preparation of 4′-epi-carbocyclic nucleosides using epoxide **17** instead of **4** and employing the same methodology.

1. Introduction

Modified nucleosides are presently the object of intense research activity in medicinal chemistry due to their potential as antiviral agents. As part of our on-going antiviral program, we have found that 2′-methyl-branched nucleosides showed particularly promising potential.[1–3] Most notably to date, a prodrug of 2′-methyl-cytidine is currently in Phase II clinical trials as an anti-hepatitis C drug.[4] It was therefore relevant to consider the preparation of carbocyclic analogues of our lead compounds. Since 2′-branched carbocycles[5] had not been reported when this work was initiated, it was necessary to design a synthetic route giving rapid access to this class of molecules. Many enantioselective syntheses of carbocycles have been reported starting with D- or L-ribose[6–9] and D- or L-ribonolactone.[10–13] All of them are non-trivial or lengthy and, appeared difficult to adapt to the preparation of branched carbocycles. Furthermore, the powerful antiviral activity of some L-nucleosides like Telbivudine[14–16] or Lamivudine[17,18] prompted us to opt for a synthesis of our targets as racemic mixtures in the first instance. Most synthetic procedures for racemic preparation of carbocycles use either Vince lactam[19–22] or cyclopentadiene.[23,24] Again, the adaptation of a known procedure to the synthesis of our molecules seemed to be problematic and would have led to synthetic routes of more than 15 steps. It was therefore decided to try and find a novel approach allowing a rapid and efficient access to 2′-branched carbocycles. This research resulted in the shortest synthesis of racemic carbocycles reported so far and is disclosed herein.

2. Results and discussion

2.1. General strategy

In every approach we considered, introduction of the 2′-branching seemed to be the weak link of the synthesis and it was therefore decided to opt for a starting compound already bearing it. The retrosynthetic analysis for purine derivatives is shown in Figure 1. Epoxide ring opening was

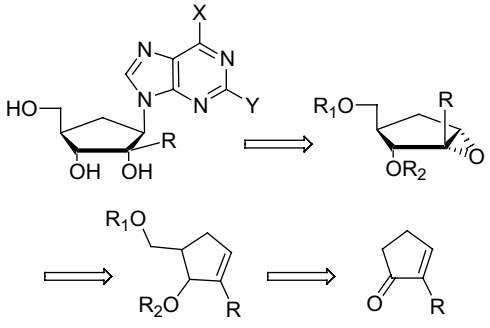

Figure 1. Retrosynthetic analysis.

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chosen as the means of introduction of the base[25–27] taking advantage of the presence of the 2′-branching to control the regioselectivity of the reaction. The core of carbocyclic pseudo-nucleosides being a cyclopentane, we were naturally led to cyclopentenones, appropriately substituted in position 2, as our starting point. This class of molecules present several key advantages (a) bearing the targeted 2′-branching, which can be changed by switching to another ketone, (b) having the 3′-oxygen of the future carbocycle, (c) having a double bond ready for epoxidation, (d) having a keto group making possible an α-alkylation for introduction of the 5′-carbon, (e) being achiral and (f) being commercially available at a reasonable price.

2.2. Preparation of key epoxide 4

Introduction of the nucleoside 4′-hydroxymethyl group on ketone **1** (Scheme 1) was not a trivial task: 2-cyclopenten-1-ones are notoriously troublesome substrates for α-alkylation reactions.[28,29] For instance, attempts to react gaseous formaldehyde on the enolate of **1** failed. The successful method came from the use of benzyloxymethyl (BOM) halides as the alkylating agent, which would potentially help introduce an already protected 4′-hydroxymethyl group. Whilst this reaction failed when attempted with BOM chloride at −50 °C and the formation of a complex mixture of products was observed at higher temperatures, freshly prepared BOM bromide[30] gave acceptable yields when it was reacted with the lithium enolate of **1** at −78 °C. When ketone **2** was treated with $LiAlH_4$ at −78 °C, alcohols **3** were obtained in 84% yield as a 2:1 mixture of diastereoisomers favoring the desired trans.

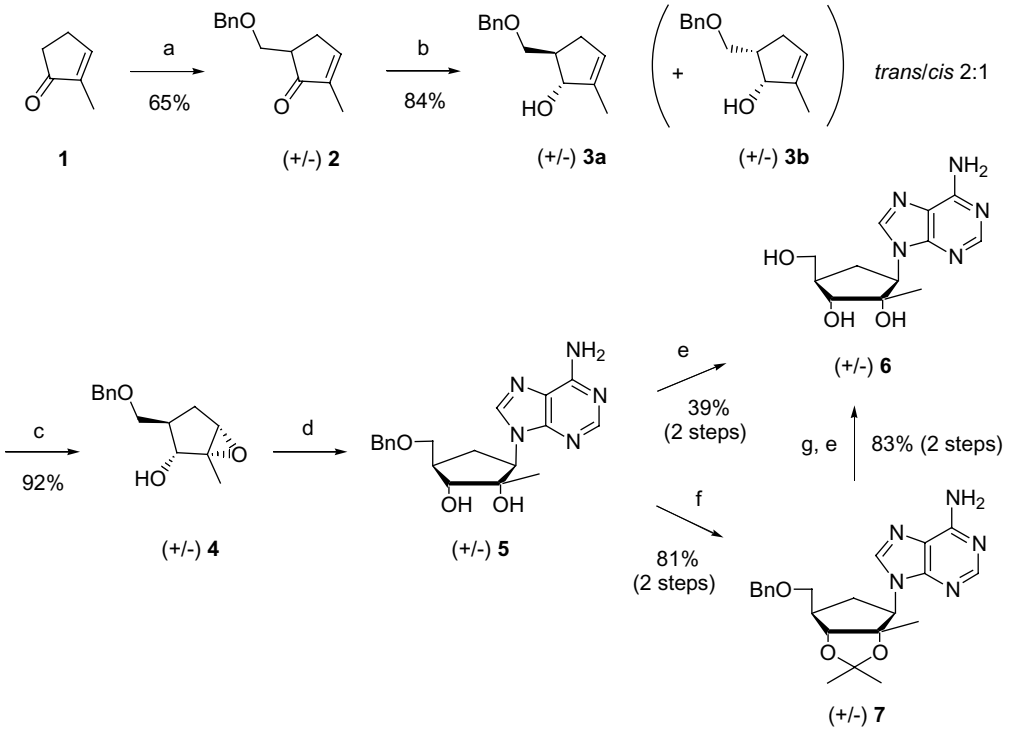
The ratio remained similar at −30 and 0 °C with the concomitant formation of side products. To our delight, alcohols **3a/3b** were very easily separated on silica gel chromatography. The two last nucleoside stereogenic carbons were introduced in one step during the peroxy acid-promoted epoxidation of **3a**. The allylic alcohol allowed perfect control on the stereochemistry of the reaction and epoxide **4** was obtained as the sole product in excellent yield.

2.3. Synthesis of carbocyclic nucleosides

Having everything in place for the introduction of the base, **4** was treated with the sodium salt of adenine in DMF at 100 °C. The 2′-methyl induced a perfect regio- and stereoselectivity, the attack occurring from the β-face on the 1′-carbon exclusively. Due to its poor solubility, purification of nucleoside **5** from the excess of adenine was not satisfactory but could be made much easier when crude **5** was directly protected as its 2′,3′-isopropylidene derivative **7**. Target compound **6** was obtained by either palladium-catalyzed hydrogenolysis of the benzyl protecting group of **5** or double deprotection of **7**. This synthesis resulted in the efficient first synthesis of (+/−)-2′-methyl-aristeromycin **6** in 5–7 steps and 23% overall yield.

A confirmation of the structure of this series of molecules was given by X-ray analysis performed on a single-crystal of **7** grown in DCM/acetone (Fig. 2).

This synthetic method is applicable to other purines, sometimes with minor changes. For instance, guanine reacted very poorly with **4** (ca. 6% yield) but after protection



Scheme 1. Reagents and conditions: (a) LDA, BOM bromide, THF, −78 to −50 °C; (b) $LiAlH_4$, ether, −78 to −60 °C; (c) *m*-CPBA, DCM, 0 °C; (d) NaH, adenine, DMF, 100 °C; (e) palladium hydroxide on charcoal, cyclohexene, MeOH, reflux; (f) *p*-toluenesulfonic acid, 2,2-dimethoxypropane, acetone, RT; (g) trifluoroacetic acid 90%, 0 °C.

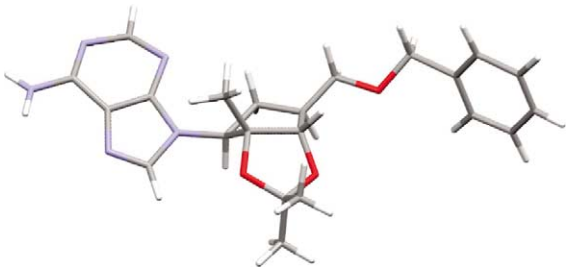
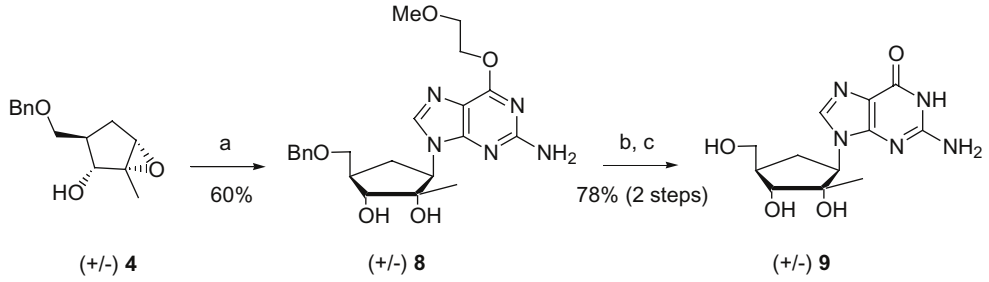


Figure 2. Single-crystal structure of fully protected carbocycle **7** (1′*S*,2′*R*,3′*S*,4′*S* enantiomer).

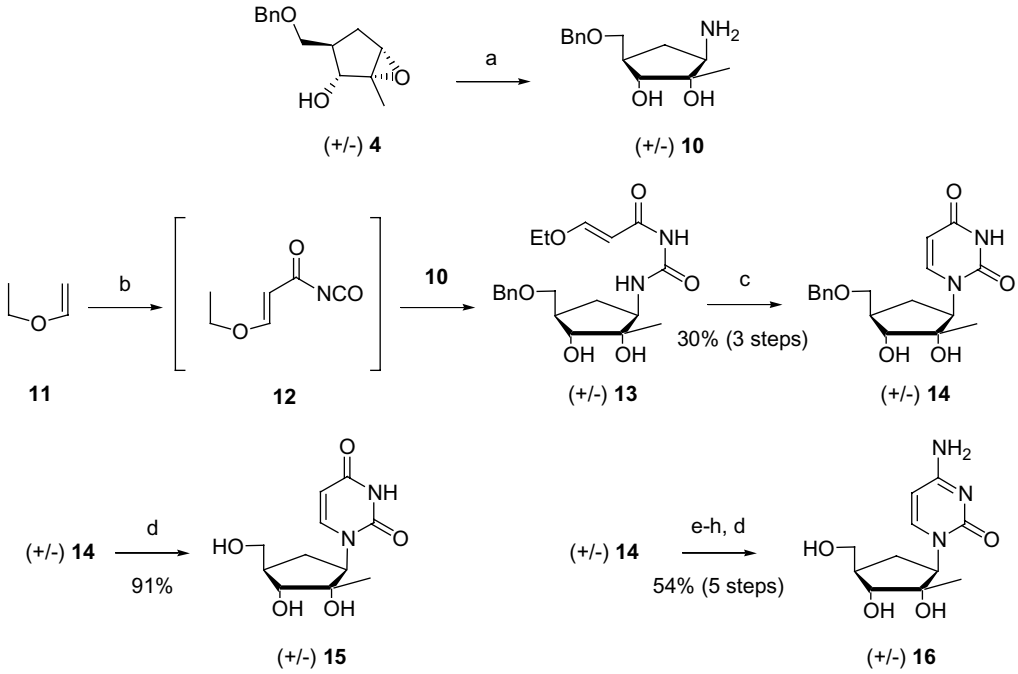
of the base with a methoxyethoxy group,[31,32] the reaction proceeded smoothly and **8** was obtained in reasonable yield (Scheme 2). Carbocycle **8** was then deprotected to afford racemic 2′-methyl-guanosine analogue **9**.

We then turned our attention to the preparation of carbocyclic nucleosides having a pyrimidine base. A slight modification to the general synthesis proved necessary to get acceptable yields. Even though uracil salts were shown to react slowly with epoxides,[32] it was found more advantageous to build the pyrimidine ring by elaboration of the amine group of **10** (Scheme 3). Key epoxide **4** was opened with ammonia with perfect regio- and stereoselective control. Cyclopentylamine **10** was used without purification in a uracil ring-construction process. In order to do that, we adapted previously described procedures:[33–35] ethylvinyl ether **11** was reacted with chlorocarbonyl isocyanate then treated with triethylamine to give isocyanate **12**. The latter compound was directly condensed with **10** in situ. Without prior purification, **13** was cyclized under acidic conditions to afford carbocycle **14**. This 3-step-1-pot synthesis gave access to two pyrimidine derivatives. First, removal of the benzyl-protecting group of **14** afforded uridine analogue **15** in 27% yield from **4**.

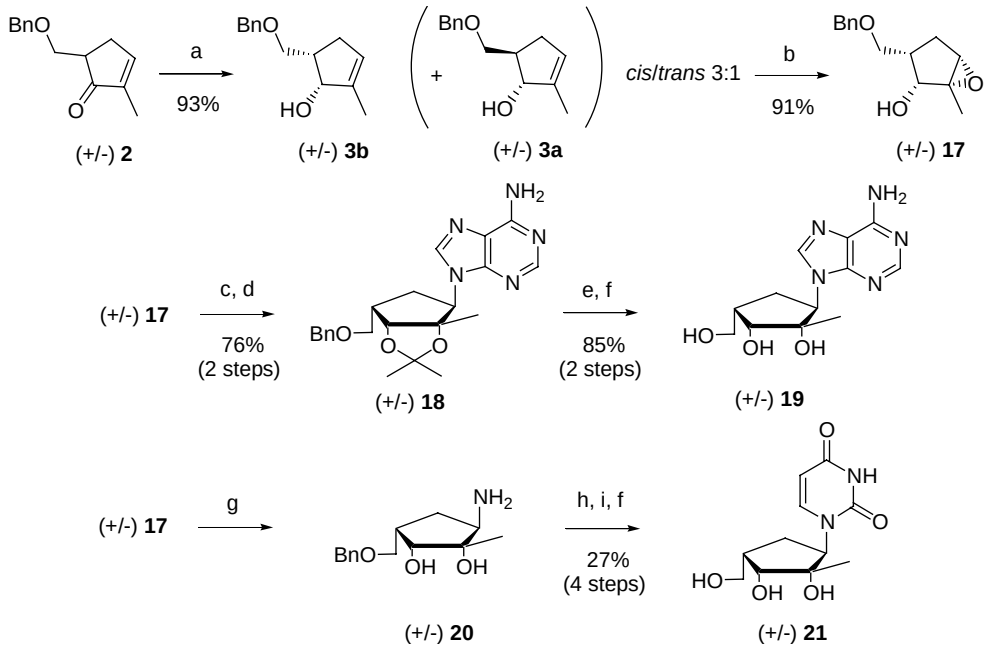
On the other hand, a simple adaptation of the method of Miah et al.[36] provided the cytidine analogue. After protection with an isopropylidene, **14** was activated with *p*-nitrophenol and treated with ammonia. The product was



Scheme 2. Reagents and conditions: (a) NaH, 2-amino-6-(methoxyethoxy)-purine, DMF, 125 °C; (b) 3 N HCl, dioxane, 80 °C; (c) palladium hydroxide on charcoal, cyclohexene, MeOH, reflux.



Scheme 3. Reagents and conditions: (a) NH_3, MeOH, 130 °C; (b) *N*-(chlorocarbonyl)-isocyanate, THF, 0 °C then Et_3N, 0 °C then **10**, −40 °C; (c) 1 N H_2SO_4, dioxane, 100 °C; (d) palladium hydroxide on charcoal, cyclohexene, MeOH, reflux; (e) *p*-toluenesulfonic acid, 2,2-dimethoxypropane, acetone, RT; (f) trifluoroacetic anhydride, *N*-methylpyrrolidine then *p*-nitrophenol, MeCN, 0 °C; (g) NH_3, MeOH, 60 °C; (h) trifluoroacetic acid 90%, 0 °C.



Scheme 4. Reagents and conditions: (a) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH, 0 °C; (b) *m*-CPBA, DCM, 0 °C; (c) NaH, adenine, DMF, 100 °C; (d) *p*-toluenesulfonic acid, 2,2-dimethoxypropane, acetone, RT; (e) trifluoroacetic acid 90%, 0 °C; (f) palladium hydroxide on charcoal, cyclohexene, MeOH, reflux; (g) NH_3, MeOH, 130 °C; (h) *N*-(chlorocarbonyl)-isocyanate, THF, 0 °C then Et_3N, 0 °C then **20**, −40 °C; (i) 1 N H_2SO_4, dioxane, 100 °C.

directly deprotected to give (+/−)-2′-methyl-carbodine **16** in 5 steps and 54% yield from **14**.

2.4. Synthesis of 4′-epi-carbocyclic nucleosides

An interesting feature of our carbocycle synthesis is the possibility of using the minor product of the reduction step of ketone **2** (Scheme 1), cis-alcohol **3b**, for the straightforward preparation of seldom reported 4′-epi-carbocycles.[37] Moreover, after reinvestigation of the reduction of **2**, it proved possible to change dramatically the stereochemical outcome of the reaction. When **2** was subjected to Luche's reduction conditions ($NaBH_4$ in presence of Ce^{3+}),[38,39] **3b** was obtained as the major product of a 3:1 mixture in excellent yield (Scheme 4). Diol **3b** was epoxidized with *m*-chloroperoxybenzoic acid to give **17** as the sole product of the reaction. Then, the chemistry previously described for **4** was applied to **17**. Reaction with adenine sodium salt followed by protection led to carbocycle **18**. In a similar fashion to **7**, the structure of this compound was confirmed by X-ray diffraction of a single crystal grown in DCM/acetone. After two deprotections, racemic 2′-methyl-4′-epi-aristeromycin **19** was obtained in good yield. On the other hand, when submitted to epoxide-opening conditions with ammonia, **17** led to cyclopentylamine **20**. The latter was used in the uracil-ring construction process described for **10** to afford uridine derivative **21** in moderate yield.

3. Conclusion

We have developed a new route for the synthesis of carbocyclic nucleosides. This method was also used for the preparation of 4′-epi-carbocycles. 2-Cyclopenten-1-ones give rapid access to a large number of compounds of potential antiviral interest through key intermediates **4** and **17**. Furthermore, the introduction of any 2′-branching-group can be achieved by using the appropriate ketone as a starting material. This versatile approach gives the shortest access to racemic carbocylic nucleosides reported so far.

Compounds **6**, **9**, **15**, **16**, **19** and **21** were evaluated for antiviral activity in cell culture experiments toward the following viruses: Bovine Viral Diarrhea, Hepatitis B, Human Immunodeficiency, Dengue and West Nile. No activity was found for any of these molecules, nor was there any cytotoxicity to the host cells.

4. Experimental

4.1. General

All ^1H chemical shifts are reported in δ relative to $CHCl_3$ (δ 7.26) or DMSO (δ 2.55). All ^{13}C chemical shifts are reported in δ relative to $CDCl_3$ (centre of triplet, δ 77.2) or DMSO-d_6 (centre of septet, δ 39.5). The spin multiplicities are indicated by the symbols s (singlet), d (doublet), t (triplet), m (multiplet) and, br (broad). Reactions were monitored by thin-layer chromatography (TLC) using Merck silica gel 60-F_{254} precoated plates with visualization by irradiation with a UV lamp or by charring after immersion in a solution of $(NH_4)_2SO_4$ and H_2SO_4 in aqueous EtOH or by charring after immersion in a 5% solution of ninhydrin in EtOH. TLC plates were developed with solvent systems (A) EtOAc/hexanes 1:1, (B) DCM/MeOH 9:1 or (C) DCM/MeOH 8:2. Column chromatographies were performed on either silica gel 60 (normal phase) or C_{18}-branched silica gel 40–63 μm (reverse phase) and eluted with the indicated solvent system. Yields refer to chromatographically and spectroscopically (NMR)

homogeneous materials. The reactions were generally carried out in an argon atmosphere using Fluka dry solvents. BOM bromide was synthesized according to Ref. 30 using either paraformaldehyde or trioxane indifferently. 2-Amino-6-(methoxyethoxy)-purine was synthesized according to Ref. 31. All other chemicals were purchased from Sigma-Aldrich or Acros.

4.1.1. (+/−)-2-Methyl-5-(benzyloxymethyl)-2-cyclopenten-1-one (2). To a solution of 2-methyl-2-cyclopenten-1-one **1** (15.0 g, 156 mmol) in THF (600 mL) was added dropwise a 1.8 M solution of LDA in hexanes (87 mL, 157 mmol) at −78 °C over 10 min. The solution was stirred for 1 h at −78 °C. Then, freshly prepared BOM bromide (purity ca. 70% by NMR) (48.0 g, 167 mmol) was added dropwise over 10 min. The solution was stirred for 3 h at −78 °C then allowed to warm up to −50 °C over 1.5 h. The reaction was quenched with sat. $NaHCO_3$ solution (300 mL) and THF was evaporated. The residue was taken up in EtOAc (400 mL) and the solution was extracted with sat. $NaHCO_3$ solution (2×400 mL) and brine (400 mL). The organic phase was dried over Na_2SO_4 and the solvent was evaporated. The residue was purified by column chromatography (hexanes/EtOAc 9:1) to afford **2** (22.0 g, 65%) as a pale yellow oil: TLC R_f=0.47 (A); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.81 (m, 3H), 2.55–2.80 (m, 3H), 3.64 (dd, 1H, J=6.4, 9.2 Hz), 3.77 (dd, 1H, J=3.8, 9.2 Hz), 4.52 (s, 2H), 7.36 (m, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 9.6, 30.6, 45.1, 69.2, 72.4, 126.9, 127.6, 137.5, 140.7, 157.2, 208.7; HRMS(FAB) Calcd $[M+H]^+$ ($C_{14}H_{17}O_2$): 217.1229, found: 217.1216.

4.1.2. (+/−)-2-Methyl-5-(benzyloxymethyl)-2-cyclopenten-1-ol (3). *Method A*. To a suspension of $LiAlH_4$ (2.2 g, 57.1 mmol) in ether (175 mL) at −78 °C was added dropwise a solution of **2** (12.3 g, 57.0 mmol) in ether (75 mL) over 10 min. The slurry was stirred and slowly warmed up to −60 °C over 2 h. Then, the reaction was quenched with successive careful additions of EtOAc (30 mL), MeOH (30 mL) and H_2O (200 mL). The milky aqueous phase was washed with ether (2×100 mL). The organic phases were pooled and washed with H_2O (2×300 mL), dried over Na_2SO_4 and the solvents were evaporated. The residue was purified by column chromatography (hexanes/EtOAc 9:1). The first eluted product was **3b** (3.5 g, 28%), which was obtained as a colorless oil: TLC R_f=0.47 (A); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.81 (m, 3H), 2.26 (m, 2H), 2.59 (m, 2H), 3.69 (m, 2H), 4.57 (s, 2H), 4.61 (br, 1H), 5.52 (m, 1H), 7.36 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.4, 33.0, 40.8, 69.8, 72.6, 79.1, 126.5, 127.1, 127.8; 137.6, 141.3; HRMS(FAB) Calcd $[M+H]^+$ ($C_{14}H_{19}O_2$): 219.1385, found: 219.1403. This product was followed by **3a** (7.0 g, 56%) as a colorless oil: TLC R_f=0.42 (A); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.78 (m, 3H), 1.96 (m, 1H), 2.12 (br, 1H), 2.37–2.59 (m, 2H), 3.56 (m, 2H), 4.46 (br, 1H), 4.58 (s, 2H), 5.45 (m, 1H), 7.35 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.0, 32.6, 47.6, 72.3, 72.4, 81.7, 125.5, 127.0, 127.1, 127.7, 137.8, 140.5; HRMS(FAB) Calcd $[M+H]^+$ ($C_{14}H_{19}O_2$): 219.1385, found: 219.1404.

Method B. To a solution of **2** (2.0 g, 9.2 mmol) in MeOH (55 mL) was added $CeCl_3\cdot 7H_2O$ (3.4 g, 14.0 mmol) at 0 °C. The solution was stirred for 30 min at this temperature. Then, $NaBH_4$ (0.7 g, 18.4 mmol) was carefully added portionwise. The milky suspension was allowed to warm up to room temperature and stirred for 3 h. The reaction was quenched by addition of acetic acid (3 mL) and MeOH was evaporated. The remaining solid was taken up in EtOAc (100 mL) and extracted with sat. NH_4Cl solution (2×100 mL), sat. $NaHCO_3$ solution (100 mL) and brine (100 mL). The organic phase was dried over Na_2SO_4 and the solvent was evaporated. The residue was purified by column chromatography (hexanes/EtOAc 9:1) to afford **3b** (1.4 g, 70%) and **3a** (0.5 g, 23%) as colorless oils.

4.1.3. (+/−)-(1α,2β,3α,5α)-1-Methyl-2-hydroxy-3-(benzyloxymethyl)-6-oxabicyclo[3.1.0]hexane (4). To a solution of **3a** (2.0 g, 9.2 mmol) in DCM (45 mL) was added *m*-chloroperoxybenzoic acid 77% (2.8 g, 12.0 mmol) at 0 °C. The solution was stirred at 0 °C for 1 h and then allowed to warm-up to room temperature over 2 h. To the white suspension was added sat. $NaHCO_3$ solution (50 mL). The mixture was extracted with EtOAc/sat. $NaHCO_3$ solution (100 mL each). The organic phase was washed with H_2O (2×100 mL), dried over Na_2SO_4 and evaporated to dryness. The residue was purified by column chromatography (hexanes/EtOAc 8:2) to afford **4** (2.0 g, 92%) as a colorless oil, which solidified in the fridge: TLC R_f=0.25 (A); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.51 (s, 3H), 1.56 (m, 1H), 1.89 (m, 1H), 2.12 (m, 1H), 2.29 (br, 1H), 3.31 (s, 1H), 3.49 (dd, 1H, J=6.3, 9.1 Hz), 3.62 (dd, 1H, J=5.1, 9.1 Hz), 3.90 (d, 1H, J=7.4 Hz), 4.54 (s, 2H), 7.36 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 27.9, 40.9, 60.7, 64.6, 69.9, 72.4, 76.6, 126.9, 127.7; 137.7; HRMS(FAB) Calcd $[M+H]^+$ ($C_{14}H_{19}O_3$): 235.1334, found: 235.1348.

4.1.4. (+/−)-2′-*C*-Methyl-5′-*O*-benzyl-aristeromycin (5). *Method A*. To a suspension of adenine (1.75 g, 12.9 mmol) in DMF (30 mL) was added NaH (60% oil dispersion) (0.43 g, 10.8 mmol) at room temperature. After the evolution of hydrogen had ceased, the creamy suspension was stirred at 80 °C for 20 min. Epoxide **4** (1.04 g, 4.3 mmol) dissolved in DMF (20 mL) was added via a syringe. The resulting suspension was stirred at 100 °C for 18 h then cooled down to room temperature. The solid was filtered over celite and rinsed with DCM. The filtrate was evaporated. The brown residue was purified by column chromatography (DCM/MeOH 94:6) to afford **5** (0.65 g, 41%) as a beige powder: TLC R_f=0.20 (B); mp 180.4–181.5 °C; ^{1}H NMR (200 MHz, DMSO) δ 0.68 (s, 3H), 2.09–2.46 (m, 3H), 3.65–3.74 (m, 3H), 4.56 (s, 2H), 4.65 (s, 1H), 4.73 (m, 1H), 4.90 (d, 1H, J=6.3 Hz), 7.23 (br, 2H), 7.32 (m, 5H), 8.12 (s, 1H), 8.16 (s, 1H); ^{13}C NMR (75.5 MHz, DMSO) δ 20.6, 28.9, 42.0, 60.8, 70.7, 72.0, 76.2, 78.4, 118.5, 127.2, 127.3, 128.1, 138.4, 139.8, 149.7, 152.0, 155.8; HRMS(FAB) Calcd $[M+H]^+$ ($C_{19}H_{24}N_5O_3$): 370.1879, found: 370.1861.

Method B. A solution of **7** (500 mg, 1.22 mmol) in TFA 90% (8 mL) was stirred for 1 h at 0 °C. Then, the solution was basified by the addition of ammonia-saturated methanol and the solvents were evaporated. The residue was taken up in cold H_2O (ca. 10 mL) and filtered. The solid was washed with cold H_2O and dried in the oven at 60 °C under vacuum. Carbocyclic nucleoside **5** was obtained (400 mg, 90%) as a white solid.

4.1.5. (+/−)-2′-*C*-Methyl-aristeromycin (6). A solution of **5** (330 mg, 0.89 mmol) in MeOH (30 mL) was treated with palladium hydroxide (20% on charcoal) (200 mg) at 0 °C. Cyclohexene (10 mL) was added and the mixture was refluxed for 15 h. The suspension was cooled down to room temperature, filtered over celite and the solvents were evaporated. The residue was crystallized from H_2O to afford **6** (228 mg, 92%) as a white powder: TLC R_f=0.21 (C); mp 209.1–210.2 °C; UV (H_2O) λ_{max}=259 nm (ε=13,100); ^{1}H NMR (300 MHz, DMSO) δ 0.68 (s, 3H), 1.95–2.22 (m, 2H), 2.38 (m, 1H), 3.58–3.77 (m, 3H), 4.62 (m, 1H), 4.68–4.89 (m, 3H), 7.23 (br, 2H), 8.14 (s, 1H), 8.26 (s, 1H); ^{13}C NMR (75.5 MHz, DMSO) δ 20.6, 28.4, 44.0, 60.6, 61.1, 75.7, 78.7, 118.4, 139.8, 149.8, 152.0, 155.8; HRMS(FAB) Calcd $[M+H]^+$ ($C_{12}H_{18}N_5O_3$): 280.1410, found: 280.1402.

4.1.6. (+/−)-2′-*C*-Methyl-2′,3′-*O*-isopropylidene-5′-*O*-benzyl-aristeromycin (7). This synthesis began like the preparation of **5** using 500 mg (2.13 mmol) of epoxide **4**. After evaporation of DMF, the brown residue was suspended in acetone (32 mL) and 2,2-dimethoxypropane (8 mL). The suspension was acidified with *p*-toluenesulfonic acid (300 mg, 1.75 mmol) and stirred for 2 h at room temperature. The mixture was filtered, the solid was washed with acetone and the filtrate was neutralized with pyridine (300 μL). The solvents were evaporated. The residue was taken up in DCM (100 mL) and extracted successively with H_2O (100 mL), 1 N HCl (100 mL), sat. $NaHCO_3$ solution (100 mL) and brine (100 mL). The organic phase was dried over Na_2SO_4 and the solvent was evaporated. The remaining solid was purified by column chromatography (DCM/MeOH 96:4) to afford **7** (695 mg, 81%) as a beige powder: TLC R_f=0.38 (B); mp 200.4–201.3 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (s, 3H), 1.39 (s, 3H), 1.68 (s, 3H), 2.46 (m, 1H), 2.57 (m, 1H), 2.85 (m, 1H), 3.65 (m, 2H), 4.27 (d, 1H, J=2.7 Hz), 4.63 (s, 2H), 5.05 (dd, 1H, J=6.7, 13.5 Hz), 5.97 (br, 2H), 7.35 (m, 5H), 7.87 (s, 1H), 8.36 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.7, 25.9, 27.8, 30.3, 40.2, 63.9, 70.1, 72.6, 86.3, 88.3, 112.4, 119.2, 127.0, 127.1, 127.8, 137.4, 139.8, 150.3, 151.5, 154.4; HRMS(FAB) Calcd $[M+H]^+$ ($C_{22}H_{28}N_5O_3$): 410.2192, found: 410.2203.

4.1.7. (+/−)-2-Amino-6-deamino-6-(methoxyethoxy)-2′-*C*-methyl-5′-*O*-benzyl-aristeromycin (8). A suspension of 2-amino-6-(methoxyethoxy)-purine (950 mg, 4.54 mmol) in DMF (8 mL) was treated with NaH (60% oil dispersion) (160 mg, 4.00 mmol) at room temperature. After the evolution of hydrogen had ceased, the suspension was stirred at 80 °C for 20 min. Epoxide **4** (375 mg, 1.60 mmol) dissolved in DMF (8 mL) was added via a syringe. The resulting brown solution was stirred at 125 °C for 48 h then cooled down to room temperature. The DMF was evaporated. The brown residue was purified by column chromatography (DCM/MeOH 96:4) to afford **8** (425 mg, 60%) as a beige powder: TLC R_f=0.45 (B); mp 175.7–176.6 °C; ^{1}H NMR (200 MHz, DMSO) δ 0.70 (s, 3H), 1.94 (m, 1H), 2.23 (m, 1H), 2.44 (m, 1H), 3.32 (s, 3H), 3.62–3.72 (m, 5H), 4.49–4.66 (s, 6H), 4.91 (d, 1H, J=6.4 Hz), 6.41 (br, 2H), 7.33 (m, 5H), 7.92 (s, 1H); ^{13}C NMR (75.5 MHz, DMSO) δ 20.6, 29.2, 41.9, 57.9, 59.8, 64.4, 69.9, 70.8, 72.0, 76.2, 78.5, 113.3, 127.2, 128.1, 138.3, 138.4, 154.5, 159.3, 160.0; HRMS(FAB) Calcd $[M+H]^+$ ($C_{22}H_{30}N_5O_5$): 444.2247, found: 444.2254.

4.1.8. (+/−)-2′-*C*-Methyl-carbocyclic guanosine (9). A solution of **8** (400 mg, 0.90 mmol) in 3 N HCl (70 mL) was stirred for 3 h at 80 °C. Then, the solution was cooled down, evaporated and the residue was basified with ammonia-saturated MeOH. The solvent was evaporated and the residue was rapidly purified by column chromatography (DCM/MeOH 88:12) to afford 2′-*C*-methyl-5′-*O*-benzyl-carbocyclic guanosine as a beige solid: TLC R_f=0.30 (C); ^{1}H NMR (200 MHz, DMSO) δ 0.71 (s, 3H), 1.88 (m, 1H), 2.23 (m, 1H), 2.40 (m, 1H), 3.59–3.66 (m, 3H), 4.49–4.55 (m, 4H), 4.93 (d, 1H, J=6.2 Hz), 6.52 (br, 2H), 7.34 (m, 5H), 7.75 (s, 1H), 10.64 (br, 1H). A solution of the above 2′-*C*-methyl-5′-*O*-benzyl-carbocyclic guanosine (295 mg, 0.77 mmol) in MeOH (20 mL) was treated with palladium hydroxide (20% on charcoal) (150 mg) at 0 °C. Cyclohexene (5 mL) was added and the mixture was refluxed for 15 h. The suspension was cooled down to room temperature, filtered over celite and the solvents were evaporated. The residue was purified by reverse phase column chromatography (H_2O/MeOH 95:5) to afford **9** (205 mg, 78% from **8**) as a white solid: TLC R_f=0.10 (C); mp >230 °C (dec); UV (H_2O) λ_{max}=252 nm (ε=11,200); ^{1}H NMR (300 MHz, DMSO) δ 0.73 (s, 3H), 1.88 (m, 1H), 2.06 (m, 1H), 2.36 (m, 1H), 3.60–3.66 (m, 3H), 4.42 (s, 1H), 4.52 (m, 1H), 4.73–4.79 (m, 2H), 6.42 (br, 2H), 7.82 (s, 1H), 10.56 (br, 1H); ^{13}C NMR (75.5 MHz, DMSO) δ 15.7, 20.6, 43.9, 59.5, 60.7, 75.6, 78.8, 116.1, 135.8, 151.5, 153.3, 157.1; HRMS(FAB) Calcd $[M+H]^+$ ($C_{12}H_{18}N_5O_4$): 296.1359, found: 296.1339.

4.1.9. (+/−)-(1β,2β,3α,5α)-1,2-Dihydroxy-1-methyl-3-(benzyloxymethyl)-5-amino-cyclopentane (10). A solution of **4** (900 mg, 3.84 mmol) in ammonia-saturated MeOH (20 mL) was heated at 130 °C under pressure for 3 h. The solution was cooled down, degassed and evaporated to dryness to get 960 mg of **10** as an oily brown residue, which was found homogeneous by TLC and used in the next step without purification: TLC R_f=0.14 (C).

4.1.10. (+/−)-2′-*C*-Methyl-5′-*O*-benzyl-carbocyclic uridine (14). To a solution of *N*-(chlorocarbonyl) isocyanate (894 mg, 8.51 mmol) in THF (9 mL) was slowly added a solution of ethylvinyl ether (804 mg, 11.15 mmol) in THF (6 mL) at 0 °C. The resulting solution was stirred for 20 min at 0 °C. Then, triethylamine (852 mg, 8.42 mmol) in THF (9 mL) was slowly added. The resulting suspension was stirred for 5 min at 0 °C and then, cooled down to −40 °C. A solution of amine **10** (1.920 g, 7.64 mmol) in THF (9 mL) was rapidly added to the mixture and the suspension was allowed to slowly warm up to room temperature. Then, THF was evaporated and the residue was dissolved in dioxane (6 mL). To this solution was added 1 N H_2SO_4 (9 mL) and the mixture was heated at 100 °C for 2 h. Then, the solution was cooled down to room temperature and basified with 3 N ammonia (7 mL). The ammonium salts were precipitated with MeOH and the suspension was filtered. The filtrate was evaporated to dryness and the crude material was purified by column chromatography (DCM/MeOH 96:4) to afford **14** (798 mg, 30%) as a white solid: TLC R_f=0.32 (B); mp

183.1–184.2 °C; ^{1}H NMR (300 MHz, DMSO) δ 0.89 (s, 3H), 1.61 (m, 1H), 2.16 (m, 1H), 2.29 (m, 1H), 3.48 (d, 1H, J=9.5 Hz), 3.62 (m, 2H), 4.52 (s, 2H), 4.67 (m, 1H), 5.25 (dd, 1H, J=2.2, 8.1 Hz), 7.34 (m, 5H), 7.66 (d, 1H, J=8.1 Hz), 11.26 (br, 1H); ^{13}C NMR (75.5 MHz, DMSO) δ 20.4, 27.5, 41.8, 61.2, 70.0, 72.2, 76.0, 78.6, 100.7, 127.3, 127.4, 128.1, 138.2, 142.9, 151.2, 162.7; HRMS(FAB) Calcd $[M+H]^+$ ($C_{18}H_{23}N_2O_5$): 347.1607, found: 347.1616.

4.1.11. (+/−)-2′-*C*-Methyl-carbocyclic uridine (15). A solution of **14** (250 mg, 0.72 mmol) in MeOH (20 mL) was cooled down to 0 °C and treated with palladium hydroxide (20% on charcoal) (180 mg). Cyclohexene (7 mL) was added and the mixture was refluxed for 15 h. The suspension was cooled down to room temperature, filtered on celite and the solvents were evaporated. The residue was crystallized from MeOH/*i*-propyl ether to afford **15** (164 mg, 91%) as white crystals: TLC R_f=0.27 (C); mp 181.6–182.5 °C; UV (H_2O) λ_{max}=267 nm (ε=9900); ^{1}H NMR (200 MHz, DMSO) δ 0.92 (s, 3H), 1.61 (m, 1H), 2.00 (m, 1H), 2.17 (m, 1H), 3.44 (m, 1H), 3.56 (m, 2H), 4.39 (s, 1H), 4.67–4.76 (m, 3H), 5.59 (d, 1H, J=8.0 Hz), 7.72 (d, 1H, J=8.0 Hz), 11.29 (br, 1H); ^{13}C NMR (75.5 MHz, DMSO) δ 20.6, 27.0, 43.6, 60.4, 61.1, 75.8, 78.6, 100.9, 142.9, 151.2, 162.8; HRMS(FAB) Calcd $[M+H]^+$ ($C_{11}H_{17}N_2O_5$): 257.1137, found: 257.1139.

4.1.12. (+/−)-2′-*C*-Methyl-carbodine (16). A suspension of **14** (300 mg, 0.87 mmol) in acetone (25 mL) and 2,2-dimethoxypropane (8 mL) was treated with *p*-toluenesulfonic acid (50 mg, 0.3 mmol). After dissolution of the materials, the solution was stirred for 1 h at room temperature. Then, the mixture was neutralized with pyridine (50 μL) and the solvents were evaporated. The residue was rapidly purified by column chromatography (DCM/MeOH 95:5) to afford 2′-*C*-methyl-2′,3′-*O*-isopropylidene-5′-*O*-benzyl-carbocyclic uridine as a white solid: TLC R_f=0.48 (B); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.27 (s, 3H), 1.37 (s, 3H), 1.61 (s, 3H), 2.12–2.22 (m, 2H), 2.47 (m, 1H), 3.51–3.67 (m, 2H), 4.17 (d, 1H, J=2.9 Hz), 4.58 (s, 2H), 5.13 (m, 1H), 5.67 (dd, 1H, J=2.3, 8.1 Hz), 7.22 (d, 1H, J=8.1 Hz), 7.36 (m, 5H), 9.29 (br, 1H). To a solution of the above 2′-*C*-methyl-2′,3′-*O*-isopropylidene-5′-*O*-benzyl-carbocyclic uridine (280 mg, 0.73 mmol) in MeCN (8 mL) was added *N*-methylpyrrolidine (700 μL) and trifluoroacetic anhydride (300 μL, 2.12 mmol) at 0 °C. The mixture was stirred for 30 min then *p*-nitrophenol (300 mg, 2.16 mmol) was added. The yellow solution was stirred for 3 h at 0 °C. The mixture was diluted with DCM (20 mL) and extracted with 1 N HCl (20 mL), sat. $NaHCO_3$ solution (3×20 mL) and brine (20 mL). The organic phase was dried over Na_2SO_4 and the solvents were evaporated. The residue was taken up in ammonia-saturated MeOH (30 mL) and stirred at 60 °C for 15 h. The solvent was evaporated and the residue was purified by column chromatography (DCM/MeOH 94:6) to afford 2′-*C*-methyl-2′,3′-*O*-isopropylidene-5′-*O*-benzyl-carbodine as a yellowish solid: TLC R_f=0.23 (B); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.23 (s, 3H), 1.36 (s, 3H), 1.60 (s, 3H), 2.09–2.22 (m, 2H), 2.44 (m, 1H), 3.51–3.64 (m, 2H), 4.15 (d, 1H, J=3.5 Hz), 4.57 (s, 2H), 5.18 (m, 1H), 5.72 (d, 1H, J=7.4 Hz), 7.21 (d, 1H, J=7.4 Hz), 7.35 (m, 5H). A solution of the above 2′-*C*-methyl-2′,3′-*O*-isopropylidene-5′-*O*-benzyl-carbodine (202 mg, 0.52 mmol) in TFA 90% (5 mL) was stirred for 1 h at 0 °C. Then, the solution was basified by the addition of ammonia-saturated methanol and the solvents were evaporated. The residue was taken up in cold H_2O and filtered. The solid was washed with cold H_2O and dried in the oven at 60 °C under vacuum. 2′-*C*-methyl-5′-*O*-benzyl-carbodine was obtained as an off-white solid and used directly in the next step: TLC R_f=0.51 (C). A solution of 2′-*C*-methyl-5′-*O*-benzyl-carbodine (172 mg, 0.50 mmol) in MeOH (20 mL) was cooled down to 0 °C and treated with palladium hydroxide (20% on charcoal) (120 mg). Cyclohexene (7 mL) was added and the mixture was refluxed for 15 h. The suspension was cooled down to room temperature, filtered on celite and the solvents were evaporated. The residue was crystallized from MeOH/*i*-propyl ether to afford **16** (112 mg, 54% from **14**) as a white powder: TLC R_f=0.20 (C); mp >200 °C (dec); UV (H_2O) λ_{max}=274 nm (ε=7400); ^{1}H NMR (200 MHz, DMSO) δ 0.85 (s, 3H), 1.60 (m, 1H), 1.92–2.19 (m, 2H), 3.49–3.63 (m, 3H), 4.54–4.79 (m, 4H), 5.73 (d, 1H, J=7.4 Hz), 7.26 (br, 2H), 7.66 (d, 1H, J=7.4 Hz); ^{13}C NMR (75.5 MHz, DMSO) δ 20.9, 27.4, 44.0, 60.8, 62.3, 76.1, 78.5, 93.4, 143.8, 155.4; 164.0; HRMS(FAB) Calcd $[M+H]^+$ ($C_{11}H_{18}N_3O_4$): 256.1297, found: 256.1302.

4.1.13. (+/−)-(1β,2β,3α,5β)-1-Methyl-2-hydroxy-3-(benzyloxymethyl)-6-oxabicyclo[3.1.0]hexane (17). The preparation was carried out as described for **4**, using **3b** in place of **3a**. Epoxide **17** was obtained in 91% yield as a colorless oil, which solidified in the fridge: TLC R_f=0.25 (A); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.53 (s, 3H), 1.75 (dd, 1H, J=2.1, 14.9 Hz), 1.98 (dd, 1H, J=9.5, 14.9 Hz), 2.51 (m, 1H), 3.29 (s, 1H), 3.38 (dd, 1H, J=5.3, 9.0 Hz), 3.94 (dd, 1H, J=9.0, 9.5 Hz), 4.29 (d, 1H, J=8.2 Hz), 4.46 (d, 1H, J=11.7 Hz), 4.58 (d, 1H, J=11.7 Hz), 7.36 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.3, 28.7, 37.0, 61.4, 66.8, 72.4, 72.5, 75.6, 127.1, 127.8; 137.1; HRMS(FAB) Calcd $[M+H]^+$ ($C_{14}H_{19}O_3$): 235.1334, found: 235.1343.

4.1.14. (+/−)-2′-*C*-Methyl-2′,3′-*O*-isopropylidene-4′-epi-5′-*O*-benzyl-aristeromycin (18). The preparation was carried out as described for **7**, using **17** in place of **4**. Carbocyclic nucleoside **18** was obtained in 76% yield (2 steps) as a beige powder: TLC R_f=0.37 (B); mp 104.8–105.7 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.01 (s, 3H), 1.40 (s, 3H), 1.56 (s, 3H), 2.34 (m, 1H), 2.48 (m, 1H), 3.11 (m, 1H), 3.74 (m, 2H), 4.44 (d, 1H, J=4.0 Hz), 4.62 (m, 2H), 5.01 (dd, 1H, J=2.2, 7.1 Hz), 6.38 (br, 2H), 7.35 (m, 5H), 7.88 (s, 1H), 8.40 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.0, 25.3, 26.9, 31.9, 42.3, 63.9, 68.9, 72.7, 85.9, 91.6, 110.5, 118.9, 127.0, 127.7, 137.6, 138.7, 149.9, 152.1, 154.7; HRMS(FAB) Calcd $[M+H]^+$ ($C_{22}H_{28}N_5O_3$): 410.2192, found: 410.2173.

4.1.15. (+/−)-2′-*C*-Methyl-4′-epi-aristeromycin (19). The preparation was carried out as described for **6**, using **18** in place of **7**. Carbocyclic nucleoside **19** was obtained in 85% yield (2 steps) as a white powder: TLC R_f=0.23 (C); mp 254.3–255.2 °C; UV (H_2O) λ_{max}=260 nm (ε=13,600); ^{1}H NMR (200 MHz, DMSO) δ 0.88 (s, 3H), 1.95 (m, 1H), 2.56 (m, 2H), 3.44 (m, 1H), 3.61 (m, 1H), 3.71 (m, 1H), 4.50 (t, 1H, J=5.1 Hz), 4.80 (s, 1H), 4.87 (m, 1H), 4.90 (d, 1H,

J=5.1 Hz), 7.21 (br, 2H), 8.12 (s, 1H), 8.17 (s, 1H); ^{13}C NMR (75.5 MHz, DMSO) δ 20.4, 27.5, 40.5, 60.9, 61.4, 76.5, 80.1, 118.7, 140.7, 150.0, 151.8, 155.8; HRMS(FAB) Calcd $[M+H]^+$ ($C_{12}H_{18}N_5O_3$): 280.1410, found: 280.1417.

4.1.16. (+/−)-(1β,2β,3β,5α)-1,2-Dihydroxy-1-methyl-3-(benzyloxymethyl)-5-amino-cyclopentane (20). The preparation was carried out as described for **10**, using **17** in place of **4**. Cyclopentylamine **20** was obtained as a brown oil and directly used in the next step without purification: TLC R_f=0.13 (C).

4.1.17. (+/−)-2′-*C*-Methyl-4′-epi-carbocyclic uridine (21). The preparation was carried out as described for **15**, using **17** in place of **4**. Carbocyclic nucleoside **21** was obtained in 27% yield (4 steps from **17**) as a white powder: TLC R_f=0.29 (C); mp 195.5–196.4 °C; UV (H_2O) λ_{max}= 267 nm (ε=10,400); ^{1}H NMR (200 MHz, DMSO) δ 1.00 (s, 3H), 1.87 (m, 2H), 2.31 (m, 1H), 3.40 (dd, 1H, J=6.8, 10.5 Hz), 3.60 (m, 2H), 4.49 (m, 2H), 4.82 (d, 1H, J= 4.2 Hz), 4.89 (m, 1H), 5.54 (d, 1H, J=8.0 Hz), 7.67 (d, 1H, J=8.0 Hz), 11.23 (br, 1H); ^{13}C NMR (75.5 MHz, DMSO) δ 20.4, 27.1, 40.5, 60.7, 61.0, 76.5, 79.9, 100.3, 143.5, 151.4, 162.9; HRMS(FAB) Calcd $[M+H]^+$ ($C_{11}H_{17}N_2O_5$): 257.1137, found: 257.1140.

4.2. X-ray crystallographic data

Crystallographic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 284302 and 284303.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.10.037

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