Stereospecific Synthesis and Antiviral Properties of Different Enantiomerically Pure Carbocyclic 2′-Deoxyribonucleoside Analogues Derived from Common Chiral Pools: (+)-(1*R*,5*S*)- and (−)-(1*S*,5*R*)-2-Oxabicyclo[3.3.0]oct-6-en-3-one

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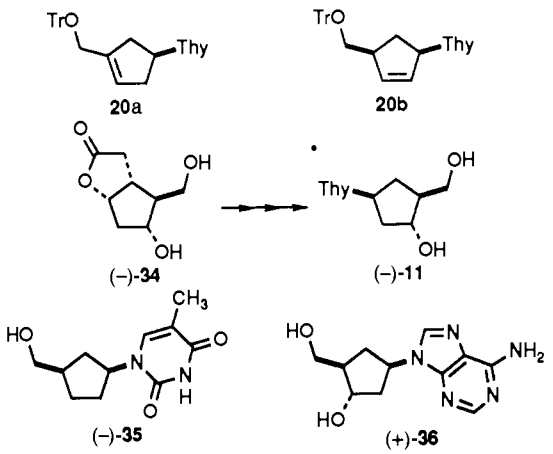
Enantiomerically pure (+)- and (−)-carbocyclic thymidine, (−)-carbocyclic 3′-*epi*-thymidine, (+)-carbocyclic 3′-deoxy-3′-azidothymidine, (+)-carbocyclic 2,3′-*O*-anhydrothymidine, (+)-carbocyclic 3′-*O*,6′-methylenethymidine, and (+)-(6′*S*)-carbocyclic 6′-methylthymidine were synthesized in a stereospecific manner from common chiral pools of (+)-(1*R*,5*S*)- and (−)-(1*S*,5*R*)-2-oxabicyclo[3.3.0]oct-6-en-3-one and evaluated for antiviral activity. (+)-Carbathymidine and, to a lesser extent, (+)-carbocyclic 2′-deoxyadenosine proved to be effective against HSV-1 [minimum inhibitory concentration (MIC): 0.2 and 2 μg/mL, respectively] and HSV-2 (MIC: 2 and 20 μg/mL, respectively), but virtually inactive against TK⁻ HSV-1 (MIC: 40 and 100 μg/mL, respectively). (+)-Carbathymidine was also active against vaccinia virus (2 μg/mL). None of the compounds had a specific effect on the replication of HIV or other RNA viruses.

Recently much attention has been focused on the carbocyclic nucleoside analogues from both a synthetic[1] and biological[2] viewpoint. The enduring interest in antiviral (e.g., anti-HSV, -HIV, etc.) agents, and the greater metabolic stability of the carba compared to the natural nucleosides, makes the preparation, especially of the enantiomerically pure compounds, an attractive synthetic goal at the present time. Chemoenzymatic approach,[3] asymmetric synthesis,[4] and enzymatic resolution[5] are the representative synthetic strategies that have appeared in the literature for the preparation of enantiomerically pure carba-2′-deoxyribonucleosides. Recently we reported the first stereospecific approach to (+)-(1*R*,2*S*,4*R*)-4-amino-2-hydroxy-1-(hydroxymethyl)cyclopentane,[6] (+)-carbathymidine,[6] (−)-carbocyclic 3′-deoxythymidine,[7] and (+)-carba-2′-deoxyadenosine[8] using a common chiral pool, (+)-(1*R*,5*S*)-2-oxabicyclo[3.3.0]oct-6-en-3-one, known from the prostanoid chemistry. Herewith we wish to report the stereospecific synthesis and antiviral activity of additional carbocyclic 2′-deoxyribonucleoside analogues derived from the same starting material and its enantiomer.

Results and Discussion

Chemistry. We describe here a number of novel alternative approaches for the synthesis of (+)-carbathymidine[6] [(+)-11] starting from the unsaturated bicyclic lactone (+)-1 (Scheme I). The main difference between these routes is the stage of the synthesis at which the configuration of the carbon atom bearing the secondary OH group is inverted. Part [(+)-1 → 3] of the whole reaction sequence has been published recently by our laboratory.[7] Esterification of 3 with full inversion of configuration (Mitsunobu reaction) could be performed either with simultaneous formation of the phosphinimine (as in 4) or with the intact azido group (as in 8). Apparently, esterification proved to be a faster process than the phosphinimine formation. Iminophosphorane 4 could be easily hydrolyzed by H_2O in THF to the corresponding cyclopentylamine 5, which in turn gave dihydroxycyclopentylamine derivative[6] (+)-7 on full deprotection (K_2CO_3/MeOH and p-TsOH/MeOH). Compound (+)-7 proved to be identical (R_f, $[\alpha]_D$, NMR, etc.) with that synthesized independently.[6,8] Alternatively, fully protected cyclopentyl azide derivative 8 was debenzoylated to 9 followed by detritylation to 10 which on reduction with H_2 over 10% Pd-C catalyst gave again (+)-7. Both routes

Chart I



afforded nearly the same overall yields (26 versus 32%, respectively) in four steps from 3. Synthesis of the heterocycle (thymine) in (+)-11 and in other congeners was completed according to the literature[9] with minor modifications. To avoid the formation of the undesired *N*-(3-methoxy-2-methylacryloyl)cyclopentylamine in considerable amount (5–20%), 1-h reflux and ≥2 equiv of AgOCN were necessary. Another synthetic variation to (+)-11 from 2 leads through (−)-carba-3′-*epi*-thymidine (−)-13. First, the azido group in 2 was smoothly reduced with H_2 over Pd-C, yielding cyclopentylamine derivative 12. After constructing the heterocyclic base of (−)-13, the primary OH group was blocked by tritylation. The secondary OH

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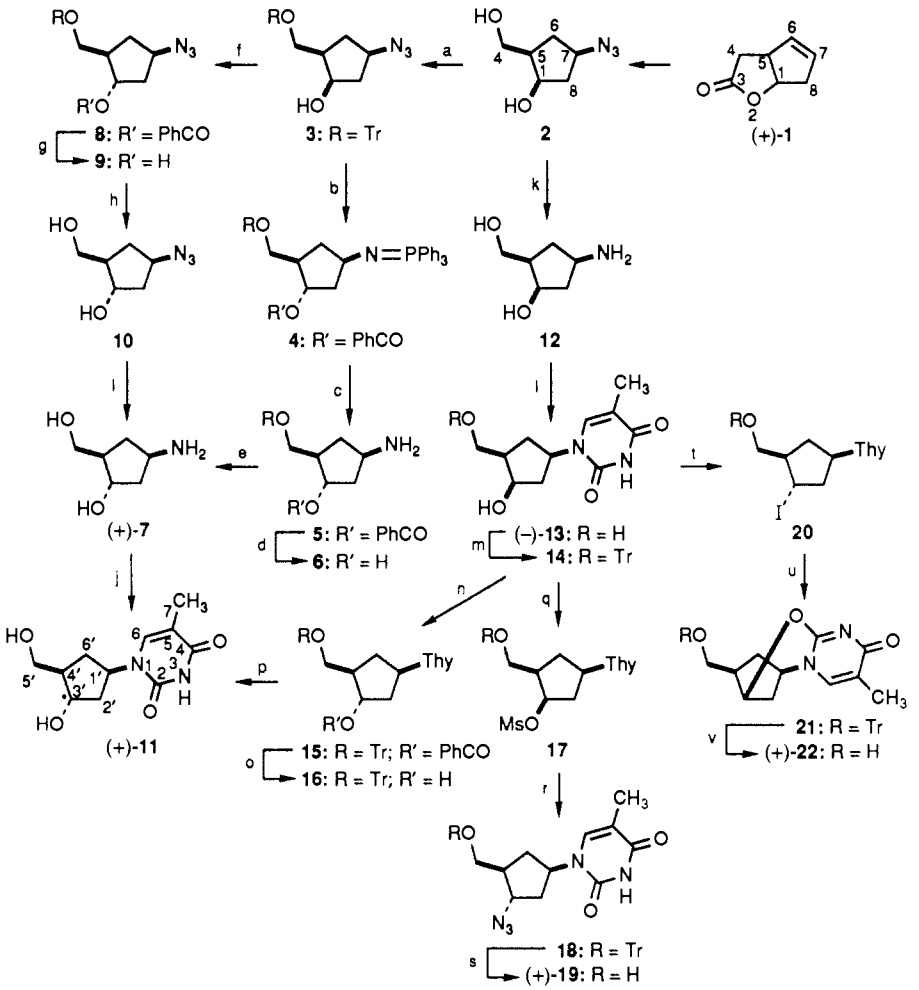
Scheme I[a]



[a] (a) TrCl, Py; (b) TPP, DEAD, $PhCO_2H$; (c) H_2O, THF; (d) K_2CO_3, MeOH; (e) p-TsOH, MeOH; (f) TPP, DEAD, $PhCO_2H$; (g) K_2CO_3, MeOH; (h) p-TsOH, MeOH; (i) H_2/10% Pd–C; (j) (i) MeOCH=C(Me)C(O)NCO, (ii) 25% aq NH_3; (k) 80% aq $NH_2NH_2 \cdot H_2O$, 10% Pd–C; (l) (i) MeOCH=C(Me)C(O)NCO, (ii) 25% aq NH_3, (m) TrCl, Py; (n) TPP, DEAD, $PhCO_2H$; (o) K_2CO_3, MeOH; (p) p-TsOH, MeOH; (q) MsCl, TEA; (r) NaN_3; (s) p-TsOH, MeOH; (t) TPP·I_2; (u) DBU; (v) p-TsOH, MeOH.

function was then benzoylated by triphenylphosphine/diethyl azodicarboxylate/$PhCO_2H$ in good yield with complete inversion of stereochemistry. Deprotection of **15** gave (+)-11 in low yield, which proved to be identical (R_f) to the product of the above-mentioned routes. The higher overall yield (17 versus 1.5%, respectively), obtained for the same length of synthesis (seven steps), suggests that the inversion of the secondary OH function should be conducted prior to the construction of the heterocyclic nucleoside base. Compound **16** (R_f = 0.13) looked more polar (SiO_2 TLC) than the corresponding 3′-*epi*-nucleoside derivative **14** (R_f = 0.26).

Carba-5′-trityl-3′-*epi*-thymidine 14 could be considered as a precursor for (+)-carbocyclic 3′-deoxy-3′-azidothymidine[10] [(+)-19]. Mesylation of **14** provided **17** in good yield, which on treatment with NaN_3 afforded protected azido derivative **18** in acceptable yield. Detritylation of **18** gave (+)-**19**, which proved to be identical with that published by Griengl et al.[10] ([α]$_D$, NMR). Compound **14** could also be converted to 3′-iodo derivative **20** in low yield by use of $Ph_3P \cdot I_2$ reagent[11] with full inversion of configuration. A minor side product of this reaction was the cyclopentene derivative **20a** (Chart I). The formation of **20a** can be explained, e.g., via the formation of 3′-*epi*-**20** followed by the trans HI elimination or through similar elimination process of the oxyphosphonium salt formed from Ph_3P and **14**. However, **20** failed to give the desired olefin **20b** (Chart I) on treatment with a strong base (DBU), but instead protected 2,3′-*O*-anhydronucleoside **21** was formed.

As we have published,[8] formation of the disubstituted 2-oxabicyclo[2.2.1]heptane **24** occurred when bis-tetrahydropyranylated iodomethyl compound **23** was treated with m-CPBA in CH_2Cl_2 in the presence of $NaHCO_3$ (Scheme II). Compound **26**, obtained from **24** after deprotection and reduction, served as precursor to afford the unusual carbocyclic nucleoside analogue (+)-**27** with a 3′-OH group masked in a covalent (ether) bond. Iodomethyl derivative **23** was also used, as a key intermediate, in the preparation of (+)-carba-6′-methylthymidine [(+)-**31**], having a substituted methylene group instead of the tetrahydrofuran oxygen of the natural nucleosides. Reduction of the iodomethyl group of **23** was achieved by $NaBH_4$ in HMPA[12] with good yield. It was followed by detetrahydropyranylation of **28** and reduction of the N_3 function of **29** to provide precursor (+)-**30**.

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Table I. Antiviral Activity of Carbocyclic 2'-Deoxyribonucleoside Analogues

	minimum inhibitory concentration,[a] μg/mL							
		PRK					Vero	HeLa
compound	MT-4 HIV-1	HSV-1 (KOS, F, McIntyre)	HSV-2 (G, 196, Lyons)	HSV-1 TK⁻ (B2006)	VV	VSV	PV-3, RV-1, SV, Coxs B4, SFV	VSV, Coxs B4, polio-1
(+)-11	>0.07 (0.07)[b] >1 (1)	0.2[c]	2[c]	40	2	>200 (200)	>100 (100)	>100 (100)
(−)-11	>160 (160)	>400	>400	>400	>400	>400	>400	>100 (100)
(−)-13	>250	>400	>400	>400	>400	>400	>200	>400
(+)-27	>250	>400	>400	>400	>400	>400	>400	>400
(+)-31	>250	>400	>400	>400	>400	>400	>400	>400
(−)-35	>250	>400	>400	>400	>400	>400	>400	>400
(+)-36	>50 (50)	2	20	100	100	>400	>100 (100)	>100 (100)
azidothymidine	0.001 (10)							
bromovinyldeoxy-uridine		0.02	7	≥200	20	>400	>400	>400
ribavirin		>400	>400	>400	10	300	150[d]	20[d]
C-c³Ado		>400	>400	150	0.7	0.7	0.7[d]	2[d]
PMEA[e]	2 (67)	7	7	150	>400	>400	>400	>400

[a] Required to reduce virus-induced cytopathogenicity by 50% (for abbreviations, see Experimental Section). [b] The minimum cytotoxic concentration of the compound for each particular cell line is indicated in parentheses, if toxicity was noted at a concentration ≤400 μg/mL. [c] For HSV-1 and HSV-2 the indicated values represent the average values each for three virus strains. [d] For ribavirin and C-c³Ado only the lowest MIC values are indicated that were obtained in each case, i.e., for ribavirin against PV-3 and VSV, and for C-c³Ado against RV-1 and VSV. [e] Data for 9-[2-(phosphonylmethoxy)ethyl]adenine (PMEA) were taken from refs 30 and 31.

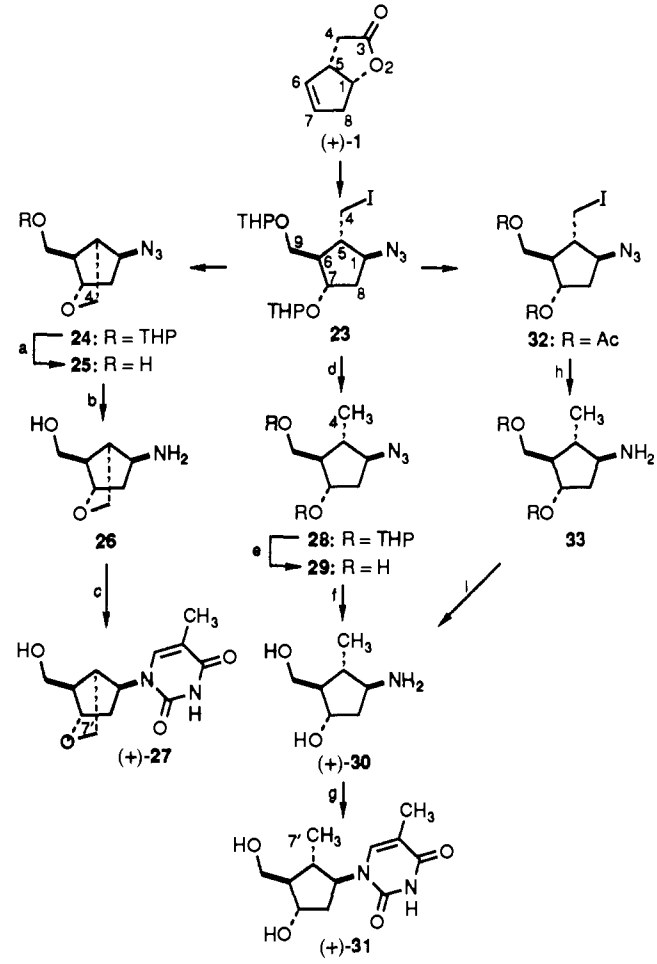
In an alternative way reductive dehalogenation and azide reduction of **32** were achieved in one step using n-Bu_3SnH. Contrary to the longer reaction sequence, this latter approach proved to be more efficient (57 versus 18% overall yield).

Enantiomerically pure isomer (−)-11 (Chart I) was synthesized starting from (−)-**34**[13] [$[\alpha]^{23}_D$ −41 ± 1° (*c* 1.5, MeOH)] following the preparation of (+)-11.[8] Preparation of (−)-**35** and (+)-**36** (Chart I) has also been described earlier by our laboratory.[7,8]

Biological Activity. Compounds (+)-**11**, (−)-**11**, (−)-**13**, (+)-**27**, (+)-**31**, (−)-**35**, and (+)-**36** were evaluated for their antiviral potential in various assay systems (Table I). In marked contrast with azidothymidine (which was included as a reference compound),[14] none of the newly synthesized compounds had a specific effect on HIV-1 replication. In fact, compound (+)-11 was highly cytotoxic to MT-4 cells: it impaired the viability of the cells at a concentration of 0.1–1 μg/mL. This contrasted with (−)-11 which was not toxic for MT-4 cells up to a concentration of 160 μg/mL. Compound (+)-11 was toxic for PRK cells only at a concentration of 200 μg/mL. In these cells it proved inhibitory to HSV-1, HSV-2, and VV replication at a concentration of 0.2, 2, and 2 μg/mL, respectively. Compound (+)-**36** was also active against HSV-1 and HSV-2 but only at a 10-fold higher concentration than (+)-11. None of the other newly synthesized compounds showed activity against HSV-1 or HSV-2.

Like bromovinyldeoxyuridine, a highly selective inhibitor of HSV-1,[15] compounds (+)-11 and (+)-**36** were much less active against a TK⁻ variant of HSV-1 (B2006) (Table I). They were also much less effective against a clinical HSV-1 isolate (VMW-1837)[16] that had a significantly reduced TK activity (data not shown). These data suggest that both (+)-11 and (+)-**36** depend on phosphorylation by the virus-induced dThd kinase to express their anti-

Scheme II[a]



[a] (a) AcOH/THF/H_2O, 4:2:1; (b) n-Bu_3SnH; (c) (i) MeOCH=C(Me)C(O)NCO, (ii) 25% aq NH_3; (d) $NaBH_4$, HMPA; (e) p-TsOH, MeOH; (f) 80% $NH_2NH_2 \cdot H_2O$, 10% Pd–C, MeOH; (g) (i) MeOCH=C(Me)C(O)NCO, (ii) 25% aq NH_3; (h) n-Bu_3SnH; (i) NH_3–MeOH.

HSV activity. This may perhaps be expected for the thymidine analogue (+)-11, but not for the adenosine analogue (+)-**36**. It would now seem worthwhile to further study the kinetic parameters of the interaction of (+)-11

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and (+)-36 with the HSV-1-encoded dThd kinase.

None of the compounds showed any appreciable activity against any of the RNA viruses tested (Table I) under conditions where ribavirin[17] and C-c^{3}Ado[18] exhibited the expected inhibitory effect, i.e., on vesicular stomatitis virus, parainfluenza virus, and reovirus.

Compound (+)-19, first described by Griengl et al.,[10] was also tested in one of our laboratories.[19] The (+)-carbocyclic analogue of AZT also proved to be inactive against HIV-1 in MT-4 cells at a concentration of 125 μM/mL and nontoxic to the host cells at a concentration of 625 μM/mL. Earlier, (±)-19 was also reported to be inactive against HIV-1.[20]

Thus, the only compounds that proved specifically active as antiviral agents were (+)-11 and (+)-36, and their activity spectrum was restricted to herpes simplex virus and vaccinia virus. The activity obtained with (+)-carbathymidine [(+)-11] against HSV-1 and HSV-2 is in agreement with those reported previously by Shealy et al.[21,22] for the racemic (±)-carbathymidine. Our results clearly show that the whole antiviral activity of (±)-carbathymidine resides in its (+)-enantiomer. Experiments have been undertaken to elucidate whether the reason(s) for the marked differences in the biological activity of (+)- and (−)-enantiomers of 11 resides (reside) in different phosphorylation patterns (in particular, the initial phosphorylation by the viral/cellular thymidine kinase) or different inhibitory effects at the DNA polymerase level.

Experimental Section

Abbreviations: HSV-1, herpes simplex virus type 1; HSV-2, herpes simplex virus type 2; HIV-1, human immunodeficiency virus type 1; VV, vaccinia virus; VSV, vesicular stomatitis virus; PV-3, parainfluenza virus type 3; RV-1, reovirus type 1; SV, Sindbis virus; Coxs B4, Coxsackie B4 virus; SFV, Semliki forest virus; polio-1, poliovirus type 1; MT-4, (human) T-4 lymphocyte (cells); PRK, primary rabbit kidney (cells); Vero, (African) green monkey kidney (cells); HeLa, (human) carcinoma cells; C-c^{3}Ado, carbocyclic 3-deazaadenosine; dThd, thymidine; AZT, 3′-deoxy-3′-azidothymidine; MIC, minimum inhibitory concentration; TK$^-$, thymidine kinase deficient; THF, tetrahydrofuran; p-TsOH·H_2O, *p*-toluenesulfonic acid monohydrate; SiO_2, silica gel; m-CPBA, 3-chloroperoxybenzoic acid; HMPA, hexamethylphosphoramide; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DEAD, diethyl azodicarboxylate; DCFC, dry column flash chromatography; TPP, triphenylphosphine; TEA, triethylamine; TrCl, triphenylmethyl chloride; Thy, thymin-1-yl; MsCl, methanesulfonyl chloride; THP, tetrahydropyran-2-yl; aq, aqueous; satd, saturated; Py, pyridine; bs, broad singlet; rt, room temperature.

Materials. Benzene, dichloromethane, ethyl acetate, and pyridine were distilled from P_2O_5, methanol was distilled from CaH_2, and tetrahydrofuran was distilled from lithium aluminum hydride. Triethylamine was distilled from and stored over KOH. Hexane and HMPA were used without purification. n-Bu_3SnH was freshly prepared from the corresponding tin chloride with $LiAlH_4$ in ether. 1,8-Diazabicyclo[5.4.0]undec-7-ene and diethyl azodicarboxylate were purchased from Fluka AG and Aldrich Chemical Co., respectively. Precoated 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.

Spectroscopy. ^1H and ^{13}C NMR spectra were recorded on Varian XL-100 and XL-400 instruments. ^1H assignments, if necessary, were performed with the aid of homonuclear spin-decoupling experiments. Mass spectrometric measurements were carried out on an AEI MS-902 double-focusing instrument with ionizing energy of 70 eV. All samples were introduced by direct probe. FAB-MS measurement was performed on the same instrument equipped with a homemade FAB source. The spectrum was taken by using a matrix of *m*-nitrobenzyl alcohol and Ar gun at 7 kV. Optical rotation measurements were performed on a Polamat A (Carl Zeiss, Jena, GDR) polarimeter.

Synthesis of (+)-Carbocyclic Thymidine [(+)-11]. [(Trityloxy)methyl]cyclopentane Derivative 3. A solution of 2 (2.09 g, 13.3 mM) and triphenylmethyl chloride (4.46 g, 16.0 mM) in pyridine (25 mL) was stirred at room temperature for 5.5 h. The reaction was near complete (SiO_2 TLC) and left to stand overnight at ambient temperature. Pyridine was then removed by evaporation, and ice–water (50 mL) was added followed by extraction with CH_2Cl_2 (5 × 20 mL). Then water was added to the organic phase in a separatory funnel, and the pH was adjusted to 3–4 by adding 2 M/L aq $NaHSO_4$ (12 mL). The latter aqueous phase was washed with CH_2Cl_2 (3 × 10 mL). The combined CH_2Cl_2 solution was shaken with brine (1 × 20 mL), dried over $MgSO_4$, and evaporated to dryness. The residue was purified by dry column flash chromatography[23] using 80 g of SiO_2 (<0.063 mm) and hexane/ethyl acetate, 10:1, followed by 5:1, as eluents. Fractions with impure 3 were evaporated, and the chromatography was repeated. Yield 4.75 g (89%); R_f (hexane/EtOAc, 5:1) = 0.23.

Phosphiniminocyclopentane Derivative 4. A solution of 3 (4.75 g, 11.9 mM), triphenylphosphine (4.67 g, 17.8 mM), benzoic acid (2.17 g, 17.8 mM), and diethyl azodicarboxylate (2.79 mL, 17.8 mM) in THF (50 mL) was stirred for 5 min at room temperature. As the conversion was not complete, the addition of the reagents in the same amount was repeated. After 5 min TLC showed no starting material. Approximately 20 min later a polar product (4) appeared. The total reaction time was 4 h. Then the solvent was removed by evaporation. The residue was dissolved in CH_2Cl_2 and applied to chromatography. DCFC: 80 g of SiO_2, CH_2Cl_2 followed by EtOAc. Compound 4 was eluted by MeOH. On evaporation the appropriate fractions gave 7.49 g (85%) of 4: R_f (butyl acetate/AcOH/EtOH/H_2O, 3:2:1:1) = 0.75; ^1H NMR (100 MHz, $CDCl_3$/DMSO-d_6)[24] δ 1.2–2.7 (5 H, m, H5, H6, and H8), 3.2 (2 H, d, J = 6 Hz, H4), 4.15 (1 H, m, H7), 5.2 (1 H, m, H1), 7.1–8.0 (35 H, m, aromatics).

Cyclopentylamine Derivative 5. A solution of 4 (4.21 g, 5.71 mM) and water (0.5 mL, 27.8 mM) in THF (70 mL) was kept at 50 °C for 3 h. Then it was left to stand overnight at room temperature. After removal of the solvent, the residue was dissolved in CH_2Cl_2 and applied to chromatography. DCFC: 80 g of SiO_2, CH_2Cl_2 followed by EtOAc. Compound 5 was eluted by MeOH. Evaporation afforded 1.29 g (47%) of pure 5: R_f (MeOH) = 0.20.

Hydroxycyclopentylamine Derivative 6. A mixture of 5 (1.29 g, 2.70 mM) and K_2CO_3 (1.38 g, 10 mM) in MeOH (30 mL) was stirred at ambient temperature for 5 h. The reaction was close to completion and left to stand at rt overnight. Then most of the MeOH was removed by evaporation (approximately 5 mL of volume remained), and this mixture was applied to DCFC (15 g SiO_2, MeOH/25% aq NH_3, 30:1). Chromatography yielded 0.978 g (97%) of 6: R_f (MeOH/25% aq NH_3, 30:1) = 0.46.

(+)-(1*R*,2*S*,4*R*)-4-Amino-2-hydroxy-1-(hydroxymethyl)cyclopentane [(+)-7]. A solution of 6 (0.978 g, 2.62 mM) in MeOH (20 mL) was treated with *p*-toluenesulfonic acid monohydrate (0.71 g, 3.73 mM) for 30 min. TLC showed complete conversion. Triethylamine (1.0 mL, 7.21 mM) was added, and the solution was evaporated to dryness. The residue in MeOH (20 mL) was applied to a Dowex 50WX8 (H^+) column (2.1 × 7 cm). The resin was first washed with MeOH (10 × 10 mL). Then crude (+)-7 (0.327 g) was eluted by using ~1 M/L aq NH_3. DCFC: 30 g of SiO_2, MeOH/25% aq NH_3, 30:1. On evaporation

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(23) Harwood, L. M. *Aldrichimica Acta* **1985**, *18*, 25.
(24) Atomic numbering refers to that of (+)-1 and 2 in Scheme I.

0.232 g (68%) of pure (+)-7 was obtained: $[\alpha]^{25}_D$ +33° (c 1.0, DMF);[6,8] R_f (MeOH/25% aq NH_3, 30:1) = 0.22; ^1H NMR (400 MHz, DMSO-d_6/$CDCl_3$)[25] δ 1.05 (1 H, m, J = 12.5 + 7.5 + 7.5 Hz, $H5_A$), 1.57 (1 H, m, J = 13 + 7 + 7 + 1.5 Hz, $H3_A$), 1.77 (1 H, m, J = 13 + 7 + 4.5 Hz, $H3_B$), 1.92 (1 H, m, J = 7.5 + 7.5 + 6 + 6 + 5 Hz, H1), 2.11 (1 H, m, J = 12.5 + 7.5 + 7.5 + 1.5 Hz, $H5_B$), 3.47 (1 H, m, J = 7.5 + 7.5 + 7 + 7 Hz, H4), 3.48 (2 H, d, J = 6 Hz, H6), 4.03 (1 H, m, J = 7 + 5 + 4.5 Hz, H2); ^{13}C NMR (100 MHz, DMSO-d_6/$CDCl_3$)[25] δ 37.90 (C5), 44.73 (C3), 49.76 (C1), 50.09 (C4), 63.47 (C6), 72.90 (C2); EI-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), 56 (62), 44 (44), 43 (38). Anal. ($C_6H_{13}NO_2$) C, H, N.

Protected Cyclopentyl Azide Derivative 8. A solution of **3** (0.81 g, 2.03 mM), TPP (0.80 g, 3.05 mM), DEAD (0.48 mL, 3.05 mM), and $PhCO_2H$ (0.37 g, 3.05 mM) in THF (10 mL) was stirred for 5 min at ambient temperature. As TLC showed about 50% conversion of **3**, the addition of the reagents was repeated followed by 5-min reaction time. Then Et_2O (40 mL) was added, and the solution was washed by satd aq $NaHCO_3$ (5 mL) and brine (5 mL) and dried over $MgSO_4$. The solvents were removed under reduced pressure. DCFC: 30 g of SiO_2, hexane/EtOAc, 13:1. The impure fractions were purified again as above but with hexane/EtOAc, 30:1. Yield 0.622 g (61%) of pure **8**; R_f (hexane/EtOAc, 15:1) = 0.44.

Hydroxycyclopentyl Azide Derivative 9. A mixture of **8** (0.449 g, 0.89 mM) and K_2CO_3 (2.46 g, 1.78 mM) in MeOH (10 mL) was stirred at rt for 1.5 h. Then the mixture was concentrated to a smaller volume (approximately 1 mL) and applied to chromatography. DCFC: 15 g of SiO_2, hexane/EtOAc, 3:1. Impure fraction was rechromatographed. On evaporation 0.299 g (84%) of pure **9** was obtained: R_f (hexane/EtOAc, 3:1) = 0.24.

Dihydroxycyclopentyl Azide Derivative 10. A solution of **9** (1.32 g, 3.30 mM) in MeOH (30 mL) was treated with p-TsOH·H_2O (0.050 g, 0.26 mM) for 2 h. TLC showed apparently complete conversion. TEA (0.5 mL, 3.61 mM) was added, and the solution was evaporated to dryness. DCFC: 15 g of SiO_2, hexane/EtOAc, 1:2. Chromatography afforded 0.481 g (93%) of **10**: R_f (hexane/EtOAc, 1:2) = 0.15.

Synthesis of (+)-7 from 10. A mixture of **10** (0.481 g, 3.06 mM) and 0.094 g of 10% Pd–C in 20 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 **10** to (+)-7 was attained in 1.33 h. Then the catalyst was filtered off through a short asbestos pad, washed with MeOH (3 × 3 mL). The MeOH solution was evaporated to dryness. DCFC: 15 g of SiO_2, MeOH/25% aq NH_3, 30:1. The impure fractions were purified again as above, but MeOH/25% aq NH_3, 100:1, followed by 30:1, was used. Yield 0.271 g (68%) of pure (+)-7; R_f (MeOH/25% aq NH_3, 30:1) = 0.22.

General Procedure for the Construction of the Thymine Base. 1. Addition. *N*-[[[(1*R*,3*S*,4*R*)-3-Hydroxy-4-(hydroxymethyl)cyclopentyl]amino]carbonyl]-3-methoxy-2-methyl-2-propenamide (11a). A mixture of 3-methoxy-2-methylacryloyl chloride (0.850 g, 6.32 mM) and silver cyanate (2.25 g, 15 mM) in benzene (30 mL) was refluxed for 1 h under N_2. After cooling to ambient temperature, 12.5 mL (~2.62 mM) of the supernatant isocyanate solution was added dropwise to a solution of (+)-7 (0.230 g, 1.75 mM) in 12 mL of DMF–Et_2O (3:1 v/v) at −20 °C under N_2 in 20 min. After 2 h TLC still showed some (+)-7 to be present in the reaction mixture. Further isocyanate solution (3 mL, 0.63 mM) was needed to drive the reaction to completion. Then ethanol (20 mL) was added, and the solution was evaporated to dryness and coevaporated with EtOH (2 × 25 mL). The yellow syrup obtained was applied to DCFC (25 g of SiO_2, gradient elution from $CHCl_3$ → $CHCl_3$/MeOH, 19:1). Chromatographically pure crystalline **11a** (0.315 g, 66%) was obtained on evaporation of the appropriate fractions: R_f ($CHCl_3$/MeOH, 9:1) = 0.22.

2. Ring Closure. (+)-Carbocyclic Thymidine [(+)-11]. A solution of **11a** (0.315 g, 1.16 mM) in 35 mL of satd aq NH_3 was stirred under reflux for 2.5 h. After cooling to rt, 30 mL of ethanol was added and the solvents were removed in vacuo. The residue was first coevaporated with EtOH (2 × 30 mL), and then the crystalline crude product was triturated with cold dry ether. The product was then filtered off, washed with a small volume of cold EtOH and Et_2O, and dried on air, providing 0.235 g of pure (+)-11. Preparative TLC of the washings afforded an additional 0.019 g of (+)-11. Yield 0.254 g (91%); R_f ($CHCl_3$/MeOH, 9:1) = 0.11; $[\alpha]^{25}_D$ +8.9° (c 1.0, MeOH);[6] CD (H_2O, 3.44 mmol/L, 0.05 cm) λ (Δε) 282.4 (−0.526), 276.8 (−0.660), 270.4 (−0.628), 268.4 (−0.614), 263.8 (−0.419) nm; ^1H NMR (100 MHz, DMSO-d_6/$CDCl_3$)[26] δ 1.40–2.35 (5 H, m, H2′, H4′, H6′), 1.86 (3 H, d, J = 1.5 Hz, H7), 3.63 (2 H, m, H5′), 4.22 (1 H, q, ∑J = 16.5 Hz, H3′), 5.06 (1 H, m, ∑J = 35 Hz, H1′), 7.24 (1 H, q, J = 1.5 Hz, H6), 10.3 (1 H, bs, H3); ^{13}C NMR (25.2 MHz, DMSO-d_6/$CDCl_3$)[26] δ 12.09 (C7), 32.26 (C6′), 39.00 (C2′), 48.81 (C4′), 53.34 (C1′), 62.69 (C5′), 71.58 (C3′), 109.34 (C5), 137.59 (C6), 151.02 (C2), 163.88 (C4); EI-MS, m/e (rel intensity %) 240 (39) M^+, 212 (17) M^+–CO, 203 (6), 191 (4), 183 (8), 181 (8), 168 (5), 153 (10) $B^+ + C_2H_4$, 127 (100) $B^+ + 2$ H, 126 (87) $B^+ + H$, 110 (15), 96 (65). Anal. ($C_{11}H_{16}N_2O_4$) C, H, N.

Cyclopentylamine Derivative 12. To a mixture of **2** (0.084 g, 0.53 mM) and 10% Pd–C (0.70 g) in 10 mL of MeOH was added 0.5 mL of 80% aq $NH_2NH_2·H_2O$. An exothermic reaction took place at once. After 30 min the catalyst was filtered off through asbestos and washed with methanol (10 × 3 mL). The solution was evaporated to dryness under reduced pressure. Yield 0.058 g (83%) of **12**; R_f (MeOH/25% aq NH_3, 30:1) = 0.10. Anal. ($C_6H_{13}NO_2$) C, H, N.

Triacetyl-12. A representative procedure for acetylations was as follows: A solution of **12** (0.058 g, 0.44 mM), 4-(dimethylamino)pyridine (0.21 g, 1.72 mM), and Ac_2O (0.14 mL, 1.45 mM) in 5 mL of CH_2Cl_2 was stirred at rt for 5 min. Then MeOH (0.5 mL, 12.3 mM) was added, and the solution was evaporated to dryness. DCFC (15 g of SiO_2, EtOAc followed by EtOAc/MeOH, 20:1) afforded 0.088 g (78%) of pure triacetyl-**12**: R_f (EtOAc) = 0.12; ^1H NMR (100 MHz, $CDCl_3$)[24] δ 1.2–2.7 (5 H, m, H5, H6, and H8), 1.95 (3 H, s, OAc), 2.02 (3 H, s, OAc), 2.05 (3 H, s, OAc), 4.14 (2 H, d, J = 7.5 Hz, H4), 4.40 (1 H, m, H7), 5.29 (1 H, m, J = 2.5 + 5.5 + 5.5 Hz, H1), 5.70 (1 H, bs, NH); ^{13}C NMR (25.2 MHz, $CDCl_3$)[24] δ 20.86 (OAc), 21.13 (OAc), 23.22 (NHAc), 34.89 (C6), 40.17 (C8), 41.96 (C5), 48.15 (C7), 62.95 (C4), 74.47 (C1), 169.66 (NHAc), 170.02 (OAc), 170.97 (OAc).

(−)-Carbocyclic 3′-*epi*-Thymidine [(−)-13]. 1. Addition. Compound **12** (0.429 g, 3.28 mM) was reacted with the isocyanate (5.44 mM), and 3.5 h was needed to drive the reaction to completion. Yield 0.750 g (84%) of **13a**; R_f ($CHCl_3$/MeOH, 9:1) = 0.33.

2. Ring Closure. Yield 0.593 g (90%); mp 178–180 °C; $[\alpha]^{27}_D$ −59° (c 1.0, MeOH); R_f ($CHCl_3$/MeOH, 9:1) = 0.19; ^1H NMR (100 MHz, $CDCl_3$/DMSO-d_6)[26] δ 1.6–2.6 (5 H, m, H2′, H4′, and H6′), 1.9 (3 H, d, J = 1 Hz, H7), 3.8 (2 H, d, J = 4 Hz, H5′), 4.36 (1 H, m, J = 4 + 3 + 3 Hz, H3′), 5.10 (1 H, m, J = 5 + 8 + 8 + 12 Hz, H1′), 7.68 (1 H, q, J = 1 Hz, H6), 9.7 (1 H, bs, H3); ^{13}C NMR (25.2 MHz, $CDCl_3$/DMSO-d_6)[26] δ 12.54 (C7), 32.36 (C6′), 40.48 (C2′), 46.91 (C4′), 53.31 (C1′), 60.76 (C5′), 71.56 (C3′), 110.62 (C5), 138.60 (C6), 151.54 (C2), 164.40 (C4); EI-MS, m/e (rel intensity %) 240 (61) M^+, 222 (4.1), 211 (0.5), 209 (0.5), 196 (6.5), 191 (3.9), 181 (70), 165 (2.2), 153 (32), 148 (5.4), 138 (12), 127 (98) $B^+ + 2$ H, 126 (100) $B^+ + H$. Anal. ($C_{11}H_{16}N_2O_4$) C, H, N.

Carbocyclic 5′-*O*-Trityl-3′-*epi*-thymidine (14). A solution of (−)-**13** (1.06 g, 4.41 mM) and triphenylmethyl chloride (1.47 g, 5.29 mM) in 10 mL of pyridine was stirred at ambient temperature for 4.75 h. As the reaction was not complete, 0.38 g (1.36 mM) of TrCl was added. Total reaction time was 5.66 h. The solvent was removed by evaporation, and 10 mL of H_2O and CH_2Cl_2 (30 mL) were added. Then the pH was adjusted to 4 by using 2 M/L aq $NaHSO_4$ (11 mL). The aqueous layer was further extracted with CH_2Cl_2 (4 × 20 mL). The combined organic phase was washed with brine (10 mL), dried over $MgSO_4$, and evaporated. The residue was refluxed in EtOAc (10 mL). After cooling, the crystalline material was filtered off and washed with EtOAc (yield 1.98 g). The mother liquid was evaporated and purified

(25) Atomic numbering follows the systematic nomenclature of (+)-7.

(26) Atomic numbering corresponds to that of the nucleosides as shown on the formula of (+)-11 in Scheme I.

by DCFC (15 g of SiO_2, the residue was dissolved in CH_2Cl_2, hexane/EtOAc, 1:1, yield 0.098 g). Yield 2.08 g (98%); mp 247–248 °C; R_f (hexane/EtOAc, 1:2) = 0.26; ^{1}H NMR (100 MHz, $CDCl_3$)[26] δ 1.6–2.6 (5 H, m, H2′, H4′, and H6′), 1.9 (3 H, d, J = 1 Hz, H7), 3.27 + 3.46 (2 H, m, J_{gem} = 10 Hz, J_{vic} = 6.5 + 5 Hz, H5′), 4.41 (1 H, m, J = 4 + 3 + 1 Hz, H3′), 5.17 (1 H, m, J = 5 + 8 + 8 + 12 Hz, H1′), 7.15–7.5 (15 H, m, aromatics), 7.60 (1 H, q, J = 1 Hz, H6), 8.50 (1 H, bs, H3).

Carbocyclic 5′-*O*-Trityl-3′-*O*-benzoylthymidine (15). A solution of 14 (0.483 g, 1.0 mM), TPP (0.787 g, 3.0 mM), DEAD (0.16 mL, 1.0 mL), and $PhCO_2H$ (0.122 g, 1.0 mM) was stirred at rt for 5 min. Then Et_2O (40 mL) was added, and the solution was washed with satd aq $NaHCO_3$ (5 mL) and brine (5 mL) and dried over $MgSO_4$. After evaporation the residue was purified by DCFC (30 g of SiO_2, hexane/EtOAc, 1:1). Yield 0.367 g (63%); R_f (hexane/EtOAc, 1:1) = 0.21.

Carbocyclic 5′-*O*-Tritylthymidine (16). A mixture of 15 (0.367 g, 0.63 mM) and K_2CO_3 (0.28 g, 2 mM) in 10 mL of MeOH was stirred at rt. As the conversion of 15 was not complete after 4 h, the same amount of K_2CO_3 was added again. The mixture was left to stand overnight at rt. Then it was concentrated to ~2-mL volume. DCFC: 15 g of SiO_2, hexane/EtOAc, 1:2. Impure fractions were purified repeatedly as above. The residue dissolved in CH_2Cl_2. Yield 0.012 g (3.9%); R_f (hexane/EtOAc, 1:2) = 0.13; ^{1}H NMR (100 MHz, $CDCl_3$)[26] δ 1.3–2.4 (5 H, m, H2′, H4′, and H6′), 1.88 (3 H, d, J = 1 Hz, H7), 3.19 + 3.42 (2 H, m, J_{gem} = 10 Hz, J_{vic} = 6.5 + 5 Hz, H5′), 4.26 (1 H, q, J = 6 Hz, H3′), 5.10 (1 H, m, J = 8 + 8 + 8.5 + 9 Hz, H1′), 6.95 (1 H, q, J = 1 Hz, H6), 7.2–7.5 (15 H, m, aromatics), 8.56 (1 H, bs, H3).

Synthesis of (+)-11 from 16. A solution of 16 (0.012 g) in 0.2 mL of MeOH was treated with a small amount (~1 mg) of p-TsOH·H_2O. After 1 h TLC showed essentially complete reaction. The cochromatography of the product with authentic sample evidenced its structure to be (+)-11. R_f (EtOAc/MeOH, 10:1) = 0.15.

(Mesyloxy)cyclopentane Derivative 17. A solution of 14 (0.483 g, 1.0 mM), TEA (0.21 mL, 1.5 mM), and MsCl (0.09 mL, 1.1 mM) in 20 mL of CH_2Cl_2 was stirred at 0 °C for 15 min. Then the stirring was continued for an additional hour at ambient temperature. TLC (EtOAc eluent) showed the reaction to be complete. CH_2Cl_2 (30 mL) was added, and the solution was washed with ice–water (3 × 10 mL) and dried over $MgSO_4$. The residue dissolved in CH_2Cl_2 was chromatographed with DCFC (15 g of SiO_2, hexane/EtOAc, 1:1). Evaporation of the appropriate fractions afforded 0.346 g (62%) of pure 17: R_f (hexane/EtOAc, 1:2) = 0.27; ^{1}H NMR (100 MHz, $CDCl_3$)[26] δ 1.3–2.8 (5 H, m, H2′, H4′, and H6′), 1.90 (3 H, d, J = 1 Hz, H7), 2.74 (3 H, s, CH_3SO_2), 3.1–3.6 (2 H, m, H5′), 5.20 (1 H, m, H1′), 5.28 (1 H, m, J = 4 + 3 + 1 Hz, H3′), 7.2–7.6 (15 H, m, aromatics), 8.65 (1 H, bs, H3).

Carbocyclic 5′-*O*-Trityl-3′-deoxy-3′-azidothymidine (18). A mixture of 17 (0.329 g, 0.59 mM) and NaN_3 (0.077 g, 1.18 mM) in 5 mL of DMF was stirred at 70–75 °C for 2 h. Then H_2O (35 mL) was added and 18 was extracted with Et_2O (5 × 20 mL). The ethereal solution was washed with brine (10 mL) and dried over $MgSO_4$. Crude 18 was purified by DCFC (15 g of SiO_2, hexane/EtOAc, 2:1). Isolated was 0.179 (60%) of 18: R_f (hexane/EtOAc, 1:1) = 0.25; ^{1}H NMR (100 MHz, $CDCl_3$)[26] δ 1.4–2.4 (5 H, m, H2′, H4′, and H6′), 1.86 (3 H, d, J = 1 Hz, H7), 3.28 (2 H, m, H5′), 4.0 (1 H, m, J = 6.5 + 6 + 6 Hz, H3′), 4.92 (1 H, m, J = 8 + 8 + 8.5 + 9 Hz, H1′), 6.94 (1 H, q, J = 1 Hz, H6), 7.1–7.5 (15 H, m, aromatics), 8.70 (1 H, bs, H3).

(+)-Carbocyclic 3′-Deoxy-3′-azidothymidine [(+)-19]. A solution of 18 (0.161 g, 0.32 mM) in 5 mL of MeOH was treated with 0.010 g (0.053 mM) of p-TsOH·H_2O at ambient temperature. After 3.5 h of reaction time TLC showed complete conversion. The acid catalyst was quenched with 0.1 mL (0.72 mM) of TEA, and the solution was evaporated to dryness. The residue was purified by DCFC (15 g of SiO_2, hexane/EtOAc, 1:2). Pure fractions gave on evaporation 0.064 g (75%) of (+)-19: R_f (EtOAc) = 0.38; $[\alpha]^{23}_D$ +16 ± 1° (c 0.98, acetone);[10] ^{1}H NMR (100 MHz, DMSO-d_6/$CDCl_3$)[26] δ 1.6–2.4 (5 H, m, H2′, H4′, and H6′), 1.88 (3 H, d, J = 1 Hz, H7), 3.66 (2 H, m, H5′), 4.1 (1 H, m, J = 6 + 6 + 5.5 Hz, H3′), 4.95 (1 H, m, J = 8 + 8 + 9 + 9 Hz, H1′), 7.24 (1 H, q, J = 1 Hz, H6), 10.2 (1 H, bs, H3); ^{13}C NMR (25.2 MHz, DMSO-d_6/$CDCl_3$)[26] δ 12.18 (C7), 31.89 (C6′), 35.99 (C2′), 46.55 (C4′), 53.75 (C1′), 61.96 (C3′), 62.08 (C5′), 109.82 (C5), 137.48 (C6), 151.04 (C2), 163.97 (C4); EI-MS, m/e (rel intensity %) 265 (7.2) M^+, 239 (0.7), 223 (0.8), 219 (2.2), 204 (0.4), 196 (1.2), 193 (4.3), 178 (24), 167 (1.6), 153 (9.5), 135 (29), 127 (40) B^+ + 2 H, 126 (100) B^+ + H.

Cyclopentyl Iodide Derivative 20. A solution of TPP (0.674 g, 2.57 mM) and I_2 (0.604 g, 2.38 mM) in 10 mL of dry CH_2Cl_2 was stirred at room temperature for 30 min. (After 5 min some precipitation occurred.) Then a suspension of 14 (0.956 g, 1.98 mM) and pyridine (0.19 mL, 2.38 mM) in 10 mL of CH_2Cl_2 was added to and washed in the above mixture with 8 mL of CH_2Cl_2 at 0 °C. The mixture was left to stand at ambient temperature overnight. After the precipitate was removed by filtration, CH_2Cl_2 (20 mL) was added and the solution was washed with H_2O (10 mL). Then 10 mL of H_2O was poured to the organic layer in a separatory funnel, and the pH was adjusted to 2 with 0.5 mL of 2 M/L aq $NaHSO_4$. The CH_2Cl_2 solution was washed with 5% aq $Na_2S_2O_3$, dried over $MgSO_4$, and evaporated to smaller volume (~15 mL). DCFC (15 g of SiO_2, hexane/EtOAc, 2:1) provided 0.201 g (17%) of 20: R_f (hexane/EtOAc, 1:1) = 0.45; ^{1}H NMR (100 MHz, $CDCl_3$)[26] δ 1.6–2.5 (3 H, m, H4′ and H6′), 1.86 (3 H, d, J = 1 Hz, H7), 2.48 (2 H, m, H2′), 3.28 (2 H, d, J = 4.5 Hz, H5′), 4.38 (1 H, q, J = 7.5 Hz, H3′), 5.08 (1 H, m, J = 8 + 8 + 9 + 9 Hz, H1′), 6.98 (1 H, q, J = 1 Hz, H6), 7.2–7.55 (15 H, m, aromatics), 8.50 (1 H, bs, H3). A minor side product (**20a**) was also isolated (4.3%): R_f (hexane/EtOAc, 1:1) = 0.24; ^{1}H NMR (100 MHz, $CDCl_3$)[16] δ 1.89 (3 H, d, J = 1 Hz, H7), 2.3–3.1 (4 H, m, H2′ and H6′), 3.73 (2 H, bs, H5′), 5.38 (1 H, m, J = 8 + 8 + 4 + 3.5 Hz, H1′), 5.78 (1 H, t, J = 2 + 1.5 Hz, H3′), 7.06 (1 H, q, J = 1 Hz, H6), 7.2–7.5 (15 H, m, aromatics), 8.52 (1 H, bs, H3).

Detritylated 20a. Yield 68%; R_f (EtOAc) = 0.20; ^{1}H NMR (100 MHz, DMSO-d_6/$CDCl_3$)[26] δ 1.82 (3 H, d, J = 1 Hz, H7), 2.3–3.05 (4 H, m, H2′ and H6′), 4.11 (2 H, bs, H5′), 5.29 (1 H, m, J = 8 + 8 + 4.5 + 4 Hz, H1′), 5.64 (1 H, t, J = 2 + 2 Hz, H3′), 7.10 (1 H, q, J = 1 Hz, H6), 10.72 (1 H, bs, H3); ^{13}C NMR (25.2 MHz, DMSO-d_6/$CDCl_3$)[26] δ 12.33 (C7), 38.83 (C6′), 38.92 (C2′), 52.76 (C1′), 60.07 (C5′), 110.46 (C5), 122.27 (C3′), 136.80 (C6), 143.67 (C4′), 150.95 (C2), 164.15 (C4).

Carbocyclic 5′-*O*-Trityl-2,3′-*O*-anhydrothymidine (21). A solution of 20 (0.183 g, 0.31 mM) and DBU (0.09 mL, 0.62 mM) in 10 mL of benzene was refluxed for 1 h. TLC showed complete conversion of 20. (Some precipitation occurred, which was very likely DBU·HI.) Total reflux time was 2 h. The reaction mixture was transferred to a DCFC column (15 g of SiO_2, EtOAc/MeOH, 5:1). Crude 21 was purified again in the same manner, but now it was dissolved in EtOAc/MeOH, 5:1, and eluted with EtOAc/MeOH, 10:1, followed by 5:1. Evaporation yielded 0.131 g (91%) of pure 21: R_f (EtOAc/MeOH, 5:1) = 0.19; ^{1}H NMR (100 MHz, $CDCl_3$)[26] δ 1.45–2.55 (5 H, m, H2′, H4′, and H6′), 1.88 (3 H, d, J = 1 Hz, H7), 3.12 + 3.48 (2 H, m, J_{gem} = 10 Hz, J_{vic} = 8 + 7 Hz, H5′), 4.12 (1 H, m, J = 3 + 3 + 4 Hz, H3′), 5.05 (1 H, m, J = 3 + 3 + 2 + 1 Hz, H1′), 6.74 (1 H, q, J = 1 Hz, H6), 7.1–7.5 (15 H, m, aromatics).

(+)-Carbocyclic 2,3′-*O*-Anhydrothymidine [(+)-(22)]. A solution of 21 (0.116 g, 0.25 mM) in 5 mL of MeOH was treated with p-TsOH·H_2O (pH ~2) and left to stand overnight. The reaction was complete and was quenched by adding TEA (0.5 mL). After evaporation DCFC (15 g of SiO_2, EtOAc/MeOH, 1:1) provided 0.032 g (57%) of (+)-22: R_f (EtOAc/MeOH, 1:1) = 0.20; mp 230–231 °C; $[\alpha]^{25}_D$ +19 ± 1° (c 0.6, MeOH); ^{1}H NMR (100 MHz, $CDCl_3$/DMSO-d_6)[26] δ 1.4–2.40 (5 H, m, H2′, H4′, and H6′), 1.48 (3 H, d, J = 1 Hz, H7), 3.2 (2 H, m, H5′), 4.02 (1 H, m, J = 3 + 3 + 4 Hz, H3′), 4.68 (1 H, m, J = 3 + 3 + 2 + 1 Hz, H1′), 6.81 (1 H, q, J = 1 Hz, H6); FAB-MS, m/e (rel intensity %) 223 (100) MH^+, 127 (39) $(B)H_2^+$. Anal. ($C_{11}H_{14}N_2O_3$) C, H, N.

5′-*O*-Acetyl-(+)-22. Yield 59%; R_f (EtOAc/MeOH, 5:1) = 0.28; ^{1}H NMR (100 MHz, $CDCl_3$/DMSO-d_6)[26] δ 1.6–2.8 (5 H, m, H2′, H4′, and H6′), 1.89 (3 H, d, J = 1 Hz, H7), 1.96 (3 H, s, OAc), 4.17 (2 H, m, H5′), 4.41 (1 H, m, J = 4 + 3 + 3 Hz, H3′), 5.04 (1 H, m, J = 3 + 3 + 2 + 1 Hz, H1′), 7.14 (1 H, q, J = 1 Hz, H6).

(Hydroxymethyl)oxabicycloheptane Derivative 25. A solution of 24 (1.55 g, 6.12 mM) in 21 mL of AcOH/THF/H_2O, 4:2:1 (v/v), was stirred at 45 °C for 8.5 h. After evaporation DCFC (30 g of SiO_2, hexane/EtOAc, 1:1) afforded 0.463 g (45%) of 25: R_f (EtOAc) = 0.29.

(1*S*,2*R*,3*S*,4*S*)-4-Amino-1-*O*,3-methylene-2-(hydroxymethyl)cyclopentanol (26). A solution of 25 (0.463 g, 2.74 mM)

in 18 mL of benzene containing ~11 mM of n-Bu_3SnH was refluxed for 1.5 h. Then the solution was evaporated, and 20 mL of CH_3CN was added to the residue. After extraction with hexane (5 × 20 mL), the CH_3CN solution was evaporated. The residue was chromatographed by DCFC (15 g of SiO_2, MeOH/25% aq NH_3, 100:1). Evaporation of the appropriate fractions gave 0.242 g (62%) of crystalline **26**: R_f (MeOH/25% aq NH_3, 100:1) = 0.10. Anal. ($C_7H_{13}NO_2$) C, H, N.

Diacetyl-26. Yield 71%; R_f (EtOAc/MeOH, 10:1) = 0.21; ^1H NMR (100 MHz, $CDCl_3$)[27] δ 1.58 (1 H, m, J = 14.5 + 5 + 1 + 1 Hz, $H8_A$), 1.92 (3 H, s, NHAc), 2.09 (3 H, s, OAc), 2.2–2.5 (2 H, m, $H8_B$ and H6), 2.50 (1 H, m, J = 2.5 + 0.5 Hz, H5), 3.58 (1 H, d, J = 7 Hz, $H4_A$), 3.72 (1 H, dd, J = 7 + 2.5 Hz, $H4_B$), 4.02 (1 H, m, J = 8 + 5 + 0.5 Hz, H1), 4.14 + 4.39 (2 H, m, J_{gem} = 11.5, J_{vic} = 7 + 9 Hz, H9), 4.20 (1 H, m, J = 1 + 1 + 1 Hz, H7), 6.44 (1 H, bs, NH); ^{13}C NMR (25.2 MHz, $CDCl_3$)[27] δ 20.94 (OAc), 23.01 (NHAc), 39.94 (C8), 43.62 (C5), 48.43 (C6), 51.33 (C1), 62.12 (C9), 72.38 (C4), 76.60 (C7), 170.22 (NHAc), 171.75 (OAc).

(+)-Carbocyclic 3'-*O*,6'-Methylenethymidine [(+)-27]. 1. **Addition.** Compound **26** (0.200 g, 1.4 mM) was reacted with the appropriate isocyanate (2.8 mM) in benzene. DCFC: 25 g of SiO_2, $CHCl_3$/MeOH, 97:3. Yield 0.186 g, 47%; R_f ($CHCl_3$/MeOH, 9:1) = 0.30.

2. Ring Closure. DCFC (15 g of SiO_2, EtOAc/MeOH, 10:1) provided 0.108 g (66%) of pure (+)-**27**: R_f (EtOAc/MeOH, 10:1) = 0.24; mp 215 °C; $[\alpha]^{25}_D$ +111° (*c* 1.0, MeOH); ^1H NMR (400 MHz, DMSO-d_6/$CDCl_3$)[26] δ 1.74 (1 H, m, J = 14.5 + 5 + 1 + 1 Hz, $H2'_A$), 1.90 (3 H, d, J = 1 Hz, H7), 2.49 (1 H, m, J = 10 + 6.5 + 1 + 1 Hz, H4'), 2.61 (1 H, m, J = 14.5 + 8 + 1 + 1 Hz, $H2'_B$), 2.98 (1 H, dd, J = 3 + 0.5 Hz, H6'), 3.28 (1 H, dd, J = 11 + 10 Hz, $H5'_A$), 3.63 (1 H, d, J = 7.5 Hz, $H7'_A$), 3.72 (1 H, dd, J = 11.0 + 6.5 Hz, $H5'_B$), 3.85 (1 H, dd, J = 7.5 + 3 Hz, $H7'_B$), 4.21 (1 H, m, J = 1 + 1 + 1 Hz, H3'), 4.25 (1 H, m, J = 8 + 5 + 1 + 0.5 Hz, H1'), 4.57 (1 H, bs, OH), 7.6 (1 H, q, J = 1 Hz, H6), 10.4 (1 H, bs, H3); ^{13}C NMR (25.2 MHz, DMSO-d_6/$CDCl_3$)[26] δ 12.28 (C7), 40.10 (C2'), 41.38 (C6'), 51.48 (C4'), 58.55 (C5'), 59.41 (C1'), 73.02 (C7'), 76.13 (C3'), 107.99 (C5), 137.87 (C6), 151.26 (C2), 164.39 (C4); EI-MS, m/e (rel intensity %) 252 (98) M^+, 235 (2.8), 234 (1.5), 223 (2.4), 221 (6.8), 203 (4.1), 191 (5.2), 181 (8.0), 179 (5.2), 165 (3.6), 153 (42), 152 (14), 148 (7.6), 127 (86) B^+ + 2 H, 126 (100) B^+ + H. Anal. ($C_{12}H_{16}N_2O_4$) C, H, N.

α-Methylcyclopentyl Azide Derivative 28. A solution of **23** (1.52 g, 3.27 mM) and $NaBH_4$ (0.24 g, 6.54 mM) in HMPA (20 mL) was kept at ambient temperature for 7 min. Then water (150 mL), Et_2O (60 mL), and some solid NaCl were added. The aqueous layer was further extracted with 3 × 20 mL of Et_2O. The organic phase was washed with brine (10 mL) and dried over $MgSO_4$. The residue obtained on evaporation was purified by DCFC (30 g of SiO_2, hexane/EtOAc, 10:1, followed by 5:1), yielding 0.67 g (60%) of **28** (observed to be an at least three-component mixture): R_f (hexane/EtOAc, 5:1) = 0.24–0.29; ^1H NMR (100 MHz, $CDCl_3$)[27] δ 1.15 (3 H, d, J = 6 Hz, H4), 1.2–2.3 (16 H, m, H5, H6, H8, and OTHP), 3.2–4.0 (7 H, m, H7, H9, and OTHP), 4.1 (1 H, m, H1), 4.62 (2 H, m, OTHP).

Dihydroxycyclopentyl Azide Derivative 29. A solution of **28** (0.67 g, 1.97 mM) in 10 mL of MeOH was treated with p-TsOH·H_2O (0.019 g, 0.099 mM) at room temperature. After 2 h the reaction was quenched with TEA (0.5 mL, 3.61 mM) and the solution was evaporated to dryness. Chromatography (DCFC: 30 g of SiO_2, hexane/EtOAc, 1:2) yielded 0.164 g (49%) of pure **29**: R_f (hexane/EtOAc, 1:2) = 0.17.

(+)-(1*R*,2*S*,4*S*,5*S*)-5-Methyl-4-amino-2-hydroxy-1-(hydroxymethyl)cyclopentane [(+)-30]. A mixture of **29** (0.164 g, 0.96 mM) and 1.44 g of 10% Pd–C in 10 mL of MeOH was treated with 0.96 mL of 80% $NH_2NH_2·H_2O$. An exothermic reaction took place at once and TLC showed—after 1 min—complete disappearance of the starting compound. Then the catalyst was filtered off through an asbestos pad, washed with MeOH/25% aq NH_3, 50:1 (10 × 5 mL). The solution thus obtained was evaporated, and the residue was coevaporated with MeOH (3 × 5 mL). On evaporation of the pure fractions, DCFC (15 g of SiO_2, MeOH/25% aq NH_3, 50:1) gave 0.086 g (62%) of pure (+)-**30**: R_f (MeOH/25% aq NH_3, 30:1) = 0.17; $[\alpha]^{23}_D$ +32 ± 1° (*c* 1.34, MeOH); ^1H NMR (100 MHz, DMSO-d_6/$CDCl_3$)[27] δ 1.02 (3 H, d, J = 6 Hz, H4), 1.1–2.0 (4 H, m, H5, H6, and H8), 2.90 (1 H, m, H1), 3.50 (2 H, m, H9), 3.99 (1 H, m, J = 4.0 + 4.5 + 7.5 Hz, H7). Anal. ($C_7H_{15}NO_2$) C, H, N.

Triacetyl-(+)-30. Yield 89%; R_f (EtOAc) = 0.15; ^1H NMR (100 MHz, $CDCl_3$)[27] δ 1.10 (3 H, d, J = 6 Hz, H4), 1.2–2.2 (4 H, m, H5, H6, and H8), 1.96 (3 H, s, NHAc), 2.03 (3 H, s, OAc), 2.04 (3 H, s, OAc), 4.10 (1 H, m, J = 9 + 9 + 9 + 8 Hz, H1), 4.14 (2 H, d, J = 5 Hz, H9), 4.98 (1 H, m, J = 3 + 5 + 8 Hz, H7), 5.74 (1 H, d, J = 8 Hz, NH); ^{13}C NMR (25.2 MHz, $CDCl_3$)[27] δ 16.61 (C4), 20.87 (OAc), 21.16 (OAc), 23.25 (NHAc), 38.54 (C8), 42.10 (C5), 50.66 (C6), 54.87 (C1), 63.73 (C9), 170.34 (NHAc), 170.70 (OAc), 171.00 (OAc).

(+)-(6'*S*)-Carbocyclic 6'-Methylthymidine [(+)-31]. 1. **Addition.** Compound (+)-**30** (0.300 g, 2.1 mM) was reacted with the isocyanate (3.47 mM) for 5 h. DCFC gave 0.435 g (73%) of crystalline **31a**: R_f ($CHCl_3$/MeOH, 9:1) = 0.21.

2. Ring Closure. Yield 0.352 g (92%) of (+)-**31**; R_f ($CHCl_3$/MeOH, 4:1) = 0.34; mp 181 °C; $[\alpha]^{25}_D$ +2.7° (*c* 1.0, MeOH); CD (H_2O, 2.85 mM/L, 0.05 cm) λ ($\Delta\epsilon$) 281.8 (–0.244), 266.8 (–0.083), 260.4 (+0.103), 243.1 (+0.267), 231.6 (–0.258); ^1H NMR (100 MHz, $CDCl_3$/DMSO-d_6)[26] δ 1.02 (3 H, d, J = 6 Hz, H7'), 1.1–2.1 (4 H, m, H2', H4', and H6'), 1.89 (3 H, d, J = 1 Hz, H7), 3.72 (2 H, m, J_{gem} = 11.5 Hz, J_{vic} = 6 + 4 Hz, H5'), 4.26 (1 H, m, J = 5.5 + 6 + 6.5 Hz, H3'), 4.71 (1 H, m, J = 9 + 9 + 9.5 Hz, H1'), 7.14 (1 H, q, J = 1 Hz, H6); ^{13}C NMR (25.2 MHz, $CDCl_3$/DMSO-d_6)[26] δ 12.41 (C7), 16.12 (C7'), 38.69 (C2'), 39.01 (C6'), 55.73 (C4'), 60.03 (C1'), 61.06 (C5'), 71.30 (C3'), 110.35 (C5), 137.04 (C6), 151.66 (C2), 164.20 (C4); EI-MS, m/e (rel intensity %) 254 (20) M^+, 236 (0.4), 205 (1.4), 183 (1.9), 181 (6), 167 (2.5), 162 (2.2), 153 (5.8), 152 (2.2), 127 (100) B^+ + 2 H, 126 (44) B^+ + H. Anal. ($C_{12}H_{18}N_2O_4$) C, H, N.

α-Methylcyclopentylamine Derivative 33. A solution of **32** (1.88 g, 4.93 mM) in 48 mL of benzene containing approximately 29 mM n-Bu_3SnH was refluxed for 30 min. The solution was evaporated to dryness, and the residue was distributed between acetonitrile (50 mL) and hexane (50 mL). The CH_3CN solution was further washed with hexane (5 × 10 mL) and then evaporated to dryness. Isolated was 1.04 g of crude **33**: R_f (MeOH/25% aq NH_3, 100:1) = 0.38.

Synthesis of (+)-30 from 33. A solution of crude **33** (1.04 g) in 20 mL of satd ammonia in methanol was kept at rt overnight. The addition of NH_3–MeOH was repeated two more times. Complete deacetylation was only observed after ~4 days. Then the solution was evaporated to dryness. The residue was purified by DCFC (30 g of SiO_2, MeOH/25% aq NH_3, 100:1): yield 0.434 g (61%, based on **32**) of pure (+)-**30**.

Biological Activity. The compounds were evaluated for antiviral activity according to a standard procedure described previously.[28] For the determination of anti-HIV activity the procedure of Pauwels et al.[29] was followed. Cytotoxicity was recorded based on either microscopically detectable alteration of normal cell morphology[28] or reduction of cell viability [as assessed by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) method].[29]

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Registry No. (+)-1, 54483-22-6; (–)-1, 43119-28-4; **2**, 125249-58-3; **3**, 125249-59-4; **4**, 125280-77-5; **5**, 125249-60-7; **6**, 125249-61-8; (+)-**7**, 100018-56-2; **8**, 125249-62-9; **9**, 125353-57-3; **10**, 125353-58-4;

(27) Atomic numbering refers to that of (+)-1 and **23** in Scheme II.

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(+)-11, 114884-15-0; (-)-11, 125353-66-4; 11a, 125353-65-3; 11a epimer, 125353-67-5; 12, 125353-59-5; 12 triacetyl derivative, 125249-79-8; (-)-13, 125353-60-8; 14, 125353-61-9; 15, 125249-63-0; 16, 125353-62-0; 17, 125353-63-1; 18, 114489-63-3; (+)-19, 116183-74-5; 20, 125249-64-1; 20 R=H, 125249-73-2; 20a, 125249-74-3; 21, 125353-64-2; (+)-22, 125408-90-4; (+)-22 acetyl derivative, 125249-75-4; 23, 121236-40-6; 24, 121236-48-4; 25, 125249-65-2; 26, 125249-66-3; 26 diacetyl derivative, 125249-76-5; (+)-27, 125249-67-4; (+)-27 ring-opened derivative, 125280-78-6; 28, 125249-68-5; 29, 125249-69-6; (+)-30, 125249-70-9; (+)-30 triacetyl derivative, 125249-77-6; (+)-31, 125249-71-0; (+)-31 ring-opened derivative, 125249-78-7; 32, 121236-42-8; 33, 125249-72-1; (-)-34, 32233-40-2; (-)-35, 117957-63-8; (+)-36, 57345-51-4; 3-methoxy-2-methylacryloyl chloride, 52410-41-0.

Antirhinovirus Activity of 6-Anilino-9-benzyl-2-chloro-9*H*-purines

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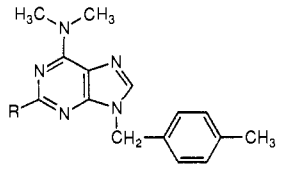
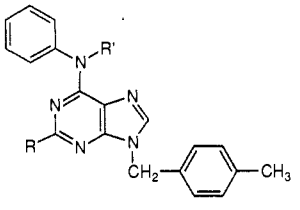
A series of 6-anilino-9-benzyl-2-chloropurines was synthesized and tested for antirhinovirus activity. Most of the compounds were prepared by reaction of the appropriate aniline with 9-benzyl-2,6-dichloro-9*H*-purine. Structure–activity relationship studies revealed that compounds with small, lipophilic para substituents were good inhibitors of serotype 1B. Several compounds had good activity against four representative serotypes.

A variety of structural types have in vitro activity against rhinoviruses,[1,2] which are recognized as the most important causative agents of the common cold.[3] Several 2-substituted 9-benzylpurines have potent in vitro activity against rhinovirus serotype 1B, but most other serotypes are less sensitive.[4,5] Two of the most active compounds are the 2-trifluoromethyl (1) and 2-chloro (2) benzylpurines, which have IC_{50} values of 0.03 and 0.08 μM, respectively.

Structure–activity studies show that optimum activity is associated with 9-benzylpurines that contain a lipophilic, electron-withdrawing 2-substituent,[5] a small lipophilic substituent on the phenyl ring,[6] and a dimethylamino group at the 6-position.[7] Although many of these compounds have potent activity against serotype 1B, none have a uniform profile of potent antirhinovirus serotype activity. The 6-anilinopurine 3 has moderate activity against serotype 1B (IC_{50} = 1.9 μM), and it is also active against many other serotypes with IC_{50}s ranging over 5-fold.[8] To develop a more active agent with a broad spectrum of rhinovirus serotype activity, we prepared a series of 6-anilino-2-chloro-9-benzylpurines related to 4. The synthesis and antirhinovirus structure–activity relationships of these new compounds are reported herein.



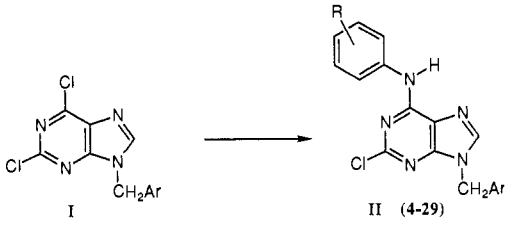
1; R = CF_3
2; R = Cl



3; R = CF_3, R' = CH_3
4; R = Cl, R' = H

Chemistry

Most of the compounds in Table I were prepared from 9-benzyl-2,6-dichloro-9*H*-purine (I) and the appropriate aniline. Reaction of the aniline and I was a facile process if the aniline was unsubstituted or contained an electron-donating substituent. Excess aniline or triethylamine served as the acid acceptor, and the reaction proceeded in high yield at solvent reflux or at ambient temperature for the amino and dimethylamino analogues. However,



I II (4-29)

in cases where the anilino substituent was an electron-withdrawing group, triethylamine was a better nucleophile and reacted with I to give a 6-(diethylamino)purine. This side reaction was circumvented by using collidine as a base or by using excess aniline. The excess aniline was removed with a hydrochloric acid wash; the 2-chloro-6-anilinopurines II are weak bases and are not soluble in acid. The 4-(methylsulfonyl)aniline was too deactivated to react under these conditions. Consequently, 4-(methylthio)aniline was reacted with I to give 11, and the sulfide was oxidized to give sulfone 19.

Biological Results and Discussion

Although 6-(dimethylamino)purines like 1 and 2 have potent activity against serotype 1B,[4-6] the 6-anilino-2-(trifluoromethyl)purine 3 had a more uniform profile of antirhinoviral activity.[8] Since the 2-chloro analogue of 3, compound 4 (Table II), had a comparable profile of activity, analogues of 4 were prepared to examine the effect of aryl substituents on antiviral activity. Compounds that contained aryl substituents with a wide range of physicochemical properties were selected for synthesis so that meaningful structure–activity relationships (SAR) might be derived.[9,10]

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