

STEREOSPECIFIC SYNTHESIS OF (+)-CARBOCYCLIC 2'-DEOXYADENOSINE. AN IMPROVED PROCEDURE FOR THE PREPARATION OF (+)-(1R,2S,4R)-4-AMINO-2-HYDROXY-1-HYDROXYMETHYLCYCLOPENTANE.

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Abstract: An improved procedure for the preparation of a versatile synthetic precursor, (+)-13, of carba-2'-deoxyribonucleosides and the first stereospecific way to enantiomerically pure carbocyclic 2'-deoxyadenosine, (+)-14, are presented from bicyclic lactone diol (+)-1. An unexpected formation of the di-substituted 2-oxabicyclo[2.2.1]heptane skeleton 15 through a hypervalent iodo species derived from 6 is also reported.

(Received in UK 14 June 1988)

Introduction

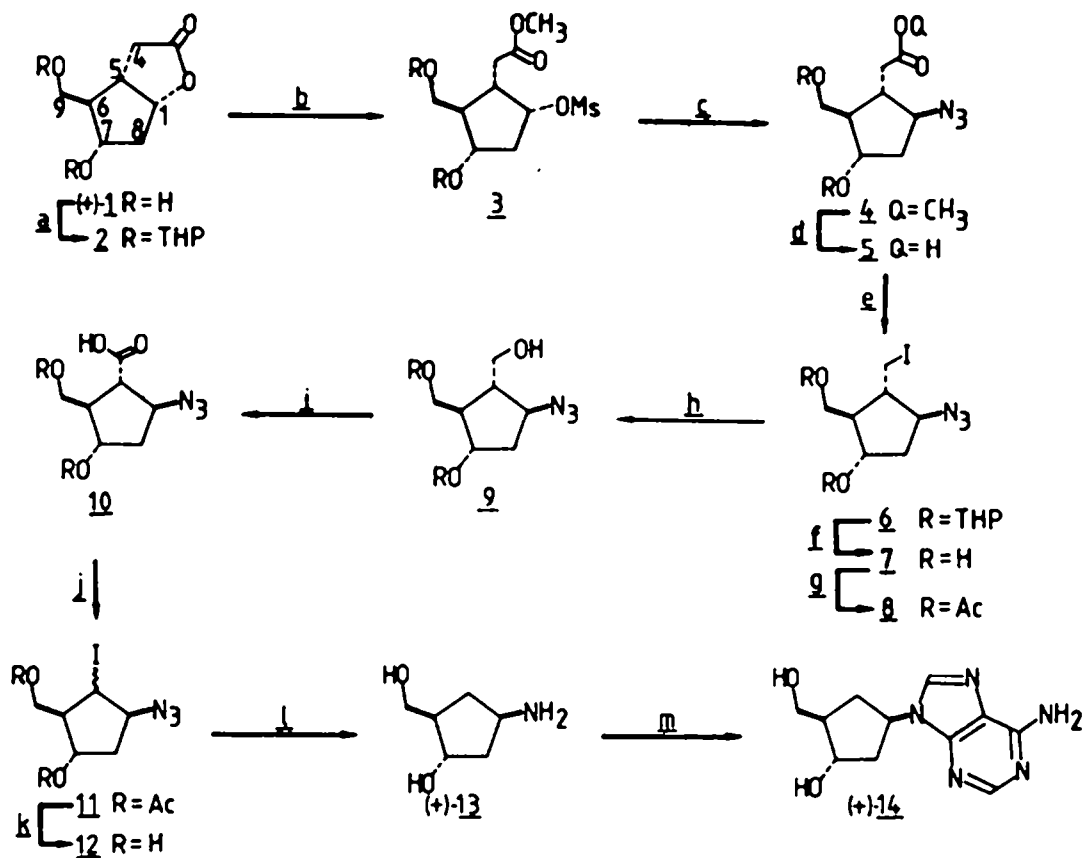
Carba-adenosine, the first representative of the carbocyclic analogues of nucleosides was synthesized in racemic form by Shealy et al.¹ over two decades ago. This pioneering step was followed by the preparations and biological evaluations of carbocyclic analogues of other naturally occurring and many unnatural nucleosides.² In several cases these compounds, likely due to their analogous structure and enhanced stability, proved to be biologically active (e.g. antiviral) agents.³ Recently much attention has been paid to the preparation of enantiomerically pure substances mainly for purposes of biological tests.^{4,5,6,7,8} These non-racemic nucleoside analogues have also the potential to be effective in viral infections (anti-AIDS drugs, etc.^{9,10}).

Recently we reported the first stereospecific synthesis of (+)-13 and the (+)-carbocyclic thymidine.⁸ However, the synthetic process used was rather protracted giving the required aminocyclopentane derivative (+)-13 from (+)-(1R,5S)-2-oxabicyclo[3.3.0]oct-6-en-3-one in 0.75% and 0.94% overall yields, respectively. In this paper we publish the first stereospecific way to the enantiomerically pure carbocyclic 2'-deoxyadenosine, (+)-14, via (+)-13 which was now obtained in an improved procedure from bicyclic lactone diol¹¹ (+)-1 in 11% overall yield.

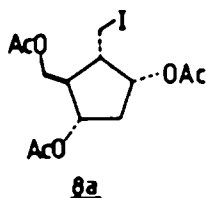
Results and Discussion

The main feature of our improved procedure (Scheme 1) is represented by two consecutive iodo-decarboxylations (e and j steps) of the appropriate carboxylic acid side chains derived from the lactone portion of (+)-1. The easily accessible tetrahydropyranyl protection of (+)-1 was thought to be compatible with the whole reaction sequence planned. Contrary to analogous cases,¹² no significant relactonization was observed when the γ -mesyloxy carboxylic ester 3 was prepared in a few steps from 2. As expected¹³ and evidenced indirectly at a later stage of the synthesis by ¹H NMR spectroscopy (comparing the data of 8 and 8a), the displacement of the secondary mesyloxy function by azide anion (transformation 3 \rightarrow 4) proceeded with full inversion of configuration. Conversion of acid-labile carboxylic acid derivative 5 to 6 needed well-controlled reaction conditions (optimal amounts of reagents, short reaction time, temperature control) to attain satisfactory yield in the iodo-

Scheme 1



\underline{a} DHP, *p*-TsOH; \underline{b} i, aq LiOH, ii, aq NaHSO₄, iii, CH₂N₂, iv, MeCl, TEA; \underline{c} NaN₃; \underline{d} i, aq LiOH, ii, aq NaHSO₄; \underline{e} IBDA, I₂, hv; \underline{f} MeOH, *p*-TsOH; \underline{g} Ac₂O, Py, DMAP; \underline{h} *m*-CPBA; \underline{i} PDC, DMF; \underline{j} IBDA, I₂, hv; \underline{k} MeOH, K₂CO₃; \underline{l} H₂/10% Pd-C; \underline{m} i, 5-amino-4,6-dichloropyrimidine, TEA, ii, (EtO)₃CH, oc HCl, iii, NH₃-MeOH.

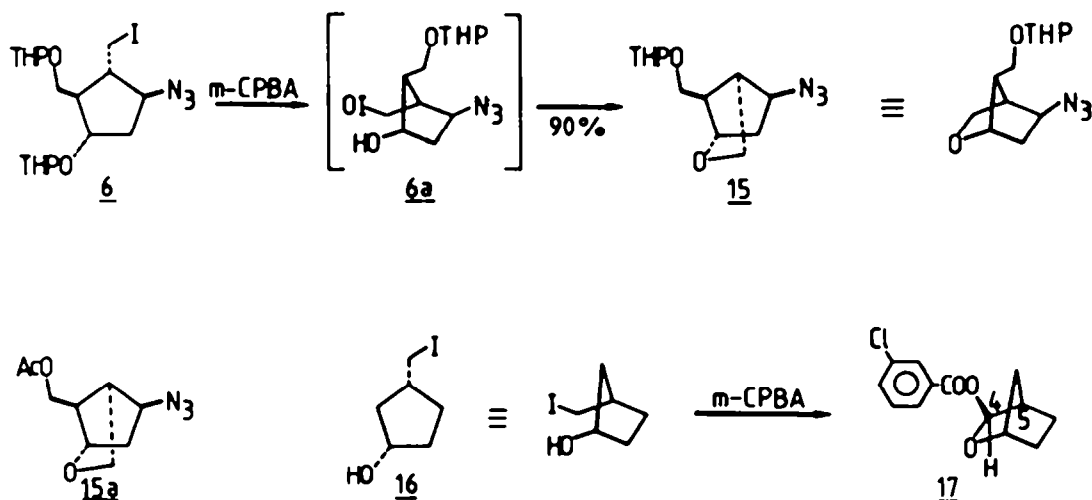


decarboxylation using iodobenzene diacetate (IBDA)^{8,10}. To overcome the formation of undesired 2-oxabicycloheptane derivative $\underline{15}$ (vide infra, Scheme 2), the THP groups in $\underline{6}$ were replaced by acetyl ones prior to treatment with *m*-CPBA^{10,14}. IBDA-decarboxylation (with 8 eq each of IBDA and I₂) of diacetoxy β-azido carboxylic acid derivative $\underline{10}$ proceeded in good yield giving chromatographically (SiO₂ TLC/column) readily separable diastereomeric iodo azides $\underline{11}$ (trans/cis ratio = 5:1, by weight). Spatial orientation (trans/cis) of iodide relative to N₃ group in $\underline{11}$ was established by NMR spectroscopy analysing the coupling constants obtained for the separated diastereoisomers. Catalytic hydrogenation of α-iodo azides $\underline{12}$ to key intermediate (+)- $\underline{13}$ afforded acceptable yield¹⁵. The heterocyclic moiety (adenine) of (+)- $\underline{14}$ was constructed according to modified literature proce-

dures¹. A novel version, which involves SnCl_2 -reduction of NO_2 to NH_2 group as developed by Bellamy and Ou¹⁶, was elaborated for the preparation of 5-amino-4,6-dichloropyrimidine¹⁷, precursor for the adenine portion of (+)-14.

As mentioned, an unexpected highly efficient formation (90% yield) of the disubstituted 2-oxabicyclo[2.2.1]heptane¹⁸ 15 occurred when bis-tetrahydropyranylated iodomethyl compound 6 was treated with *m*-CPBA in CH_2Cl_2 in the presence of NaHCO_3 in order to obtain the corresponding hydroxymethyl derivative (Scheme 2). (Unlikely formation of the alternative *trans*-fused 3-oxabicyclo[3.3.0]octane ring-system could be excluded by NMR spectroscopy.) In contrast, no ring closure was noticed for unblocked 7 in the absence of *m*-CPBA even under basic (acetylation) condition¹⁹. Fortunately, however, conversion of diacetoxy iodomethyl compound 8 went smoothly to the desired hydroxymethyl derivative 9 using *m*-CPBA. On this basis we assume that the above anomalous reaction likely proceeds through a hypervalent iodo species (6a) derived from 6, losing THP group selectively from the secondary OH function prior to or in the cyclization process.

Scheme 2



To expand the applicability of this ring closure, appropriately substituted cyclopentanol derivative 16 (prepared in 8 steps from (+)-(1*R*,5*S*)-2-oxabicyclo[3.3.0]oct-6-en-3-one) was treated with *m*-CPBA in CH_2Cl_2 in order to obtain unsubstituted 2-oxabicyclo[2.2.1]heptane skeleton. Surprisingly, however, one isomer (17) of the *m*-chlorobenzoate of the bicyclic lactol was isolated (Scheme 2) as the main TLC-detectable product. The stereochemistry of the *m*-chlorobenzoate moiety derives from the ¹H NMR data. The absence of detectable splitting on the signal of 4-H (6.97 ppm) indicates that the dihedral angle between 4-H and 5-H is close to 90°. The low isolated yield (5%) was likely due to the loss of the volatile material during evaporation. Oxidation of the iodomethyl function to a formyl one seems to be plausible in this process. So far, this kind of oxidation was only noted for secondary alkyl iodides.¹⁴

Experimental

Materials. Dichloromethane and pyridine were distilled from P_2O_5 , carbon tetrachloride and methanol from CaH_2 . Triethylamine was distilled from and stored over KOH. Iodobenzene diacetate was prepared as described in the literature.²⁰ Pyridinium dichromate and 90% *m*-CPBA were purchased from Fluka AG and 85% *m*-CPBA from Aldrich. Pre-coated SiO_2 TLC plates (DC-Alufolien, Kieselgel 60 F_{254} , 0.2 mm) were purchased from Merck, Darmstadt. UV-light and phosphomolybdic acid in methanol were used to detect compounds on TLC plates.

Equipments. 1H and ^{13}C NMR spectra were recorded on Varian XL-100 and XL-400 instruments. Non-trivial 1H assignments were confirmed by extensive spin-decoupling experiments. Connectivities between identified protons and protonated carbons, if necessary, were obtained by means of two-dimensional (HETCOR) measurements. Mass spectrometric measurements were carried out on an ABI MB-902 double focusing instrument with ionizing energy of 70 eV. All samples were introduced by direct probe. Optical rotation measurements were performed on a Polamat A (Carl Zeiss, Jena, GDR) polarimeter.

Synthesis of (+)-(1R,2S,4R)-4-Amino-2-Hydroxy-1-Hydroxymethylcyclopentane, (+)-13.

Bis-Tetrahydropyranyl Bicyclic Lactone Diol (2).

A mixture of lactone diol (+)-1 (20.44 g, 119 mM), 3,4-dihydro-2H-pyran (32.6 mL, 357 mM) and *p*-toluenesulfonic acid monohydrate (0.23 g, 1.19 mM) in 200 mL of CH_2Cl_2 was stirred with cooling in water bath ($\sim 15^\circ C$) for 10 min. Stirring was continued at room temperature until complete dissolution occurred (approx. 50 min) and TLC showed full conversion of (+)-1. After addition of triethylamine (0.5 mL, 3.61 mM), the solvent was removed in vacuo. The residue was then dissolved in 400 mL of Et_2O , washed with 40 mL of H_2O , 30 mL of brine, dried over $MgSO_4$ and evaporated to dryness to yield 40.10 g (99%) of 2. R_f (hexane (H): ethyl acetate (E) = 1:1, v/v) = 0.22.

γ -Mesyloxy Carboxylic Ester (3)

A solution of 2 (30.19 g, 88.7 mM) and 1 M/L aq LiOH (133 mL) in 250 mL of methanol was stirred at ambient temperature (pH=13). After 5 min TLC showed complete saponification. MeOH was then removed by evaporation. Water (150 mL) was added followed by extraction with EtOAc (3x50 mL). Then EtOAc (300 mL) was added to the aq solution in a separatory funnel and the pH was adjusted to 3-4 using 2 M/L aq $NaHSO_4$. The aq solution was further extracted with EtOAc (3x50 mL). The combined organic phase was washed with brine (30 mL) and dried over $MgSO_4$. The filtrate was cooled to $0^\circ C$. The above solution was treated with ethereal CH_2N_2 (250 mL, 190mM) generated from *N*-methyl-*N*-nitrosourea. After complete esterification the solution was concentrated, dried over $MgSO_4$ and evaporated to dryness. The residue thus obtained was taken up in 400 mL of CH_2Cl_2 and cooled to $0^\circ C$. Triethylamine (18.3 mL, 132 mM) was added followed by dropwise addition (5 min) of methanesulfonyl chloride (7.50 mL, 96.9 mM). The mixture was kept at $0^\circ C$ for additional 15 min. Then it was stirred at room temperature for 0.5h. The mixture was then washed into a separatory funnel with 50 mL of CH_2Cl_2 , washed with ice-water (3x50 mL), 2M/L aq $NaHSO_4$ (2x10 mL, pH=3), saturated aq $NaHCO_3$ (10 mL, pH=10), 40 mL of brine and evaporated to dryness, yielding 39.55 g (99%) of 3. R_f (H:E=1:1) = 0.24.

$^1\text{H NMR}$ (100 MHz, CDCl_3)²¹: δ 1.4–2.4 (m, 5-H, 6-H, 8-H₂, 4'-H₂, 4''-H₂, 5'-H₂, 5''-H₂, 6'-H₂ and 6''-H₂), 2.65 (m, 4-H₂), 2.96+2.98 (m, CH_2SO_2), 3.68 (s, CO_2CH_3), 3.3–4.2 (overlapped multiplets, 7-H, 9-H₂, 3'-H₂ and 3''-H₂), 4.59+4.62 (overlapped multiplets, 1'-H and 1''-H), 5.19 (m, $J=6+4+1$ Hz, 1-H).

γ -Azido Carboxylic Ester (4)

A mixture of **3** (2.33 g, 5.17 mM) and NaN_3 (0.67 g, 10.3 mM) in 40 mL of dry DMF was stirred at 70–75°C for 2.75 h. The solvent was then removed under reduced pressure and 50 mL of H_2O was added to the residue. Compound **4** was extracted with Et_2O (3x20 mL). The ethereal solution was washed with brine (10 mL), dried over MgSO_4 and evaporated affording 1.92 g of crude **4**. The residue was purified by dry column flash chromatography²² (DCFC) using 30 g of SiO_2 (<0.063 mm), H:E=3:1 as eluent. Isolated was 1.82 g (89%) of pure **4**. R_f (H:E=3:1)=0.23.

γ -Azido Carboxylic Acid (5)

A solution of **4** (7.38 g, 18.6 mM) and 1 M/L aq LiOH (37 mL) in 200 mL MeOH- H_2O (3:1, v/v) was left to stand overnight at ambient temperature (pH=12). Then TLC showed full saponification. MeOH was removed by evaporation and water (70 mL) was added followed by extractions with Et_2O (3x30 mL). Then Et_2O (80 mL) was added to the aq layer in a separatory funnel and the pH was adjusted to 3 with 2 M/L aq NaH_2PO_4 (20 mL). The aq solution was further extracted with Et_2O (3x20 mL). The combined Et_2O solution was washed with brine (20 mL) and dried over MgSO_4 . On evaporation isolated was 7.05 g (99%) of pure **5**. R_f (H:acetone=2:1)=0.29.

$^1\text{H NMR}$ (100 MHz, CDCl_3)²¹: δ 1.3–2.2 (m, 5-H, 6-H, 8-H₂, 4'-H₂, 4''-H₂, 5'-H₂, 5''-H₂, 6'-H₂ and 6''-H₂), 2.60 (m, 4-H₂), 3.3–4.2 (overlapped multiplets, 1-H, 7-H, 9-H₂, 3'-H₂ and 3''-H₂), 4.63 (overlapped multiplets, 1'-H and 1''-H), 8.54 (s, CO_2H).

Iodoethylcyclopentane Derivative (6)

A mixture of **5** (5.22 g, 13.6 mM), iodobenzene diacetate²⁰ (8.76 g, 27.2 mM) and I_2 (6.90 g, 27.2 mM) in 370 mL of dry CCl_4 was refluxed over a 250-W tungsten-filament lamp for 10 min. The cooled solution was washed with 5% aq $\text{Na}_2\text{S}_2\text{O}_3$ (90 mL), sat'd aq NaHCO_3 (40 mL, pH=10), dried over MgSO_4 and evaporated. The residue was purified twice by DCFC (80 g SiO_2 , H:E=10:1). Chromatography yielded 3.48 g (55%) of pure **6**. R_f (H:E=5:1)=0.21.

$^1\text{H NMR}$ (100 MHz, CDCl_3)²¹: δ 1.4–2.3 (m, 5-H, 6-H, 4'-H₂, 4''-H₂, 5'-H₂, 5''-H₂, 6'-H₂, 6''-H₂ and 8-H₂), 3.3–4.0 (overlapped multiplets, 9-H₂, 4-H₂, 1-H, 3'-H₂ and 3''-H₂), 4.16 (m, $J=7+4.5+4$ Hz, 7-H), 4.62 (overlapped multiplets, 1'-H and 1''-H).

Synthesis of 7

A solution of **6** (3.24 g, 6.96 mM) and *p*-toluenesulfonic acid monohydrate (0.200 g, 1.06 mM) in 100 mL of methanol was kept at room temperature for 1 h. Then the catalyst was quenched with triethylamine (0.20 mL, 1.44 mM). The solution was evaporated under reduced pressure and the residue was purified by DCFC (30 g SiO_2 , H:E=1:2). Evaporation of the appropriate fractions gave 1.99 g (96%) of pure **7**. R_f (H:E=1:2)=0.25.

$^1\text{H NMR}$ (400 MHz, CDCl_3)²¹: δ 1.58 (m, $J=9+6.5+6.5+5$ Hz, 5-H), 1.84 (m, $J=9+7.5+6+5$ Hz, 6-H), 2.06 (t, $J=6.5$ Hz, 8-H₂), 3.33 (dd, $J=10.5+6.5$ Hz, 4-H_A), 3.44 (dd, $J=10.5+5$ Hz, 4-H_B), 3.68 (dd, $J=10.5+7.5$ Hz, 9-H_A), 3.85 (m, $J=6.5+6.5+6.5$ Hz, 1-H), 3.87 (dd, $J=10.5+5$ Hz, 9-H_B), 4.29 (m, $J=6.5+6.5+6$ Hz, 7-H).

Acetylation of **7** to **8**.

A solution of **7** (8.24 g, 27.7 mM), pyridine (6.69 mL, 83.1 mM) and 4-dimethylaminopyridine (0.68 g, 5.54 mM) in 140 mL of dichloromethane was treated with acetic anhydride (6.60 mL, 69.3 mM) using tap-water cooling for 10 min. Then the solution was kept at ambient temperature for additional 10 min. The excess of Ac_2O was quenched by adding MeOH (5.0 mL, 123 mM). The solution was evaporated and the residue coevaporated with toluene (3x20 mL). DCPC: 100 g SiO_2 , H:E=4:1. Yield: 10.28 g (97%).

R_f (H:E=3:1)=0.36.

$^1\text{H NMR}$ (400 MHz, CDCl_3)²¹: δ 1.49 (m, $J=9+8.5+4+4$ Hz, 5-H), 2.06-2.15 (overlapped multiplets, 8-H₂+6-H), 2.06 (s, OAc), 2.07 (s, OAc), 3.38 (dd, $J=10.5+4$ Hz, 4-H_A), 3.48 (dd, $J=10.5+4$ Hz, 4-H_B), 3.84 (m, $J=8.5+8+7.5$ Hz, 1-H), 4.12 (dd, $J=11.5+4.5$ Hz, 9-H_A), 4.21 (dd, $J=11.5+5$ Hz, 9-H_B), 5.04 (m, $J=7.5+4+3.5$ Hz, 7-H).

8a: $^1\text{H NMR}$ (400 MHz, CDCl_3)²¹: δ 1.87 (m, $J=16+3+1.5$ Hz, 8-H_A), 2.21 (m, $J=11+10+4.5+4.3$ Hz, 5-H), 2.27 (m, $J=11+5.5+4.5+4$ Hz, 6-H), 2.39 (m, $J=16+8.5+5.2$ Hz, 8-H_B), 3.22 (dd, $J=10+9.5$ Hz, 4-H_A), 3.33 (dd, $J=9.5+4.5$ Hz, 4-H_B), 4.18 (dd, $J=11.5+4.5$ Hz, 9-H_A), 4.24 (dd, $J=11.5+4$ Hz, 9-H_B), 5.09 (m, $J=8.5+6.5+3$ Hz, 7-H), 5.23 (m, $J=5.2+4.3+1.5$ Hz, 1-H).

Hydroxymethylcyclopentane Derivative (**9**).

A solution of **8** (10.26 g, 28.9 mM) in 150 mL of dichloromethane was treated with 90% m-CPBA (15.13 g, 78.9 mM) employing cold water cooling for 10 min. Then the solution was kept at r.t. for 30 min. TLC showed complete conversion of **8**. The solution was then washed with 120 mL of 1.1 M/L aq NaHCO_3 (pH=9). The aq phase was extracted with CH_2Cl_2 (5x20 mL). The combined organic solution was washed with 5% aq $\text{Na}_2\text{S}_2\text{O}_3$ (30 mL). The aq layer was repeatedly extracted with CH_2Cl_2 (3x20 mL). The combined CH_2Cl_2 solution was dried over MgSO_4 and evaporated to dryness. DCPC: 100 g SiO_2 , H:E = 2:1 → 1:1. Fractions with impure **9** were evaporated and chromatography was repeated. Yield: 5.18 g (69%). R_f (H:E=1:1)=0.27.

O-Acetyl-9: $^1\text{H NMR}$ (100 MHz, CDCl_3)²¹: δ 1.8-2.4 (overlapped multiplets, 8-H₂, 5-H and 6-H), 3.87 (m, $J=8+8+7.5$ Hz, 1-H), 2.03 (s, OAc), 2.06 (s, OAc), 2.09 (s, OAc), 4.16 (d, $J=5$ Hz, 9-H₂), 4.20 (d, $J=5.6$ Hz, 4-H₂), 5.05 (m, $J=8.5+4.0+4.0$ Hz, 7-H).

Cyclopentanecarboxylic Acid Derivative (**10**).

A solution of **9** (2.28 g, 8.40 mM) and pyridinium dichromate (11.06 g, 29.4 mM) in 40 mL of dry DMF was left at ambient temperature overnight (22 h). TLC showed almost full conversion of **9** to **10**. The mixture was poured into 300 mL of water and extracted with ether (13x60 mL). The ethereal layer was then washed with 5 mL of 2 M/L NaHSO_4 in 10 mL of water (pH=3), brine (20 mL) and dried over MgSO_4 . Evaporation afforded 2.38 g (99%) of pure **10**. R_f (H:E=1:2)=0.19.

α -Azidocyclopentylidide Derivatives (11).

A mixture of 10 (5.97 g, 20.93 mM), IBDA (13.50 g, 41.9 mM) and I_2 (10.63 g, 41.9 mM) in 600 mL of carbon tetrachloride was refluxed over a 250-W tungsten-filament lamp for 10 min. The addition of IBDA and I_2 was repeated (three times, each followed by 10 min reflux) until full conversion of 10 was observed (TLC). The cooled solution was washed with 5% aq $Na_2S_2O_3$ (240 mL), water (50 mL), sat'd aq $NaHCO_3$ (50 mL, pH=10), water (50 mL) and dried over $MgSO_4$. After removal of the solvent, the residue was purified by DCPC (100 g SiO_2 , H:E=4:1). Chromatography afforded 5.22 g (68%) of pure isomeric 11. R_f (H:E=3:1)=0.17 (cis), 0.24 (trans).

trans-11: 1H NMR (400 MHz, $CDCl_3$)²¹: δ 1.93 (m, J=14+9.5+7.5 Hz, 8- H_A), 2.06 (m, 14+7.5+2.8 Hz, 8- H_B), 2.07 (s, OAc), 2.08 (s, OAc), 2.53 (m, J=10+6+5+6 Hz, 6-H), 3.73 (dd, J=10+9 Hz, 5-H), 4.24 (m, J=9.5+9+7.5 Hz, 1-H), 4.25 (d, J=5 Hz, 9- H_2), 6.02 (m, J=7.5+5+2.8 Hz, 7-H).

cis-11: 1H NMR (400 MHz, $CDCl_3$)²¹: δ 1.96 (m, J=14.6+8+3+2 Hz, 8- H_A), 2.05 (s, OAc), 2.06 (s, OAc), 2.15 (m, J=8.5+7+6.5+5 Hz, 6-H), 2.45 (m, J=14.5+9.5+9.5 Hz, 8- H_B), 3.75 (m, J=9.5+8+4.5 Hz, 1-H), 4.13 (dd, J=11+8.5 Hz, 9- H_A), 4.35 (dd, J=11+6.5 Hz, 9- H_B), 4.64 (m, 5+4.5+2 Hz, 5-H), 5.04 (m, 9.5+7+3 Hz, 7-H).

Deacetylation of 11 to 12.

A mixture of trans- α -azidocyclopentylidide derivative, trans-11 (5.06 g, 13.76 mM) and K_2CO_3 (3.80 g, 27.52 mM) in 136 mL of MeOH was stirred at room temperature for 5 min. Then it was concentrated to approx. 10 mL volume and purified by DCPC (80 g SiO_2 , H:E=1:2). Isolated was 3.46 g (89%) of trans-12. R_f (H:E=1:2)=0.33.

(+)-(1R,2S,4R)-4-Amino-2-Hydroxy-1-Hydroxymethylcyclopentane, (+)-13.

A mixture of trans-12 (3.46 g, 12.22 mM) and 0.44 g of 10% Pd-C in 110 mL of methanol was stirred at ambient temperature under argon for a short time (5 min). Then H_2 was bubbled through the mixture at atmospheric pressure. Nearly complete reduction of trans-12 to (+)-13 was attained in 10 hrs. Then the catalyst was filtered off through a short asbestos pad, washed with MeOH (5x5 mL) and H_2O (5x5 mL). The combined MeOH solution was evaporated to dryness and the residue was dissolved in the above aq washing and applied to a DOWEX 50 WXB (H^+) column (1.2x18 cm). The column was first washed with water (10x20 mL) and crude (+)-13 (1.22 g, 76%) was eluted with 1 M/L aq NH_4OH . DCPC (30 g SiO_2 , MeOH: 25% aq NH_4OH :30:1) provided 0.927 g (56%) of pure (+)-13. $[\alpha]_D^{25} + 31^\circ$ (c 1.0, DMF), lit.⁸ $[\alpha]_D^{26} + 34^\circ$ (c 1.0, DMF). R_f (MeOH: 25% aq NH_4OH :30:1)=0.20.

1H NMR (400 MHz, $DMSO-d_6/CDCl_3$)²³: δ 1.05 (m, J=12.5+7.5+7.5+ Hz, 5- H_A), 1.57 (m, J=13+7+7+1.5 Hz, 3- H_A), 1.77 (m, J=13+7+4.5 Hz, 3- H_B), 1.92 (m, J=7.5+7.5+6+6+6 Hz, 1-H), 2.11 (m, J=12.5+7.5+7.5+1.5 Hz, 6- H_B), 3.47 (m, J=7.5+7.5+7+7 Hz, 4-H), 3.48 (d, J=6 Hz, 6- H_2), 4.03 (m, J=7+6+4.5 Hz, 2-H).

^{13}C NMR (100 MHz, $DMSO-d_6/CDCl_3$)²³: δ 37.90(C5), 44.73 (C3), 49.76(C1), 50.09(C4), 63.47(C6), 72.90(C2).

EL-MS, m/e (rel. intensity%): 131(9) M^+ , 114(15), 101(10), 100(12), 96(10), 86(36), 84(9), 83(9), 82(8), 72(100), 69(31), 66(62), 44(44), 43(38).

Synthesis of (+)-Carbocyclic 2'-Deoxyadenosine, (+)-14.

5-Amino-4,6-Dichloropyrimidine.

A mixture of 4,6-dichloro-5-nitropyrimidine¹⁷ (13.00 g, 67.0 mM) and $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (76.60 g, 0.335 M) in 136 mL ethanol was refluxed under N_2 for 20 min. After cooling, the solution was poured over crushed ice (450 mL). Then the pH was adjusted to ~8 by adding solid NaHCO_3 . The suspension thus obtained was extracted with EtOAc (3x200 mL). The organic layer was washed with brine (3x150 mL), treated with charcoal and dried over MgSO_4 . The crystalline residue obtained on evaporation was recrystallized from hexane affording white crystals. Yield: 10.03 g (91%), m.p. 145°C (lit.²⁴, 147°C). Anal. calcd. for $\text{C}_4\text{H}_3\text{Cl}_2\text{N}_3$: C: 29.27; H: 1.83; Cl: 43.29; N: 25.61. Found: C: 29.22; H: 2.03; Cl: 43.36; N: 25.41.

(1R,2S,4R)-4-(5-Amino-6-chloro-4-pyrimidinylamino)-2-Hydroxy-1-Hydroxymethylcyclopentane, 14a.

A solution of (+)-13 (0.536 g, 4.09 mM), 5-amino-4,6-dichloropyrimidine (1.34 g, 8.20 mM) and triethylamine (1.8 mL) in 45 mL of dry n-butanol was refluxed for 3 days. After removal of the solvent, the oily residue was partitioned between 60 mL of water and 50 mL of chloroform. The aq layer was further extracted with CHCl_3 (2x25 mL), then treated with Amberlite IRA-400 (OH^-) to adjust pH~8. The resin was filtered off and washed with H_2O and EtOH. The filtrate was evaporated and the residue was coevaporated with EtOH (2x25 mL). The residue was purified by DCPC (45 g SiO_2 , $\text{CHCl}_3 \rightarrow \text{CHCl}_3:\text{MeOH}=9:1$ gradient). The appropriate fractions were concentrated and gave on treatment with cold, dry Et_2O 0.845 g (80%) of pure 14a. $R_f(\text{CHCl}_3:\text{MeOH}=9:1)=0.06$, ($\text{EtOH}:25\% \text{ aq } \text{NH}_4\text{OH}=9:1$)=0.62.

(+)-Carbocyclic 2'-Deoxyadenosine, (+)-14.

A mixture of 14a (0.825 g, 3.19 mM), triethyl orthoformate (40 mL) and cc aq HCl (0.43 mL) was stirred at room temperature for 20 hrs. After addition of triethylamine (1.0 mL), the solution was evaporated in vacuo and the residue was coevaporated with toluene (3x30 mL). The brown oil obtained was heated with sat'd ammonia in methanol (60 mL) in a stainless steel bomb at 100°C for 20 hrs. After removal of the solvent, the syrup was dissolved in 60 mL of 1 M/L aq HCl and stirred at 60 °C for an hour. The solution was then evaporated to dryness. The residue was dissolved in methanol (80 mL) and treated with Amberlite IRA-400 (OH^-). Purification by DCPC (35 g SiO_2 , $\text{CHCl}_3:\text{MeOH}=9:1$) afforded 0.549 g (69%) of pure (+)-14. $[\alpha]_D^{23} + 15.5^\circ \pm 1$ (c 1.0, MeOH). M.p.: 182°C. $[\text{CD}]_{20}(\text{H}_2\text{O}, 3.29 \text{ mmol/L}, 0.05 \text{ cm})$: $\lambda(\Delta\epsilon)$ 202.0(+0.092), 225.0(-0.137) nm.

$^1\text{H NMR}$: (400 MHz, $\text{DMSO}-d_6/\text{CDCl}_3$)²⁵: δ 1.88(m, J=12.5+10+9 Hz, 6'- H_A), 2.16 (overlapped multiplet, 4'-H), 2.19 (overlapped multiplet, 2'- H_A), 2.31(m, J=13.5+8.5+6.5 Hz, 2'- H_B), 2.47(m, J=12.5+7.5+7.5 Hz, 6'- H_B), 3.64(d, J=5.5 Hz, 6'- H_2), 4.28(m, J=6.5+4.5+4 Hz, 3'-H), 5.13(m, J=9.0+8.5+8+7.5 Hz, 1'-H), 7.05(s, NH_2), 8.11(s, 2-H), 8.20(s, 8-H).

^{13}C NMR (100 MHz, $\text{Me}_2\text{SO}-d_6/\text{CDCl}_3$)²⁵: δ 32.66 (C6'), 40.10 (C2'), 48.36 (C4'), 52.54 (C1'), 62.49 (C5'), 72.00 (C3'), 118.85 (C5), 138.14 (C8), 148.68 (C4), 151.30 (C2), 154.90 (C6).

RI-MS (direct inlet, 180°C), m/e (rel. intensity%): 249(20) M^+ , 232(5) $\text{M}^+ - \text{OH}$, 218(20) $\text{M}^+ - \text{CH}_2\text{OH}$, 205(3), 202(5), 162(50), 136(100) $\text{B}^+ + 2\text{H}$, 135(50) $\text{B}^+ + \text{H}$, 119(5), 108(40).

Formation of 15.

A mixture of **6** (3.49 g, 7.50 mM), NaHCO_3 (4.16 g, 49.5 mM) and 90% m-CPBA (4.76 g, 24.8 mM) in 75 mL of CH_2Cl_2 was stirred at room temperature for 30 min. The mixture was then washed with 20 mL of water, 1 M/L aq LiOH (4x15 mL, pH=13). The aq layer was extracted with ether (2x30 mL). The combined organic phase was washed with brine (20 mL) and dried over MgSO_4 . After removal of the solvents, the residue was further purified by DCFC (30 g SiO_2 , H:E=4:1). Chromatography afforded 1.71 g (90%) of pure **15**. $R_f(\text{H:E}=2:1)=0.20$.

^1H NMR (100 MHz, CDCl_3)²¹: δ 1.3-1.9(m, 4'- H_2 , 5'- H_2 , 6'- H_2), 1.7(m, 8- H_A), 2.20(m, 8- H_B), 2.4(m, 6-H), 2.55(m, 5-H), 3.55+3.9+4.51 (overlapped multiplets, 1'-H, 3'- H_2), 3.9 (m, 9- H_2). 3.46 (d, J=7.2 Hz, 4- H_A), 3.77 (dd, J=7.2+3 Hz, 4- H_B), 3.9(m, 1-H), 4.31 (m, J=2+1+0.5 Hz, 7-H).

^{13}C NMR (25.16 MHz, CDCl_3)²¹: δ 19.41+19.67(C5'), 25.48(C4'), 30.65+30.69 (C-6'), 38.61+38.67(C8), 43.39+43.59(C5), 48.80+49.07(C6), 62.14+62.27(C1), 62.39+62.43(C3'), 64.73+64.87(C9), 70.99+ 71.02 (C4), 76.98+77.01(C7), 99.00(C1').

15a: ^1H NMR (400 MHz, C_6D_6)²¹: δ 1.39 (m, J=14+3.5+2 Hz, 8- H_A), 1.67(m, OAc), 1.72 (m, J=14+8+1+0.5 Hz, 8- H_B), 1.78(m, J=3+1+0.5 Hz, 5-H), 2.07 (m, J=9+6.2+1+1 Hz, 6-H), 2.8 (d, J=7.2 Hz, 4- H_A), 3.07 (m, J=8+3.5+0.5 Hz, 1-H), 3.2 (dd, J=7.2+3 Hz, 4- H_B), 3.98 (m, J=2+1+0.5 Hz, 7-H), 4.07 (dd, J=11.5+6.2 Hz, 9- H_A), 4.16 (dd, J=11.5+9 Hz, 9- H_B).

^{13}C NMR (100 MHz, CDCl_3)²¹: δ 20.86(OAc), 38.53(C8), 43.84(C5), 48.00(C6), 61.95(C9), 62.19(C1), 70.72(C4), 76.92(C7), 170.86(OAc).

RI-MS of **15a** (direct inlet, 120°C), m/e (rel. intensity%): 211(0.2) M^+ , 182(0.6), 169(2.3) $\text{M}^+ - \text{N}_3$, 122(2.1), 109(12), 43(100) CH_3CO^+ .

Formation of 17.

A solution of **16** (0.452 g, 2.00 mM) and 85% m-CPBA (0.812 g, 4.00 mM) in 200 mL of CH_2Cl_2 was kept at ambient temperature for 30 min. Then 20 mL of CH_2Cl_2 was added and the solution was washed with sat'd aq NaHCO_3 (10 mL, pH=9), 5% aq $\text{Na}_2\text{S}_2\text{O}_3$ (10 mL) and dried over MgSO_4 . The solvent was removed at atmospheric pressure (480°C). Repeated purification by DCFC (15 g SiO_2 , H:E=15:1) gave 0.025 g (5%) of volatile **17**. $R_f(\text{H:E}=10:1)=0.20$.

^1H NMR (400 MHz, CDCl_3)²¹: δ 1.42 (dd, J=10.5+1.5 Hz, 6- H_A), 1.45-1.76 (m, 1- H_2 + 8- H_2), 2.04 (m, J=10.5+2.2+2 Hz, 6- H_B), 2.69(m, J=4+2.2+2 Hz, 5-H), 4.59 (m, J=2+1.5+1.5 Hz, 7-H), 6.97 (m, 4-H), 7.38 (dd, J=8+7.5 Hz, 5'-H), 7.53 (m, J=7.5+2+1.5 Hz, 4'-H), 7.91 (m, J=8+1.5+1.5 Hz, 6'-H), 8.01 (dd, J=2+1.5 Hz, 2'-H).

^{13}C NMR (25.16 MHz, CDCl_3)²¹: δ 22.80(C1), 29.75(C8), 34.17(C6), 41.34(C5), 78.46(C7), 100.36(C4), 127.87(C8'), 129.65+129.72(C2'+C5'), 132.0(C1'), 133.07(C4'), 134.48(C3').

RI-MS (direct inlet, 100°C), m/e (rel. intensity%): 252 (2.2)M⁺, 156(3.5), 139(100), 113(38), 111(19), 97(80).

Acknowledgement.

Thanks are due to Dr.J.Tamás for the mass spectra and Mmes.P.Bartók and É.Löffler for the excellent technical assistance.

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