# SYNTHESIS OF CARBOCYCLIC 4′-*C*-HYDROXYMETHYL ANALOGUES OF AZIDODEOXYTHYMIDINE, DEOXYTHYMIDINE, DEOXYDIDEHYDROTHYMIDINE AND THYMIDINE CARBA ANALOGUE WITH FUSED OXETANE RING

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Tosylation of (±)-1-[*trans*-4-hydroxy-3,3-bis(hydroxymethyl)cyclopentyl]-5-methylpyrimidine-2(1*H*),4(3*H*)-dione (**1**) and (±)-1-[*cis*-4-hydroxy-3,3-bis(hydroxymethyl)cyclopentyl]-5-methylpyrimidine-2(1*H*),4(3*H*)-dione (**2**) and treatment of the obtained 1-{(1*R**,3*R**,4*S**)-4-hydroxy-3-(hydroxymethyl)-3-[(tosyloxy)methyl]cyclopentyl}-5-methylpyrimidine-2(1*H*),4(3*H*)-dione (**6**) and 1-{(1*R**,3*S**,4*R**)-4-hydroxy-3-(hydroxymethyl)-3-[(tosyloxy)-methyl]cyclopentyl}-5-methylpyrimidine-2(1*H*),4(3*H*)-dione (**9**) with methanolic sodium methoxide gave 1-[(1*R**,4*S**,6*S**)-4-hydroxymethyl-2-oxabicyclo[3.2.0]hept-6-yl]-5-methyl-pyrimidine-2(1*H*),4(3*H*)-dione (**7**) and 1-[(1*R**,4*S**,6*R**)-4-hydroxymethyl-2-oxabicyclo-[3.2.0]hept-6-yl]-5-methylpyrimidine-2(1*H*),4(3*H*)-dione (**10**), respectively. Treatment of (±)-1-{*cis*-4-mesyloxy-3,3-bis[(trityloxy)methyl]cyclopentyl}-5-methylpyrimidine-2(1*H*),4(3*H*)-dione (**11**), which was prepared from **2** by tritylation and mesylation, with 1,8-diaza-bicyclo[5.4.0]undec-7-ene in dimethylformamide afforded after deprotection (±)-1-[4,4-bis-(hydroxymethyl)cyclopent-2-en-1-yl]-5-methylpyrimidine-2(1*H*),4(3*H*)-dione (**14**). Hydrogenation of **14** led to (±)-1-[3,3-bis(hydroxymethyl)cyclopentyl]-5-methylpyrimidine-2(1*H*),4(3*H*)-dione (**15**). (±)-1-{*trans*-4-Mesyloxy-3,3-bis[(trityloxy)methyl]cyclopentyl}-5-methylpyrimidine-2(1*H*),4(3*H*)-dione (**17**), which was prepared from **1**, was converted to (1*R**,9*R**)-6-methyl-5-oxo-11,11-bis(trityloxymethyl)-2-oxa-4,8-diazatricyclo[7.2.1.$0^{3,8}$]dodec-3,6-diene (**18**). The compound **18** was deprotected and heated with lithium azide in dimethylformamide to give (±)-1-[*trans*-4-azido-3,3-bis(hydroxymethyl)cyclopentyl]-5-methylpyrimidine-2(1*H*),4(3*H*)-dione (**21**).

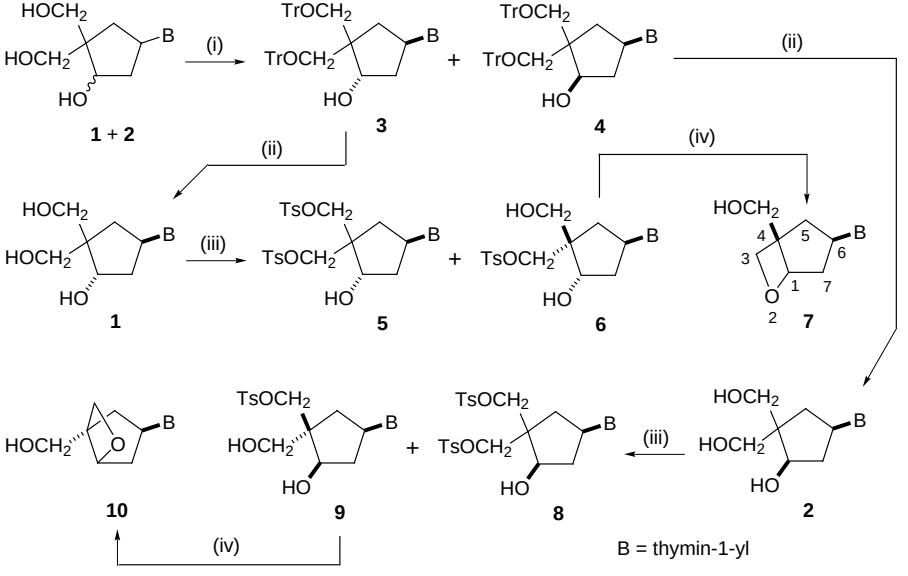
**Key words**: Carbanucleosides; Carbocyclic nucleosides; 4′-C-Branched nucleosides; Cyclopentanes; Nucleosides; Pyrimidines.

Replacement of the oxygen in the sugar portion of the nucleoside with a methylene unit results in carbocyclic nucleoside analogues which show enhanced biostability. The discovery of the antibiotic and antitumor activity of the natural carbocyclic nucleosides aristeromycin and neplanocin A stimulated the search for other carbocyclic nucleoside analogues with bio-

logical activity. Later on, additional synthetic carbocyclic nucleosides with important therapeutic properties were discovered. Development in the area of synthetic approaches to carbocyclic nucleosides is the subject of several reviews[1].

This communication is a continuation of our program aimed at the synthesis of 2′-deoxy-4′-*C*-substituted nucleosides and at structure–antiviral activity relationship studies[2] and deals with the synthesis of racemic carba analogues of 2′-deoxy-4′-*C*-(hydroxymethyl)nucleosides. The present paper concerns the synthesis of racemic carbocyclic 4′-*C*-hydroxymethyl analogues of 3′-azido-3′-deoxy-, 3′-deoxy-, and 3′-deoxy-2′,3′-didehydrothymidine and an analogue with fused oxetane ring in the position 3′,4′. The same oxetane derivative of thymidine inhibits HIV replication in A301 (Alex) cells with remarkably low bone marrow toxicity[3]. Most recently a racemic carbocyclic analogue of 2′,3′-didehydro-2′,3′-dideoxy-4′-*C*-(hydroxymethyl)guanosine was synthesized[4] by a multistep procedure from 2-azabicyclo[2.2.1]hept-5-en-3-one.

Since the separation of the starting stereoisomeric carbocyclic nucleosides **1** and **2** is difficult (*cf.* ref.[2h]), a mixture of the isomers was tritylated (Scheme 1). The obtained mixture of trityl derivatives was easily separated

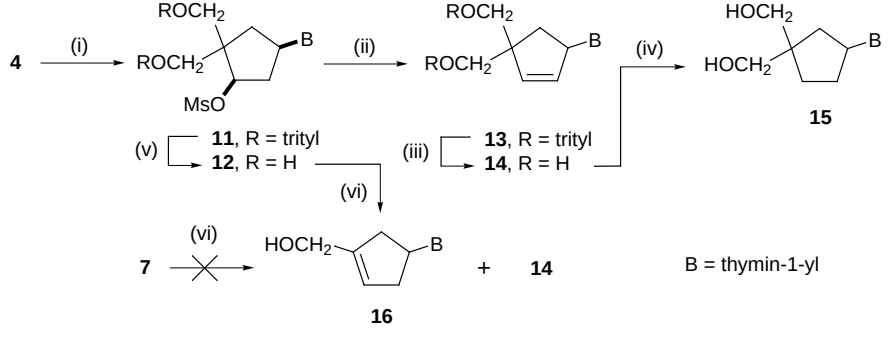



(i) TrCl/pyridine, 38% of **3**, 34% of **4**; (ii) 80% aqueous $CF_3COOH$, 92% of **1** and 94% of **2**; (iii) TsCl/pyridine, 20% of **5**, 68% of **6**, 17% of **8** and 69% of **9**; (iv) 0.25 M MeONa/MeOH, 53% of **7** (19% of recovered **6**), 33% of **10** (25% of recovered **9**)

SCHEME 1

on silica gel to give pure (±)-*trans* isomer **3** (38% yield) and (±)-*cis* isomer **4** (34% yield). Treatment of the trityl derivatives with 80% aqueous trifluoroacetic acid afforded free nucleoside analogues **1** and **2** (*cf.* ref.[2h]). Tosylation of the (±)-*trans* isomer **1** led to a mixture of the ditosyl derivative **5** (20% yield) and the monotosyl derivative **6** (68% yield) with hydroxy and (tosyloxy)methyl groups in *cis* position. The ditosyl derivative **8** (17% yield) and the monotosyl derivative **9** (69% yield) were obtained in the same manner from *cis* isomer **2**. The greater reactivity of the 4′-(hydroxymethyl) group was also observed in 4′-hydroxymethylthymidine[3]. Monotosylates **6** and **7** were treated with methanolic sodium methoxide giving compounds with fused oxetane rings **7** (53% yield) and **10** (33% yield), respectively. The starting monotosyl derivatives were also recovered from the reaction mixture: 19% of **6** and 25% of **9**. This reaction is accompanied by the cleavage of the C–N bond. The positions of absorption bands in UV spectra of the oxetanes **7** and **10** remained virtually unchanged independently of pH whereas in alkaline medium, the absorption decreased: such pattern is characteristic of $N^1$-substituted uracil derivatives[5]. Using the same procedure, the analogue of 2′-deoxyuridine with fused oxetane ring in the position 3′,4′ was prepared (*cf.* ref.[2e]). In this case, cleavage of the C–N bond was not observed.

Mesylation of the ditrityl derivative **4** and treatment of the obtained mesylate **11** with 1,8-diazabicyclo[5.4.0]undec-7-ene in dimethylformamide at 125 °C (Scheme 2) led to the cyclopentene derivative **13** (89% yield).



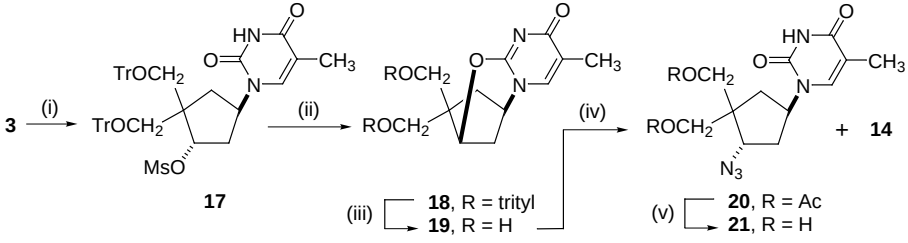

(i) MsCl/pyridine, 95%; (ii) DBU/DMF, 125 °C, 89%; (iii) 80% aqueous $CH_3COOH$, 84%; (iv) Pd/C, $H_2$, 81%; (v) 80% aqueous $CF_3COOH$, 92%; (vi) NaH/DMF, 47% of **13**, 24% of **14**

SCHEME 2

Deprotection of **13** with 80% aqueous acetic acid afforded the free analogue **14**. Hydrogenation of **14** over palladium on activated carbon gave the carbocyclic dideoxynucleoside **15** (81% yield).

The dityrityl derivative **11** was deprotected with 80% aqueous trifluoroacetic acid and the obtained compound **12** was treated with sodium hydride in dimethylformamide giving unsaturated analogue **14** (24% yield) and the unsaturated hydroxymethyl derivative **16** (47% yield) instead of the expected oxetane **7**. The oxetane **7** was not involved as an intermediate in this reaction, because it remained unchanged under the reaction conditions.

Mesylation of compound **3** and treatment of the obtained mesyl derivative **17** with 1,8-diazabicyclo[5.4.0]undec-7-ene in acetonitrile at 60 °C (Scheme 3) afforded the anhydro derivative **18** (74% yield). The opening of 2,3′-bond with lithium azide in dimethylformamide at 150 °C resulting in a relatively high yield of 1-(3-azido-2,3-dideoxy-5-*O*-trityl-β-D-ribofuranosyl)-5-ethyluridine is described in the literature (see, *e.g.*, ref.[6]). However, the reaction of the anhydro derivative **19** with lithium azide under described




(i) MsCl/pyridine, 85%; (ii) DBU/acetonitrile, 60 °C, 74%; (iii) 80% aqueous $CF_3COOH$, 83%; (iv) 1. $LiN_3$/DMF, 150 °C, 2. $Ac_2O$/DMAP/MeCN, 17.5% of **14** and 49% of **20**; (v) MeONa/MeOH, 99%

SCHEME 3

conditions led to a complex unseparable mixture of products. The compound **19**, which was obtained by deprotection of **18** with 80% aqueous trifluoroacetic acid, was treated with lithium azide in dimethylformamide at 150 °C. Chromatography of products of the reaction afforded 17.5% of the unsaturated derivative **14** and the crude azido analogue **21**. This product was acetylated and the obtained acetate **20** was easily purified by chromatography on silica gel. The free azido nucleoside analogue **21** was obtained by methanolysis of **20**. The anhydro ring opening was not accompanied by N-1 to N-3 migration, which has been described for cleavage of some 2,2′-anhydronucleosides with hydrogen chloride and of 2,3′-anhydronucleosides with azide (see ref.[7] and references therein), because infrared spectrum of the acetate **20** exhibits NH band at 3 391 $cm^{-1}$, in agreement with the literature data[8] for N-1 isomer. UV spectrum of the free azido derivative **21** was also characteristic of $N^1$-substituted uracil derivatives[5].

In conclusion, new racemic carbocyclic 4′-*C*-hydroxymethyl analogues of azidodeoxythymidine, deoxydidehydrothymidine, deoxythymidine, and 1-[(1*R**,4*S**,6*S**)-4-hydroxymethyl-2-oxabicyclo[3.2.0]heptan-6-yl]-5-methylpyrimidine-2(1*H*),4(3*H*)-dione (**7**) (the carba analogue of the anti-HIV compound, thymidine derivative with 3′,4′-fused oxetane ring) were prepared. The synthesized compounds will be tested for antiviral activity.

## EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. IR spectra were recorded on a Zeiss UR 20 spectrophotometer (wavenumbers in $cm^{-1}$) and UV spectra on a Unicam SP 8000 spectrometer. $^1$H NMR spectra (δ, ppm; *J*, Hz) were measured on a Varian XL-200 (200 MHz) instrument in hexadeuteriodimethyl sulfoxide with tetramethylsilane as internal standard. Column chromatography was performed on 30–60 μm silica gel (Service Laboratories of the Institute) and thin-layer chromatography (TLC) on Silufol UV 254 foils (Kavalier, Votice). Solvents were evaporated at 2 kPa and bath temperature 30–60 °C; the compounds prepared were dried at 13 Pa and 50 °C.

(±)-1-{*trans*-4-Hydroxy-3,3-bis[(trityloxy)methyl]cyclopentyl}-5-methylpyrimidine-2(1*H*),4(3*H*)-dione (**3**) and (±)-1-{*cis*-4-hydroxy-3,3-bis[(trityloxy)methyl]cyclopentyl}-5-methylpyrimidine-2(1*H*),4(3*H*)-dione (**4**)

A solution of a mixture of **1** and **2** (1.89 g, 7 mmol; *cf.* ref.[2h]) and triphenylmethyl chloride (4.74 g, 17 mmol) in pyridine (40 ml) was heated at 100 °C for 1 h. The solvent was evaporated and the residue was partitioned between ethyl acetate (200 ml) and water (100 ml). The organic layer was separated, washed with water (3 × 100 ml), dried over sodium sulfate and the solvent was evaporated. Chromatography of the residue on silica gel (600 g) in toluene–ethyl acetate (2 : 1) afforded 1.79 g (34% yield) of *cis* isomer **4** and 2.01 g (38% yield) of *trans* isomer **3** (both after crystallization from ethanol).

*Isomer* **3**. M.p. 228–229 °C. For $C_{50}H_{46}N_2O_5$ (754.9) calculated: 79.55% C, 6.14% H, 3.71% N; found: 79.26% C, 6.22% H, 3.49% N. $^1$H NMR: 1.44 dd, 1 H, *J*(2a′,1′) = 9.5, *J*(2a′,2b′) = 13.1 (H-2a′); 1.54–1.63 m, 1 H (H-5a′); 1.68–1.82 m, 1 H (H-5b′); 1.73 s, 3 H ($CH_3$); 2.02 dd, 1 H, *J*(2b′,4′) = 9.2 (H-2b′); 3.00 d, 1 H and 3.41 d, 1 H, $J_{gem}$ = 8.9 ($CH_2O$); 3.08 d, 1 H and 3.42 d, 1 H, $J_{gem}$ = 9.2 ($CH_2O$); 4.14–4 20 m, 1 H (H-4′); 4.65–4.83 m, 1 H (H-1′); 4.71 d, 1 H, *J*(4′,OH) = 4.6 (4′-OH); 7.12 s, 1 H (H-6); 7.29 m, 30 H (H-arom.); 11.16 s, 1 H (NH).

*Isomer* **4**. M.p. 265–266 °C. For $C_{50}H_{46}N_2O_5$ (754.9) calculated: 79.55% C, 6.14% H, 3.71% N; found: 79.32% C, 6.27% H, 3.60% N. $^1$H NMR: 1.35–1.49 m, 2 H (H-2a′, H-5a′); 1.68 s, 3 H ($CH_3$); 1.75 ddd, 1 H, *J*(5b′,4′) = 4.9, *J*(5b′,5a′) = 14.2, *J*(5b′,1′) = 9.1 (H-5b′); 1.99 dd, 1 H, *J*(2b′,1′) = 8.5, *J*(2b′,2a′) = 13.1 (H-2b′); 2.90 d, 1 H and 3.29 d, 1 H , $J_{gem}$ = 9.2 ($CH_2O$); 3.27 d, 1 H and 3.49 d, 1 H, $J_{gem}$ = 8.0 ($CH_2O$); 3.91 m, 1 H (H-4′); 4.60–4.76 m, 1 H (H-1′); 5.11 d, 1 H, *J*(OH,4′) = 4.3 (4′-OH); 7.22–7.41 m, 31 H (H-6, H-arom.); 11.16 s, 1 H (NH).

(±)-1-[*trans*-4-Hydroxy-3,3-bis(hydroxymethyl)cyclopentyl]-5-methylpyrimidine-2(1*H*),4(3*H*)-dione (**1**)

A solution of trityl derivative **3** (1.51 g, 2 mmol) in 80% aqueous trifluoroacetic acid (25 ml) was set aside at room temperature for 15 min. The solvent was evaporated and the residue was partitioned between ether (20 ml) and water (30 ml). The aqueous layer was separated, washed with ether (2 × 10 ml) and neutralized with Dowex 1 ($HCO_3^-$ form). The ion exchanger was filtered off, washed with water and the combined filtrates were taken down giving 497 mg (92%) of **1**. For $C_{12}H_{18}N_2O_5$ (270.3) calculated: 53.32% C, 6.71% H, 10.36% N; found: 53.10% C, 6.83% H, 10.21% N. The $^1$H NMR spectra of **1** and compound prepared before[2h] were identical.

(±)-1-[*cis*-4-Hydroxy-3,3-bis(hydroxymethyl)cyclopentyl]-5-methylpyrimidine-2(1*H*),4(3*H*)-dione (**2**)

Using the same procedure as in the preparation of **1**, trityl derivative **4** (1.51 g, 2 mmol) was deprotected giving 510 mg (94%) of **2**. For $C_{12}H_{18}N_2O_5$ (270.3) calculated: 53.32% C, 6.71% H, 10.36% N; found: 53.15% C, 6.64% H, 10.30% N.
The $^1$H NMR spectra of **2** and compound prepared before[2h] were identical.

(±)-1-{*trans*-4-Hydroxy-3,3-bis[(tosyloxy)methyl]cyclopentyl}-5-methylpyrimidine-2(1*H*),4(3*H*)-dione (**5**) and 1-{(1*R**,3*R**,4*S**)-4-Hydroxy-3-(hydroxymethyl)-3-[(tosyloxy)methyl]cyclopentyl}-5-methylpyrimidine-2(1*H*),4(3*H*)-dione (**6**)

A solution of **1** (270 mg, 1 mmol) and tosyl chloride (210 mg, 1.1 mmol) in pyridine (3.5 ml) was allowed to stand at room temperature for 5 h and then water (50 µl) was added. After standing at room temperature for 10 min, the solvent was evaporated. Chromatography of the residue on a silica gel column afforded 110 mg (20%) of ditosyl derivative **5** as a solid foam and 290 mg (68%) of monotosyl derivative **6** (after crystallization from ethanol).

*Racemate* **5**. For $C_{26}H_{30}N_2O_7S_2$ (546.7) calculated: 57.13% C, 5.53% H, 5.12% N, 11.73% S; found: 56.80% C, 5.44% H, 4.88% N, 11.46 % S. $^1$H NMR: 1.37 dd, 1 H, *J*(2a′,1′) = 9.9, *J*(2a′,2b′) = 13.9 (H-2a′); 1.70–1.86 m, 2 H (H-2b′, H-5a′); 1.75 s, 3 H ($CH_3$); 2.11 m, 1 H, *J*(5b′,4′) = 6.8, *J*(5b′,4′) = 7.7, *J*(5b′,5a′) = 14.7 (H-5b′); 2.43 s, 6 H (2 × $CH_3$, tosyl); 3.88 d, 1 H and 4.05 d, 1 H, $J_{gem}$ = 10.1 ($CH_2O$); 3.93 s, 2 H ($CH_2O$); 3.98 m, 1 H (H-4′); 4.85 m, 1 H, Σ*J* = 35.4 (H-1′); 5.23 d, 1 H, *J*(OH,4′) = 4.3 (4′-OH); 7.47 d, 2 H and 7.73 d, 2 H, *J* = 8.2 (H-tosyl); 7.49 d, 2 H and 7.75 d, 2 H, *J* = 8.2 (H-tosyl); 7.50 s, 1 H (H-6); 11.21 s, 1 H (NH).

*Racemate* **6**. M.p. 167–170 °C. For $C_{19}H_{24}N_2O_7S$ (424.5) calculated: 53.76% C, 5.70% H, 6.60% N, 7.55% S; found: 53.63% C, 5.81% H, 6.71% N, 7.39% S. $^1$H NMR: 1.31 dd, 1 H, *J*(2a′,1′) = 10.2, *J*(2a′,2b′) = 13.7 (H-2a′); 1.70–2.15 m, 3 H (2 × H-5′, H-2b′); 1.77 d, 3 H, *J* = 0.9 ($CH_3$); 2.42 s, 3 H ($CH_3$, tosyl); 3.33–3.46 m, 2 H ($CH_2O$); 3.93–4.07 m, 2 H (H-4′, $CH_2O$**H**); 4.02 s, 2 H ($CH_2OTs$); 4.84–5.02 m, 2 H (4′-OH, H-1′); 7.49 d, 2 H, *J* = 8.2 and 7.79 dd, 2 H, *J* = 8.2, 3.5 (H-tosyl); 7.50 s, 1 H (H-6); 11.20 s, 1 H (NH).

1-[(1*R**,4*S**,6*S**)-4-Hydroxymethyl-2-oxabicyclo[3.2.0]hept-6-yl]-5-methylpyrimidine-2(1*H*),4(3*H*)-dione (**7**)

A solution of **6** (212 mg, 0.5 mmol) in 0.25 M methanolic sodium methoxide (6 ml) was set aside at room temperature for 20 h and then Dowex 50 ($H^+$) was added (to pH ≈ 2). The ion exchanger was filtered off, washed with methanol and the combined filtrates were neutralized with Dowex 1 ($HClO_3^-$ form). The resin was filtered off, washed with methanol and the combined filtrates were evaporated. Chromatography of the residue on silica gel (20 g) in ethyl acetate–acetone–ethanol–water (19 : 3 : 2 : 1) gave 40 mg (19%) of starting **6**, 10 mg (16%) of thymine, and 67 mg (53%) of **7** (after crystallization from ethanol), m.p. 184–186 °C. For $C_{12}H_{16}N_2O_4$ (252.3) calculated: 57.13% C, 6.39% H, 11.10% N; found: 57.09% C, 6.59% H, 11.02% N. UV (water): $\lambda_{max}$ 274 nm (ε 10 500); (0.1 M NaOH): $\lambda_{max}$ 272 nm (ε 7 700). $^1$H NMR: 1.63–2.03 m, 4 H (2 × H-5′, 2 × H-7′); 1.78 s, 3 H ($CH_3$); 3.45–3.60 m, 2 H ($CH_2O$); 4.11 d, 1 H and 4.54 d, 1 H, $J_{gem}$ = 5.8 (2 × H-3′); 4.90 d, 1 H, *J*(1′,7a′) = 3.1 (H-1′); 4.94 t, 1 H, *J*(OH,$CH_2$) = 5.5 ($CH_2$O**H**); 5.46 m, 1 H, Σ*J* = 34.8 (H-6′); 7.65 d, 1 H, *J* = 0.8 (H-6); 11.28 s, 1 H (NH).

(±)-1-{*cis*-4-Hydroxy-3,3-bis[(tosyloxy)methyl]cyclopentyl}-5-methylpyrimidine-2(1*H*),4(3*H*)-dione (**8**) and 1-{(1*R**,3*R**,4*S**)-4-Hydroxy-3-(hydroxymethyl)-3-[(tosyloxy)methyl]cyclopentyl}-5-methylpyrimidine-2(1*H*),4(3*H*)-dione (**9**)

Using the same procedure as described in the preparation of tosylates **5** and **6**, the trihydroxy compound **2** (270 mg, 1 mmol) was converted into ditosylate **8** (92 mg; 17%) and monotosylate **9** (295 mg; 69%).

*Racemate* **8**. For $C_{26}H_{30}N_2O_7S_2$ (546.7) calculated: 57.13% C, 5.53% H, 5.12% N, 11.73% S; found: 56.80% C, 5.44% H, 4.88% N, 11.46 % S. $^1$H NMR: 1.51 dd, 1 H, *J*(2a′,1′) = 9.6, *J*(2a′,2b′) = 13.9 (H-2a′); 1.68–1.82 m, 2 H (H-5a′, H-2b′); 1.76 s, 3 H ($CH_3$); 2.18 ddd, 1 H, *J*(5b′,4′) = 5.5, *J*(5b′,5a′) = 14.0, *J*(5b′,1′) = 7.9 (H-5b′); 2.41 s, 3 H ($CH_3$, tosyl); 2.43 s, 3 H ($CH_3$, tosyl); 3.77–3.91 m, 1 H (H-4′); 3.83 s, 2 H ($CH_2O$); 4.05 s, 2 H ($CH_2O$); 4.70–4.87 m, 1 H (H-1′); 5.45 d, 1 H, *J*(OH,4′) = 4.6 (4′-OH); 7.46 d, 2 H and 7.72 d, 2 H, *J* = 8.2 (H-tosyl); 7.50 d, 2 H and 7.78 d, 2 H, *J* = 8.2 (H-tosyl); 7.55 s, 1 H (H-6); 11.21 s, 1 H (NH).

*Racemate* **9**. M.p. 188–189 °C. For $C_{19}H_{24}N_2O_7S$ (424.5) calculated: 53.76% C, 5.70% H, 6.60% N, 7.55% S; found: 53.79% C, 5.82% H, 6.50% N, 7.63% S. $^1$H NMR: 1.40 dd, 1 H, *J*(2a′,1′) = 9.5, *J*(2a′,2b′) = 13.1 (H-2a′); 1.68 ddd, 1 H, *J*(5a′,4′) = 5.3, *J*(5a′,5b′) = 14.1, *J*(5a′,1′) = 7.9 (H-5a′); 1.77 s, 3 H ($CH_3$); 1.83 dd, 1 H, *J*(2b′,1) = 8.6 (H-2b′); 2.29 ddd, 1 H, *J*(5b′,4′) = 5.5, *J*(5b′,1′) = 8.7 (H-5b′); 2.40 s, 3 H ($CH_3$, tosyl); 3.20 d, 2 H, *J*($CH_2$,OH) = 4.9 ($CH_2O$); 3.94 ddd, 1 H (H-4′); 4.09 s, 2 H ($CH_2$OTs); 4.79–4.96 m, 1 H (H-1′); 4.87 t, 1 H ($CH_2$O**H**); 5.22 d, 1 H, *J*(OH,4′) = 4.3 (4′-OH); 7.47d, 2 H and 7.78 d, 2 H, *J* = 8.2 (H-tosyl); 7.60 s, 1 H (H-6); 11.20 s, 1 H (NH).

1-[(1*R**,4*S**,6*R**)-4-Hydroxymethyl-2-oxabicyclo[3.2.0]hept-6-yl]-5-methylpyrimidine-2(1*H*),4(3*H*)-dione (**10**)

Using the same procedure as in the preparation of the oxetane **7**, tosylate **9** (212 mg, 0.5 mmol) produced oxetane **10** (42 mg; 33%). Starting **9** (53 mg; 25%) was recovered and thymine (22 mg; 35%) was formed.

*Racemate* **10**. M.p. 157–158 °C. For $C_{12}H_{16}N_2O_4$ (252.3) calculated: 57.13% C, 6.39% H, 11.10% N; found: 57.01% C, 6.48% H, 11.03% N. UV (water): $\lambda_{max}$ 275 nm (ε 10 750); (0.1 M

NaOH): $\lambda_{max}$ 273 nm (ε 8 200). $^1$H NMR: 1.78 d, 3 H, *J* = 1.2 ($CH_3$); 1.99–2.26 m, 4 H (2 × H-5′, 2 × H-7′); 3.36–3.52 m, 2 H ($CH_2O$); 4.12 d, 1 H and 4.47 d, $J_{gem}$ = 6.1 (2 × H-3′); 4.90 m, 1 H, Σ*J* = 30.0 (H-6′); 4.94 t, 1 H, *J*(OH,$CH_2$) = 5.4 ($CH_2$O**H**); 4.94 dd, 1 H, *J*(1′,7a′) = 3.7, *J*(1′,7b′) = 4.3 (H-1′); 8.00 d, 1 H, *J* = 1.2 (H-6); 11.23 s, 1 H (NH).

(±)-1-{*cis*-4-Mesyloxy-3,3-bis[(trityloxy)methyl]cyclopentyl}-5-methylpyrimidine-2(1*H*),4(3*H*)-dione (**11**)

Methanesulfonyl chloride (1.24 ml, 16 mmol) was added to a stirred solution of trityl derivative **4** (3.02 g, 4 mmol) in pyridine (28 ml). After standing at room temperature for 5 h, water (1 ml) was added and, after standing for 10 min, the solvent was evaporated and the residue was partitioned between ethyl acetate (100 ml) and water (100 ml). The organic layer was washed with water (3 × 100 ml), dried over anhydrous sodium sulfate and evaporated. Chromatography of the residue on a column of silica gel (250 g) in ethyl acetate–toluene (2 : 3) afforded 2.97 g (89%) of mesylate **11**. For $C_{51}H_{48}N_2O_7S$ (833.0) calculated: 73.53% C, 5.81% H, 3.36% N, 3.85% S; found: 73.25% C, 5.92% H, 3.17% N, 3.70% S. $^1$H NMR: 1.63 s, 3 H ($CH_3$); 1.54–1.68 m, 1 H; 2.00–2.30 m, 3 H; 2.97 s, 3 H ($CH_3SO_2$); 2.99 d, 1 H and 3.28 d, 1 H, $J_{gem}$ ≈ 8 ($CH_2O$); 3.26 s, 2 H ($CH_2O$); 4.71–4.89 m, 1 H (H-1′); 4.82 t, 1 H, *J*(4′,5a′) ≈ *J*(4′,5b′) ≈ 6.1 (H-4′); 7.29 m, 31 H (H-arom., H-6); 11.26 s, 1 H (NH).

(±)-1-[*cis*-3,3-Bis(hydroxymethyl)-4-(mesyloxy)cyclopentyl]-5-methylpyrimidine-2(1*H*),4(3*H*)-dione (**12**)

A solution of trityl derivative **11** (833 mg, 1 mmol) in 80% aqueous trifluoroacetic acid (12 ml) was set aside at room temperature for 10 min. The solvent was evaporated and the residue was partitioned between ether (10 ml) and water (20 ml). The aqueous layer was separated, washed with ether (2 × 10 ml) and neutralized with Dowex 1 ($HCO_3^-$ form). The ion exchanger was filtered off, washed with water and the combined filtrates were taken down. Crystallization of the residue from ethanol gave 320 mg (92%) of mesylate **12**, m.p. 131–133 °C. For $C_{13}H_{20}N_2O_7S$ (348.4) calculated: 44.82% C, 5.79% H, 8.04% N, 9.20% S; found: 44.80% C, 6.04% H, 7.80% N, 8.95% S. $^1$H NMR: 1.73 dd, 1 H, *J*(2a′,1′) = 10.3, *J*(2a′,2b′) = 13.1 (H-2a′); 1.78 s, 3 H ($CH_3$); 1.93 dd, 1 H, *J*(2b′,1′) = 8.6 (H-2b′); 2.17 ddd, 1 H, *J*(5a′,4′) = 6.5, *J*(5a′,5b′) = 13.1, *J*(5a′,1′) = 9.5 (H-5a′); 2.41–2.55 m, 1 H (H-5b′); 3.19 s, 3 H ($CH_3SO_2$); 3.36 s, 2 H ($CH_2O$); 3.45 d, 1 H and 3.54 d, 1 H, $J_{gem}$ = 10.5 ($CH_2O$); 4.23 brs (OH groups); 4.88 t, 1 H, *J*(4′,5b′) = 6.4 (H-4′); 4.91 m, 1 H (H-4); 7.59 s, 1 H (H-6); 11.24 s, 1 H (NH).

(±)-1-{4,4-Bis[(trityloxy)methyl]cyclopent-2-en-1-yl}-5-methylpyrimidine-2(1*H*),4(3*H*)-dione (**13**)

A solution of mesylate **11** (1.67 g, 2 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.47 ml, 3 mmol) in dimethylformamide (17 ml) was heated at 125 °C for 6 h. The residue was partitioned between ethyl acetate (100 ml) and water (50 ml). The organic layer was separated, washed with water (3 × 50 ml), dried over anhydrous sodium sulfate and concentrated to a small volume. The crystalline product was filtered off to give 1.31 g (89%) of **13**, m.p. 119–121 °C. For $C_{50}H_{44}N_2O_4$ (736.9) calculated: 81.50% C, 6.02% H, 3.80% N; found: 81.21% C, 5.99% H, 3.64% N. $^1$H NMR: 1.25 dd, 1 H, *J*(5a′,1′) = 6.1, *J*(5a′,5b′) = 14.0 (H-5a′); 1.58 s, 3 H ($CH_3$); 2.04 dd, 1 H, *J*(5b′,1′) = 8.5 (H-5b′); 3.01 d, 1 H and 3.25 d, 1 H, $J_{gem}$ = 8.5

($CH_2O$); 3.08 s, 2 H ($CH_2O$); 5.36 m, 1 H (H-1′); 5.88 dd, 1 H, *J*(3′,2′) = 5.5, *J*(3′,1′) = 1.9 (H-3′); 6.23 dd, 1 H, *J*(2′,1′) = 2.0 (H-2′); 6.85 d, 1 H, *J* = 0.9 (H-6); 7.30 s, 15 H and 7.26 s, 15 H (trityl); 11.23 s, 1 H (NH).

(±)-1-[4,4-Bis(hydroxymethyl)cyclopent-2-en-1-yl]-5-methylpyrimidine-2(1*H*),4(3*H*)-dione (**14**)

A solution of the trityl derivative **13** (1.11 g, 1.5 mmol) in 80% aqueous acetic acid was heated at 60 °C for 2 h. The mixture was concentrated, the residue was washed with toluene (2 × 5 ml) and crystallized from methanol to obtain 215 mg (57%) of the racemic diol **14**, m.p. 119–121 °C. Column chromatography of mother liquors on silica gel (40 g) in ethyl acetate–acetone–ethanol–water (19 : 3 : 2 : 1) afforded additional 103 mg (27%) of **14**. For $C_{12}H_{16}N_2O_4$ (252.3) calculated: 57.13% C, 6.39% H, 11.10% N; found: 56.99% C, 6.36% H, 11.02% N. $^1$H NMR: 1.47 dd, 1 H, *J*(5a,1) = 5.9, *J*(5a,5b) = 13.8 (H-5a); 1.74 s, 3 H ($CH_3$); 2.18 dd, 1 H, *J*(5b,1) = 9.0 (H-5b); 3.30 d, 2 H, *J*($CH_2$,OH) = 5.5 ($CH_2O$); 3.53 dd, 1 H, *J*($CH_2$,OH) = 5.5 and 3.49 dd, 1 H, *J*($CH_2$,OH) = 5.1, $J_{gem}$ = 10.5 ($CH_2O$); 4.65 t, 1 H, *J*(OH,$CH_2$) = 5.5 ($CH_2O$**H**); 4.71 t, 1 H, *J*(OH,$CH_2$) = 5.3 ($CH_2O$**H**); 5.53 m, 1 H (H-1); 5.65 dd, 1 H, *J*(3,2) = 5.6, *J*(3,1) = 2.0 (H-3); 5.91 dd, 1 H, *J*(2,1) = 2.0 (H-2); 7.38 s, 1 H (H-6′); 11.21 s, 1 H (NH).

(±)-1-[3,3-Bis(hydroxymethyl)cyclopentyl]-5-methylpyrimidine-2(1*H*),4(3*H*)-dione (**15**)

Pd/C (20 mg; 10%) was added to a solution of **14** (76 mg, 0.3 mmol) in methanol (2 ml) and the mixture was hydrogenated at 50 °C and atmospheric pressure for 5 h. The solids were removed by filtration through Celite washed with a hot mixture of methanol–ethyl acetate (1 : 1; 5 × 2 ml) and the combined filtrates were evaporated. Crystallization of the residue from methanol afforded 62 mg (81%) of racemic **15**, m.p. 216–218 °C. For $C_{12}H_{18}N_2O_4$ (254.3) calculated: 56.68% C, 7.14% H, 11.02% N; found: 56.61% C, 7.12% H, 10.94% N. $^1$H NMR: 1.28–1.83 m, 6 H (2 × H-2′, 2 × H-5′, 2 × H-4′); 1.78 s, 1 H ($CH_3$); 3.24 dd, 2 H, *J*($CH_2$,OH) = 5.0, *J* = 1.7 ($CH_2O$); 3.33 d, 2 H, *J*($CH_2$,OH) = 5.0 ($CH_2O$); 4.60 t, 1 H, *J*(OH,$CH_2$) = 5.0 ($CH_2O$**H**); 4.61 t, 1 H, *J*(OH,$CH_2$) = 5.0 ($CH_2O$**H**); 4.66–4.84 m, 1 H (H-1′); 7.57 d, 1 H, *J* = 0.8 (H-6); 11.18 s, 1 H (NH).

(±)-1-[3-(Hydroxymethyl)cyclopent-3-en-1-yl]-5-methylpyrimidine-2(1*H*),4(3*H*)-dione (**16**)

Sodium hydride (160 mg, 4 mmol; 60% dispersion) was added to a stirred solution of mesylate **12** (348 mg, 1 mmol) in dimethylformamide (5 ml). The mixture was stirred at room temperature for 2 h, then neutralized with acetic acid and evaporated. Chromatography of the residue on a silica gel column (35 g) in ethyl acetate–acetone–ethanol–water (100 : 15 : 6 : 4) afforded 98 mg (47%) of **16** and 60 mg (24%) of **14** (both after crystallization from ethanol).

*Racemate* **16**. M.p. 192–195 °C. For $C_{11}H_{14}N_2O_3$ (222.3) calculated: 59.45% C, 6.35% H, 12.60% N; found: 59.45% C, 6.45% H, 12.53% N. UV (water): $\lambda_{max}$ 276 nm (ε 10 100); (0.1 M NaOH): $\lambda_{max}$ 274 nm (ε 8 000). $^1$H NMR: 1.75 d, 3 H, *J* = 1.0 ($CH_3$); 2.29–2.45 m, 2 H (2 × H-5′); 2.61–2.80 m, 2 H (2 × H-2′); 3.99 d, 2 H, *J*($CH_2$,OH) = 5.5 ($CH_2O$); 4.82 t, 1 H ($CH_2O$**H**); 5.13 m, 1 H, *J*(1′,5a′) ≈ *J*(1′,5b′) ≈ 4.5, *J*(1′,2a′) ≈ *J*(1′,2b′) ≈ 9.0 (H-1′); 5.55 t, 1 H, *J*(4′,5a′) = *J*(4′,5b′) = 2.1 (H-4′); 7.28 d, 1 H, *J* = 1.0 (H-6); 11.22 s, 1 H (NH).

Treatment of Oxetane Derivative **7** with Sodium Hydride

Sodium hydride (32 mg, 0.8 mmol; 60% dispersion) was added to a stirred solution of **7** (50 mg, 0.2 mmol) in dimethylformamide (1 ml). The mixture was stirred at room temperature for 2 h, then neutralized with acetic acid and evaporated. Chromatography of the residue on silica gel (5 g) in ethyl acetate–acetone–ethanol–water (100 : 15 : 6 : 4) afforded 48 mg (96%) of the starting oxetane **7**.

(±)-1-{*trans*-4-Mesyloxy-3,3-bis[(trityloxy)methyl]cyclopentyl}-5-methylpyrimidine-2(1*H*),4(3*H*)-dione (**17**)

Methanesulfonyl chloride (1.24 ml, 16 mmol) was added to a stirred solution of trityl drivative **3** (3.02 g, 4 mmol) in pyridine (28 ml). After standing at room temperature for 5 h, water (1 ml) was added. After standing for 10 min, the solvent was evaporated and the residue was partitioned between ethyl acetate (100 ml) and water (100 ml). The organic layer was washed with water (3 × 100 ml), dried over anhydrous sodium sulfate and evaporated. Crystallization of the residue from ethanol afforded 2.83 g (85%) of the mesyl derivative **17**, m.p. 185–185.5 °C. For $C_{51}H_{48}N_2O_7S$ (833.0) calculated: 73.53% C, 5.81% H, 3.36% N, 3.85% S; found: 73.42% C, 5.92% H, 3.28% N, 4.18% S. $^1$H NMR: 1.67 dd, 1 H, $J$(2a′,1′) = 10.0, $J$(2a′,2b′) = 13.1 (H-2a′); 1.75 s, 3 H ($CH_3$); 1.98–2.17 m, 3 H (2 × H-5′, H-2b′); 2.94 s, 3 H ($CH_3SO_2$); 3.06 d, 1 H and 3.09 d, 1 H, $J_{gem}$ = 6.4 ($CH_2$); 3.35 d, 1 H and 3.40 d, 1 H, $J_{gem}$ = 9.5 ($CH_2$); 4.71 m, 1 H, Σ$J$ = 38.8 (H-1′); 5.09 t, 1 H, $J$(4′,5a′) = $J$(4′,5b′) = 5.5 (H-4′); 7.25–7.36 m, 31 H (H-6, H-arom.); 11.22 s, 1 H (HN).

(1*R**,9*R**)-6-Methyl-5-oxo-11,11-bis(trityloxymethyl)-2-oxa-4,8-diazatricyclo-[7.2.1.0$^{3,8}$]dodec-3,6-diene (**18**)

To a solution of the mesylate **17** (1.67g, 2 mmol) in acetonitrile (25 ml) 1,8-diazabicyclo-[5.4.0]undec-7-ene (0.6 ml, 4 mmol) was added. The mixture was heated to 60 °C for 6 h, then cooled and the crystalline compound was filtered off, washed with acetonitrile, then with ether. It was obtained 1.09 g (74%) of **18**, m.p. 300–302 °C. For $C_{50}H_{44}N_2O_4$ (736.9) calculated: 81.50% C, 6.02% H, 3.80% N; found: 81.21% C, 5.87% H, 3.65% N. $^1$H NMR: 1.32–1.15 m, 2 H (2 × H-10); 1.75 brs, 4 H ($CH_3$, H-12a); 2.05 brd, 1 H, $J$(12b,12a) = 12.8 (H-12b); 2.69 d, 1 H and 3.79 d, 1 H, $J_{gem}$ = 9.2 ($CH_2O$); 2.84 d, 1 H and 3.39 d, 1 H, $J_{gem}$ = 9.5 ($CH_2O$); 4.15 brs, 1 H (H-1); 4.84 brs, 1 H (H-9); 7.14 d, 1 H, $J \approx 1$ (H-7); 7.20 m, 15 H and 7.35 m, 15 H (2 × trityl).

(1*R**,9*R**)-11,11-Bis(hydroxymethyl)-6-methyl-5-oxo-2-oxa-4,8-diazatricyclo-[7.2.1.0$^{3,8}$]dodec-3,6-diene (**19**)

A solution of trityl derivative **18** (737 mg, 1 mmol) in 80% aqueous trifluoroacetic acid (10 ml) was set aside at room temperature for 10 min. The solvent was evaporated and the residue was partitioned between ether (10 ml) and water (20 ml). The aqueous layer was separated, washed with ether (2 × 10 ml) and neutralized with Dowex 1 ($HCO_3^-$ form). The ion exchanger was filtered off, washed with water and the combined filtrates were taken down. Crystallization of the residue from methanol gave 210 mg (83%) of racemic anhydro derivative **19**, m.p. 244–247 °C. For $C_{12}H_{16}N_2O_4$ (252.3) calculated: 57.13% C, 6.39% H, 11.10% N; found: 56.96% C, 6.50% H, 10.92% N. $^1$H NMR: 1.61 dd, 1 H, $J$(12a,9) = 4.3,

*J*(12a,12b) = 14.0 (H-12a); 1.75 d, 3 H, *J* = 0.9 ($CH_3$); 1.83 dd, 1 H, *J*(12b,9) = 2.4 (H-12b); 2.13 dt, 1 H, *J*(10a,1) ≈ *J*(10a,9) ≈ 1, *J*(10a,10b) = 13.1 (H-10a); 2.32 dt, 1 H, *J*(10b,1) = *J*(10b,9) = 3.1 (H-10b); 3.22–3.50 m, 4 H (2 × $CH_2O$); 4.39 m, 1 H (H-9); 4.72 m, 2 H (H-1, OH); 4.91 brs, 1 H (OH); 7.43 d, 1 H, *J* = 1.2 (H-7).

(±)-1-[*trans*-4-Azido-3,3-bis(acetoxymethyl)cyclopentyl]-5-methylpyrimidine-2(1*H*),4(3*H*)-dione (**20**)

A solution of the anhydro derivative **19** (252 mg, 1 mmol) and lithium azide (490 mg, 10 mmol) in dimethylformamide (7 ml) was heated at 150 °C for 8 h. The solvent was evaporated and the residue was chromatographed on a silica gel column in ethyl acetate–acetone–ethanol–water (200 : 30 : 12 : 8) giving 198 mg of crude azido nucleoside **21** and 44 mg (17.5%) of cyclopentyl derivative **14**. To a solution of crude **21** in acetonitrile (3 ml), acetic anhydride (0.4 ml) and 4-(dimethylamino)pyridine (50 mg) were added and the solution was allowed to stand for 2 h at room temperature. Methanol (0.5 ml) was added and, after 10 min, the solvent was evaporated. Chromatography of the residue on a silica gel column in ethyl acetate–toluene (4 : 1) afforded 186 mg (49%) of acetate **20**. For $C_{16}H_{21}N_5O_6$ (379.4) calculated: 50.66% C, 5.58% H, 18.46% N; found: 50.39% C, 5.70% H, 18.18% N. IR (*c* = 2%, $CHCl_3$): 3 391 (NH); 2 111, 1 273 ($N_3$); 1 741 (C=O, ester); 1 705, 1 689 (C=O, thymine); 1 238, 1 045 (C–O, ester). $^1$H NMR: 1.68 dd, 1 H, *J*(2a′,1′) = 9.8, *J*(2a′,2b′) = 13.7 (H-2a′); 1.78 s, 3 H ($CH_3$); 1.98–2.18 m, 2 H (H-5a′, H-2b′); 2.05 s, 3 H and 2.06 s, 3 H ($CH_3CO$); 2.33 dt, 1 H, *J*(5b′,2′) = *J*(5b′,4′) = 7.0, *J*(5b′,5a′) = 14.9 (H-5b′); 4.06 s, 2 H ($CH_2O$); 4.10 s, 2 H ($CH_2O$); 4.90 m, 1 H, Σ*J* = 35.0 (H-1′); 7.58 d, 1 H, *J* = 0.8 (H-6); 11.25 s, 1 H (NH).

(±)-1-[*trans*-4-Azido-3,3-bis(hydroxymethyl)cyclopentyl]-5-methylpyrimidine-2(1*H*),4(3*H*)-dione (**21**)

A solution of diacetate **20** (112 mg, 0.3 mmol) in 0.1 M methanolic sodium methoxide (2 ml) was allowed to stand for 2 h at room temperature. Neutralization with Dowex 50 ($H^+$) and evaporation afforded 88 mg (99%) of the azido nucleoside **21** as a solid foam. For $C_{12}H_{17}N_5O_4$ (295.3) calculated: 48.81% C, 5.80% H, 23.72% N; found: 48.52% C, 6.01% H, 23.41% N. UV (water): $\lambda_{max}$ 275 nm (ε 10 400); (0.1 M NaOH): $\lambda_{max}$ 273 nm (ε 7 800). $^1$H NMR: 1.51 dd, 1 H, *J*(2a′,1′) = 9.6, *J*(2a′,2b′) = 13.3 (H-2a′); 1.78 d, 3 H, *J* = 1.0 ($CH_3$); 1.94 dd, 1 H, *J*(2b′,1′) = 7.7 (H-2b′); 1.90–2.28 m, 2 H (2 × H-5′); 3.40 d, 4 H, *J* = 4.9 (2 × $CH_2O$); 4.23 dd, 1 H, *J*(4′,5a′) = 6.5, *J*(4′,5b′) = 7.8 (H-4′); 4.67 t, 1 H, *J*(OH,$CH_2$) = 4.9 ($CH_2O$**H**); 4.67 t, 1 H, *J*(OH,$CH_2$) = 5.4 ($CH_2O$**H**); 4.93 pentet, 1 H, *J* = 8.5 (H-1′); 7.54 d, 1 H, *J* = 1.0 (H-6); 11.20 s, 1 H (NH).

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