A Short and Stereoselective Synthesis of Carbocyclic *alpha*-L-Dideoxyhomonucleosides

F. Girard, M.-G. Lee and L. A. Agrofoglio*

I.C.O.A., associé au CNRS, Faculté des Sciences, 45067 Orléans, France

A. Fridland

Department of Infectious Diseases, St. Jude Children's Research Hospital, Memphis, TN 38105-2794, USA

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A stereoselective five-step total synthesis of the hitherto unknown carbocyclic *alpha*-L-dideoxyhomonucleosides starting from readily available (1*R*,5*S*)-2-oxabicyclo[3.3.0]oct-6-en-3-one is described.

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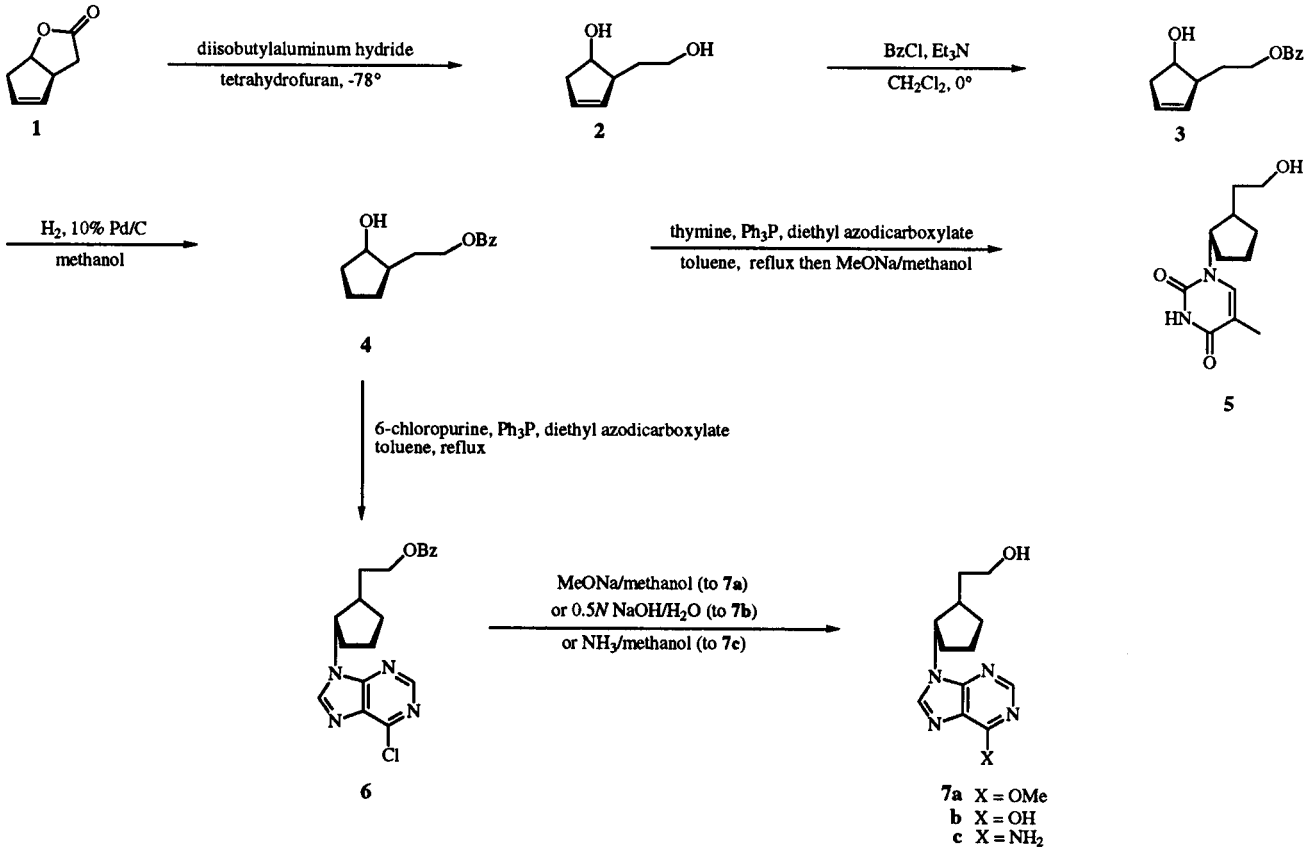
During the most recent period, research on the chemistry of carbocyclic nucleoside analogues, in which the oxygen of the furanosyl ring has been replaced by a methylene group, has been directed towards the development of agents showing activities against human immunodeficiency virus (HIV), hepatitis B virus (HBV), herpes simplex virus (HSV), and certain forms of cancer [1-4]. The pharmaceutical importance of carbocyclic nucleoside analogues has prompted the design and synthesis of many new examples of these compounds [5,6]. As part of our drug discovery program, in this communication we wish to report the synthesis of the hitherto unknown optically pure carbocyclic *alpha*-L-isomeric dideoxyhomonucleosides [7].

Our synthetic strategy is outlined in Scheme 1 and utilized the known compound, (1*R*,5*S*)-2-oxabicyclo[3.3.0]-oct-6-en-3-one **1** as a chiral starting material, which could be prepared in 3 steps from cyclopentadiene [8]. Reduction of the lactone moiety of **1** with diisobutylaluminium hydride afforded diol **2** in 95% yield [9]. Benzoylation of the primary alcohol of **2** to **3**, followed by reductive hydrogenation in the presence of 10% Pd/C pro-

Scheme 1



vided *cis*-2-(2-hydroxycyclopentyl)ethanol benzoyl ester **4** in 60% yield (two steps). The *N*-alkylation of thymine with the cyclopentanol **4** was achieved under Mitsunobu conditions [10] and afforded after deprotection the desired carbocyclic (-)-*alpha*-L-thymine nucleoside **5** (35% on two steps). The same approach was used to reach the 6-chloropurine nucleoside **6** (32%). On one hand, deprotection of **6** with a solution of sodium methoxide in methanol afforded the 6-methoxypurine derivative **7a** (92%). The hypoxanthine analogue **7b** was obtained directly by treatment of **6** with a 1*N* aqueous sodium hydroxide in 52% yield. On the other hand, deprotection of **6** with a solution of methanolic ammonia resulted in the carbocyclic (-)-*alpha*-L-adenine nucleoside **7c** in 30% yield.

In conclusion, compounds **5** and **7a-c** can be considered as isomeric forms of carbocyclic 2',3'-dideoxyhomonucleosides. We are also applying this methodology to synthesize other carbocyclic nucleosides. These results will be published in due course.

EXPERIMENTAL

Commercially available chemicals and solvents were reagent grade and used as received. 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. 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.

(1*R*,2*S*)-2-(2-Hydroxyethyl)cyclopent-3-enol (**2**).

A solution of (1*R*,5*S*)-2-oxabicyclo[3.3.0]oct-6-en-3-one **1** (1 g, 8.05 mmoles) dissolved in dry tetrahydrofuran (25 ml) was cooled to -78°. The lactone **1** was reduced by slowly adding a 1*M* solution of diisobutylaluminum hydride in tetrahydrofuran (24.1 ml, 24.1 mmoles). The solution was allowed to warm to room temperature for six hours. The reaction mixture was then quenched by slowing adding methanol (20 ml). The solution was then neutralized with 1*M* of aqueous hydrochloric acid. The solution was evaporated to dryness. The residual solid was washed with ethyl acetate (4 x 100 ml) and filtered. Evaporation of ethyl acetate *in vacuo* gave a residue which was purified by column chromatography (silica gel-dichloromethane/methanol, 9:1, v/v) to give **2** as a colorless syrup (982 mg, 95%); $[\alpha]_D^{20}$ +71° (*c* 1, methanol); ^{1}H nmr (deuteriochloroform): δ 5.70 (m, 1H), 5.55 (m, 1H), 4.50 (td, 1H, J = 6.28 Hz, 2.51 Hz), 4.00 (broad s, 2H, deuterium oxide-exchangeable), 3.76 (m, 1H), 3.67 (m, 1H), 2.69 (m, 1H), 2.60-2.31 (m, 2H), 1.80 (m, 2H). Its spectral data are identical to the known compound [9].

(1*S*,5*R*)-Benzoic Acid 2-(5-Hydroxycyclopent-2-enyl)ethyl Ester (**3**).

To a stirred solution of the diol **2** (969 mg, 7.57 mmoles) and triethylamine (3.50 ml) dissolved in anhydrous dichloromethane (20 ml), benzoyl chloride (0.97 ml, 8.32 mmoles) was added under argon. Stirring was continued at room temperature for 3 hours. The organic phase was washed successively with saturated aqueous sodium hydrogencarbonate (15 ml) and water to neutrality. After drying (sodium sulfate) and evaporation of the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel-hexane/ethyl acetate, 6:4, v/v) to give **3** as a yellow syrup (1.3 g, 74%); $[\alpha]_D^{20}$ +29° (*c* 5, chloroform); ^{1}H nmr (deuteriochloroform): 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, 1H, deuterium oxide-exchangeable), 2.20-1.85 (m, 2H).

(1*R*,2*R*)-2-(2-Hydroxycyclopentyl)ethanol Benzoyl Ester (**4**).

The alcohol **3** (300 mg, 1.29 mmoles) was dissolved in methanol (10 ml) and added to a suspension of 10% Pd/C (100 mg, 0.09 mmole) in methanol (5 ml). The mixture was hydrogenated in a Parr shaker at 20 psi pressure overnight, and then filtered through celite to remove the catalyst. The solvent was evaporated to dryness and the residue was chromatographed on silica gel using 6:4 hexane/ethyl acetate as eluant. All fractions containing the desired product were combined and concentrated to yield **4** as an oil (240 mg, 80%); $[\alpha]_D^{20}$ -13° (*c* 5, chloroform); ^{1}H nmr (deuteriochloroform): δ 8.02 (m, 2H), 7.57 (m, 1H), 7.45 (m, 2H), 4.42 (m, 2H), 4.19 (m, 1H), 2.12-1.38 (m, 10H).

(1*S*,2*R*)-1-[2-(2-Hydroxyethyl)cyclopentyl)]-5-methyl-1*H*-pyrimidine-2,4-dione (**5**).

Dried thymine (315 mg, 2.50 mmoles) was added to a stirring solution of triphenylphosphine (664 mg, 2.50 mmoles) and diethyl azodicarboxylate (0.40 ml, 2.50 mmoles) in dry tetrahydrofuran (6 ml) at 0°. The resulting suspension was stirred for 10 minutes, followed by addition of a solution of the alcohol **4** (391 mg, 0.15 mmole) dissolved in dry tetrahydrofuran (4 ml). The reaction mixture was stirred for one hour. The solvent was evaporated to leave a residue. The residue was chromatographed on silica gel using 1:1 hexane/ethyl acetate as eluant to give the benzoylated thymine analogue as an orange oil; ^{1}H nmr (deuteriochloroform): δ 11.45 (broad s, 1H, deuterium oxide-exchangeable), 7.87 (m, 2H), 7.54 (m, 1H), 7.48 (s, 1H), 7.40 (m, 2H), 4.63 (m, 1H), 4.46 (m, 2H), 2.53 (s, 3H), 2.50-1.55 (m, 9H). The compound obtained was dissolved in a saturated solution of ammonia in methanol and stirred at room temperature overnight. The solvent was evaporated to leave a residue that was chromatographed on silica gel using dichloromethane/methanol 9:1 as eluant to afford the desired carbocyclic *alpha*-L-thymine homonucleoside (**5**), (221 mg, 35% two steps); $[\alpha]_D^{20}$ -4.8° (*c* 5, chloroform); uv (water): λ max nm (ε) 270.5 (10821) (*p*H 2), 270.5 (10367) (*p*H 7), 269.5 (10851) (*p*H 11); ^{1}H nmr (deuteriochloroform): δ 11.53 (broad s, 1H, deuterium oxide-exchangeable), 7.54 (s, 1H), 4.85 (broad s, 1H, deuterium oxide-exchangeable), 4.58 (q, 1H, J = 7.75 Hz), 3.60 (m, 2H), 2.82-1.05 (m, 10H); ms: m/z 248 (M^++1).

Anal. Calcd. for $C_{12}H_{18}N_2O_3$: C, 60.48; H, 7.62; N, 11.76. Found: C, 60.52; H, 7.58; N, 11.58.

(1*R*,2*S*)-Benzoic Acid 2-(2-[6-Chloro-9*H*-purin-9yl]-2-cyclopentyl)ethyl Ester (**6**).

Dried 6-chloropurine (185 mg, 1.47 mmoles) was added to a stirring solution of triphenylphosphine (390 mg, 1.47 mmoles) and diethyl azodicarboxylate (0.23 ml, 1.47 mmoles) in dry tetrahydrofuran (6 ml) at 0°. The resulting suspension was stirred for 10 minutes, followed by addition of a solution of the alcohol **4** (230 mg, 0.09 mmole) dissolved in dry tetrahydrofuran (4 ml). The reaction mixture was stirred for one hour. The solvent was evaporated to leave a residue. The residue was chromatographed on silica gel using 1:1 hexane/ethyl acetate as eluant to give **6** as an orange syrup (130 mg, 32%); ^{1}H nmr (deuteriochloroform): δ 8.69 (s, 1H), 8.19 (s, 1H), 7.87 (m, 2H), 7.54 (m, 1H), 7.40 (m, 2H), 4.65 (m, 1H), 4.46 (m, 2H), 2.67 (m, 1H), 2.45-1.78 (m, 7H), 1.62-1.48 (m, 1H).

(1*R*,2*S*)-2-[2-(6-Methoxy-9*H*-purin-9yl)cyclopentyl)]ethanol (**7a**).

A solution of 6-chloropurine derivative **6** (70 mg, 0.18 mmole) dissolved in methanol (2 ml) was treated with a 1*M* solution of sodium methoxide in methanol (0.3 ml). The resulting mixture was stirred at room temperature for 12 hours. The organic phase was washed with brine. After drying (magnesium sulfate) and evaporation of the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel-dichloromethane/methanol, 95:5, v/v) to afford **7a** as a colorless syrup (43 mg, 92%); $[\alpha]_D^{20}$ -7.6° (*c* 5, chloroform); uv (water): λ max nm (ε) 260.1 (12432) (*p*H 2), 260.5 (9585) (*p*H 7), 261.0 (10640) (*p*H 11); ^{1}H nmr (deuteriochloroform): δ 8.52 and 7.99 (two s, 1H), 4.70 (q, 1H, J = 7.75 Hz), 4.17 (s, 3H), 3.65 (m, 2H), 2.95 (broad s, 1H, deuterium oxide-exchangeable), 2.53 (m, 1H), 2.30 (m, 1H), 2.20-1.18 (m, 5H), 1.65 (m, 2H); ms: m/z 263 (M^++1).

Anal. Calcd. for $C_{13}H_{18}N_4O_2$: C, 59.53; H, 6.92; N, 21.36. Found: C, 59.56; H, 6.89; N, 21.22.

(1*S*,2*R*)-9-[2-(2-Hydroxyethyl)cyclopentyl)]-9*H*-purin-6-ol (**7b**).

The 6-chloropurine derivative **6** (100 mg, 0.26 mmole) dissolved in a 1*N* aqueous solution of sodium hydroxide (10 ml) was refluxed for 3 hours. The reaction was cooled to room temperature and acidified to *p*H 5 with 2*M* of aqueous hydrochloric acid. The mixture was evaporated to dryness. The residue was purified by column chromatography (silica gel-dichloromethane/methanol, 9:1, v/v) to afford **7b** as a oil (33 mg, 52%); $[\alpha]_D^{20}$ -6.2° (*c* 2.5, methanol); uv (water): λ max nm (ε) 254.5 (14568) (*p*H 7), 250.1 (13847) (*p*H 2), 250.0 (13010) (*p*H 11); ^{1}H nmr (deuteriomethanol): δ 8.07 (s, 1H), 8.03 (s, 1H), 4.58 (m, 1H), 3.54 (m, 2H), 2.75-1.05 (m, 9H); ms: m/z 248 (M^++1).

Anal. Calcd. for $C_{12}H_{15}N_4O_2$: C, 58.28; H, 6.11; N, 22.65. Found: C, 58.20; H, 6.05; N, 22.55.

(1*S*,2*R*)-2-[2-(6-Amino-9*H*-purin-9yl)cyclopentyl)]ethanol (**7c**).

The 6-chloropurine derivative **6** (100 mg, 0.26 mmole) was dissolved in a saturated solution of ammonia in methanol and the mixture was stirred at room temperature for 20 hours. The solvent was removed under reduced pressure and the residue purified by column chromatography (silica gel-dichloromethane/methanol, 9:1, v/v) to provide **7c** as a white solid (20 mg, 30%); $[\alpha]_D^{20}$ -5.6° (*c* 5, chloroform); uv (methanol) λ max nm 260.5; ^{1}H nmr (deuteriochloroform): δ 8.33 and 7.85 (two s, 2H), 5.72 (broad s, 2H, deuterium oxide-exchangeable), 4.70 (q, 1H, J = 7.75 Hz), 3.66 (m, 2H), 2.75-1.00 (m, 10H); ms: m/z 248 (M^++1).

Anal. Calcd. for $C_{12}H_{17}N_5O$: C, 58.28; H, 6.93; N, 28.32. Found: C, 58.19; H, 6.89; N, 28.14.

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