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Rapid synthesis of (±)-*r*-7-benzyloxymethyl-cyclopenta-*cis*-[4,5][1,3]-oxazolo[3,2-*a*]pyrimidinones versatile carbocyclic nucleoside precursors

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Abstract—(±)-*r*-7-Benzyloxymethyl-cyclopenta-*cis*-[4,5][1,3]-oxazolo[3,2-*a*]pyrimidinones were synthesized in two steps from 1-hydroxymethyl-3-cyclopentene. These compounds are versatile intermediates for the synthesis of carbocyclic nucleosides. The synthesis has been accomplished by the iodofunctionalization of olefins as a method of coupling the pyrimidine bases and the carbocycle.

1. Introduction

A very active field of research in chemistry since last decade is the synthesis of nucleoside analogues with antiviral properties against diseases such as the human virus immunodeficiency (HIV) syndrome and the Herpes simplex virus (HSV) infection. Of particular interest are those nucleoside analogues that are modified in the furanose ring where the oxygen atom has been changed by a methylene group, named carbocyclic nucleosides, because they exhibit biological activities similar to their parent furanose nucleosides with the advantage of having good metabolic stability to the phosphorylases and hydrolases, enzymes that cleave the glycosidic bond of parent nucleosides.[1] The most active carbocyclic nucleosides contain in their structure purine bases, some examples are shown in Figure 1. Carbovir (**1**)[2] and abacavir (**2**)[3] have been approved for their therapeutical use against HIV, and entecavir (**3**)[4,5] is currently in clinical trials for the treatment of HSV infection. On the other hand, the antiviral activity of carbocyclic pyrimidine nucleosides have not attracted much attention, however, their triphosphates display good inhibitory activities against HIV reverse transcriptase like the compound **4** (Fig. 1).[6]

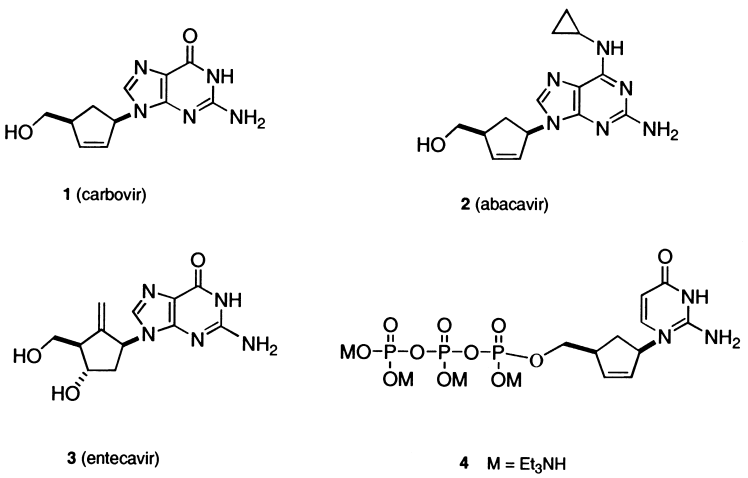

Figure 1. Antiviral carbocyclic nucleosides.

Keywords: carbocyclic nucleosides; iodofunctionalization; cyclopenta-oxazolo pyrimidinones.

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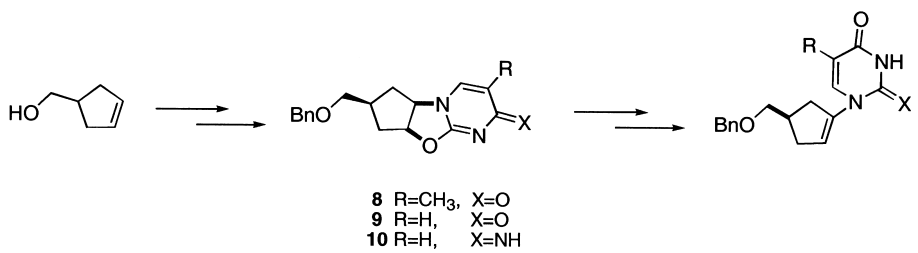
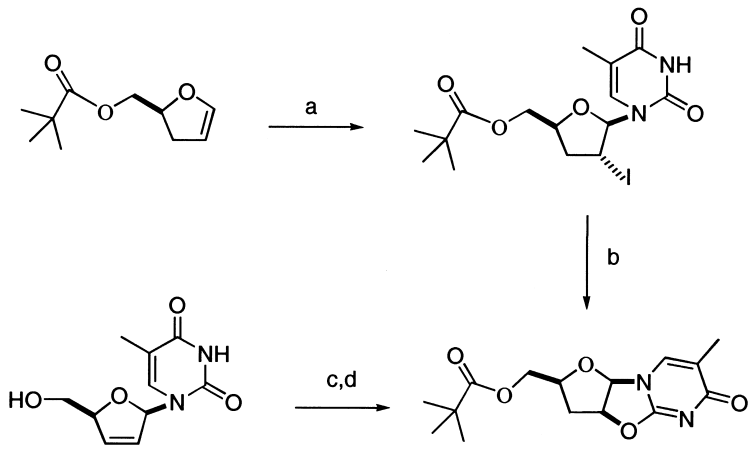
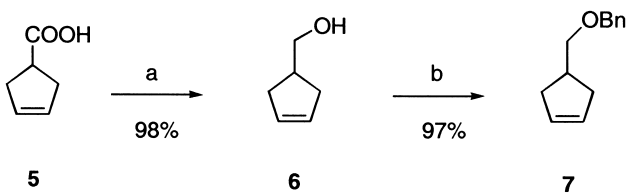


Figure 2.



Scheme 1. (a) Thymine $(TMS)_2$, NIS, THF, −15°C, 2 h; (b) DBU, CH_2Cl_2, 0°C, 1 h; (c) potassium *t*-butoxide, THF, 0°C, 1 h; (d) CH_3OH, 23°C, 4 h.

In this paper, we propose an efficient method for the preparation of (±)-*r*-7-benzyloxymethyl-cyclopenta-*cis*-[4,5][1,3]-oxazolo[3,2-*a*]pyrimidinones (**8**–**10**) as precursors of pyrimidine carbocyclic nucleosides (Fig. 2). The method is based in a convergent strategy that involves the coupling of thymine, uracil or cytosine, and the carbocycle through the nucleophilic opening of a iodonium intermediate prepared from 1-(hydroxymethyl)-3-cyclopentene.

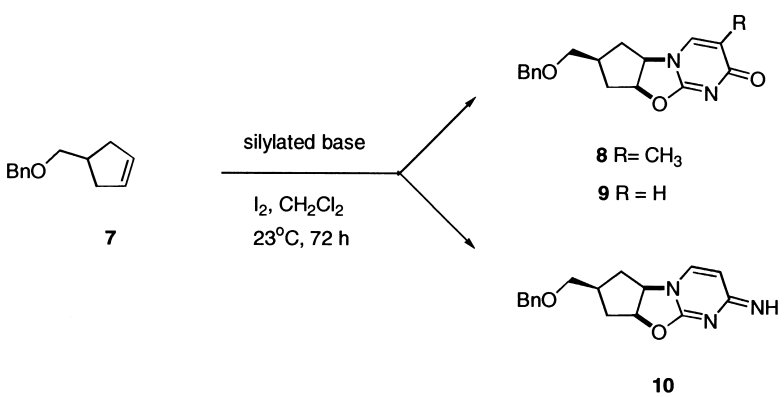


Scheme 2. (a) $LiAlH_4$, THF, 23°C, 30 min; (b) NaH, BnBr, THF, 23°C, 8 h.

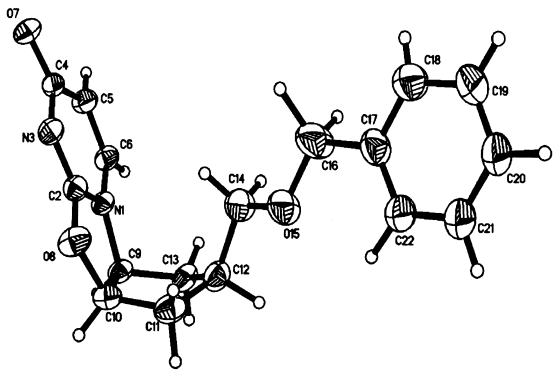
It is worth of mention that Kim and Misco[7] reported, previously, the direct coupling of a thymine with a cyclic iodonium furanoid glycal as a key intermediate step for the synthesis of 2′,3′-dideoxy- and 2′,3′-didehydro-2′,3′-dideoxy nucleosides; an example is shown in Scheme 1.

2. Results and discussion

1-(Hydroxymethyl)-3-cyclopentene **6** was prepared from 3-cyclopentenecarboxylic acid **5** according to a literature procedure.[8] Reaction of this alcohol with benzyl bromide in the presence of sodium hydride afforded the benzyl ether derivative **7** in excellent yield (Scheme 2). In order to prove if the conditions described by Kim and Misco were suitable for the coupling of the pyrimidine bases and compound **7**, the reaction between **7**, *N*-iodosuccinimide and the silylated pyrimidine bases was maintained for 2 h at −15°C.



Scheme 3. Formation of compounds **8**, **9** and **10** from 3-hydroxymethyl-3-cyclopentene by iodofunctionalization.

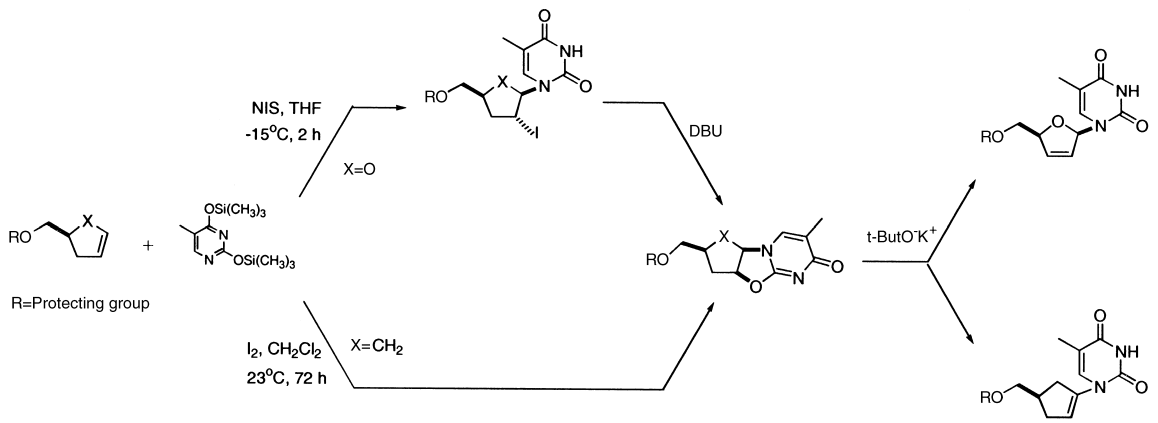


Scheme 4. ORTEP projection of the molecular structure of compound **9**, showing the atomic numbering as in the CIF file.

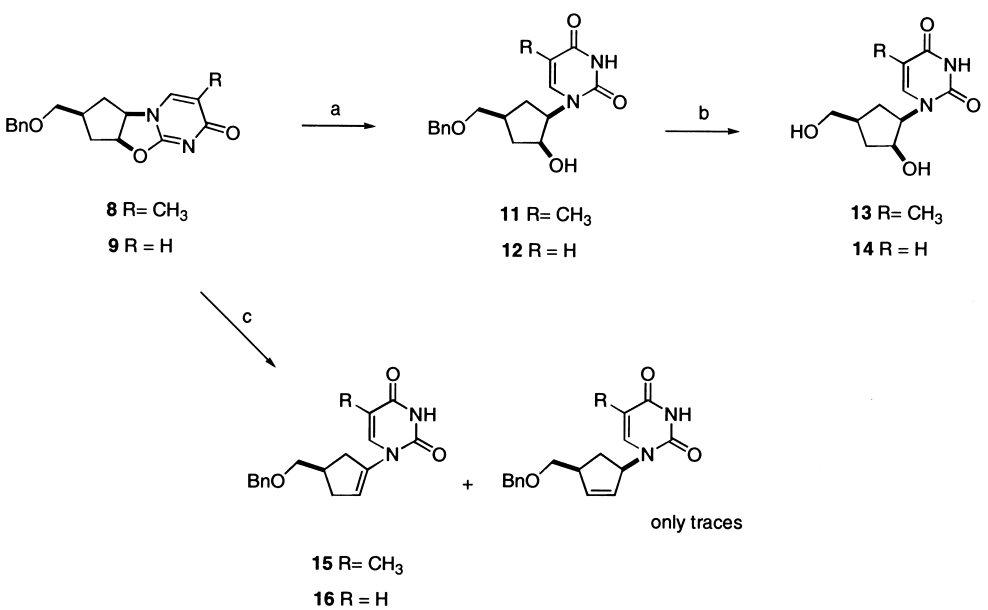
Nevertheless, the reactions did not proceed in any case and the starting material was recovered. However, when the reactions were run at room temperature for 72 h in the presence of iodine, Scheme 3, we observed the formation of only one product, with good yield, for the thymine and uracil bases. In the case of the cytosine derivate, the yield was only of 26%. The mass analyses of compounds **8**–**10** were indicative of the absence of iodine; therefore the cyclopenta-oxazolo pyrimidinones of Scheme 3 were proposed, as the products of the reaction.

Indeed the structure of compounds **8**–**10** was corroborated by NMR and X-ray diffraction analysis of compound **9**. The ORTEP structure of this compound is shown in Scheme 4, the *syn* orientation of the pyrimidine base and the benzyloxymethyl group, which is characteristic of the groups at C1′ and C4′ of natural nucleosides, confirms the stereochemistry assigned to these intermediates.

The cyclopentane ring conformation in the solid state is an envelope with C-11, C-10, C-9 and C-13 atoms in a plane and C-12 puckered by 12°. The pyrimidine base and the oxazolo five-membered ring are planar and both are coplanar and perpendicular to the cyclopentane. Previously two analogues of **9** were reported as intermediates in the synthesis of 2,3-dihydroxy-4-(hydroxymethyl)cyclopentyl-thymine[9] and the 2′-deoxy-neplanocin,[10] however, there are no report on the X-ray diffraction study of these kinds of structures in the literature.



Scheme 5. Synthetic pathway for the obtention of natural nucleosides and carbonucleosides through fused anhydro intermediates.



Scheme 6. (a) 1N NaOH, EtOH, 23°C; (b) H_2, Pd/C, MeOH, AcOH; (c) *t*-BuO^-K^+, *t*-BuOH, 40°C, 2 h.

In natural nucleosides the formation of the key anhydro intermediates is through the iodonucleoside (Scheme 5), in this work we found that the iodocabonucleoside is not stable enough to be isolated, thus the formation of the cyclopenta-oxazolo pyrimidinones is straightforward in the only one step of reaction. The opening of the anhydro intermediates in alkaline media lead to the nucleoside or carbonucleoside dihydro analogues in a precise a practical manner (Scheme 5). In the natural nucleoside the less substituted alkene is obtained meanwhile in the carbonucleoside the more substituted is preferred.

The utility of compounds **8** and **9** as intermediates for the synthesis of carbocyclic nucleosides was also explored in this work. Summarized in Scheme 6 are the reactions that were performed with these intermediates. The 2′-hydroxy-2′deoxypyrimidin carbonucleosides **13** and **14** are already known.[11,12] In additions we obtained the new carbocyclic nucleoside analogues **11**, **12**, **15** and **16**.

3. Conclusions

We have developed a simple and efficient method for the synthesis of (±)-*r*-7-benzyloxymethyl-cyclopenta-*cis*-[4,5][1,3]-oxazolo[3,2-*a*]pyrimidinones **8**–**10** as precursors of carbocyclic nucleosides using cheap and readily available reagents, i.e. elemental iodine. Several carbocyclic nucleosides were produced under mild reaction conditions, in high yields, by using this method.

4. Experimental

4.1. General

Melting points (uncorrected) were recorded using a Mel-Temp II apparatus. Infrared spectra were recorded in a Perkin Elmer 16F PC FTIR spectrophotometer and UV spectra were determined on a Perkin Elmer Lambda 12 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in a Jeol Eclipse spectrometer at 400 and 100.5 MHz, respectively. The chemical shifts of the NMR spectra are given in parts per million (ppm) and constant couplings in hertz (Hz). Mass spectra were recorded on a Hewlett Packard 5989A spectrometer using electron impact (EI) at 70 eV. Elemental analysis were performed by Galbraith Laboratories, Inc., Knoxville, T N. for compounds **8**–**10**, and were recorded in Thermo Finnigan Flash 1112 analyzer for compounds **11**, **12**, **15** and **16**. X-Ray diffraction data were collected in an Enraf-Nonius Kappa CCD. Data collection: COLLECT software (Nonius BV 1997).[13] Cell refinement and data reduction: Denzo/Scalepack software.[14] An integer system of programs was used for the solution, refinement and analysis of X-ray diffraction data, WinGX v-1.64.[15] The structure was solved by direct methods with Shelxs-97 (Sheldrick 1997)[16] and refined with Shelxs-97 (Sheldrick 1997).[17] Molecular graphics with WinGX software.[15] Florisil was purchased from Merk. All chemicals used here were of reagent grade and were obtained from Aldrich Chemical Co.

4.1.1. 1-Hydroxymethyl-3-cyclopentene 6. To a solution of 10.96 g (280 mmol) of $LiAlH_4$ in 100 mL of dry THF, was added dropwise 7.95 g (70 mmol) of **5** under ice-cooling. When the addition was completed, the temperature of the mixture was raised to room temperature and maintained under stirring for 30 min. To quench the reaction, a solution of 10% of NaOH and 10 mL of H_2O were added slowly and the mixture was stirred for 1 h. The mixture was filtered, dried over Na_2SO_4 (anh.) and concentrated in a rotary evaporator. Yield 6.81 g (98%). IR ν_{max} (film) (cm^{-1}): 3400 (s), 2930 (s), 1650 (m), 1080 (m), 950 (m), 900 (m). ^{1}H NMR ($CDCl_3$) δ (ppm): 5.68 (2H, s, CH═CH), 3.57 (2H, d, J=6.2 Hz, CH_2O), 2.54 (3H, m, CH+CH_2), 2.15 (2H, m, CH_2). ^{13}C NMR ($CDCl_3$), δ (ppm): 129.9 (CH═CH), 67.3 (CH_2O), 39.5 (CH), 36.0 ($2CH_2$).

4.1.2. 4-[(Phenylmethoxy)methyl]-3-cyclopentene 7. To a solution of 0.55 g (23 mmol) of NaH in dry THF (15 mL) was added 1.96 g (20 mmol) of alcohol **6**. After stirring at room temperature for 30 min, 2.4 mL (20 mmol) of benzyl bromide was added to the solution followed by the addition of a catalytic amount of tetrabutyl iodide resulting a mixture, which was stirred for 8 h. The mixture was quenched with H_2O (10 mL) and the organic layer was separated. The aqueous layer was extracted with ethyl ether (2×20 mL). The combination of extracts were dried over $NaSO_4$ (anh.), filtered, and concentrated in a rotary evaporator. The resulting residue was chromatographed over silica gel in hexanes to afford 3.62 g (97%) of compound **7** as a colorless liquid. IR ν_{max} (film) (cm^{-1}): 3055 (m), 2925 (m), 1610 (s), 1490 (w), 1452 (m), 1270 (m), 1100 (s), 1020 (m), 735 (w), 695 (w). ^{1}H NMR ($CDCl_3$), δ (ppm): 7.25–7.45 (5H, m, arom.), 5.68 (2H, s, CH═CH), 4.55 (2H, s, CH_2Ph) 3.40 (2H, d, J=7.1 Hz, CH_2O), 2.61 (1H, m, CH), 2.15–2.50 (4H, m, $2CH_2$). ^{13}C NMR ($CDCl_3$), δ (ppm) 139.1 (arom.), 130.0 (CH═CH), 128.8 (arom.), 128.1 (arom.), 128.0 (arom.), 75.2 (CH_2Ph), 72.5 (OCH_2), 37.3 (CH), 36.5 ($2CH_2$).

4.2. General procedure for the coupling of pyrimidine nucleobases with 4-[(phenylmethoxy)methyl]-3-cyclopentene 7

To a solution of 1.46 g (5 mmol) of iodine in dry CH_2Cl_2 (10 mL), was added 1 g (5 mmol) of the ether **7** followed by the addition of the silylated nucleobase (6.25 mmol). The reaction mixture was stirred for 48 h at room temperature. The mixture was diluted with CH_2Cl_2 (20 mL) and a saturated aqueous solution of sodium thiosulfate was added vigorously until disappearance of the brown color. The organic layer was separated, washed with H_2O, filtered and concentrated in a rotary evaporator. The resulting residue was purified by successive recrystallization from CH_2Cl_2/hexanes.

4.2.1. (±)-*r*-7-Benzyloxymethyl-3-methyl-cyclopenta-*cis*-[4,5][1,3]oxazolo[3,2-*a*]pyrimidin-2-one 8. Yield: 2.50 g (71%). White solid, mp 165–167°C. IR (KBr) ν (cm^{-1}): 3504 (m), 2998 (m), 2990 (w), 1774 (s), 1666 (s), 1630 (s), 1546 (s), 1490 (s), 1238 (s), 1194 (s), 1164 (m), 830 (m), 762 (w). UV λ_{max} (MeOH) (nm): 260. MS, *m*/*z* (%): 313 [M+H]$^+$ (13), 312 (17), 206 (35), 174 (70), 148 (100), 122 (55), 91 (57), 85 (27). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.27 (5H, m, arom.), 7.06 (1H, d, J=1.0 Hz, H-4), 5.33 (1H,

ddd, J=7.5, 7.5, 4.2 Hz, H-8a), 4.77 (1H, ddd, J=7.7, 7.7, 4.2 Hz, H-5a), 4.42/4.33 (2H, AB system, J=11.8 Hz, CH_2Ph), 3.34 (1H, dd, J=9.1, 6.2 Hz, CH_2O), 3.22 (1H, dd, J=9.1, 7.3 Hz, CH_2O), 2.41 (1H, m, H-7), 2.32 (1H, ddd, J=6.9, 7.1, 14.0 Hz, H-6′), 2.30 (1H, ddd, J=7.4, 7.3, 14.5 Hz, H-8′), 2.00 (1H, ddd, J=4.1, 6.3, 14.5 Hz, H-8″), 1.93 (3H, s, CH_3), 1.90 (1H, ddd, J=4.3, 5.5, 14.0 Hz, H-6″). ^{13}C NMR δ (ppm) ($CDCl_3$): 173.0 (C-2), 160.3 (C-9a), 138.1 (arom.), 131.4 (C-4), 128.8 (arom.), 128.1 (arom.), 128.0 (arom.), 119.1 (C-3), 85.0 (C-8a), 73.6 (CH_2Ph), 72.3 (CH_2O), 63.3 (C-5a), 38.9 (C-7), 36.5 (C-8), 35.6 (C-6), 14.5 (CH_3). Anal. calcd for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97. Found: C, 69.39; H, 6.41; N 8.73.

4.2.2. (±)-*r*-7-Benzyloxymethyl-cyclopenta-*cis*-[4,5][1,3]-oxazolo[3,2-*a*]pyrimidin-2-one 9. Yield: 2.56 g (76.5%). White solid, mp 144–145°C. IR (KBr) ν (cm^{-1}): 3072 (m), 3024 (w), 2924 (w), 1648 (s), 1624 (s), 1516 (s), 1472 (s), 1442 (s), 1430 (m), 1260 (m), 1234 (m), 1104 (m), 1028 (m), 1016 (m), 938 (w), 838 (w), 732 (m). UV λ_{max} (MeOH) (nm): 264. MS, m/z (%), 299 $[M+H]^+$ (15), 192 (77), 164 (92), 151 (100), 136 (45), 108 (57), 91 (70), 81 (40). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.27 (5H, m, arom.), 7.17 (1H, d, J=7.3 Hz, H-4), 6.02 (1H, d, J=7.3 Hz, H-3), 5.35 (1H, ddd, J=7.6, 6.7, 3.6 Hz, H-8a), 4.76 (1H, ddd, J=7.7, 7.6, 3.6 Hz, H-5a), 4.42/4.39 (2H, AB system, J=12.0 Hz, CH_2Ph), 3.36 (1H, dd, J=9.2, 5.6 Hz, CH_2O), 3.20 (1H, dd, J=9.2, 46.9 Hz, CH_2O), 2.44 (1H, m, H-7), 2.33 (1H, ddd, J=6.5, 6.4, 14.1 Hz, H-6′), 2.30 (1H, ddd, J=7.3, 7.1, 14.1 Hz, H-8′), 2.04 (1H, ddd, J=3.6, 5.8, 14.5 Hz, H-8″), 1.93 (1H, ddd, J=5.6, 14.1 Hz, H-6″). ^{13}C NMR ($CDCl_3$) δ (ppm): 172.4 (C-2), 160.4 (C-9a), 137.1 (arom.), 135.4 (C-4), 128.6 (arom.), 128.0 (arom.), 127.9 (arom.), 110.14 (C-3), 85.0 (C-8a), 73.5 (CH_2Ph), 71.9 (CH_2O), 63.2 (C-5a), 38.7 (C-7), 36.5 (C-8), 35.5 (C-6). Anal. calcd for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.54; H, 6.21, 9.45. *Crystal data for* **9**. $C_{17}H_{18}N_2O_3$, M=298.3, monoclinic, P 21/a, a=12.076 (3), b=7.410 (2), c=17.294 (4), Z=4, D_c=1.365 mg cm^{-1}, μ (Cu Kα)=0.095 mm^{-1}, T=293 K, colourless rectangular, 3478 independent measured reflections, F^2 refinement, R_1=0.056, wR_2=0.147, 2243 observed reflections [$F>4\sigma(F)$, $\leq 2\theta^\circ$], 271 parameters. Crystallographic data (excluding structure factors) for this structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 195232.

4.2.3. (±)-*r*-7-Benzyloxymethyl-3-cyclopenta-*cis*-[4,5]-[1,3]oxazolo[3,2-*a*]pyrimidin-2-ylideneamine 10. Yield: 0.41 g (26%). Yellow solid, mp 175–176°C. IR (KBr) ν (cm^{-1}): 3283 (m), 3153 (m), 2861 (m), 1677 (s), 1525 (s), 1497 (s), 1241 (s), 1101 (m), 1027 (m), 948 (w), 829 (w), 753 (w), 699 (w). UV λ_{max} (MeOH) (nm): 272. MS, m/z (%) 298 $[M+H]^+$ (25), 190 (100), 201 (18), 176 (15), 128, (34), 91 (100). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.62 (1H, d, J=7.3 Hz, H-4), 7.30 (5H, m, arom.), 7.28 (1H, br s, NH), 6.38 (1H, d, J=7.3 Hz, H-3), 5.58 (1H, ddd, J=11.5, 7.3, 3.5 Hz, H-5a), 5.08 (1H, ddd, J=11.2, 7.8, 4.1 Hz, H-8a), 4.38/4.26 (2H, AB system, J=12.0 Hz, CH_2Ph), 3.31 (1H, dd, J=8.7, 4.7 Hz, CH_2O), 3.22 (1H, dd, J=9.5, 4.7 Hz, CH_2O), 2.50–2.40 (3H, m, H-7 and 2H-8), 2.03–1.98 (2H, m, 2H-6). ^{13}C NMR ($CDCl_3$) δ (ppm): 167.8 (C-2), 160.9 (C-9a), 139.6 (arom.), 141.3 (C-4), 128.7 (arom.), 128.6 (arom.), 128.4 (arom.), 101.6 (C-3), 88.2 (C-8a), 73.2 ($PhCH_2$), 72.2 (CH_2O), 65.1 (C-5a), 38.8 (C-7), 36.1 (C-8), 34.5 (C-6). Anal. calcd for: $C_{17}H_{19}N_3O_2$: C, 68.67; H, 6.44; N, 14.13. Found: C, 68.98; H, 6.47; N 14.33.

4.3. General procedure for the hydrolysis of compounds 8 and 9

An aqueous solution of 1N NaOH (2 mL) was added to a solution of 0.5 g of 8 or **9** in 30 mL of ethanol. The resulting mixture was stirred for 8 h and neutralized with an aqueous solution of 5% HCl. The reaction mixture was diluted with 40 mL of CH_2Cl_2 and the organic layer was dried with Na_2SO_4 (anh.), filtered and concentrated in a rotary evaporator. The solid residue was purified by recrystallization from CH_2Cl_2–hexane (1:9).

4.3.1. (±)-1-(4-Benzyloxymethyl-2-hydroxy-cyclopentyl)-5-methyl-1*H*-pyrimidine-2,4-dione 11. Yield: 0.51 g (96.5%). White solid, mp 138–140°C. IR (KBr) ν (cm^{-1}) 3420 (s), 3143 (w), 2925 (s), 2853 (s), 1692 (s), 1474 (s), 1365 (m), 1276 (m), 1094 (s), 1036 (s), 746 (s), 695 (m), 606 (m). MS, m/z (%): 331 $[M+H]^+$ (13), 315 (100), 237 (34), 127 (28), 91 (85), 69 (58), 41 (67). ^{1}H NMR ($CDCl_3$) δ (ppm): 9.64 (1H, br s, NH), 7.35 (5H, m, arom. and H-6), 4.72 (1H, ddd, J=12.3, 7.8, 4.1 Hz, H1′), 4.61 (2H, s, CH_2Ph), 4.25 (1H, m, H-2′), 4.01 (1H, br s, OH), 3.55 (2H, m, CH_2O), 2.45 (1H, m, H-4′), 2.23 (1H, ddd, J=5.4, 10.2, 14.2 Hz, H3′), 2.05 (1H, m, H5′), 1.90 (1H, m, H5″), 1.79 (3H, s, CH_3), 1.57 (1H, dd, J=5.4, 14.6 Hz, H3″). ^{13}C NMR ($CDCl_3$), δ (ppm): 164.6 (C-4), 152.2 (C-2), 139.6 (arom.), 137.9 (C-6), 129.0 (arom.), 128.4 (arom.), 128.3 (arom.), 109.2 (C-5), 73.9 ($PhCH_2O$), 73.7 (CH_2O), 71.5 (C-2′), 59.0 (C-1′), 36.5 (C-3′), 34.5 (C-4′), 29.4 (C-5′), 12.9 (CH_3). Anal. calcd for $C_{18}H_{22}N_2O_4$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.27; H, 6.67; N 8.37.

4.3.2. (±)-1-(4-Benzyloxymethyl-2-hydroxy-cyclopentyl)-1*H*-pyrimidine-2,4-dione 12. Yield: 0.46 g (88%). White solid, mp 131–132°C. IR (KBr) ν (cm^{-1}) 3444 (s), 3109 (m), 2910 (m), 2890 (m), 1690 (s), 1533 (s), 1456 (s), 1345 (m), 1221 (m), 1216 (m), 1012 (m), 765 (s), 720 (w). MS, m/z (%): 317 $[M+H^+]$ (19), 301 (100), 223 (41), 113 (38), 91 (85), 69 (58), 41 (67). ^{1}H NMR ($CDCl_3$) δ (ppm): 9.41 (1H, br s, NH), 7.34 (1H, d, J=7.5 Hz, H6), 7.21 (5H, m, arom.), 6.02 (1H, d, J=7.5 Hz, H5), 4.78 (1H, ddd, J=12.1, 7.5, 4.1 Hz, H1′), 4.51 (2H, s, CH_2Ph), 4.22 (1H, m, H-2′), 4.10 (1H, br s, OH), 3.50 (2H, m, CH_2O), 2.35 (1H, m, H-4′), 2.20 (1H, ddd, J=5.4, 9.8, 14.1 Hz, H3′), 2.03 (1H, m, H5′), 1.92 (1H, m, H5″), 1.48 (1H, dd, J=5.3, 14.2 Hz, H3″). ^{13}C NMR ($CDCl_3$), δ (ppm): 163.9 (C-4), 151.4 (C-2), 138.0 (arom.), 137.5 (C-6), 129.1 (arom.), 128.4 (arom.), 128.3 (arom.), 107.2 (C-5), 73.0 ($PhCH_2$), 72.7 (CH_2O), 70.1 (C-2′), 58.5 (C-1′), 36.4 (C-3′), 34.0 (C-4′), 29.7 (C-5′). Anal. calcd for $C_{17}H_{20}N_2O_4$: C, 64.54; H, 6.37; N, 8.85. Found: C, 64.73; H, 6.41; N, 8.67.

4.4. General procedure for the hydrogenation of compounds 11 and 12

A solution of 0.5 g of compound **11** or **12** in 10 mL of methanol was hydrogenated in the presence of 61 mg of Pd–C and acetic acid, at room temperature and 1 atm

of pressure for 12 h. The catalyst was filtered out and the solvent was evaporated in a rotary evaporator. Purification by flash chromatography (EtOAc/hexane, 2:8) afforded product **13** or **14**, respectively.

4.4.1. (±)-1-(2-Hydroxy-4-hydroxymethyl-cyclopentyl)-5-methyl-1*H*-pyrimidine-2,4-dione 13.[11] Yield: 0.32 g (90%). White solid, mp 210–211°C. ^{1}H NMR ($CDCl_3$) δ (ppm): 9.64 (1H, br s, NH), 7.13 (1H, s, H6), 4.88 (1H, br s, CHOH), 4.80 (1H, br s, CH_2OH), 4.61 (1H, m, H1′), 4.25 (1H, m, H-2′), 3.55 (2H, m, CH_2O), 2.45–2.28 (3H, m, H-4′, H3′ and H5′), 1.86–1.22 (2H, m, H3″ and 5″), 1.64 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$), δ (ppm): 164.1 (C-4), 151.0 (C-2), 138.1 (C-6), 107.8 (C-5), 73.9 (CH_2O), 71.5 (C-2′), 60.5 (C-1′), 36.1 (C-3′), 34.5 (C-4′), 28.8 (C-5′), 12.5 (CH_3).

4.4.2. (±)-1-(2-Hydroxy-4-hydroxymethyl-cyclopentyl)-1*H*-pyrimidine-2,4-dione 14.[12] Yield: 0.31 g (88%). White solid, mp 157–158°C. ^{1}H NMR (Me_2SO-d_6) δ (ppm): 10.8 (1H, br s, NH), 7.58 (1H, d, J=7.8 Hz, H6), 5.51 (1H, d, J=7.8 Hz, H5), 4.90 (1H, d, J=4.3 Hz, CHOH), 4.51 (1H, t, J=4.8 Hz, CH_2OH), 4.42 (1H, m, H1′), 4.10 (1H, m, H-2′), 3.50 (2H, m, CH_2O), 2.25–1.90 (2H, m, H-3″ and H-5″), 1.58–1.87 (2H, m, H4′ and H5′), 1.36 (1H, m, H3″). ^{13}C NMR ($CDCl_3$) δ (ppm): 163.2 (C-4), 152.0 (C-2), 138.0 (C-6), 105.9 (C-5), 64.7 (C1′), 62.3 (CH_2OH), 61.2 (C2′), 35.4 (C-3′), 34.0 (C-4′), 30.7 (C-5′).

4.5. General procedure for the rearrangement of compounds 8 and 9 to give 15 and 16, respectively

To a solution of 1 g of **8** or **9** in 8 mL of dry *t*-BuOH was added 0.40 g of potassium *t*-butoxide and the mixture was stirred at 40°C for 2 h. The reaction was quenched with 2 mL of water and was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $NaSO_4$ (anh.) and concentrated in a rotary evaporator. Purification by flash chromatography (EtOAc/hexane, 2:8) gave the corresponding product.

4.5.1. (±)-1-(4-Benzyloxymethyl-cyclopent-1-enyl)-5-methyl-1*H*-pyrimidine-2,4-dione 15. Yield: 0.91 g (91%). Yellow oil. IR (film) ν (cm^{-1}): 3330 (m), 3100 (m), 2950 (m), 2942 (m), 1670 (s), 1648 (s), 1507 (m), 1309 (w), 1221 (w), 1216 (m), 1110 (m), 765 (s), 620 (s). MS, *m*/*z* (%): 313 [M+H]$^+$ (25), 206 (100), 127 (45), 81 (40), 77 (78). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.01 (1H, br s, NH), 7.33 (5H, m, arom.), 7.01 (1H, s, H6), 5.8 (1H, t, J=2.0 Hz, H-2′), 4.86 (2H, d, J=5.3 Hz, $PhCH_2$), 3.45 (2H, d, J=6.6 Hz, CH_2O), 2.78–1.95 (5H, m, 2H-3′, H-4′, 2H-5′), 2.15 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$) δ (ppm): 164.2 (C-4), 149.7 (C-2), 140.0 (C-1′), 139.4 (C-6), 138.5 (arom.), 128.8 (arom.), 128.8 (arom.), 128.4 (arom.), 127.8 (C-2′), 110.6 (C-5), 73.7 ($PhCH_2$), 73.0 (CH_2O), 36.4 (C-4′), 36.1 (C-3′), 33.8 (C-5′), 12.4 (CH_3). Anal. calcd for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97. Found: C, 69.66; H, 6.51; N, 8.88.

4.5.2. (±)-1-(4-Benzyloxymethyl-cyclopent-1-enyl)-1*H*-pyrimidine-2,4-dione 16. Yield: 0.90 g (90%). Yellow oil. IR (film) ν (cm^{-1}): 3455 (m), 3321 (w), 2980 (w), 2969 (m), 1688 (s), 1656 (s), 1510 (s), 1309 (m), 1216 (w), 1110 (m), 789 (s), 645 (s). MS, *m*/*z* (%): 299 [M+H]$^+$ (13), 192 (98), 112 (45), 81 (60), 77 (67). ^{1}H NMR ($CDCl_3$) δ (ppm): 9.5 (1H, br s, NH), 7.51 (1H, d, J=7.8 Hz, H6), 7.35 (5H, m, arom.), 6.23 (1H, d, J=7.8 Hz, H5), 6.10 (1H, t, J=2.5 Hz, H-2′), 4.88 (2H, s, $PhCH_2$), 3.10 (1H, d, J=7.1 Hz, CH_2O), 2.50–1.35 (5H, m, 2H-3′, H-4′, 2H-5′). ^{13}C NMR ($CDCl_3$) δ (ppm): 163.5 (C-4), 151.2 (C-2), 141.4 (C-1′), 138.0 (arom.), 136.6 (C-6), 129.2 (arom.), 128.8 (arom.), 128.6 (arom.), 127.8 (C-2′), 106.6 (C-5), 74.0 ($PhCH_2$), 63.2 (CH_2O) 36.5 (C-4′), 36.11 (C-3′), 34.0 (C-5′). Anal. calcd for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.88; H, 6.16; N, 9.52.

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