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Synthesis of Enantiomerically Pure Carbocyclic α-L-Isomeric Homonucleosides.

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Abstract: *Synthesis of hitherto unknown carbocyclic α-L-isomeric homonucleosides (**8a-b, 9a-b**) is described. The key intermediate **6** was synthesized from the known compound **1** as a chiral starting material. Construction of the heterocyclic moiety around the amino group of **6** afforded carbocyclic α-L-isomeric 2',3'-dideoxyhomonucleosides **8a-b** and their 2',3'-didehydro-2',3'-dideoxy derivatives **9a-b**.*

Introduction

Research on the chemistry of the carbocyclic nucleosides, in which the ring oxygen is replaced by a methylene group, has been directed towards the development of agents showing activities against HIV, HSV-1, HSV-2, VZV, HCMV and EBV.[1-4] For example, carbovir, carbocylic 2',3'-didehydro-2',3'-dideoxyguanosine, has been found to show significant anti-HIV activity, and a congener 1592U89 (abacavir) having a better toxicological profile is currently undergoing clinical trials for the treatment of HIV infections.[5-6] Recently, a number of L-nucleosides have been synthesized, among which 3TC,[7] FTC,[8] L-FddC[9] and L-FMAU[10] have shown to be the most promising as antiviral agents. Although in most cases the β-anomer has been considered to have more important biological activity, there are a number of examples of the corresponding α-anomers having significant activity,[11] as for instance α-L-dioxolane-5-fluorocytidine that is more potent and less toxic to cells than its β-L-counterparts.

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As part of our drug discovery program, we have been interested in the synthesis and biological evaluation of L-cyclopentyl carbocyclic nucleosides.[12] Thus, herein we wish to report the synthesis of enantiomerically pure novel α-L-cyclopentanyl- and α-L-cyclopentenyl carbocyclic homonucleosides from chiral starting material.

Discussion

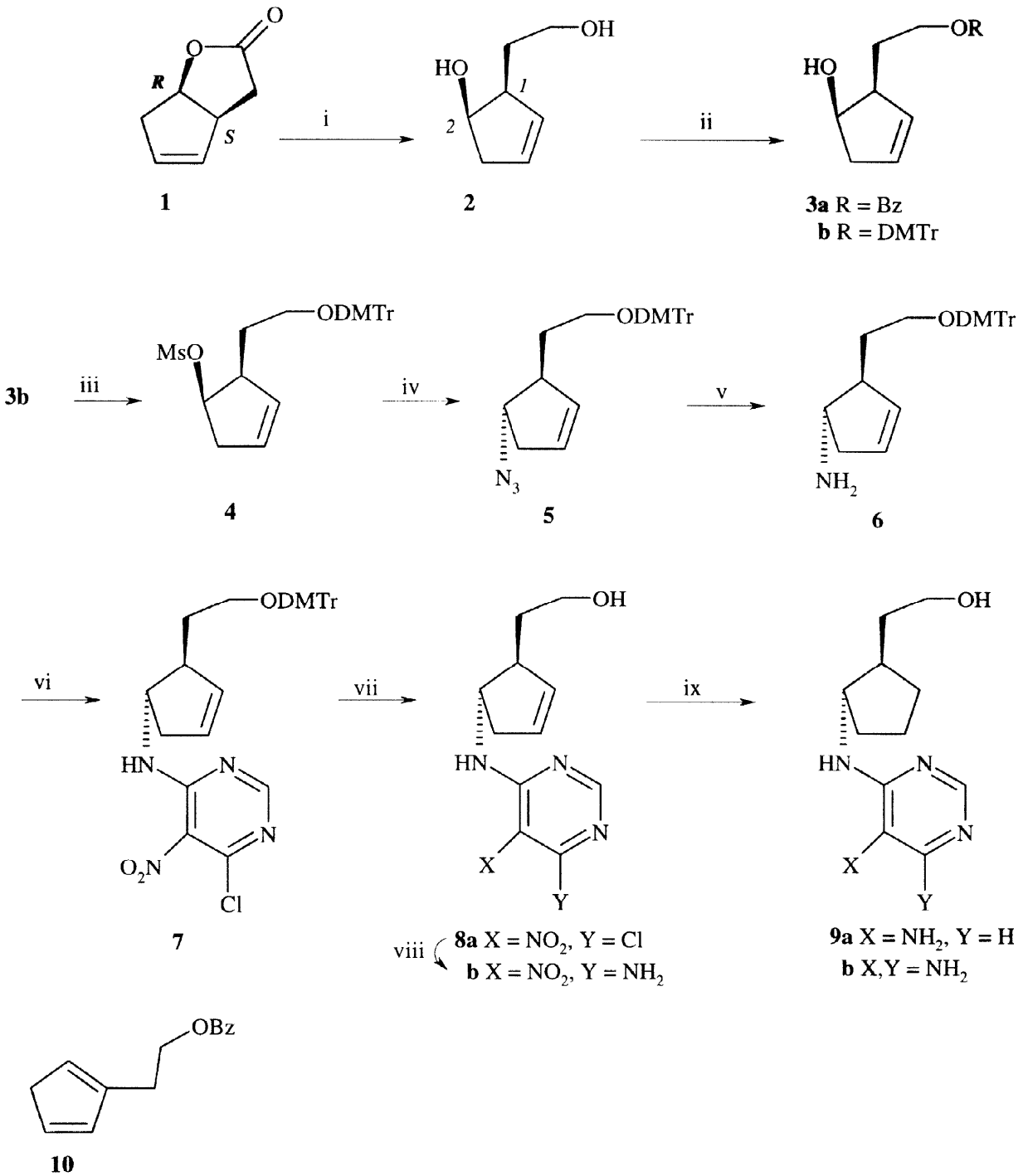
Our synthetic strategy (Scheme 1) utilized the known intermediate **1**, (*1R,5S*)-2-oxabicyclo[3.3.0]oct-6-en-3-one, which could be prepared in 3 steps from cyclopentadiene.[13] Reduction of the lactone moiety of **1** with diisobutylaluminum hydride afforded diol **2** in 95% yield, which was benzoylated to **3a** (74%). All our preliminary attempts to condense a heterocycle (purines or pyrimidines) on **3a** under Mitsunobu conditions,[14] as well as under nucleophilic substitution *via* the tosylate displacement of **3a** by a heterocycle sodium salt,[15] resulted exclusively in the product of *trans*-elimination **10**. To circumvent this problem and to increase the yield of the coupling step, we decided to protect the primary alcohol of **2** by a dimethoxytrityl group and to build up the heterocycle moiety around an amino group.

Thus, selective protection of the primary alcohol was achieved by reacting **2** with 4,4'-dimethoxytriphenylmethyl chloride in dichloromethane in the presence of DMAP and triethylamine to give **3b** in 80% yield. The cyclopentenol **3b** was quantitatively mesylated to **4** (82%) by the usual reaction procedures. The desired stereochemistry in the synthesis of the title compounds was achieved by nucleophilic substitution of the mesylate **4** by NaN_3 to yield **5** (86%). Selective reduction of the azide was achieved by a modified Staudinger reaction.[16] Thus, reduction of **5** with triphenylphosphine and hydrolysis of the resulting phosphine imino derivative with water gave the cyclopentylamine **6** (86%). The amine **6** was coupled with 4,6-dichloro-5-nitropyrimidine to afford **7** (75%). Deprotection of the dimethoxytrityl group with a solution of 2% TFA/MeOH gave **8a** in 65% yield. The substitution of the aromatic chlorine in **8a** with methanolic ammonia gave **8b** in 90% yield. The obtained carbocyclic **8a-b** can be considered an isomeric form of carbocyclic 2',3'-didehydro-2',3'-dideoxy homonucleosides. Finally, hydrogenation of **8a** and **8b** gave quantitatively two new exocyclic amino carbocyclic 2',3'-dideoxyhomonucleosides **9a** and **9b**, respectively.

In summary, the first asymmetric synthesis of the hitherto unknown isomeric form of α-L-carbocyclic homonucleosides (**8a-b**, **9a-b**) has been accomplished.

Biological Results

Compounds were evaluated for antiviral activity against HIV-1 *in vitro*. However, compounds did not show any significant antiviral activity. Other biological evaluations are in progress.



Reagents: i) DIBAL-H, THF, -78°C to rt; ii) BzCl, Et_3N, CH_2Cl_2, 0°C (to 3a) or DMTrCl, DMAP, Et_3N, CH_2Cl_2, 0°C (to 3b); iii) MsCl, Et_3N, CH_2Cl_2, 0°C; iv) NaN_3, DMF, 75°C; v) PPh_3, THF then H_2O, 45°C; vi) 4,6-dichloro-5-nitropyrimidine, Et_3N, CH_2Cl_2, 0°C; vii) 2% TFA in CH_2Cl_2, 0°C; viii) MeOH/NH_3, rt; ix) H_2, Pd/C 10%, 20 psi, rt.

Scheme 1

Experimental

General

Commercially available chemicals and solvents were reagent grade and used as received. Dry tetrahydrofuran, pyridine and dichloromethane were obtained by distillation from CaH_2, N,N-dimethylformamide from BaO. Melting points were determined on a Büchi (Tottoli) and are uncorrected. Proton NMR spectra were recorded on a Bruker AVANCE DPX 250 Fourier Transform spectrometer for 250 MHz, using tetramethylsilane as the internal standard ; signals are reported as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Mass spectra were recorded on Perkin-Elmer SCIEX API-300 (heated nebullizer) spectrometer. Optical rotations were performed on a Perkin-Elmer 241 polarimeter. Elemental analyses were performed by the CNRS, Vernaison, and are within ± 0.4% of the theorical values.

(*1S,2R*)-2-(2-Hydroxycyclopent-4-enyl)ethanol (2). A solution of (*1R,5S*)-2-oxabicyclo[3.3.0]oct-6-en-3-one **1** (1 g, 8.05 mmol) dissolved in dry THF (25 mL) was cooled to -78 °C. The lactone **1** was reduced by slowly adding a 1M solution of DIBAL-H in THF (24.1 mL, 24.1 mmol). The reaction mixture was allowed to warm to room temperature for 6 h and quenched by slowing adding MeOH (20 mL). The mixture was then neutralized with 1M HCl and the solvent was removed under reduced pressure. The residual solid was filtered, washed with EtOAc (4 x 100 mL), and the combined filtrate was evaporated *in vacuo* to give a residue which was purified by column chromatography (silica gel- CH_2Cl_2/MeOH, 9:1) to give **2** as a colorless oil (982 mg, 95%). $[\alpha]^{20}_D$ +71° (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$) δ 5.70 (m, 1H), 5.55 (m, 1H), 4.50 (td, 1H, *J*=6.28 Hz, 2.51 Hz), 4.00 (broad s, 2 x OH, D_2O-exchangeable), 3.76 (m, 1H), 3.67 (m, 1H), 2.69 (m, 1H), 2.60-2.31 (m, 2H), 1.80 (m, 2H). Its physical data were identical to the known compound.[13]

(*1S,2R*)-Benzoic acid 2-(2-hydroxycyclopent-4-enyl)ethyl ester (3a). To a stirred solution of the diol **2** (969 mg, 7.57 mmol) and Et_3N (3.50 mL) in anhydrous CH_2Cl_2 (20 mL), benzoyl chloride (0.97 mL, 8.32 mmol) was added under argon atmosphere. The reaction mixture was stirred at room temperature for 3 h. The mixture was washed successively with sat. Aqueous $NaHCO_3$ (15 mL) and water to neutrality. The organic layer was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The obtained residue was purified by column chromatography (silica gel- hexane/EtOAc, 6:4) to give **3a** as a yellow syrup (1.3 g, 74%). $[\alpha]^{20}_D$ +29° (*c* 5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.04 (m, 2H), 7.55 (m, 1H), 7.49 (m, 2H), 5.77 (m, 1H), 5.68 (m, 1H), 4.51-4.41 (m, 3H), 2.83-2.57 (m, 2H), 2.43-2.30 (m, 1H), 2.24 (broad s, OH, D_2O-exchangeable), 2.20-1.85 (m, 2H); Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.40; H, 6.94. Found: C, 72.47; H, 6.99.

(*1S,2R*)-2-(2-Hydroxycyclopent-4-enyl)ethanol (4,4'-Dimethoxy)triphenylmethyl ether (3b). A solution of **2** (1.02 g, 7.96 mmol), 4,4'-dimethoxytriphenylmethyl chloride (2.97 g, 8.35 mmol), Et_3N (2.25 mL, 15.92

mmol), and DMAP (48 mg, 0.40 mmol) in anhydrous CH_2Cl_2 (10 mL) was stirred at 0 °C for 2 h. The reaction mixture was washed successively with sat. aqueous $NaHCO_3$ (15 mL) and brine to neutrality. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by column chromatography (silica gel- hexane/EtOAc, 9:1 containing 1% Et_3N) to give **3b** as a yellow oil (1.145 g, 80%). $[\alpha]^{20}_D$ +24° (*c* 10, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 7.50-6.70 (m, 13H), 5.69 (m, 1H), 5.49 (m, 1H), 4.37 (m, 1H), 3.76 (s, 6H), 3.36 (m, 1H), 3.15 (m, 1H), 3.00-2.50 (m, 2H and OH, D_2O-exchangeable), 2.42 (m, 1H), 2.03 (m, 1H), 1.84 (m, 1H); Anal. Calcd for $C_{28}H_{30}O_4$: C, 78.11; H, 7.02. Found: C, 78.04; H, 7.03.

(*1S,2R*)-2-[2-[(Methylsulfonyl)oxy]cyclopent-4-enyl]ethanol (4,4'-Dimethoxy)triphenylmethyl ether (4). A solution of diol **3b** (2.52 g, 5.80 mmol) and Et_3N (1.45 mL, 10.35 mmol) in CH_2Cl_2 (20 mL) was stirred at 0 °C. To this cooling mixture, methanesulfonyl chloride (615 μL, 7.96 mmol) was added dropwise and stirring was continued for 2 h. The reaction mixture was washed successively with sat. aqueous $NaHCO_3$ (10 mL) and brine to neutrality. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by column chromatography (silica gel- hexane/EtOAc, 8:2 containing 1% Et_3N) to give **4** as a colorless syrup (2.35 g, 82%). ^{1}H-NMR ($CDCl_3$) δ 7.50-6.74 (m, 13H), 5.66 (m, 2H), 5.22 (m, 1H), 3.85 (s, 6H), 3.25-2.95 (m, 3H), 2.87 (s, 3H), 2.69 (m, 2H), 1.98 (m, 1H), 1.73 (m, 1H). The product was subjected to the next reaction without further purification.

(*1S,2S*)-2-(2-Azidocyclopent-4-enyl)ethanol (4,4'-Dimethoxy)triphenylmethyl ether (5). A solution of **4** (1.35 g, 2.65 mmol) and NaN_3 (2.59 g, 39.80 mmol) in DMF (15 mL) was stirred at 75 °C for 10 h. After cooling, the mixture was diluted with EtOAc (20 mL) and washed with brine (20 mL). The organic phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The obtained residue was purified by column chromatography (silica gel- hexane/EtOAc, 95:5) to yield **5** as a colorless syrup (1.04 g, 86%). $[\alpha]^{20}_D$ +42° (*c* 10, $CHCl_3$); IR (KBr) 2096 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.50-7.15 (m, 13H), 5.59 (s, 2H), 3.65 (m, 1H), 3.16 (td, 2H, *J*=6.2, 2.2 Hz), 2.84-2.32 (m, 3H), 1.65 (m, 2H).

(*1S,2S*)-2-(2-Aminocyclopent-4-enyl)ethanol (4,4'-Dimethoxy)triphenylmethyl ether (6). A solution of azido derivative **5** (1.40 g, 3.0 mmol) and PPh_3 (1.07 g, 4.0 mmol) in THF (15 mL) was stirred at room temperature for 12 h. To this solution H_2O (0.8 mL) was added and the mixture was stirred at 45°C for 3h and then under reflux for 1h. After cooling, the mixture was diluted with EtOAc and the organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The obtained residue was purified by column chromatography (silica gel- EtOAc/hexane, 8:2). The desired product **6** was obtained as a yellow oil (1.10 g, 86%). $[\alpha]^{20}_D$ +53° (*c* 5, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 7.50-6.75 (m, 13H), 5.57 (m, 2H), 3.78 (s, 6H),

3.16 (m, 3H), 2.75-1.85 (m, 3H), 1.80-1.50 (m, 2H), 1.34 (broad s, NH_2, D_2O-exchangeable); Anal. Calcd for $C_{28}H_{31}NO_3$: C, 78.30; H, 7.27; N, 3.26. Found: C, 78.11; H, 7.22; N, 3.09.

(*1S,2S*)-2-[2-(6-Chloro-5-nitropyrimidin-4-ylamino)cyclopent-4-enyl]ethanol (4,4'-Dimethoxy)triphenylmethyl ether (7). The intermediate **6** (1.03 g, 2.39 mmol) dissolved in anhydrous CH_2Cl_2 (10 mL) was introduced to a suspension of 4,6-dichloro-5-nitropyrimidine (525 mg, 2.63 mmol) and Et_3N (500 µL, 3.59 mmol) in anhydrous CH_2Cl_2 (10 mL) at 0 °C. The mixture was stirred at 0 °C for 2 h. After filtration over celite, the filtrate was evaporated to dryness under reduced pressure without heating. The obtained residue was purified by column chromatography (silica gel- hexane/EtOAc, 8:2). The desired nucleoside **7** was isolated as a yellow oil (1.05 g, 75%). $[\alpha]^{20}_D$ +68° (*c* 5, $CHCl_3$); UV ($CHCl_3$) λ_{max} 263 nm; ^{1}H-NMR ($CDCl_3$) δ 8.24 (s, 1H), 7.61 (d, 1H, *J*=7.2 Hz), 7.45-6.50 (m, 13H), 5.66 (m, 2H), 4.55 (m, 1H), 3.77 (s, 6H), 3.16 (m, 2H), 3.00-2.65 (m, 2H), 2.15 (m, 1H), 1.75 (m, 2H); MS : m/z 587 (M^++1); Anal. Calcd for $C_{32}H_{31}ClN_4O_5$: C, 65.47; H, 5.32; N, 9.54. Found: C, 65.61; H, 5.35; N, 9.44.

(*1S,2S*)-2-[2-(6-Chloro-5-nitropyrimidin-4-ylamino)cyclopent-4-enyl]ethanol (8a). A solution of protected carbocyclic nucleoside **7** (300 mg, 0.52 mmol) in a mixture of 2% trifluoroacetic acid in CH_2Cl_2 (15 mL) was stirred at -20 °C for 2h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel- CH_2Cl_2/MeOH, 9:1) to give **8a** (95 mg, 65%) as a yellow oil. $[\alpha]^{20}_D$ +45° (*c* 5, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 8.40 (s, 1H), 7.64 (broad s, NH), 5.76 (s, 2H), 4.61 (m, 1H), 3.80 (m, 2H), 3.10-2.50 (m, 2H and OH, D_2O exchangeable), 2.28 (m, 1H), 1.65 (m, 2H); MS : m/z 285 (M^++1); Anal. Calcd for $C_{11}H_{13}ClN_3O_3$: C, 48.81; H, 4.84; N, 15.52. Found: C, 48.95; H, 4.88; N, 15.33.

(*1S,2S*)-2-[2-(6-Amino-5-nitropyrimidin-4-ylamino)cyclopent-4-enyl]ethanol (8b). A solution of the intermediate **8a** (500 mg, 1.76 mmol) in saturated NH_3/MeOH (15 mL) was stirred at room temperature for 2 h. The solution was concentrated under reduced pressure and the obtained residue was purified by column chromatography (silica gel- CH_2Cl_2/MeOH, 9:1) to give **8b** as a white solid (420 mg, 90%). $[\alpha]^{20}_D$ +104° (*c* 5, $CHCl_3$); UV ($CHCl_3$) λ_{max} 245 nm; ^{1}H-NMR ($CDCl_3$) δ 9.24 (broad s, N<u>H</u>$_2$), 8.60 (broad s, NH), 8.05 (s, 1H), 6.49 (broad s, N<u>H</u>$_2$), 5.90-5.50 (m, 2H), 4.84 (OH, D_2O exchangeable), 4.67 (m, 1H), 3.83 (m, 2H), 3.10-2.25 (m, 3H), 1.75-1.50 (m, 2H). MS : m/z 266 (M^++1); Anal. Calcd for $C_{11}H_{15}N_5O_3$: C, 49.81; H, 5.70; N, 26.41. Found: C, 49.72; H, 5.81; N, 26.31.

(*1R,2S*)-2-[2-(5-Aminopyrimidin-4-ylamino)cyclopentyl]ethanol (9a). The 6-chloropyrimidine alcohol **8a** (63 mg, 0.22 mmol) was dissolved in methanol (10 mL) and then introduced to a suspension of 10% Pd/C (10 mg) in methanol (5 mL). The mixture was hydrogenated in a Parr shaker at 25 psi pressure for 5 h and then filtered through celite to remove the catalyst. The solvent was evaporated to dryness to leave a residue which was purified by column chromatography (silica gel- CH_2Cl_2/MeOH, 9:1) to yield **9b** (48 mg, 98%). $[\alpha]^{20}_D$ +41.5° (*c* 11, MeOH); UV (MeOH) λ_{max} 221 nm; ^{1}H-NMR (MeOD-*d4*) δ 7.93 (s, 1H), 4.10 (m, 1H), 3.50 (m, 2H), 3.30 (m, 1H), 2.15 (m, 1H), 1.95 (m, 2H), 1.75 (m, 3H), 1.48 (m, 2H); MS : m/z 223 (M^++1); Anal. Calcd for $C_{11}H_{17}N_4O$: C, 59.71; H, 7.74; N, 25.32. Found: C, 59.51; H, 7.67; N, 25.21.

(*1R,2S*)-2-[2-(5,6-Diaminopyrimidin-4-ylamino)cyclopentyl]ethanol (9b). The 6-amino-5-nitropyrimidine alcohol **8b** (35 mg, 0.13 mmol) was dissolved in methanol (10 mL) and then introduced to a suspension of 10% Pd/C (10 mg) in methanol (5 mL). The mixture was hydrogenated in a Parr shaker at 25 psi pressure for 5 h and then filtered through celite to remove the catalyst. The solvent was evaporated to dryness to leave a residue which was purified by column chromatography (silica gel- CH_2Cl_2/MeOH, 9:1) to yield **9b** (34 mg, 97%). $[\alpha]^{20}_D$ +75° (*c* 5, MeOH); UV (MeOH) λ_{max} 241 nm; ^{1}H-NMR (MeOD-*d4*) δ 7.65 (s, 1H), 3.90 to 4.10 (m, 1H), 3.50 to 3.70 (m, 2H), 1.2 to 2.2 (m, 9H); MS : m/z 238 (M^++1); Anal. Calcd for $C_{11}H_{19}N_5O$: C, 55.68; H, 8.07; N, 29.51. Found: C, 55.49; H, 8.38; N, 29.79.

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