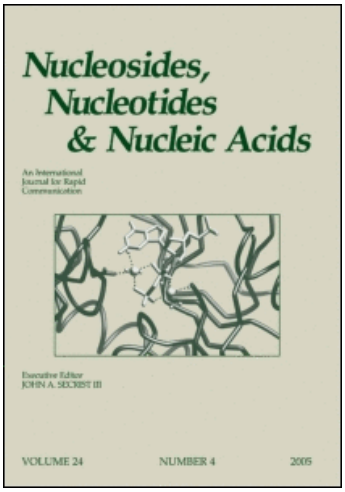

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A NOVEL APPROACH TO ENANTIOMERICALLY PURE CARBOCYCLIC NUCLEOSIDE ANALOGUES

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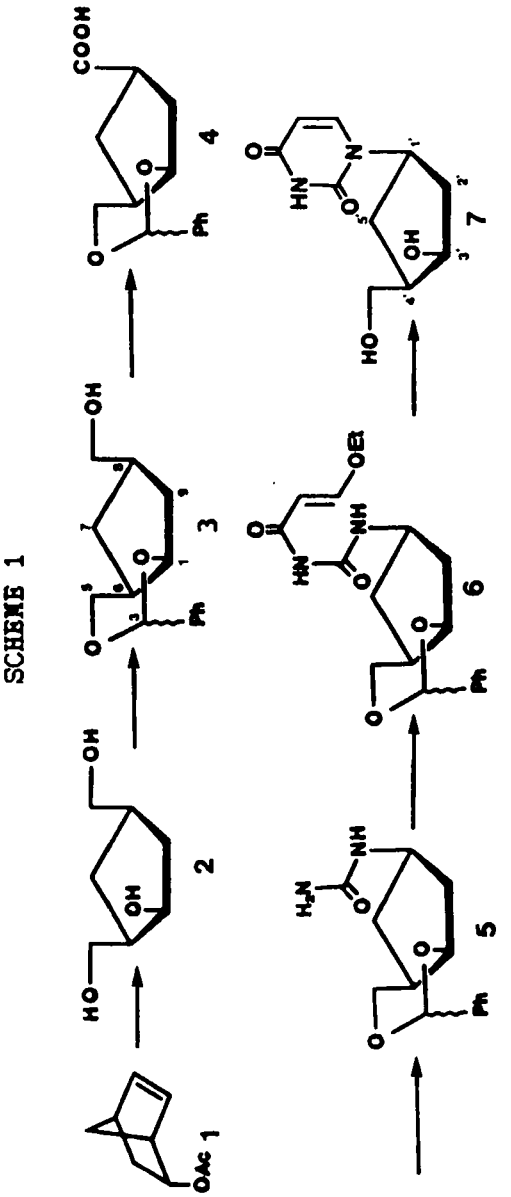
Abstract: Starting from (+)-*endo*-5-norbornen-2-yl acetate (1) (-)-1-[(1*R*,3*R*,4*R*)-3-hydroxy-4-hydroxymethylcyclopentyl]-1*H*,3*H*-pyrimidine-2,4-dione (7) was synthesized in a 6-step sequence.

Carbocyclic analogues of nucleosides have been the topic of a variety of investigations[1-5] in the last years. The majority of compounds synthesized were racemic and only a few enantiomerically pure carbocyclic nucleoside analogues have been obtained either by chemoenzymatic approach[2], by multistep synthesis[6] or by enzymatic resolution of the monophosphate of racemic aristeromycin[4]. As expected, in the case of aristeromycin only the (-)-enantiomer, mimicking the natural configuration of adenosine, showed antiviral activity while the corresponding (+)-enantiomer was completely inactive.

Making use of our recently published enzymatic resolution of racemic 1[7] we developed a short and efficient synthesis leading to carbocyclic nucleoside analogues of (-)-configuration, being equivalent to the natural occuring nucleosides. The synthetic sequence as shown in scheme 1 was published for the racemic compound in a preliminary communication[8].

We want to report here the application of this approach to the synthesis of (-)-1-[(1*R*,3*R*,4*R*)-3-hydroxy-4-hydroxymethylcyclopentyl]-1*H*,3*H*-pyrimidine-2,4-dione (7): Ozonolysis of (+)-1[7] (enantiomeric purity 82%) followed by reductive workup[9] using $LiAlH_4$ furnished triol 2 in 91% yield. Selective protection via transacetalisation with benzaldehyde dimethylacetal/HBF_4[10] gave quantitatively the benzylidene acetal 3. Oxidation of this material using pyridinium dichromate (PDC) in DMF[11] led to the



SCHEME 1

carboxylic acid **4** as a sirup (yield >90%). A neat sample of this acid crystallized spontaneously after some days of storage showing an enhanced optical rotation, which corresponds to >98% optical purity. Transformation of the sirupy material (82% e.e.) to the urea derivative **5** was achieved by successive treatment with ethyl chloroformate and NaN_3, followed by Curtius rearrangement in benzene and trapping of the intermediate isocyanate by addition of gaseous NH_3. Acylation of **5** with ethoxyacryloyl chloride[12] led to intermediate **6**. Finally, cyclisation under acidic conditions and simultaneous removal of the protective group furnished **7** ($[\alpha]_D^{20}$ -55°, 82% e.e.) which could be obtained optically pure by a single recrystallisation ($[\alpha]_D^{20}$ -67°).

Experimental Section

Melting points were determined on a Tottoli apparatus (Büchi) and are uncorrected. Analytical TLC was performed on Merck 60 F_{254} silica gel plates. Medium pressure column chromatography was carried out on silica gel Merck 60, 230-400 mesh. ^{1}H-NMR (90 MHz) and ^{13}C-NMR (23 MHz) spectra were recorded on a Bruker WM-90 spectrometer with TMS as internal standard, chemical shifts (δ) are reported in ppm. Optical rotation values were determined on a Perkin-Elmer 141 polarimeter. All solvents were dried and distilled before use.

(-)-(1*R*,3*R*,4*R*)-4-Hydroxycyclopentane-1,3-dimethanol (**2**).

Through a solution of (+)-*endo*-5-norbornen-2-yl acetate (**1**) (7.7g, 51mmol, 82%e.e.) in 400 ml of methanol at -70° ozone was bubbled until the mixture turned blue (about 2h). Excess ozone was removed by a stream of dry N_2. The solvent was evaporated *in vacuo* at room temperature, last traces were removed at <0.1mbar. The remaining foam was dissolved in THF (100ml) and added dropwise with stirring to a cooled (-30°) suspension of $LiAlH_4$ (7.7g, 200mmol) in 400ml of THF. When the reaction ceased the mixture was heated at reflux for 1h. Quenching was accomplished by cautious addition of saturated aqueous $MgSO_4$-solution (29ml) at -10° and stirring was continued for 24h. The precipitate was filtered and extracted with boiling THF for 30min. Evaporation of the combined organic phase yielded 6.43g of **2** (91%) as a colorless oil. An analytical sample was obtained by chromatography ($CHCl_3$/MeOH 9:1 v/v); $[\alpha]_D^{20}$ -26° (c 4.95, MeOH). ^{1}H-NMR (DMSO-d_6): 0.9-1.9(m,6H,H-1,H-2,H-3,H-5), 2.94(d,J=5Hz,2H,C*H*$_2$OH), 3.11(dd,J=10 and 4Hz,2H,C*H*$_2$OH), 3.3-3.9(m,4H,H-4,OH). ^{13}C-NMR (DMSO-d_6): 29.9, 38.2, 39.0, 47.7, 61.0, 66.1, 71.6.

(-)-(1*R*,6*R*,8*R*)-3-Phenyl-2,4-dioxabicyclo[4.3.0]nonane-8-methanol (**3**).

To a solution of triol **2** (6.1g, 42mmol) in 70ml of DMF benzaldehyde dimethylacetal (7.4g, 7.3ml, 48mmol) and HBF_4 (0.3ml, 54% in ether) were added successively. The reaction was monitored by TLC (toluene/ethyl acetate 4:1 v/v) and quenched after completion (about 2h) by addition of NEt_3 (1ml). The solvents were evaporated and the residue was partitioned between ether/water. After reextraction of the aqueous phase the combined organic phase was dried (Na_2SO_4) and taken to dryness. The remaining oil was coevaporated twice with toluene and last traces of solvent were removed *in vacuo* (<0.1mbar) at 50° to give 9.7g of **3** (99%) as an oil. An analytical sample was obtained by chromatography (toluene/ethyl acetate 4:1 v/v). $[\alpha]_D^{20}$ -17° (c 6.0, MeOH). ^{1}H-NMR ($CDCl_3$): 1.6-2.25(m,6H), 2.5(s

br,1H,OH), 3.61(d,J=6Hz,2H,H-5), 4.13(s br,2H,C*H*$_2$OH), 4.2-4.35(m,1H,H-1), 5.43(s,1H,H-3), 7.15-7.4(m,5H,ar-H). ^{13}C-NMR ($CDCl_3$): 28.5, 36.5, 39.5, 40.0, 67.2, 67.4, 80.0, 100.9, 125.4, 126.2, 128.4, 129.0, 138.0.

(-)-(1*R*,6*R*,8*R*)-3-Phenyl-2,4-dioxabicyclo[4.3.0]nonane-8-carboxylic acid (**4**).

PDC (22.5g, 60mmol, 3.5eq.) was added to a solution of **3** (4.0g, 17mmol) in 30ml of DMF. After stirring for 5h (monitored by TLC, $CHCl_3$/MeOH 9:1 v/v) the mixture was poured into 300ml of water and extracted repeatedly with ether. The organic phase was dried (Na_2SO_4) and evaporated to give 3.9g of **4** (93%). An analytical sample was prepared by chromatography ($CHCl_3$/MeOH 9:1 v/v), $[\alpha]_D^{20}$ -10° (c 4.9, MeOH), 82%e.e. Prolonged storage of the latter led to spontaneous crystallisation yielding material which showed enhanced optical rotation $[\alpha]_D^{20}$ -12.7°, (c 5.4, MeOH), >98%e.e., mp 104-6°. ^{1}H-NMR (DMSO-d_6): 1.9-2.8(m,6H), 4.1(s br,2H,H-5), 4.3(s br,1H,H-1), 5.4(s,1H,H-3), 7.15(s,5H,ar-H), 11.5(s br,1H,COOH).

(-)-N-[(1*R*,6*R*,8*R*)-3-Phenyl-2,4-dioxabicyclo[4.3.0]non-8-yl] urea (**5**).

To a stirred solution of **4** (3.77g, 15mmol) in acetone (80ml) was added NEt_3 (2.34ml, 18mmol) and ethyl chloroformate (1.63ml, 18mmol) at -70° successively. The mixture was allowed to reach -40° where it was kept for 30min and then treated with saturated aqueous NaN_3 solution (1.4g, 24mmol) at -10° for 30min. It was then poured into cold brine and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and evaporated to give an oily residue which was dissolved in benzene and heated at reflux for 30min followed by treatment with gaseous NH_3. Column chromatography ($CHCl_3$/MeOH 9:1 v/v) furnished 2.3g of the crystalline urea derivative **5** (58%). Attempts to enhance the optical purity by recrystallisation from 2-propanol were unsuccessful. mp 166-8°, $[\alpha]_D^{20}$ -15° (c 4.2, MeOH), ^{1}H-NMR (acetone-d_6): 1.2-2.5(m,6H), 3.8-4.3(m,4H,H-1,H-5,H-8), 5.25(s br,2H,NH_2), 5.35(s,1H,H-3), 5.84(d,J=8.5Hz,1H,NH), 7.1-7.4(m,5H,ar-H).
(-)-3-Ethoxy-N-(N'-[(1*R*,6*R*,8*R*)-3-phenyl-2,4-dioxabicyclo[4.3.0]non-8-yl]-carbamoyl) propenamide (**6**).

To a stirred suspension of urea **5** (1.2g, 4.6mmol) in pyridine (3ml) and $CHCl_3$ (10ml) ethoxyacryloyl chloride[12] (0.92g, 6.9mmol) was added and stirring was continued for 24h. After partitioning between CH_2Cl_2/water the organic phase was dried (Na_2SO_4) and taken to dryness. The residue was purified by column chromatography (toluene/ethyl acetate 1:1 v/v) to give 1.34g (82%) of **6** as a foam. $[\alpha]_D^{20}$ -1.8° (c 2.9, CH_2Cl_2). ^{1}H-NMR (DMSO-d_6): 1.25(t,J=7Hz,3H,CH_3), 1.45-2.6(m,5H), 3.85-4.5(m,6H,O-C*H*$_2$CH$_3$,H-1,H-5,H-8), 5.45(s,1H,H-3), 5.50(d,J=13Hz,1H,CO-C*H*=CH-), 7.1-7.6(m,5H,ar-H), 7.60(d,J=13Hz,1H,CO-CH=C*H*-), 8.8(d,J=8Hz,1H,NH), 10.0(s,1H,NH).

(-)-1-[(1*R*,3*R*,4*R*)-3-Hydroxy-4-hydroxymethylcyclopentyl]-1*H*,3*H*-pyrimidine-2,4-dione (**7**).

A suspension of **6** (0.32g, 0.9mmol) in 10ml of 2*N* H_2SO_4 was heated at 80-5° for 2.5h. The pH of the resulting solution was adjusted near 7 by addition of dil. NaOH and the solvent was removed *in vacuo*. The solid residue was extracted twice with hot ethanol (20ml each) followed by column chromatography ($CHCl_3$/MeOH 6:1 v/v) yielding 0.15g (74%) of **7**. $[\alpha]_D^{20}$ -55° (c=1.4, MeOH) e.e.=82%. A single recrystallisation from 2-propanol raised the optical rotation to $[\alpha]_D^{20}$ -67° (c 0.7, MeOH) e.e.>98%. mp 183-5° [lit[5]: 155-7° (racemic)]. ^{1}H-NMR (acetone-d_6): 1.0-2.55(m,5H,H-2',H-4',H-5'), 3.2-3.8(m,3H,H-3',C*H*$_2$OH), 4.21(m,1H,OH), 5.1(m,1H,H-1'), 5.65(d,J=8Hz,1H,H-5), 7.3(m,1H,OH), 7.98(d,J=8Hz,1H,H-6).

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