Synthesis and Antiviral Activity of the Enantiomeric Forms of Carba-5-iodo-2′-deoxyuridine and Carba-(*E*)-5-(2-bromovinyl)-2′-deoxyuridine

Jan Balzarini,† Harald Baumgartner,‡ Michael Bodenteich,‡ Erik De Clercq,*,† and Herfried Griengl*,‡

Institute of Organic Chemistry, Graz University of Technology, A-8010 Graz, Austria, and Rega Institute for Medical Research, Katholieke Universiteit Leuven, B-3000 Leuven, Belgium. *Received November 28, 1988*

Both enantiomers of the carbocyclic analogues of 5-iodo-2′-deoxyuridine (**14** and *ent*-**14**) and of (*E*)-5-(2-bromovinyl)-2′-deoxyuridine (**16** and *ent*-**16**) were synthesized by using (+)- or (−)-*endo*-norborn-5-en-2-yl acetate or butyrate, respectively, as starting materials. Against herpes simplex virus type 1 (+)-C-BVDU (**16**) was only slightly less active than BVDU itself, whereas (−)-C-BVDU (*ent*-**16**) proved to be 10–400-fold less effective, depending on the strain investigated. Against HSV-2 both (+)- and (−)-C-BVDU as well as (+)- and (−)-C-IDU showed minor activity. All carbocyclic analogues were inactive against TK⁻ HSV-1 strains, pointing to the prerequisite of phosphorylation (activation) by the viral thymidine kinase (TK).

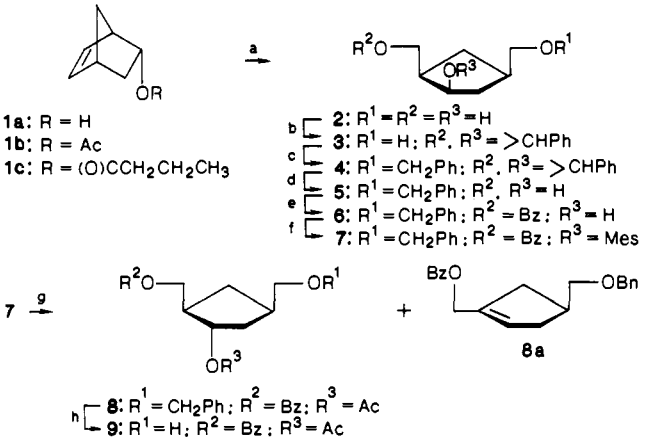
Several carbocyclic nucleoside analogues, in which the furanose oxygen atom has been replaced by carbon atoms, have been synthesized and shown to exhibit significant biological (i.e., cytostatic or antiviral) activity.[1-21] (For an overview see ref 13.)

In particular, the carbocyclic analogues of (*E*)-5-(2-bromovinyl)-2′-deoxyuridine [(±)-C-BVDU] and (*E*)-5-(2-iodovinyl)-2′-deoxyuridine [(±)-C-IVDU] are, like their parent compounds BVDU and IVDU, potent and selective inhibitors of herpes simplex virus type 1 (HSV-1) and, to a lesser extent, herpes simplex virus type 2 (HSV-2) replication.[8,9] The general synthetic routes to the cyclopentane precursors of carbocyclic analogues of nucleosides lead to the racemic forms of the target nucleoside analogues. Thus, biological evaluation of these compounds was mostly done with a mixture of the (+)- and (−)-enantiomers. Only in a few studies have the biological activities of the individual (+)- and (−)-enantiomers been investigated.[19,22-27] Generally, the biological activities of the racemic carbocyclic analogues of the nucleosides [e.g., aristeromycin (C-adenosine), C-2,6-diaminopurine-2′-deoxyriboside (C-DAPdR), and C-2′-deoxyguanosine] could be attributed to the enantiomer that is analogous to the β-nucleoside structure. We now have synthesized the enantiomerically pure analogues of (±)-C-BVDU and (±)-C-IDU and evaluated these compounds for their antiviral activity. We found that both (+)- and (−)-enantiomers of C-BVDU and C-IDU have marked activity against HSV-1, the (+)-enantiomer being the more active in both series.

Chemistry

Racemic (*E*)-5-(2-bromovinyl)-2′-deoxyuridine has been prepared[8] from (±)-(4-amino-2,3-dihydroxycyclopentyl)-methanol, which is accessible[28] via 2-azabicyclo[2.2.1]-hept-5-en-3-one,[29,30] obtained by cycloaddition of tosyl cyanide to 1,3-cyclopentadiene and subsequent hydrolysis. Another approach[31] (see also ref 32) starts from norborn-5-en-2-ol and involves a syn-dihydroxylation/oxidation/ozonation sequence to construct the functionalized cyclopentane ring. For the synthesis of both enantiomers of C-BVDU we used (±)-*endo*-norborn-5-en-2-yl butyrate as starting material, which as resolved enzymatically with *Candida cylindracea* lipase.[33] By this means, (+)-(1*R*,2*R*,4*R*)-*endo*-bicyclo[2.2.1]hept-5-en-2-yl acetate (**1b**) (configuration[33] as shown in Scheme I, ee 89.7%) and (−)-(1*S*,2*S*,4*S*)-*endo*-bicyclo[2.2.1]hept-5-en-2-yl butyrate (**1c**) (configuration[34] opposite to that shown in Scheme I, ee 86.5%) were obtained. The synthetic sequence followed was the same for the (+)- and (−)-series. In principle, the strategy already published[27] in a short communication for (+)-C-BVDU was used. Thus, **1b** gave on ozonation with

Scheme I[a]



[a] (a) O_3, MeOH, −70 °C; $LiAlH_4$, THF; (b) $PhCH(OMe)_2$, HBF_4, DMF; (c) KH, THF, $PhCH_2Br$; (d) aqueous H_2SO_4, 100 °C; (e) BzCl, Pyr, CH_2Cl_2; (f) MesCl, Et_3N, CH_2Cl_2; (g) CsOAc, DMSO, 40–45 °C; (h) Pd–C, EtOH.

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† Katholieke Universiteit Leuven.
‡ Graz University of Technology.

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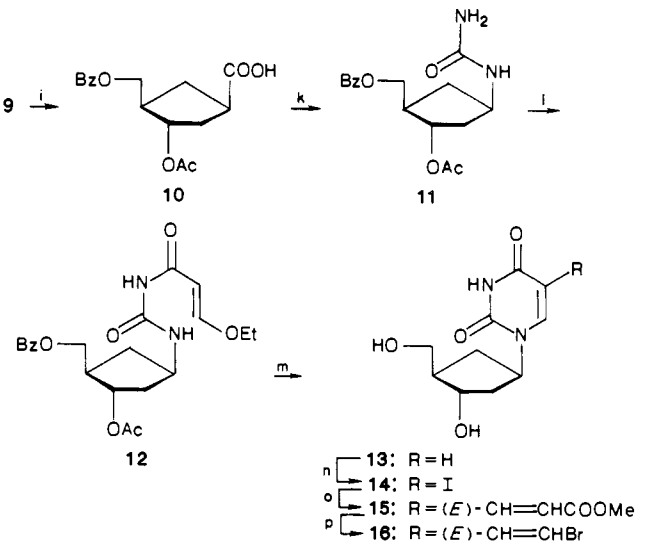
Table I. Cytotoxicity and Antiviral Activity of Carbocyclic BVDU and IDU Enantiomers in Primary Rabbit Kidney Cell Cultures

		min inhibitory concn,[b] μg/mL									
compd	min cytotoxic concn,[a] μg/mL	herpes symplex virus-1 (KOS)	herpes simplex virus-1 (F)	herpes simplex virus-1 (McIntyre)	herpes simplex virus-2 (G)	herpes simplex virus-2 (196)	herpes simplex virus-2 (Lyons)	vaccinia virus	vesicular stomatitis virus	TK⁻ herpes simplex virus-1 (B2006)	TK⁻ herpes simplex virus-1 (VMW 1837)
(−)-C-BVDU	≥400	0.7	10	10	20	100	100	>400	>400	>400	>400
(+)-C-BVDU	≥400	0.05	0.02	0.02	7	100	20	≥400	>400	>400	>400
(±)-C-BVDU	≥400	0.02	0.06	0.07	7	70	20	≥400	>400	>400	>400
(−)-C-IDU	≥400	1.0	7	20	70	≥400	>400	≥400	>400	>400	>400
(+)-C-IDU	>400	0.07	0.07	0.2	10	≥400	>400	40	>400	>400	>400
(±)-C-IDU	>400	0.1	0.1	0.1	20	>400	>400	150	>400	>400	>400
BVDU	>400	0.01	0.02	0.025	2	70	7	15	>400	150	≥400
IDU	>400	0.1	0.07	0.1	0.4	2.0	1.0	0.2	>400	>400	≥400

[a] Required to cause a microscopically detectable alteration of cell morphology. [b] Required to reduce virus-induced cytopathogenicity by 50%. The data represent average values for three to four separate experiments.

reductive workup (−)-(1*R*,2*R*,4*R*)-4-hydroxycyclopentane-1,3-dimethanol (2)[35] as a precursor for (+)-C-BVDU (16), the enantiomer that mimics the configuration of natural nucleosides. Analogously, the (+)-enantiomer *ent*-2 for the "unnatural" series leading to (−)-C-BVDU (*ent*-16) was obtained. Protection as the benzylidene acetal, benzylation, and deprotection gave crystalline monobenzylated triol 5. By one single recrystallization the optical rotation for 5 was raised from $[\alpha]_D^{20} = -23.9°$ (ee 89.7%) to $[\alpha]_D^{20} = -28.3°$ and for *ent*-5 from $[\alpha]_D^{20} = +23.0°$ (ee 86.5%) to $[\alpha]_D^{20} = +28.3°$. These values indicate an enrichment of optical purity up to 100% for both enantiomers. Since further recrystallization did not change optical rotations, we concluded that both compounds were enantiomerically pure. In addition, enantiomeric purity was checked by HPLC using the chiral column Nucleosil Chiral 2. Benzoylation of the primary and mesylation of the secondary hydroxyl group, followed by inversion at the latter center, gave protected triol 8 (together with the corresponding elimination product 8a). By this last step the sign of optical rotation changed, the "natural" series now being dextrorotatory. After hydrogenolytic removal of the benzyl group, oxidation,[36] Curtius degradation,[37] and trapping the intermediate isocyanate by using gaseous ammonia,[35] urea derivative 11 (see Scheme II) was obtained. This was converted into carbocyclic 2′-deoxyuridine 13 and C-BVDU 16, respectively, according to methods[8,38] given in the literature for the corresponding deoxyribo derivatives. Recently, (+)-C-IDU (14) has been prepared by another synthetic route.[20]

Scheme II[a]



[a] (i) PDC, DMF, room temperature; (k) DPPA, C_6H_6; NH_3; (l) 3-ethoxyacryloyl chloride, pyr, CH_2Cl_2; (m) aqueous NH_3, 90 °C, 4 h; (n) I_2, 0.75 N HNO_3, dioxane, reflux, 1 h; (o) methyl acrylate, dioxane, $Pd(OAc)_2$, Ph_3P, Et_3N, 85 °C, 15 h; (p) 1.8 N KOH, room temperature, 2 h; $KHCO_3$, NBS, DMF, room temperature.

Antiviral Activity

The carbocyclic enantiomers of IDU and BVDU were evaluated for their inhibitory effect on the replication of a number of viruses including herpes simplex virus type 1 (HSV-1) (strains KOS, F, McIntyre), HSV-2 (strains G, 196, Lyons), the thymidine kinase (TK) deficient (TK⁻) HSV-1 virus strains (B2006 and VMW1837), vaccinia virus,

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and vesicular stomatitis virus (Table I).

The racemic mixture (±)-C-BVDU strongly inhibited the replication of all strains of HSV-1, the minimum inhibitory concentration (MIC) ranging from 0.02 to 0.07 μg/mL. The anti-HSV-1 activity of the (+)-C-BVDU enantiomer was similar to that of (±)-C-BVDU, while the (−)-C-BVDU enantiomer proved to be ~10-fold less effective against HSV-1 (KOS) and ~400-fold less effective against HSV-1 (F) and HSV-1 (McIntyre). (±)-C-BVDU exhibited much less inhibition with HSV-2 than with HSV-1 (MIC: 7–70 μg/mL). Both (+)-C-BVDU and (−)-C-BVDU enantiomers showed an anti-HSV-2 activity of the same order of magnitude as that of the racemic mixture. None of the BVDU derivatives showed any inhibitory activity against the TK^- HSV-1 strains, pointing to the absolute prerequisite of phosphorylation (activation) by the viral thymidine kinase.

Basically, similar observations were made for the carbocyclic enantiomers of IDU. As a rule, the concentrations of (±)-C-IDU and (+)-C-IDU required to inhibit HSV-1 replication were within the same order of magnitude (MIC between 0.07 and 0.2 μg/mL), while the anti-HSV-1 activity of (−)-C-IDU was 10–30 times less pronounced. Again, no striking differences were oserved in the anti-HSV-2 activities of (+)-, (−)-, and (±)-C-IDU. None of the IDU derivatives showed any activity against the TK^- HSV-1 strains.

While (±)-C-IDU and (±)-C-BVDU exhibited similar or slightly inferior anti-HSV-1 activity than their 2′-deoxyribofuranosyl counterparts IDU and BVDU, the carbocyclic compounds were considerably less effective against HSV-2. Also, the carbocyclic BVDU and IDU derivatives showed poor, if any, activity against vaccinia virus and were devoid of any activity against vesicular stomatitis virus.

Discussion

This is the first report on the preparation of carbocyclic BVDU and IDU in both enantiomerically pure forms. As could be deduced from the antiviral activity spectrum of (±)-C-BVDU and (±)-C-IDU (Table I), both compounds (in their racemic form) require phosphorylation by the herpes virus induced TK to exert their antiviral activity. Surprising, however, was the finding that both the (+)- and (−)-enantiomers of C-BVDU and C-IDU were active against HSV-1. This indicates that both enantiomers may act as substrates for the HSV-1 thymidine kinase.

In 1985, we efficiently separated the optical enantiomers of (±)-C-adenosine [(±)-C-Ado] after selective enzymatic degradation of (−)-C-adenosine 5′-monophosphate [(−)-C-AMP] to (−)-C-Ado in a reaction mixture containing (±)-C-AMP and 5′-nucleosidase (EC 3.1.3.5). (−)-C-Ado could subsequently be obtained upon treatment of the remaining (+)-C-AMP with alkaline phosphatase. Of the two enantiomers, only the (−)-form showed significant cytostatic and antiviral activity. The (+)-enantiomer was totally inactive.[23] From these experiments it was also clear that only the (−)-enantiomer and not the (+)-enantiomer of C-AMP could act as a substrate for 5′-nucleosidase. Recently,[19] similar results were obtained with carbocyclic 2′-fluoro-*ara*-guanosine.

Secrist and co-workers[25] separated the carbocyclic enantiomers of 2,6-diaminopurine 2′-deoxyribofuranoside [(±)-C-DAPdR] and C-Ado by enzymatic deamination and found that the (−)-enantiomer of C-Ado (that is, the analogue of β-D-adenosine) and the (+)-enantiomer of C-DAPdR (that is, the analogue of β-D-2,6-diaminopurine 2′-deoxyribofuranoside) were rapidly deaminated to their corresponding inosine and 2′-deoxyguanosine derivatives, whereas the L-enantiomers remained largely unaltered. Moreover, in contrast to (±)-C-DAPdR, L-C-DAPdR was devoid of any anti-HSV-1 and -HSV-2 activity, while L-C-2′-deoxyguanosine proved to be much less effective as an antiviral agent than its corresponding D-C-2′-deoxyguanosine and the racemic mixture (±)-C-2′-deoxyguanosine.

These data indicate that, among the (+)- and (−)-enantiomers of the carbocyclic purine nucleoside analogues studied, one enantiomer is as effective as the racemic mixture, while the other has poor, if any, biological activity. In the present study, we demonstrated that both (+)- and (−)-enantiomers of C-BVDU and C-IDU are active against HSV-1. We also found that both enantiomers of C-BVDU and C-IDU have a strong affinity for the HSV-1 thymidine kinase (as evident from the K_i values for the enzyme). The detailed kinetics of inhibition of the HSV-1 TK by the (+)- and (−)-enantiomers of C-BVDU and C-IDU will be reported elsewhere.

Experimental Section

General Procedures. Melting points were determined on a Büchi–Tottoli apparatus and are uncorrected. Column chromatography was performed on silica gel 60, 230–400 mesh, ASTM, Merck, Darmstadt, and TLC on aluminium sheets, silica gel 60 F_{254}, Merck, Darmstadt. Optical rotations were determined on a Perkin-Elmer 141 polarimeter. ^1H and ^{13}C NMR spectra were recorded on a Bruker MSL 300, and chemical shifts (δ) are reported in ppm with TMS as internal standard. UV spectra were recorded on a Perkin-Elmer 550 SE spectrometer. HPLC: Merck-Hitachi, column ET 250/8/4 Nucleosil Chiral 2 (Macherey-Nagel), elution with hexane/THF, 80/20, UV detection (254 nm).

(−)-(1*R*,3*R*,4*R*)-4-Hydroxycyclopentane-1,3-dimethanol (2) and (+)-(1*S*,3*S*,4*S*)-4-Hydroxycyclopentane-1,3-dimethanol (*ent*-2). Ozone was passed through a cooled (−70 °C) solution of **1b** (30.4 g, 0.20 mol, $[\alpha]_D^{20}$ = +115°, ee 89.7%[6]) or *ent*-**1c** (36.0 g, 0.20 mol, $[\alpha]_D^{20}$ −106°, ee 86.5%[7]), respectively, in MeOH (500 mL) until the reaction mixture turned blue. Excess ozone was removed by bubbling nitrogen through the solution for 15 min, followed by evaporation of the solvent in vacuo at maximum 40 °C. The last traces of solvent were removed at 0.01 mbar, leaving the methyl hydroperoxide as a highly viscous oil. After dissolving this intermediate in 100 mL of anhydrous THF, the resulting solution was added dropwise to a suspension of $LiAlH_4$ (30.5 g, 0.80 mol) in 200 mL of THF at −25 °C and refluxed for 1 h to complete reaction. After quenching the mixture at −15 °C with saturated aqueous $MgSO_4$ (120 mL) and stirring overnight at room temperature, the precipitate was removed by filtration and treated twice with hot THF (100 mL each), and the combined organic layers were evaporated in vacuo, yielding 24.2 g (83%) crude **2** or *ent*-**2**, respectively, as colorless, viscous oils. An analytical sample was obtained by chromatography (eluent $CHCl_3$/MeOH, 9/1 v/v). **2**: $[\alpha]_D^{20}$ = −28.5° (*c* 5.24, MeOH), ee = 89.7%. *ent*-**2**: $[\alpha]_D^{20}$ = +27.5° (*c* 3.98, MeOH), ee = 86.5%. ^1H NMR (DMSO-d_6) δ 0.9–1.9 (overlapping multiplets, 6 H, 2 × CH_2, 2 × C*H*CH_2OH), 2.94 (d, *J* = 5.0 Hz, 2 H, C-3-CH_2OH), 3.11 (dd, *J* = 10.0 Hz and 4.0 Hz, 2 H, CH_2OH), 3.3–3.9 (overlapping multiplets, 4 H, C*H*OH, 3 × OH).

(−)-(1*R*,6*R*,8*R*)-3-Phenyl-2,4-dioxabicyclo[4.3.0]nonane-8-methanol (3) and (+)-(1*S*,6*S*,8*S*)-3-Phenyl-2,4-dioxabicyclo[4.3.0]nonane-8-methanol (*ent*-3). A solution of **2** or *ent*-**2** (18.6 g, 0.13 mol), respectively, in anhydrous DMF (200 mL) was stirred with benzaldehyde dimethyl acetal (22 mL, 0.15 mol) and 1 mL of HBF_4 (54% in ether) for 3.5 h at room temperature. After quenching the reaction by addition of 3 mL of triethylamine, removal of the solvent in vacuo, and partitioning of the residue between ether and water, the organic layer was dried (Na_2SO_4) and evaporated in vacuo, and the resulting oil was purified by column chromatography (eluent toluene/ethyl acetate, 4/1 v/v), giving 24.1 g (81%) **3** or *ent*-**3**, respectively, as colorless oils. **3**: $[\alpha]_D^{20}$ = −18.5° (*c* 3.78, MeOH), ee = 89.7%. *ent*-**3**: $[\alpha]_D^{20}$ = +18.0° (*c* 7.49, MeOH), ee = 86.5%. ^1H NMR ($CDCl_3$) δ 1.61–1.71 (overlapping multiplets, 6 H, CH_2-7, CH_2-9, H-6, H-8), 2.50 (s, 1 H, OH), 3.53 (d, *J* = 6.0 Hz, 2 H, CH_2-5), 4.10 (s, 2 H, CH_2OH),

4.2–4.38 (m, 1 H, H-1), 5.37 (s, 1 H, H-3), 7.12–7.57 (m, 5 H, Ar-H).

(−)-(1*R*,6*R*,8*R*)-8-[(Benzyloxy)methyl]-3-phenyl-2,4-dioxabicyclo[4.3.0]nonane (4) and (+)-(1*S*,6*S*,8*S*)-8-[(Benzyloxy)methyl]-3-phenyl-2,4-dioxabicyclo[4.3.0]nonane (*ent*-4). After addition of **3** or *ent*-**3** (24.0 g, 0.10 mol), respectively, to a cooled (−15 °C) suspension of potassium hydride (6.5 g, 0.16 mol) in anhydrous THF (150 mL) and stirring under nitrogen for 20 min at room temperature, benzyl bromide (16 mL, 0.13 mol) was added dropwise. Stirring was continued for 12 h. Excess potassium hydride was destroyed with 1-butanol (10 mL), the mixture was partitioned between water and ether, the organic layer was separated, and the aqueous layer was reextracted twice with ether. Removal of the solvent in vacuo and subsequent column chromatography [eluent petroleum ether (bp 60–80 °C)/ethyl acetate, 9/1 v/v] yielded 29.9 g (90%) **4** or *ent*-**4**, respectively, as colorless oils. **4**: $[\alpha]_D^{20}$ = −11.9° (*c* 8.97, CH_2Cl_2), ee = 89.7%. *ent*-**4**: $[\alpha]_D^{20}$ = +10.7° (*c* 5.87, CH_2Cl_2), ee = 86.5%. ^1H NMR ($CDCl_3$) δ 1.48–2.66 (overlapping multiplets, 6 H, CH_2-7, CH_2-9, H-6, H-8), 3.50 (d, *J* = 7.8 Hz, 2 H, CH_2-5), 4.11 (s, 2 H, CH_2OCH_2Ph), 4.25 (s, 1 H, H-1), 4.50 (s, 2 H, CH_2Ph), 5.36 (s, 1 H, H-3), 7.29 (s, 10 H, Ar-H).

(−)-(1*R*,2*R*,4*R*)-4-[(Benzyloxy)methyl]-2-hydroxycyclopentanemethanol (5) and (+)-(1*S*,2*S*,4*S*)-4-[(Benzyloxy)methyl]-2-hydroxycyclopentanemethanol (*ent*-5). Refluxing **4** or *ent*-**4** (29.9 g, 0.09 mol), respectively, in 200 mL of water containing 1 mL of concentrated H_2SO_4 for 10 min and azeotropic distillation of the benzaldehyde formed, followed by extraction of the aqueous residue 3 times with CH_2Cl_2, drying of the organic layer (Na_2SO_4), and evaporation of the solvent in vacuo, yielded 21.2 g (98%) of crystalline **5** or *ent*-**5**, respectively. **5**: mp 57–8 °C, $[\alpha]_D^{20}$ = −23.9° (*c* 6.13, CH_2Cl_2), ee = 89.7%. *ent*-**5**: mp 56–8 °C, $[\alpha]_D^{20}$ = +23.0° (*c* 5.47, CH_2Cl_2), ee = 86.5%.

One single recrystallization from ether afforded optically pure material. **5**: mp 58–60 °C, $[\alpha]_D^{20}$ = −28.3° (*c* 6.54, CH_2Cl_2). *ent*-**5**: mp 58–60 °C, $[\alpha]_D^{20}$ = +28.3° (*c* 5.99, CH_2Cl_2). ^1H NMR ($CDCl_3$) δ 1.34–2.43 (overlapping multiplets, 6 H, 2 × CH_2, $CHCH_2OH$, $CHCH_2OCH_2Ph$), 3.08 (s, 2 H, 2 × OH), 3.44 (d, *J* = 5.0 Hz, 2 H, CH_2OCH_2Ph), 3.78 (m, 2 H, CH_2OH), 4.20 (m, 1 H, CHOH), 4.54 (s, 2 H, CH_2Ph), 7.34 (s, 5 H, Ar-H). Anal. ($C_{14}H_{20}O_3$) C, H, N.

(−)-[(1*R*,2*R*,4*R*)-4-[(Benzyloxy)methyl]-2-hydroxycyclopentyl]methyl Benzoate (6) and (+)-[(1*S*,2*S*,4*S*)-4-[(Benzyloxy)methyl]-2-hydroxycyclopentyl]methyl Benzoate (*ent*-6). Benzoyl chloride (5.4 mL, 46.5 mmol) was added dropwise to a stirred ice-cold solution of **5** or *ent*-**5** (10.0 g, 42.3 mmol), respectively, and pyridine (6.9 mL, 85.0 mmol) in 150 mL of anhydrous CH_2Cl_2. TLC (eluent $CHCl_3$/MeOH, 19/1 v/v) proved the reaction to be complete within 10 min. Excess benzoyl chloride was destroyed with 10 mL of MeOH, the mixture extracted with 1 N HCl, and the organic layer washed with water, dried (Na_2SO_4), and evaporated in vacuo. Subsequent chromatography (eluent $CHCl_3$/MeOH, 19/1 v/v) yielded 14.3 g (99%) **6** or *ent*-**6**, respectively, as colorless oils. **6**: $[\alpha]_D^{20}$ = −18.2° (*c* 6.24, CH_2Cl_2). *ent*-**6**: $[\alpha]_D^{20}$ = +18.1° (*c* 5.24, CH_2Cl_2). ^1H NMR ($CDCl_3$) δ 1.18–2.61 [overlapping multiplets, 6 H, 2 × CH_2, $CHCH_2OC(O)Ph$, $CHCH_2OCH_2Ph$], 3.45 (d, *J* = 5.0 Hz, 2 H, CH_2OCH_2Ph), 4.13 (s, 1 H, OH), 4.25–4.80 [overlapping multiplets, 3 H, CHOH, $CH_2OC(O)Ph$], 4.54 (s, 2 H, CH_2Ph), 7.18–8.13 (m, 10 H, Ar-H).

(−)-(1*R*,2*R*,4*R*)-2-[(Benzoyloxy)methyl]-4-[(benzyloxy)methyl]cyclopentyl Methanesulfonate (7) and (+)-(1*S*,2*S*,4*S*)-2-[(Benzoyloxy)methyl]-4-[(benzyloxy)methyl]cyclopentyl Methanesulfonate (*ent*-7). An ice-cooled solution of **6** or *ent*-**6** (7.0 g, 20.6 mmol), respectively, and Et_3N (4.5 mL, 32.0 mmol) in CH_2Cl_2 (100 mL) was treated dropwise with mesyl chloride (2.4 mL, 30.8 mmol), warmed to room temperature, and kept at this temperature for 3 h. Extraction with 2 N HCl, washing the organic layer with water, drying (Na_2SO_4), and removal of the solvent at reduced pressure followed by chromatography (eluent toluene/ethyl acetate, 9/1 v/v) gave 7.8 g (90%) of **7** or *ent*-**7**, respectively, as colorless crystals. **7**: mp 41–2 °C, $[\alpha]_D^{20}$ = −52.2° (*c* 4.03, CH_2Cl_2). *ent*-**7**: mp 41–2 °C, $[\alpha]_D^{20}$ = +52.0° (*c* 5.86, CH_2Cl_2). ^1H NMR ($CDCl_3$) δ 1.13–2.78 [overlapping multiplets, 6 H, 2 × CH_2, $CHCH_2OC(O)Ph$, $CHCH_2OCH_2Ph$], 2.89 (s, 3 H, CH_3), 3.43 (d, *J* = 7.8 Hz, 2 H, CH_2OCH_2Ph), 4.37 [d, *J* = 7.8 Hz, 2 H, $CH_2OC(O)Ph$], 4.54 (s, 2 H, CH_2Ph), 5.24 (s, 1 H, CHOS), 7.02–8.17 (m, 10 H, Ar-H). Anal. ($C_{22}H_{26}O_6S$) C, H, N.

(+)-[(1*R*,2*S*,4*R*)-2-Acetoxy-4-[(benzyloxy)methyl]cyclopentyl]methyl Benzoate (8) and (−)-[(1*S*,2*R*,4*S*)-2-Acetoxy-4-[(benzyloxy)methyl]cyclopentyl]methyl Benzoate (*ent*-8). A mixture of **7** or *ent*-**7** (20.0 g, 48.0 mmol), respectively, and anhydrous cesium acetate (18.3 g, 96 mmol) in 150 mL of DMSO was kept overnight at 40–45 °C. The solvent was removed at 0.05 mbar, the residue was treated with 100 mL of ether, and the precipitated inorganic salts were filtered off. This procedure was repeated until by treatment with ether no more precipitate was formed. The resulting oily residue was purified by column chromatography [eluent petroleum ether (bp 60–80 °C)/ethyl acetate, 4/1 v/v] to yield 10.6 g (58%) of **8** or *ent*-**8**, respectively, and 3.2 g (21%) of the corresponding eliminated products **8a** or *ent*-**8a**, respectively, as colorless oils. **8**: $[\alpha]_D^{20}$ = +12.9 (*c* 5.31, MeOH). *ent*-**8**: $[\alpha]_D^{20}$ = −13.0° (*c* 2.45, MeOH). ^1H NMR ($CDCl_3$) δ 1.11–2.67 [overlapping multiplets, 6 H, 2 × CH_2, $CHCH_2OPh$, $CHCH_2OC(O)Ph$], 2.0 [s, 3 H, $C(O)CH_3$], 3.35 (d, *J* = 6.5 Hz, 2 H, CH_2OCH_2Ph), 4.30 [d, *J* = 6.5 Hz, 2 H, $CH_2C(O)Ph$], 4.48 (s, 2 H, CH_2Ph), 5.07 [m, 1 H, $CHOC(O)CH_3$], 7.21–8.10 (m, 10 H, Ar-H). **8a**: $[\alpha]_D^{20}$ = +6.72° (*c* 4.78, CH_2Cl_2). *ent*-**8a**: $[\alpha]_D^{20}$ = −6.73° (*c* 5.78, CH_2Cl_2). ^1H NMR ($CDCl_3$) δ 2.12–2.30 (m, 2 H, CH_2-4), 2.39–2.63 (m, 2 H, CH_2-2), 2.69–2.80 (m, 1 H, $CHCH_2OCH_2Ph$), 3.48 (d, *J* = 12 Hz, CH_2OCH_2Ph), 4.51 (s, 2 H, CH_2Ph), 4.85 [s, 2 H, $CH_2OC(O)Ph$], 5.68 (s, 1 H, olefinic H), 7.20–8.10 (m, 10 H, Ar-H).

(+)-(1*R*,3*S*,4*R*)-3-Acetoxy-4-[(benzoyloxy)methyl]cyclopentanemethanol (9) and (−)-(1*S*,3*R*,4*S*)-3-Acetoxy-4-[(benzoyloxy)methyl]cyclopentanemethanol (*ent*-9). A shaken solution of **8** or *ent*-**8** (9.0 g, 23.6 mmol), respectively, in 100 mL of ethanol containing 250 mg of Pd/C (5%) was hydrogenated overnight at 4 bar. Filtration through Celite and removal of the solvent in vacuo furnished 6.9 g (100%) of **9** or *ent*-**9**, respectively, as colorless oils. **9**: $[\alpha]_D^{20}$ = +21.5° (*c* 6.35, MeOH). *ent*-**9**: $[\alpha]_D^{20}$ = −21.5° (*c* 5.86, MeOH). ^1H NMR ($CDCl_3$) δ 1.00–2.43 [overlapping multiplets, 6 H, 2 × CH_2, $CHCH_2OH$, $CHCH_2OC(O)Ph$], 1.79 [s, 3 H, $C(O)CH_3$], 2.67 (s, 1 H, OH), 3.21 (d, *J* = 6.0 Hz, 2 H, CH_2OH), 3.88 [d, *J* = 6.5 Hz, 2 H, $CH_2OC(O)Ph$], 4.57 [m, 1 H, $CHOC(O)CH_3$], 6.54–7.33 (m, 5 H, Ar-H).

(+)-(1*R*,3*S*,4*R*)-3-Acetoxy-4-[(benzoyloxy)methyl]cyclopentanecarboxylic Acid (10) and (−)-(1*S*,3*R*,4*S*)-3-Acetoxy-4-[(benzoyloxy)methyl]cyclopentanecarboxylic Acid (*ent*-10). A solution of **9** or *ent*-**9** (7.9 g, 27.0 mmol), respectively, in 100 mL of DMF was stirred with pyridinium dichromate (PDC, 35.5 g, 95.0 mmol) for 30 h at room temperature. In the initial phase of the slightly exothermic reaction cooling to 20 °C was required. After quenching with water (300 mL), the mixture was extracted 3 times with ether (100 mL each). The combined organic layers were dried (Na_SO_4) and evaporated, and the residue was purified by column chromatography (eluent $CHCl_3$/MeOH, 9/1 v/v) to yield 7.0 g (85%) of **10** and *ent*-**10**, respectively, as colorless oils. **10**: $[\alpha]_D^{20}$ = +9.6° (*c* 7.40, MeOH). *ent*-**10**: $[\alpha]_D^{20}$ = −9.6° (*c* 4.48, MeOH). ^1H NMR (DMSO-d_6) δ 1.14–2.79 [overlapping multiplets, 6 H, 2 × CH_2, CHCOOH, $CHCH_2OC(O)Ph$], 1.76 [s, 3 H, $C(O)CH_3$], 3.86 [d, *J* = 6.5 Hz, 2 H, $CH_2OC(O)Ph$], 4.48 [m, 1 H, $CHOC(O)CH_3$], 6.57–7.29 (5 H, Ar-H), 11.0 (s, 1 H, COOH).

(+)-(1*R*,3*S*,4*R*)-*N*-[3-Acetoxy-4-[(benzyloxy)methyl]cyclopentyl]urea (11) and (−)-(1*S*,3*R*,4*S*)-*N*-[3-Acetoxy-4-[(benzoyloxy)methyl]cyclopentyl]urea (*ent*-11). Refluxing a mixture of **10** or *ent*-**10** (5.9 g, 19.0 mmol), respectively, with diphenyl phosphorazidate (4.2 mL, 19.0 mmol) in 100 mL of benzene under nitrogen for 45 min and cooling to room temperature followed by treatment with gaseous ammonia for 10 min, removal of the solvent, and column chromatography (eluent $CHCl_3$/MeOH, 9/1 v/v) yielded the crude urea derivatives, which were recrystallized from 2-propanol to give 3.6 g (58%) **11** or *ent*-**11**, respectively, as colorless crystals. **11**: mp 111–3 °C, $[\alpha]_D^{20}$ = +8.0° (*c* 1.87, MeOH). *ent*-**11**: mp 111–3 °C, $[\alpha]_D^{20}$ = −8.1° (*c* 2.05, MeOH). ^1H NMR (DMSO-d_6) δ 1.0–2.29 [overlapping multiplets, 5 H, 2 × CH_2, $CHCH_2OC(O)Ph$], 1.71 [s, 3 H, $C(O)CH_3$], 3.0 (s, 1 H, D_2O exchangeable), 3.62 (m, 1 H, CHN), 3.86 [d, *J* = 6.5 Hz, 2 H, $CH_2OC(O)Ph$], 4.50 (m, 1 H, $CHOC(O)CH_3$], 4.81 (s, 1 H, D_2O exchangeable), 5.48 (d, *J* = 6.5 Hz, 1 H, NH), 6.64–7.29 (m, 5 H, Ar-H). Anal. ($C_{16}H_{20}N_2O_5$) C, H, N.

(+)-3-Ethoxy-*N*-[*N*'-[(1*R*,3*S*,4*R*)-3-acetoxy-4-[(benzoyl-

oxy)methyl]cyclopentyl]carbamoyl}propenamide (12) and (−)-3-Ethoxy-*N*-{*N*'-[(1*S*,3*R*,4*S*)-3-acetoxy-4-[(benzoyloxy)methyl]cyclopentyl]carbamoyl}propenamide (*ent*-12). A solution of 11 or *ent*-11 (1.8 g, 5.6 mmol), respectively, and 3-ethoxyacryloyl chloride (0.9 g, 6.8 mmol) in CH_2Cl_2 (15 mL) containing pyridine (2.5 mL, 30.9 mmol) was kept overnight at room temperature. Extraction with 1 N HCl and water, drying of the organic layer (Na_2SO_4), evaporation of the solvent in vacuo, column chromatography (eluent $CHCl_3$/acetone, 9/1 v/v), and recrystallization from 2-propanol yielded 1.6 g (68%) of 12 or *ent*-12, respectively, as colorless crystals. 12: mp 107–9 °C; $[\alpha]_D^{20}$ = +3.6° (*c* 2.72, CH_2Cl_2). *ent*-12: mp 107–9 °C, $[\alpha]_D^{20}$ = −3.6° (*c* 2.94, CH_2Cl_2). ^1H NMR (DMSO-D_6) δ 1.0–2.6 [overlapping multiplets, 6 H, 2 × CH_2, CHN, C*H*CH_2C(O)Ph], 1.31 (t, *J* = 7.0 Hz, 3 H, CH_2CH_3), 2.0 [s, 3 H, C(O)CH_3], 3.96 (q, *J* = 7.0 Hz, 2 H, CH_2CH_3), 4.35 [d, *J* = 6.5 Hz, 2 H, CH_2OC(O)Ph], 5.09 [m, 1 H, C*H*OC(O)CH_3], 5.31 (d, *J* = 12 Hz, 1 H, olefinic H), 7.31 (d, *J* = 12.0 Hz, 1 H, olefinic H), 7.31–8.13 (m, 5 H, Ar-H), 8.74 (d, *J* = 7.0 Hz, 1 H, NH), 9.11 (s, 1 H, NH). Anal. ($C_{21}H_{26}N_2O_7$) C, H, N.

(+)-1-[(1*R*,3*S*,4*R*)-3-Hydroxy-4-(hydroxymethyl)cyclopentyl]-1*H*,3*H*-pyrimidine-2,4-dione (13) and (−)-1-[(1*S*,3*R*,4*S*)-3-Hydroxy-4-(hydroxymethyl)cyclopentyl]-1*H*,3*H*-pyrimidine-2,4-dione (*ent*-13). A suspension of 12 or *ent*-12 (1.4 g, 3.3 mmol), respectively, in concentrated aqueous ammonia was heated to 90 °C for 4 h. The resulting solution was evaporated to dryness, and the residue was treated with 10 mL of $CHCl_3$/MeOH, 3/1, filtered, subjected to column chromatography (eluent $CHCl_3$/MeOH, 9/1 v/v), and recrystallized from 2-propanol to give 0.64 g (85%) of 13 or *ent*-13, respectively, as colorless crystals. 13: mp 145–7 °C, $[\alpha]_D^{20}$ = +3.0° (*c* 2.12, MeOH). *ent*-13: mp 145–7 °C, $[\alpha]_D^{20}$ = −3.0° (*c* 3.01, MeOH). ^1H NMR (DMSO-d_6) δ 1.00–2.33 (overlapping multiplets, 5 H, 2 × CH_2, C*H*CH_2OH) 3.39 (m, 2 H, CH_2OH), 4.0 (m, 1 H, C*H*OH), 4.72 (s, 2 H, 2 × OH), 4.96 (m, 1 H, CHN), 5.56 (d, *J* = 7.8 Hz, 1 H, H-5), 7.69 (d, *J* = 7.8 Hz, 1 H, H-6), 11.22 (s, 1 H, NH); UV (H_2O) λ_{max} 268 nm, ε = 10 000. Anal. ($C_{10}H_{14}N_2O_4$) C, H, N.

(+)-1-[(1*R*,3*S*,4*R*)-3-Hydroxy-4-(hydroxymethyl)cyclopentyl]-5-iodo-1*H*,3*H*-pyrimidine-2,4-dione (14) and (−)-1-[(1*S*,3*R*,4*S*)-3-Hydroxy-4-(hydroxymethyl)cyclopentyl]-5-iodo-1*H*,3*H*-pyrimidine-2,4-dione (*ent*-14). A mixture of 13 or *ent*-13 (0.440 g, 1.95 mmol), respectively, iodine (1.0 g, 4.0 mmol), 0.75 N HNO_3 (2.63 mL), and dioxane (20 mL) was refluxed for 1 h. The solvent was removed in vacuo and the residue coevaporated repeatedly with EtOH and taken to dryness. Trituration with $CHCl_3$ yielded the crude crystalline 5-iodouridine derivatives, which were recrystallized from ethanol to give 0.51 g (75%) of 14 or *ent*-14, respectively, as colorless crystals. 14: mp 165–6 °C, $[\alpha]_D^{20}$ = +6.9° (*c* 2.75, MeOH) [lit.[20] $[\alpha]_D^{22}$ = +7° (DMSO)]. *ent*-14: mp 165–6 °C, $[\alpha]_D^{20}$ = −7.0° (*c* 4.56, MeOH). ^1H NMR (DMSO-d_6) δ 1.09–2.26 (overlapping multiplets, 5 H, 2 × CH_2, C*H*CH_2OH), 3.40 (m, 2 H, CH_2OH), 4.00 (m, 1 H, C*H*OH), 4.43–5.05 (overlapping multiplets, 3 H, CHN, 2 × OH), 8.13 (s, 1 H, H-6), 11.2 (s, 1 H, NH); UV (H_2O) λ_{max} 242 nm, ε = 11 500. Anal. ($C_{10}H_{13}IN_2O_4$) C, H, N.

(+)-1-[(1*R*,3*S*,4*R*)-3-Hydroxy-4-(hydroxymethyl)cyclopentyl]-5-[(*E*)-2-carbomethoxyvinyl]-1*H*,3*H*-pyrimidine-2,4-dione (15) and (−)-1-[(1*S*,3*R*,4*S*)-3-Hydroxy-4-(hydroxymethyl)cyclopentyl]-5-[(*E*)-2-carbomethoxyvinyl]-1*H*,3*H*-pyrimidine-2,4-dione (*ent*-15). A suspension of 14 or *ent*-14 (0.491 g, 1.4 mmol), respectively, and methyl acrylate (0.25 mL, 2.8 mmol) in dioxane (10 mL) was added to a mixture of $Pd(OAc)_2$ (20 mg, 0.1 mmol), triphenylphosphine (47 mg, 0.2 mmol), and triethylamine (0.31 mL, 2.2 mmol) in dioxane (20 mL), which had been kept at 85 °C for 15 min. Heating to 85 °C overnight, filtration, removal of the solvents in vacuo, and subsequent column chromatography (eluent $CHCl_3$/MeOH, 9/1 v/v, until the dark byproducts were eluted, followed by $CHCl_3$/MeOH, 3/1 v/v) furnished 0.31 g (72%) of 15 or *ent*-15, respectively, as a crystalline solid. 15: mp 135–7 °C, $[\alpha]_D^{20}$ = +2.4° (*c* 1.84, MeOH). *ent*-15: mp 135–7 °C, $[\alpha]_D^{20}$ = −2.4° (*c* 2.36, MeOH). ^1H NMR (MeOD) δ 1.60–2.35 (overlapping multiplets, 5 H, 2 × CH_2, C*H*CH_2OH), 3.67 (m, 2 H, CH_2OH), 4.15 (m, 1 H, C*H*OH), 4.18 (s, 3 H, CH_3), 5.02 (m, 1 H, CHN), 6.92 (d, *J* = 15 Hz, 1 H, vinylic H), 7.47 (d, *J* = 15 Hz, 1 H, vinylic H), 8.32 (s, 1 H, H-6). Anal. ($C_{14}H_{18}N_2O_6$) C, H, N.

(+)-1-[(1*R*,3*S*,4*R*)-3-Hydroxy-4-(hydroxymethyl)cyclopentyl]-5-[(*E*)-2-bromovinyl]-1*H*,3*H*-pyrimidine-2,4-dione (16) and (−)-1-[(1*S*,3*R*,4*S*)-3-Hydroxy-4-(hydroxymethyl)cyclopentyl]-5-[(*E*)-2-bromovinyl]-1*H*,3*H*-pyrimidine-2,4-dione (*ent*-16). A suspension of 15 or *ent*-15 (0.308 g, 1.0 mmol), respectively, in 1.8 N KOH (4.0 mL) was stirred for 2 h at room temperature, cooled to 0 °C, and acidified with HCl to pH 2. After the first crop of the precipitated carboxylic acid had been filtered off, a second crop could be obtained by concentration of the mother liquor (combined crops 0.210 g, 71.4%). This acrylic acid (0.154 g, 0.5 mmol) was stirred with $KHCO_3$ (0.156 g) in DMF (2.8 mL) at room temperature for 5 min. A solution of *N*-bromosuccinimide (0.093 g, 0.5 mmol) in 1 mL of DMF was added dropwise to the mixture over a period of 10 min, and stirring was continued for an additional 90 min followed by filtration of the precipitate. The filtrate was concentrated in vacuo and coevaporated with water 3 times. The crystalline residue was purified by recrystallization from MeOH to give 97 mg (59%) of the title compounds 16 or *ent*-16, respectively, as colorless crystals. 16: mp 184–5 °C dec, $[\alpha]_D^{20}$ = +4.9° (*c* 1.58, MeOH). *ent*-16: mp 184–5 °C dec, $[\alpha]_D^{20}$ = −4.9° (*c* 1.73, MeOH). ^1H NMR (MeOD) δ 1.60–2.31 (overlapping multiplets, 5 H, 2 × CH_2, C*H*CH_2OH), 3.67 (m, 2 H, CH_2OH), 4.15 (m, 1 H, C*H*OH), 5.08 (m, 1 H, CHN), 6.79 (d, *J* = 13.6 Hz, 1 H, vinylic H), 7.34 (d, *J* = 13.6 Hz, 1 H, vinylic H), 7.75 (s, 1 H, H-6); ^{13}C NMR (MeOD) δ 33.55 (C-5′), 40.43 (C-2′), 50.20 (C-4′), 56.62 (C-1′), 64.24 (C-6′), 73.79 (C-3′), 109.17 (C-α), 112.48 (C-5), 130.14 (C-β), 141.82 (C-6), 151.84 (C-4), 163.66 (C-2); UV (H_2O) λ_{max} 254 nm, ε = 14 500. Anal. ($C_{12}H_{15}BrN_2O_4$) C, H, N.

Antiviral Test Procedures. The antiviral test procedures were based on an inhibition of virus-induced cytopathogenicity in primary rabbit kidney cell cultures following previously established procedures.[24] Briefly, confluent cell cultures in microtiter trays were inoculated with 100 $CCID_{50}$ of virus [herpes simplex virus type 1 (HSV-1) (strain KOS, F, or McIntyre), HSV-2 (strain G, 196, or Lyons), thymidine kinase deficient HSV-1 (strain B2006 or VMW 1837), vaccinia virus, or vesicular stomatitis virus], 1 $CCID_{50}$ being the virus dose required to infect 50% of the cell cultures. After 1 h of virus adsorption, residual virus was removed and the cell cultures were incubated in the presence of varying concentrations of the test compounds. Viral cytopathogenicity was recorded as soon as it reached completion in the control virus-infected cell cultures. The origin of the viruses (except for VMW 1837) has been described in ref 39. The TK$^-$ HSV-1 variant VMW 1837 was a clinical HSV-1 isolate, obtained from an immunocompromised patient with a chronic HSV-1 infection that had become resistant to acyclovir.[40,41]

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Registry No. 1b, 112836-09-6; *ent*-1c, 120963-33-9; 2, 114129-19-0; *ent*-2, 120963-34-0; 3, 108275-94-1; 4, 120905-28-4; 5, 120236-98-8; *ent*-5, 120963-35-1; 6, 120236-99-9; *ent*-6, 120963-36-2; 7, 116142-70-2; *ent*-7, 120963-37-3; 8, 120905-29-5; *ent*-8, 120963-38-4; 8a, 120905-30-8; *ent*-8a, 120905-31-9; 9, 120905-32-0; *ent*-9, 120963-39-5; 10, 120905-33-1; *ent*-10, 120963-40-8; 11, 120905-34-2; *ent*-11, 120963-41-9; 12, 120905-35-3; *ent*-12, 120963-42-0; 13, 120963-43-1; *ent*-13, 120963-44-2; 14, 114179-59-8; *ent*-14, 120963-45-3; 15, 120963-46-4; 15 acid, 120963-48-6; *ent*-15, 120963-47-5; *ent*-15 acid, 120963-49-7; 16, 95463-56-2; *ent*-16, 120963-50-0; 3-ethoxyacryloyl chloride, 6191-99-7; methyl acrylate, 96-33-3.

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