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# ENANTIOSELECTIVE SYNTHESIS OF NEW ANALOGS OF NEPLANOCIN A AND THEIR BIOLOGICAL ACTIVITY

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ABSTRACT

Various carbocyclic nucleosides analogs of neplanocin A (such as 5-aminoimidazole-4-carboxamide riboside, uridine, 5-iodouridine, 4-thiouridine, cytidine, thymidine, 2′-deoxyguanosine, ribofuranosylthymine, a 2,2′-anhydroderivative, 2′-deoxycytidine, 2′-deoxythiouridine, and D-arabinofuranosylcytosine analogs) were synthesized from (1*R*, 2*S*, 3*R*)-2,3-isopropylidenedioxy-4-methoxymethyloxymethyl-4-cyclopentenylamine. The cytidine analog was found the most active in inhibiting mouse lymphoma L5178Y cells *in vitro* at a concentration as low as 0.8 μg/mL.


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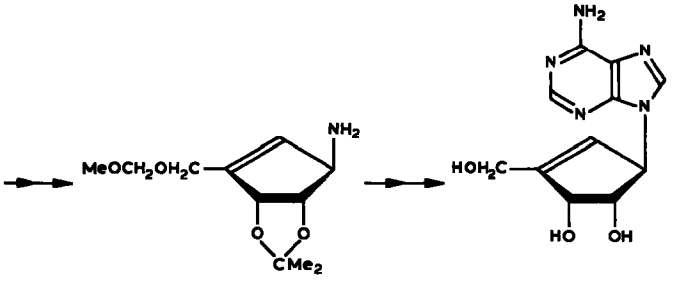


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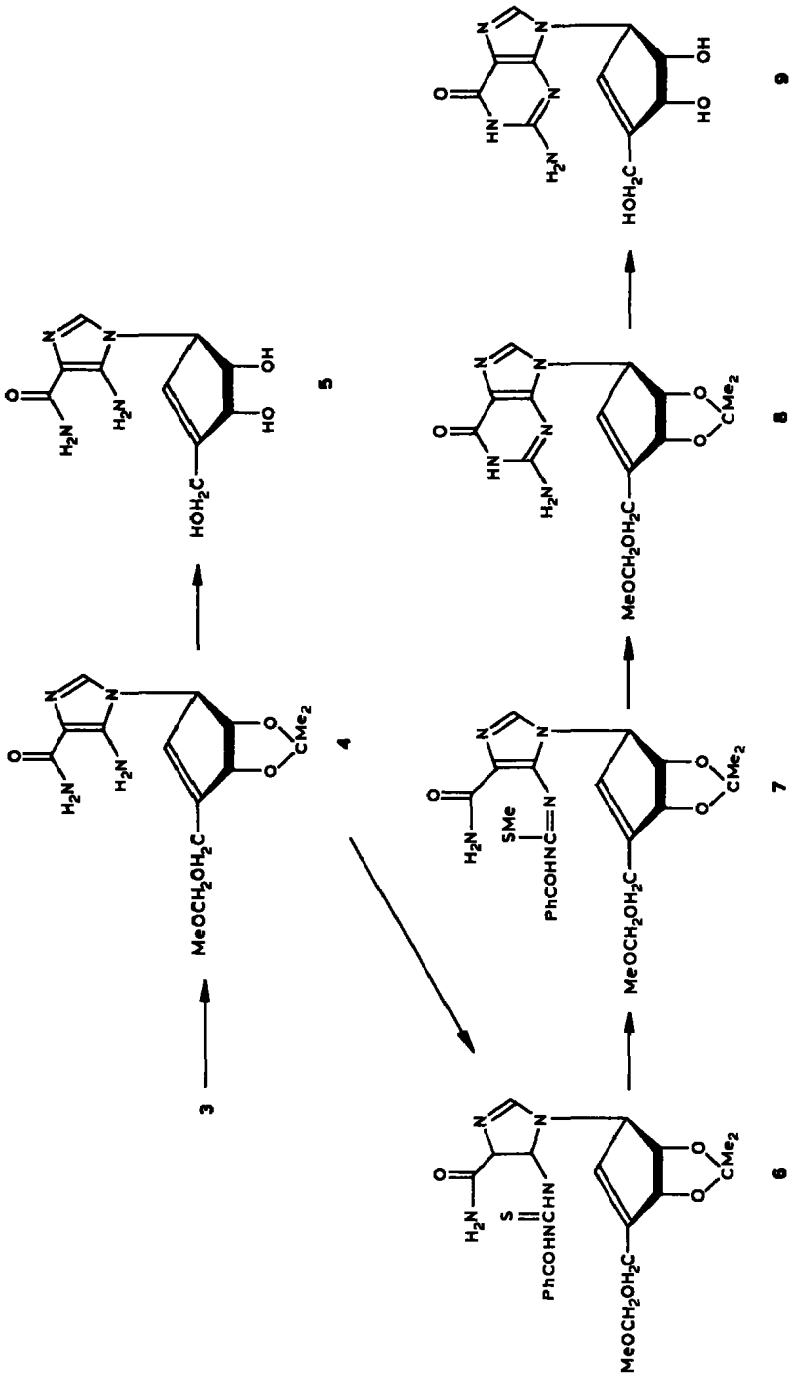
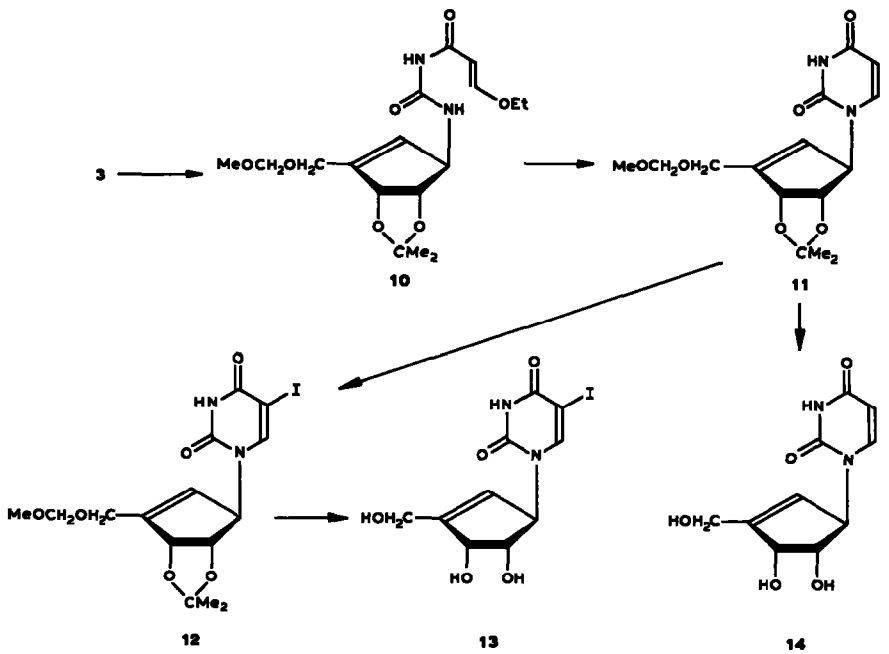


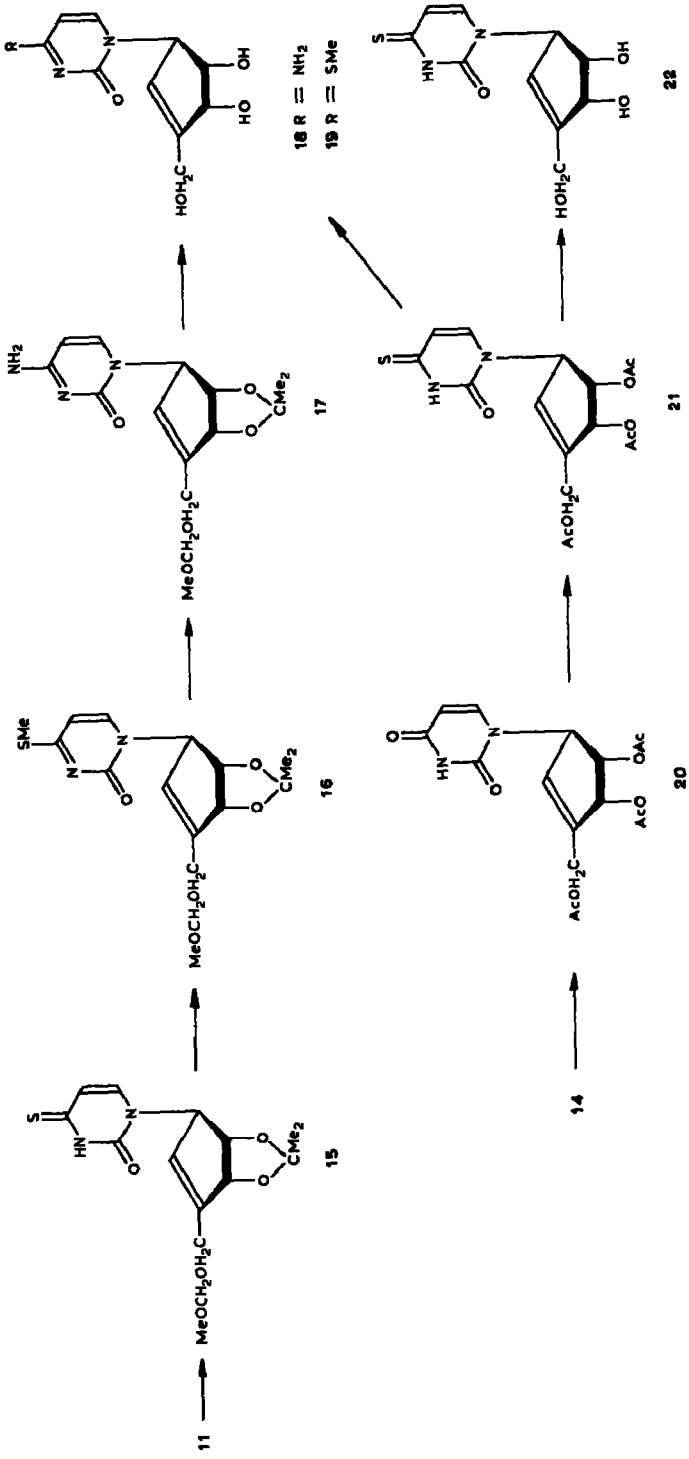
## INTRODUCTION

Neplanocin A, isolated from *Actinoplanacea ampullariella sp.* in 1981, is a carbocyclic analog of adenosine having a cyclopentene moiety and exhibits a remarkable antitumor activity against L1210 leukemia in mice[1]. We undertook the selective synthesis of the enantiomer and reported[2] the first and efficient total synthesis of (−)-neplanocin A in 1983 through an optically active half-ester **2**, enzymically generated from a symmetric unsaturated diester **1**. A key intermediate of the synthesis was (1*R*, 2*S*, 3*R*)-2,3-isopropylidenedioxy-4-methoxymethyloxymethyl-4-cyclopentenylamine (**3**), which can be used as a common precursor for the preparation of analogs of neplanocin A. We present herein the enantioselective synthesis of analogs of neplancocin A and their biological activity.

## RESULTS AND DISCUSSION

5-Aminoimidazole-4-carboxamide riboside is a key intermediate of the *de novo* biosynthesis of purine nucleosides. Therefore, derivatives of this riboside have been considered as important antimetabolites. Thus, a 5-aminoimidazole-4-carboxamide analog was first synthesized in three steps from **3** according to Shaw and Wilson[3]. The key intermediate **3** was treated with α-amino-α-cyanoacetamide and ethyl orthoformate in acetonitrile to afford the 5-aminoimidazole-4-carboxamide derivative **4** in 72% yield. After deprotection with dilute hydrochloric acid, crude **5** was purified by ion-exchange chromatography to afford pure **5** in 93% yield.



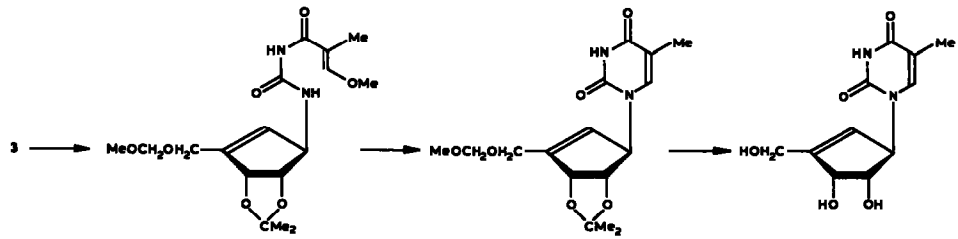

18 R = NH2
19 R = SMe

The guanosine analog **10** was synthesized in five steps from **3** according to Yamazaki and Okutsu[4]. Treatment of **4** with benzoylisothiocyanate in acetone at room temperature afforded the thiourea derivative **6** in 78% yield. Its methylation proceeded smoothly, to give the methylthio derivative **7** as a colorless oil, after chromatography on silica gel. Treatments with sodium hydroxide gave **9** in 61% yield, and deprotection with hydrochloric acid afforded the guanosine analog **9** in 92% yield.

The uridine analogs were obtained as follows. The cyclopentenylamine **3** was treated with 3-ethoxyacryloylisocyanate[5], generated *in situ* from 3-ethoxyacrolyl chloride and silver isocyanate, to afford the acryloylurea derivative **10** in 91% yield. Cyclization of **10** gave the uridine derivative **11** as a colorless oil in 91% yield. This was deprotected and crude **14** was treated with an ion-exchange resin to afford the pure uridine analog **14** as a colorless syrup in 98% yield. The 5-iodouridine analog **13** was synthesized in four steps from **3** according to Tai-Shun Lin and You-Song Gao[6]. Treatment of **11** with iodine and silver trifluoroacetate afforded **12** in 34% yield, and deprotection, followed by neutralization with an anion-exchange resin, gave **13** in 49% yield.

Various cytidine analogs, such as AraC, cyclo C, and 5-FC, are in clinical use as antitumor agents and a carbocyclic cytidine analog (Carbodine) was found to be active against L1210 leukemia[7]. Therefore, we investigated the biological activity of the cytidine analog of the cyclopentenylnucleoside, neplanocin A. In a first approach to the preparation of the cytidine analog **18**, thiation[8] of the uridine derivative **11** produced the 4-thiouridine derivative **15** in 45% yield with a 50% recovery of **11**. Methylation of **15** in 89% yield, followed by amination of **16** ammonia to give **17** in 91% yield, and finally deprotection with hydrochloric acid afforded the cytidine analog **18** in 94% yield. As the yield of the first step was low, a second approach was investigated. Acetylation of the uridine analog **14** afforded the tri-*O*-acetyl derivative **20** in 91% yield, in addition to the $N^3$,2′,3′,6′-tetraacetyl derivative in 7% yield. Treatment of **20** with phosphorus pentasulfide afforded the 4-thio derivative **21** in 83% yield, which was methylated to give **19**, further aminated to afford the crystalline cytidine analog **18** in 94% yield. The 4-thiouridine analog **22** was obtained from **21** by treatment with ammonia.

The thymine base was introduced in the same manner as the uracil base. Treatment of the free amine **3** with 3-methoxy-2-methylacryloyl isocyanate[9] afford-

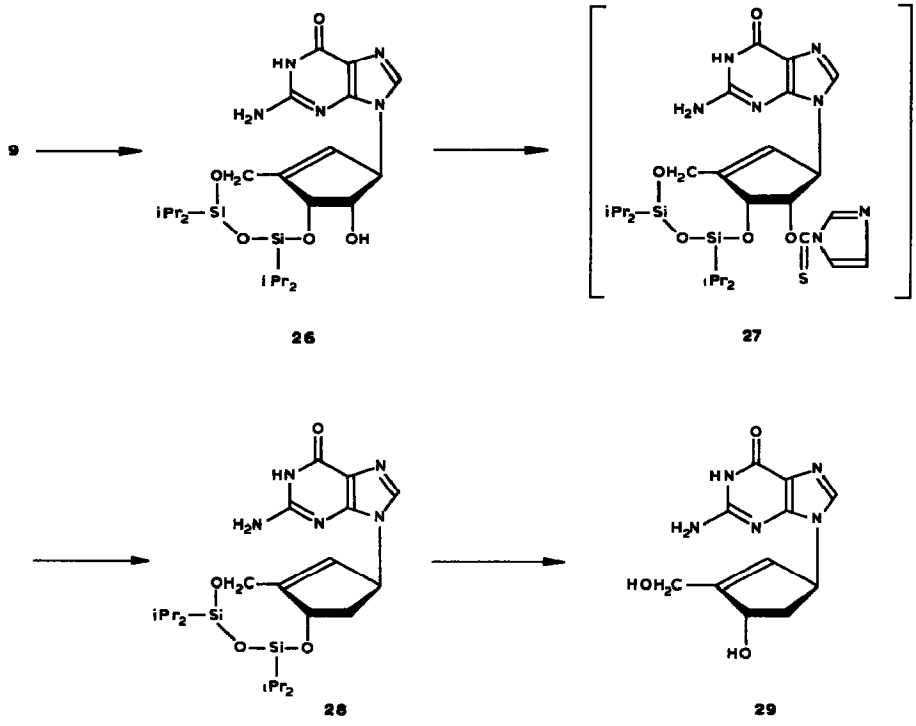



23 24 25

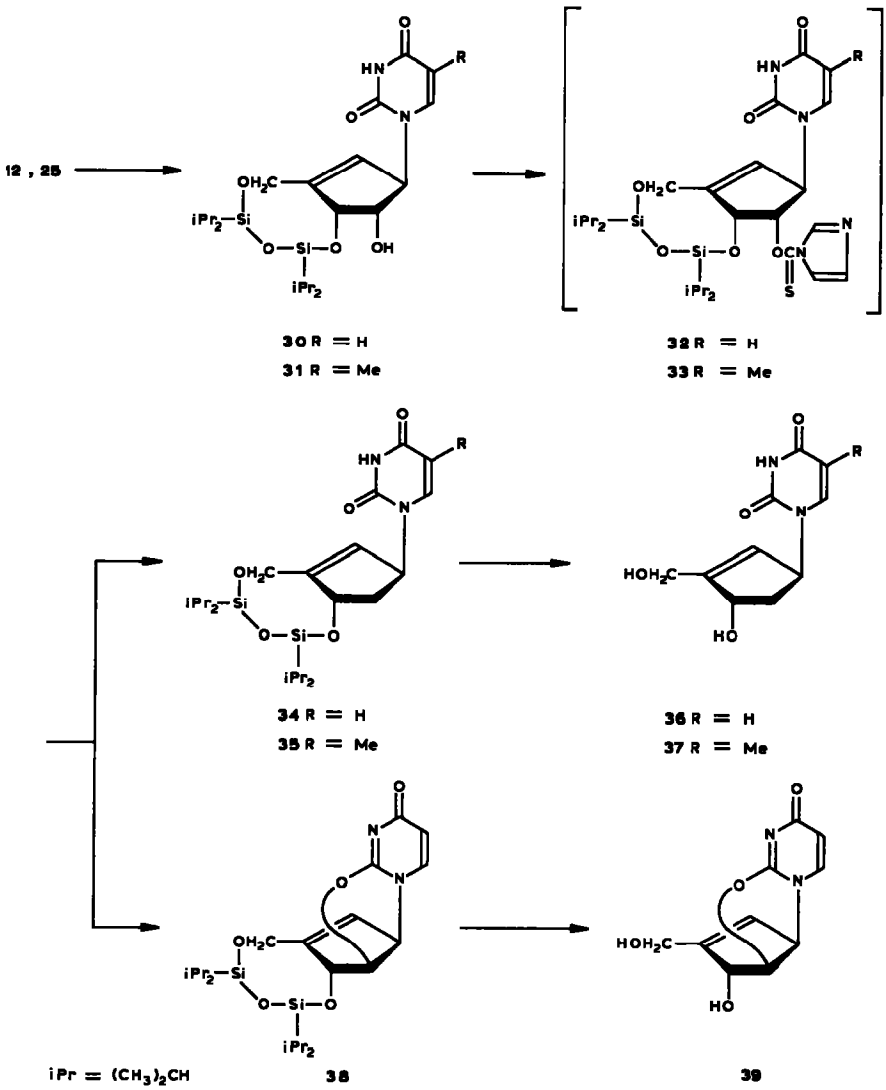
ed the ureido derivative **23** in 87% yield. Cyclization was achieved in acetone with ammonium hydroxide to give, in a fairly good yield, **24** the structure of which was readily established by the u.v. spectrum and other analyses as for the uracil derivative **11**. Hydrolysis of **24** with trifluoroacetic acid gave **25** in crystalline form, in 75% yield after chromatographic purification.

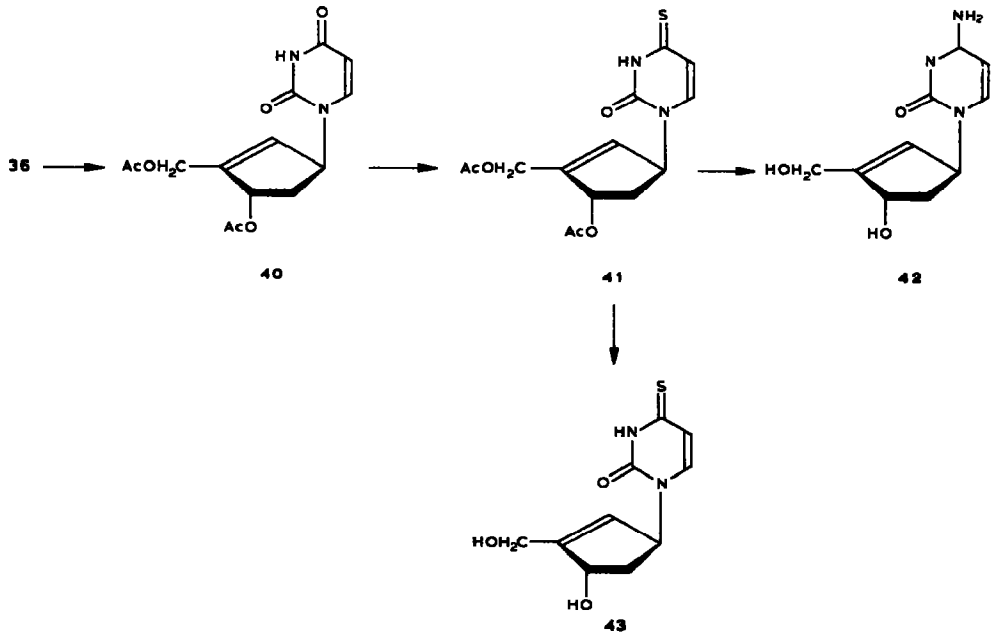
The easy 2′-deoxygenation of ribonucleosides and neplanocin A[10], by a radical reduction of a 2′-deoxy-2′-halogeno or thiocarbonyl derivative with tributyltin hydride in the presence of azo(isobutyronitrile) (Barton reaction), was also applied successfully in the present work. First, OH-3- and -6 of **9** of the cyclopentene moiety were protected by the Markiewicz reagent[10,11], 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane, in the presence of imidazole to give **20** in 58% yield. Deoxygenation of **20** was performed without isolation of the intermediate **27** by treatment with *N,N*-thiocarbonyldiimidazole, followed by reduction with tributyltin hydride, in the presence of a catalytic amount of azo(isobutyronitrile), to give **28** in 40% yield from **26**. The $^1$H-n.m.r. spectrum of **28** exhibited a characteristic signal for H-2′ at $\delta$ 2.32 as a multiplet. Deprotection with tetrabutylammonium fluoride in THF afforded the desired compound **29** in 85% yield.

The deoxygenation reported in our previous study[10] was also applied to the uracil (**12**) and thymine (**25**) analogs. They were protected in the usual manner to give **30** (71%) and **31** (68%), respectively. Attempts to deoxygenate **30** in acetonitrile through *O*-thiocarbonylation, followed by homolytic cleavage, gave **34** (45%) to-



gether with the 2,2′-anhydro derivative **38** (30%), which were readily separated by silica gel column chromatography. In the $^1$H-n.m.r. spectrum, **34** showed signals for H-2′a (ddd) and H-2′b (ddd) at $\delta$ 2.06 and 2.44, respectively. The structure was further confirmed by mass spectrometry (*m/z* 466, $M^+$) and other analyses. The $^1$H-n.m.r. spectrum of **38** exhibited a signal for H-2′ at $\delta$ 5.21–5.41 (m), overlapped by the signals for H-1′ and H-3′, as well as a parent peak in the f.a.b. mass spectrum at *m/z* 465 ($MH^+$). The ratio of **38** to **34** seemed to increase with higher temperatures. The 2,2′-anhydro derivative **38** was used for the synthesis of the *arabino*-pyrimidine nucleoside **49**. Treatment of **30** with *N,N′*-thiocarbonyldiimidazole, followed by homolytic cleavage of **32** with tributyltin hydride furnished **34** (76%)





exclusively. Similarly, **35** was obtained from **31** in 77% yield; its $^1$H-n.m.r. spectrum showed the characteristic signals of H-2'a(m) and H-2'b(m) at $\delta$ 2.12 and 2.35, respectively. Both **34** and **35** were deprotected with tetrabutylammonium fluoride to afford crystalline **36** and **37** in 71 and 92% yield, respectively, and similarly **38** furnished **39** in a quantitative yield.

The di-*O*-acetyl derivative **40** of the 2'-deoxyuridine derivative **36** was thiated with phosphorus pentasulfide to give **41** in 87% yield, and successive methylation and ammonolysis afforded the 2'-deoxycytidine analog **42**. The 2'-deoxy-4-thiouridine analog **43** was obtained from **41** by treatment with ammonia.

In general, D-arabinosylnucleosides are recognized as deoxynucleosides by the cell system[13], but it is noteworthy that the cytidine analog **18** possesses a marked activity against L-1210 and B-16 melanoma system *in vivo* (Table I). Therefore, we synthesized the analog **48** having the D-arabino configuration in order to compare its activity with that of AraC and the cytidine analog **18**. Among the many methods of synthesis of arabinosylpyrimidine nucleosides[14], that using the hydrolytic cleavage of the 2,2'-anhydro derivative **39** seemed the most suitable. Treatment of 3',5'-*O*-silyl protected uridine compounds with trifluoromethanesulfonyl chloride furnished the 2,2'-*O*-anhydrouridine exclusively[12]. This reaction may proceed by the intramolecular SN2 attack of the oxygen atom of the uridine base to the 2'-position (2'-OTf group) of the sugar residue. Therefore, **30** was treated with trifluoromethanesulfonyl chloride in the presence of *N,N*-dimethylaminopyridine to give, in 53% yield, **38** which was identical in all respects with the compound obtained as a

TABLE I

EFFECT OF NEPLANOCIN A AND CYTIDINE ANALOG (18) ON THE LIFE SPAN OF MICE BEARING L1210 LEUKEMIA AND B16 MELANOMA[a]

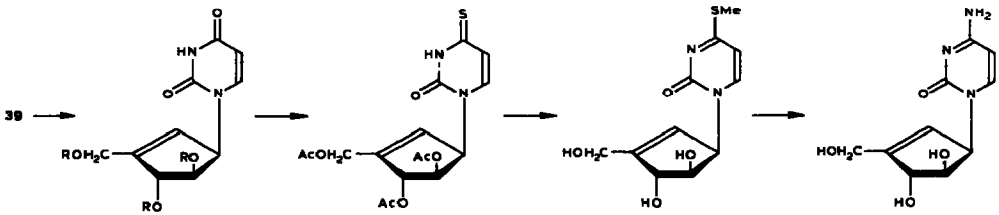
| *Compound* | *L1210 Leukemia* | | *B16 Melanoma* | |
|---|---|---|---|---|
| | *Dose (mg/kg/day)* | T/C *(%)* | *Dose (mg/kg/day)* | T/C *(%)* |
| Neplanocin A | 0.25 | 140 | | |
| | 0.5 | 147 | 0.5 | 106 |
| | 1.0 | 138 | 1.0 | 106 |
| | 2.5 | 159 | 2.5 | 114 |
| | 5.0 | Toxic | | |
| Cytidine analog 18 | 0.1 | 108 | 0.1 | 119 |
| | 0.25 | 131 | 0.25 | 128 |
| | 0.5 | 149 | 0.5 | 133 |
| | 1.0 | 177 | 1.0 | 144 |
| | 2.5 | Toxic | | |
| Ara-C | 50 | 185 | 50 | 122 |
| | 100 | 193 | 100 | 125 |
| | 250 | 207 | 250 | 119 |
| | 500 | 218 | 500 | Toxic |
| | 1000 | Toxic | | |
| 5-Fu | 5 | 219 | | |
| | 10 | 220 | 10 | 119 |
| | 25 | 225 | 25 | 125 |
| | 50 | 146 | 50 | Toxic |
| | 100 | Toxic | | |

[a] Groups of 6 female $CD_2F_1$ mice or male $B_6D_2F_2$ mice received intraperitoneal implants of L1210 leukemia cells ($10^5$/mouse), or B16 melanoma homogenates (0.5 mL/mouse), respectively, on day 0, according to the protocols described by Geran *et al.*[17]. Compounds were given intraperitoneally on days 1–5. The results are expressed as *T/C* values calculated from median survival times, where *T* and *C* are values of treated and untreated groups, respectively.

by-product in the radical reduction of **32**. After deprotection of **38** in the usual manner, alkaline hydrolysis of **39** gave **44** which was acetylated without purification to exclusively furnish the triacetate **45** as a syrup in 98% yield; no $N^3$,2′,3′,6′-tetra-acetyl by-product was observed in this case. Thiation of **45** gave **46** in 90% yield, and methylation, followed by treatment with a large excess of saturated methanolic ammonia, afforded crystalline **48** in 43% yield from **46**; its structure was assertained by $^1$H-n.m.r. spectroscopy and mass spectrometry.

*Biological activity*. — Compounds, **5**, **9**, **13**, **14**, **18**, **22**, **25**, **29**, **36**, **30**, **39**, **42**, **43**, and **48** were evaluated for growth-inhibitory activity of mouse lymphoma L5178Y cells *in vitro*. As shown in Table II, the cytidine analog **18** and neplanocin A inhibited the growth at a concentration as low as 0.8 μg/mL, whereas the other 13 analogs had no effect, even at the highest concentration tested, 100 μg/mL. Recent-

ly, **18** was synthesized also from D-ribono-1,4-lactone by Marquez and assoc.[15] and shown to exhibit potent cytotoxicity. It seems worthwhile to note that **18** acts as inhibitors of uridine kinase[15] and CTP synthesis[16]. The antitumor activities of **18** and neplanocin A, compounds having potent cytotoxicity for L5178Y cells cultures, were tested against mouse leukemia L1210 and mouse melanoma B16. In the present study, the compounds were given intraperitoneally to mice, inoculated intraperitoneally with tumors; the results are shown in Table I. The cytidine analog **18**




44 R = H
45 R = Ac

46 47 48

and neplanocin A increased the life span of the leukemic mice by 77% at a dose of 1 mg/kg/day and 59% at 2.5 mg/kg/day, respectively, over the controls. Ara-C and 5-FU, used as reference antitumor drugs, were more effective in increasing the life span of leukemic mice than **18** and neplanocin A. Against mouse melanoma B16, **18** was found to be the most active among the tested compounds; it increased the life

TABLE II

INHIBITION OF GROWTH OF CULTURED L5178Y CELLS BY NEPLANOCIN A ANALOGS[a]

| *Compound* | *Cytotoxic concentration (μg/mL)* |
|---|---|
| **5** | >100 |
| **9** | >100 |
| **14** | >100 |
| **13** | >100 |
| **18** | 0.8 |
| **22** | >100 |
| **25** | >100 |
| **29** | >100 |
| **36** | >100 |
| **37** | >100 |
| **39** | >100 |
| **42** | >100 |
| **43** | >100 |
| **48** | >100 |
| Neplanocin A | 0.8 |

[a] L5178Y cells were suspended in Fischer's medium supplemented with 10% fetal bovine serum at cell concentrations ranging from 5 to 10 × $10^4$ cells/mL. Cell growth was checked 24 h after incubating at 37° in a humidified incubator passing 5% $CO_2$–95% air with or without test compounds.

span of tumor-bearing mice by 44% over the control at a dose of 1 mg/kg/day. The other three compounds tested were found to be inactive (ILS, increase in the life span over control, ≧125%). On the basis of these findings, a further evaluation study on the antitumor activity of the cytidine analog **18** in a variety of tumors is now under progress.

## EXPERIMENTAL

*General methods.* — Melting points were determined with Yanagimoto (MP-3) and Yamato (MP-21) micromelting point apparatus and are uncorrected. Optical rotations were measured with a Horiba SEPA-200 or JASCO DIP-360 polarimeter. U.v. spectra were recorded with a Shimadzu UV-250 or Hitachi 320 spectrophotometer. I.r. spectra were recorded with a Hitachi 260-50, JASCO IR-810, or Shimadzu IR-435 spectrophotometer. $^1$H-N.m.r. spectra were recorded for solutions in (2H)chloroform of di($^2H_3$)methyl sulfoxide with tetramethylsilane and sodium 4,4-dimethyl-4-silapentane-1-sulfonate (DDS) as an internal standard, with a JEOL FX-100-FT, JNM-PS-100, or Hitachi R-90 spectrometer. All exchangeable protons were confirmed by addition of $D_2O$. Mass spectra (m.s.) were measured on JEOL JMS D-300 (CI, FAB or EI) or JMS-01SG spectrometers. T.l.c. was carried out on Merck pre-coated silica gel $60F_{254}$ plates, and silica gel column chromatography was performed on Wako-gel C-200, Merck Kieselgel 60 Art 7734 or 9385.

*5 - Amino - 1[(1R, 2S, 3R) - 2,3 - isopropylidenedioxy - 4 - methoxymethyloxy - methyl-4-cyclopenten-1-yl]imidazole-4-carboxamide* (**4**). — To a solution of α-amino-α-cyanoacetamide (1.0 g, 0.01 mol) in dry acetonitrile (40 mL) was added triethyl orthoformate (1.64 g, 0.011 mol), and the mixture was refluxed with stirring for 30 min under an Ar atmosphere. A solution of **3** (1.10 g) and triethylamine (0.60 mL) in dry acetonitrile (25 mL) was added dropwise to the cooled mixture, which was refluxed with stirring for 3 h. The solvent was removed under reduced pressure, and the residue purified by silica gel column chromatography (20:1 chloroform–methanol) to give **4** (1.16 g, 72% yield), yellow crystals, m.p. 141.5–143°; $[\alpha]_D^{20}$ −34.2° (*c* 0.96, chloroform); $R_F$ 0.67 (3:1:1 ethyl acetate–ethanol–water 0.67; $\nu_{max}^{KBr}$ 3425, 3330, 3175, 1650, 1615, 1547, 1468, and 1385 cm$^{-1}$; $^1$H-n.m.r. ($CDCl_3$–$Me_4Si$): δ 1.35 and 1.47 [2 s, 6 H, $C(CH_3)_2$], 3.41 (s, 3 H, OMe), 4.30 (br.s, 2 H, $CH_2O$), 4.58 and 5.25 (2 d, 2 H, *J* 5.8 Hz, 2OCH), 4.71 (s, 2 H, $OCH_2O$), 4.94 (br.s, 1 H, NCH), 5.07 (br.s, 4 H, $CONH_2$, $NH_2$), 5.82 (br.s, 1 H, –CH=), and 6.86 (s, 1 H, arom.); e.i.m.s.: *m/z* 338 ($M^+$), 281, and 149.

*Anal.* Calc. for $C_{15}H_{22}N_4O_5$: C, 53.25; H, 6.55; N, 16.56. Found: C, 52.99; H, 6.52; N, 16.64.

*5-Amino-1-[(1R, 2S, 3R)-2,3-dihydroxy-4-hydroxymethyl-4-cyclopenten-1-yl]imidazole-4-carboxamide* (**5**). — Compound **4** (244 mg) was dissolved in methanol (20 mL) and 2M HCl (20 mL), and the solution stirred at 30–35° for 1 day. Methanol was removed under reduced pressure, and the residual solution passed through Amberlite CG-120 ($H^+$) cation-exchange resin. Elution with 0.07M $NH_4OH$

subsequent to washing with water and evaporation of the eluent under reduced pressure gave **5** (170 mg, 93% yield), pale-yellow crystals, m.p. > 220° (dec.); $[\alpha]_D^{20}$ −87.1° (*c* 0.16, dimethyl sulfoxide; $R_F$ (3:1:1 ethyl acetate–ethanol–water) 0.46; $\nu_{max}^{KBr}$ 3450, 3350, 3250, 1655, 1635, 1550, and 1455 $cm^{-1}$; $^1$H-n.m.r. [$(CD_3)_2SO$–$CDCl_3$; $Me_4Si$)]: δ 3.91 (t, 1 H, *J* 5.5 Hz, OCH), 4.12 (br.s, 2 H, $CH_2OH$), 4.35 (d, 1 H, *J* 5.5 Hz, OCH), 4.90 (br.s, 1 H, NCH), 5.74 (br.s, 1 H, –CH=), 5.64 and 6.68 (br, 4 H, $CONH_2$, $NH_2$), and 7.02 (s, 1 H, arom.); e.i.m.s.: *m/z* 222, 220 ($M^+$ − 2OH) 207, and 205.

*Anal.* Calc. for $C_{10}H_{14}N_4O_4 \cdot 0.5\ H_2O$: C, 45.63; H, 5.74; N, 21.28. Found: C, 45.76; H, 5.37; N, 20.83.

*5-(N-Benzoylthiocarbamoyl)amino-1-[(1R,2S,3R)-2,3-isopropylidenedioxy-4-methoxymethyloxymethyl-4-cyclopenten-1-yl]imidazole-4-carboxamide* (**6**). — To a solution of **4** (50 mg) in dry acetone (3 mL) was added dropwise benzoyl isothiocyanate (150 mg) in dry acetone (4 mL). The mixture was stirred at room temperature for 4 h, poured into saturated aqueous $NaHCO_3$ and extracted with dichloromethane several times. The organic layer was washed with water until neutral, and evaporated under reduced pressure, after being dried by passing through a phase-separating paper (Whatman 1PS), to afford a crude syrup. This was purified by silica gel column chromatography with stepwise elution with dichloromethane–methanol 50:1 to 30:1 to 20:1) to give **6** (70 mg, 95% yield) foam, $R_F$ (9:1 dichloromethane–methanol) 0.53; $\nu_{max}^{film}$ 3500, 3350, 3200, 1670, 1605, 1490, and 1380 $cm^{-1}$; $^1$H-n.m.r. ($CDCl_3$; $Me_4Si$): δ 1.32 and 1.40 [2 s, 6 H, $C(CH_3)_2$], 3.38 (s, 3 H, OMe), 4.27 (br.s, 2 H, $CH_2O$) 4.65 (s, 2 H, $OCH_2O$), 4.70 and 5.26 (d, 2 H, *J* unknown, 2 OCH), 5.24 (br. s, 1 H, NCH), 5.68 (br.s, 1 H, –CSN*H*–), 5.86 (br. s, 1 H, –CH=), 6.95 (br, 2 H, $CONH_2$), 7.29 (s, 1 H, imidazole proton), 7.52 and 7.88 (m, 5 H, PhCO), and 9.56 (br.s, 1 H, CSN*H*CO); e.i.m.s.: *m/z* 501 ($M^+$) and 486 ($M^+$ − Me).

*5-(N-Benzoyl-S-methylisothiocarbamoyl)amino-1-[(1R, 2S, 3R)-2,3-isopropylidenedioxy-4-methoxymethyloxymethyl-4-cyclopenten-1-yl]imidazole-4-carboxamide* (**7**). — To a solution of **6** (50 mg) and iodemethane (60 μL) in methanol (5 mL) was added M NaOH (0.2 mL) dropwise under stirring at room temperature. The mixture was stirred for 1 h at ambient temperature, the reaction quenched by addition of acetic acid to neutrality, and the solvent removed under reduced pressure. The residue was extracted with ethyl acetate several times and the extract washed with water. The organic layer was passed through Whatman 1PS filter paper and evaporated under reduced pressure. The residue was purified by silica gel column chromatography with ethyl acetate as an eluent to give **7** (43 mg, 84% yield) as a colorless syrup by evaporation of the eluate under reduced pressure, $R_F$ (9:1 dichloromethane–methanol) 0.66; $\nu_{max}^{film}$ 3460, 3350, 1650, 1610, 1575, and 1370 $cm^{-1}$; $^1$H-n.m.r. ($CDCl_3$; $Me_4Si$) 1.32 and 1.41 [2 s, 6 H, $C(CH_3)_2$], 2.60 (s, 3 H, SMe), 3.39 (s, 3 H, OMe), 4.29 (br.s, 2 H, $CH_2O$), 4.59 and 5.16 (2 d, *J* 6 Hz, 2 H, 2 OCH), 4.68 (s, 2 H, $OCH_2O$), 5.24 (br.s, 1 H, NCH), 5.72 (br.s, 1 H, –CH=), 5.84 (br.s, 1 H, CONH–), 7.11 (s, 1 H, imidazole H), 7.34 and 7.83 (m, 5 H, PhCO); e.i.m.s.:

*m/z* 515 ($M^+$), 468 ($M^+$ − SMe), 467, 320, and 262.

*9-[(1R, 2S, 3R)-2,3-Isopropylidenedioxy-4-methoxymethyloxymethyl-4-cyclopenten-1-yl]guanine* (**8**). — To a solution of **7** (75 mg) in methanol (4 mL) was added 6M NaOH (4 mL), and the mixture stirred for 4 h at 100–110°. After the mixture had been cooled in an ice bath, rapid crystallization occurred on neutralization with dilute HCl. Methanol was removed under reduced pressure, and filtration gave **8**(37 mg, 70% yield), colorless crystals, m.p. >270° (dec.), $R_F$ (3:1:1 ethylacetate–ethanol–water) 0.60; $\lambda_{max}^{MeOH}$ 256.5 and 232 nm; $\nu_{max}^{KBr}$ 3400, 3200, 1700, 1640, 1605, 1540, and 1380 $cm^{-1}$; $^1$H-n.m.r. [$(CD_3)_2SO$–$CDCl_3$; MeSi]: δ 1.29 and 1.37 [2 s, 6 H, $C(CH_3)_2$], 3.31 (s, 3 H, OMe), 4.20 (s, 2 H, $CH_2O$), 4.59 and 5.38 (2 d, *J* 5.5 Hz, 2 H, 2 OCH), 4.64 (s, 2 H, $OCH_2O$) 5.26 (br.s, 1 H, NCH), 5.70 (s, 1 H, –CH=), 6.48 (br.s, 1 H, CONH), and 7.44 (s, 1 H, arom.); e.i.m.s.: *m/z* 363 ($M^+$), 348 ($M^+$ − Me), 311, 284, 152 (G + 2), and 151 (G + 1).

*9-[(1R, 2S, 3R)-2,3-Dihydroxy-4-hydroxymethyl-4-cyclopenten-1-yl]guanine* (**9**). — Compound **8** (33 mg) was dissolved in methanol (1 mL) and 2M HCl (1 mL), and the mixture was stirred for 2 days at room temperature. Methanol was removed by evaporation under reduced pressure and the residual solution was applied to a column of Dowex 50 ($H^+$) cation-exchange resin. Elution with 0.1M $NH_4OH$, subsequent to washing with water, followed by evaporation under reduced pressure afforded **9** (20 mg, 81% yield), colorless needles after crystallization from water, m.p. >220° (dec.), $[\alpha]_D^{20}$ −87° (*c* 0.15, *N,N*-dimethylformamide); $R_F$ (3:1:1 ethyl acetate–ethanol–water) 0.26; $\lambda_{max}^{H_2O}$ 254.5, $\lambda_{min}^{H_2O}$ 229.5nm; $\nu_{max}^{KBr}$ 3400, 3200, 1740, 1692, 1640, 1613, and 1540 $cm^{-1}$; $^1$H-n.m.r. [$(CD_3)_2SO$–$CDCl_3$; $Me_4Si$]: δ 3.32 (br, 2 H, 2 OH), 4.10 (s, 2 H, $CH_2OH$), 4.16 and 4.23 (t, 1 H, *J* 5.3 Hz; d, 1 H, *J* 5.3 Hz; 2 OCH), 5.14 (br.s, 1 H, NCH), 5.64 (d, 1 H, *J* 1.8 Hz, –CH=), 6.60 (br.s, 1 H, CONH), and 7.55 (s, 1 H, arom.); e.i.m.s.: *m/z* 279 ($M^+$), 207, 183, 165, and 152 (G + 2).

*(1R, 2S, 3R)-1-[N-(3-Ethoxyacryloyl)ureido]-2,3-isopropylidenedioxy-4-methoxymethyloxymethyl-4-cyclopentene* (**10**). — Compound **3** (544 mg) was dissolved in dry *N,N*-dimethylformamide (20 mL) and the solution cooled to −30 to −45° in a dry ice–acetone bath. To this mixture was added a solution of 3-ethoxy-2-propenoyl isocyanate [prepared from 3-ethoxy-2-propenoyl chloride (650 mg) and AgNCO (1.44 g) by heating in dry benzene] dropwise under an Ar atmosphere. The mixture was stirred for 1 h each at −30° and at room temperature, and then poured into ice-cooled, satd. $NaHCO_3$ with vigorous stirring and extracted with ethyl acetate three times. The combined organic layer was washed with water, dried by passing through Whatman 1PS, and evaporated under reduced pressure. The residue was chromatographed in a column of silica gel with 1:2 ethyl acetate–hexane to give **10** (800 mg, 91% yield), colorless syrup, $R_F$ (1:1 ethyl acetate–hexane) 0.27; $\nu_{max}^{film}$ 3250, 3100, 1700, 1675, 1615, 1535, and 1380 $cm^{-1}$; $^1$H-n.m.r. ($CDCl_3$; $Me_4Si$): δ 1.32 and 1.39 [2 s, 6 H, $C(CH_3)_2$], 1.35 (t, 3 H, *J* 6.8 Hz, $CH_2CH_3$), 3.38 (s, 3 H, OMe), 3.97 (q, 2 H, *J* 6.8 Hz, $OCH_2CH_3$), 4.19 (s, 2 H, $CH_2O$), 4.55 and 4.79 (d, 1 H, *J* 6 Hz; m, 1 H, 2 OCH), 4.67 (s, 2 H, $OCH_2O$), 5.14 (br.d, 1H, *J* 5.5 Hz, NCH),

5.38 (d, 1 H, *J* 12.5 Hz, -COCH=), 5.66 (s, 1 H, -CH=), 7.61 (d, 1 H, *J* 12.5 Hz, =C*H*-OEt), 8.63 (d, 1 H, *J* 7 Hz, CHN*H*CO), and 9.26 (s, 1 H, CONHCO); e.i.m.s.: *m/z* 355 ($M^+$ − Me), 309, 281, 267, 257, and 252.

*1-[(1*R*, 2*S*, 3*R*)-2,3-Isopropylidenedioxy-4-methoxymethyloxymethyl-4-cyclopenten-1-yl]-2,4-(1*H*, 3*H*)-pyrimidinedione* (**11**). — To a solution of **10** (404 mg) in acetone (10 mL) was added 2.8% $NH_4OH$, (30 mL), and the mixture stirred with reflux for 10 h. After being cooled to ambient temperature, the mixture was evaporated under reduced pressure. The residue was chromatographed in a column of silica gel with 1:2 ethyl acetate–hexane to give **11** (321 mg, 91% yield), colorless foam, $[\alpha]_D^{20}$ −53.5° (*c* 0.66, chloroform), $R_F$ (ethyl acetate) 0.34; $\nu_{max}^{film}$ 3200, 1680, 1450, 1370, and 1230 $cm^{-1}$; $^1$H-n.m.r. ($CDCl_3$; $Me_4Si$): δ 1.35 and 1.44 [2 s, 6 H, $C(CH_3)_2$], 3.40 (s, 3 H, OMe), 4.28 (br.s, 2 H, $CH_2O$), 4.59 and 5.23 (2 d, 2 H, *J* 5.8 Hz, 2 OCH), 4.70 (s, 2 H, $OCH_2O$), 5.38 (br.s, 1 H, NCH), 5.59 (br.s, 1 H, -CH=), 5.68 (dd, 1 H, *J* 1.5, 8 Hz, COCH=), 7.05 (d, 1 H, *J* 8 Hz, NCH=), and 9.67 (br.s, 1 H, CONHCO); e.i.m.s.: *m/z* 309 ($M^+$ − Me), 267, 263, and 235.

*1-[(1*R*, 2*S*, 3*R*)-2,3-Dihydroxy-4-hydroxymethyl-4-cyclopenten-1-yl]-2,4(1*H*, 3*H*)-pyrimidinedione* (**14**). — (*a*). A solution of **11** (3.0 g) in trifluoroacetic acid (30 mL) and water (30 mL) was stirred for 2 days at room temperature. The mixture was evaporated and the residue coevaporated to dryness with ethanol several times under reduced pressure. It was purified by silica gel column chromatography with 4:1 chloroform–methanol as an eluent to give **14** (1.71 g, 77% yield), colorless foam, $[\alpha]_D^{20}$ −84° (*c* 1.19, methanol), $R_F$ (3:1:1 ethyl acetate–ethanol–water) 0.41; $\lambda_{max}^{MeOH}$ 270 nm; $\nu_{max}^{film}$ 3350, 1675, 1460, 1388, and 1255 $cm^{-1}$; $^1$H-n.m.r. ($CD_3OD$–$CDCl_3$; $Me_4Si$): δ 4.04 (t, 1 H, *J* 5.5 Hz, OCH), 4.27 (br.s, 2 H, $CH_2OH$), 4.52 (d, 1 H, *J* 5.5 Hz, OCH), 5.48 (br.s, 1 H, NCH), 5.69 (d, 1 H, *J* 2 Hz, -CH=), 5.70 (d, 1 H, *J* 8 Hz, -COCH=), and 7.38 (d, 1 H, *J* 8 Hz, -NCH=); e.i.m.s.: *m/z* 223 ($M^+$ − OH), 207 ($M^+$ − 2 OH), 167, 161, 112 (U + 1), and 110 (U − 1).

(*b*). A mixture of **11** (47 mg) in methanol (4 mL) and 2M HCl (4 mL) was stirred for 1 day at 30–35°. Methanol was removed under reduced pressure, and the residual solution made neutral with Diaion WA30 ($OH^-$) ion-exchange resin. After filtration, the solution was concentrated to dryness under reduced pressure to furnish **14** (34 mg, 98% yield) as a colorless foam.

*5-Iodo-1-[(1*R*, 2*S*, 3*R*)-2,3-isopropylidenedioxy-4-methoxymethyloxymethyl-4-cyclopenten-1-yl]-2,4-(1*H*, 3*H*)-pyrimidinedione* (**12**). — To a solution of **11** (2.00 g) in dry dichloromethane (120 mL) was added silver trifluoroacetate (2.70 g), and a solution of $I_2$ (2.30 g) in dichloromethane (15 mL) was added dropwise under cooling in an ice bath under an $N_2$ atmosphere. After being stirred for 1 h at the same temperature, the mixture was poured into ice-cold, satd. $NaHCO_3$, and the insoluble material was filtered off with Celite. The filtrate was partitioned with ethyl acetate several times, and the combined organic layer dried by passing through Whatman 1PS and evaporated to dryness under reduced pressure. The residue was purified by chromatography in a silica gel column with 1:1 ethyl acetate–hexane, to give **12** (1.00 g, 34% yield), m.p. 195–196°, $[\alpha]_D^{23}$ −87.5° (*c* 0.3, chloroform); $R_F$ (1:1

ethyl acetate–hexane) 0.26; $\lambda_{max}^{MeOH}$ 290, $\lambda_{min}^{MeOH}$ 247 nm; $\nu_{max}^{KBr}$ 3160, 3040, 1695, 1690, 1608, 1440, 1090, and 1040 $cm^{-1}$; $^1$H-n.m.r. ($CDCl_3$; $Me_4Si$): $\delta$ 1.35 and 1.44 [2 s, 6 H, $C(CH_3)_2$], 3.40 (s, 3 H, OMe), 4.29 (br.s, 2 H, $-CH_2O$), 4.57 and 5.23 (2 d, 2 H, *J* 6 Hz, 2 OCH), 4.70 (s, 2 H, $OCH_2O$), 5.36 (br.s, 1 H, NCH), 5.58 (br.s, 1 H, –CH=), 7.41 (s, 1 H, N–CH=), and 8.78 (br.s, 1 H, CONHCO); e.i.m.s.: *m/z* 450 ($M^+$), 435 ($M^+$ – Me), 331, 283, 156, 155, and 123.

*Anal.* Calc. for $C_{15}H_{19}IN_2O_6$: C, 40.02; H, 4.25; N, 6.22. Found: C, 39.83; H, 4.23; N, 6.21.

*1-[(1R, 2S, 3R)-2,3-Dihydroxy-4-hydromethyl-4-cyclopenten-1-yl]-5-iodo-2,4-(1H, 3H)*-pyrimidinedione (**13**). — Compound **12** (1.0 g) was dissolved in methanol (10 mL) and 3M HCl (10 mL), and the mixture stirred for 24 h at ambient temperature. Methanol was removed by evaporation under reduced pressure, and the residual solution was applied onto a column of Diaion WA30 ($OH^-$) ion-exchange resin. Elution with water, followed by evaporation under reduced pressure gave **13** (425 mg, 52% yield) which was crystallized from 4:1 ethanol–methanol, needles, m.p. 123–124°, $[\alpha]_D^{23}$ −114° (*c* 0.195, methanol, $R_F$ (3:1:1 ethyl acetate–ethanol–water) 0.64; $\lambda_{max}^{MeOH}$ 292, $\lambda_{min}^{MeOH}$ 246.5nm; $\nu_{max}^{KBr}$ 3380, 1680, 1610, 1425, 1260, and 1118 $cm^{-1}$; $^1$H-n.m.r. [$(CD_3)_2SO$; $Me_4Si$]: $\delta$ 3.92 (t, 1 H, *J* 5.5 Hz, OCH), 4.08 (br.s, 2 H, $CH_2OH$), 4.33 (d, 1 H, *J* 5.5 Hz, OCH), 4.88 (br, 3 H, 3 OH), 5.30 (br.s, 1 H, NCH), 5.53 (br.s, 1 H, –CH=), 7.70 (s, 1 H, N–CH=), and 11.52 (br, 1 H, CONHCO); 366 ($M^+$), 348 ($M^+ - H_2O$), 330 ($M^+ - 2\,H_2O$), 287, 276, 254, and 238 (5 – IU + 1).

*Anal.* Calc. for $C_{10}H_{11}IN_2O_5$·EtOH: C, 34.97; H, 4.16; N, 6.80. Found: C, 34.63; H, 4.12; N, 6.77.

*1-[(1R, 2S, 3R)-2,3-Isopropylidenedioxy-4-methoxymethyloxymethyl-4-cyclopenten-1-yl]-2-oxo-4-thioxo-(1H, 3H)-pyrimidine* (**15**). — To a solution of compound **11** (40 mg) in dry pyridine (1 mL) was added $P_2S_5$ (67 mg), and the mixture stirred for 2 h at 95–100°. After being cooled to room temperature, the mixture was evaporated under reduced pressure and the residue extracted several times with dichloromethane. The combined organic layer was washed with water and evaporated to dryness under reduced pressure. The residue was applied onto a silica gel column which was developed with 1:1 ethyl acetate–hexane to give [along with recovered starting material **11** (20 mg, 50% yield)] **15** (18 mg, 45% yield), slightly yellow syrup, $R_F$ (ethyl acetate) 0.77; $\nu_{max}^{film}$ 1705, 1610, 1450, 1380, and 1235 $cm^{-1}$; $^1$H-n.m.r. ($CDCl_3$;$Me_4Si$): $\delta$ 1.36 and 1.44 [2 s, 6 H, $C(CH_3)_2$], 3.40 (s, 3 H, OMe), 4.29 (s, 2 H, $CH_2O$), 4.59 and 5.23 (2 d, 2 H, *J* 5.8 Hz, 2 OCH), 4.70 (s, 2 H, $OCH_2O$), 5.34 (br.s, 1 H, NCH), 5.58 (br.s, 1 H, –CH=), 6.34 (d, 1 H, *J* 7.5 Hz, –COCH=), and 6.87 (d, 1 H, *J* 7.5 Hz, –NCH=); e.i.m.s.: *m/z* 340 ($M^+$), 325 ($M^+$ – Me), 279 ($M^+$ – 2 Me, OMe), 221, 214, and 172.

*1-[(1R, 2S, 3R)-2,3-Isopropylidenedioxy-4-methoxymethyloxymethyl-4-cyclopenten-1-yl]-4-methylthio-2(1H)-pyrimidinone* (**16**). — To a solution of **15** (54 mg) in methanol (2.5 mL) and water (0.5 mL) was added iodomethane (45 mg), followed by the dropwise addition of M NaOH (0.18 mL) under stirring at room temperature.

After the mixture had been stirred for 1 h at ambient temperature, acetic acid was added until neutral and the solvents were evaporated under reduced pressure. The residue was partitioned between ethyl acetate and water. The organic layer was concentrated under reduced pressure, and the residue chromatographed in a column of silica gel with 1:1 ethyl acetate–hexane, to give **16** (50 mg, 89% yield), pale-yellow crystal which were recrystallized from 1:1 ehter–hexane to afford colorless needles, m.p. 49–51°, $[\alpha]_D^{20}$ −16° (*c* 1.12, chloroform); $R_F$ (ethyl acetate) 0.47; $\nu_{max}^{KBr}$ 1645, 1610, 1502, 1430, 1385, and 1372 $cm^{-1}$; $^1$H-n.m.r. ($CDCl_3$; $Me_4Si$): δ 1.35 and 1.44 [2 s, 6 H, $C(CH_3)_2$], 2.56 (s, 3 H, SMe), 3.40 (s, 3 H, OMe), 4.29 (br.s, 2 H, $CH_2O$), 4.62 and 5.23 (2 d, 2 H, *J* 5.7 Hz, 2 OCH), 4.70 (s, 2 H, $OCH_2O$), 5.42 (t, 1 H, *J* 1.7 Hz, NCH), 5.60 (br.s, 1 H, –CH=), 6.16 (d, 1 H, *J* 7.1 Hz, NCH=C*H*–), and 7.15 (d, 1 H, *J* 7.1 Hz, NC*H*=CH–); e.i.m.s.: *m/z* 354 ($M^+$), 339 ($M^+$ − Me), 293, 234, and 187.

*Anal.* Calc. for $C_{16}H_{22}N_2O_5S$: C, 54.22; H, 6.25; N, 7.90. Found: C, 54.62; H, 6.55; N, 7.84.

*4-Amino-1-[(1R, 2S, 3R)-2,3-isopropylidenedioxy-4-methoxymethyloxymethyl-4-cyclopenten-1-yl]-2(1H)-pyrimidinone* (**17**). — A solution of **16** (25 mg) in methanol (2 mL), was saturated with $NH_3$, under cooling at −78°, in a stainless steel tube. The mixture was kept for 10 h at 100–110°. The solvent was removed under reduced pressure, the residue was purified by silica gel column chromatography (19:1 dichloromethane–methanol) to afford **17** (21 mg, 91% yield), colorless crystals, m.p. 84–85°, $[\alpha]_D^{20}$ −81°(*c* 1.77, chloroform), $R_F$ (3:4:4 ethyl acetate–ethanol–water) 0.43; $\lambda_{max}^{MeOH}$ 277, $\lambda_{min}^{MeOH}$ 257 nm; $\nu_{max}^{film}$ 3350, 3125, 1660, 1625, 1485, 1390, and 1215 $cm^{-1}$; $^1$H-n.m.r. ($CDCl_3$; $Me_4Si$): δ 1.34 and 1.43 [2 s, 6 H, $C(CH_3)_2$], 3.40 (s, 3 H, OMe), 4.28 (br.s, 2 H, $CH_2O$), 4.58 and 5.21 (2 d, 2 H, *J* 5.7 Hz, 2 OCH), 4.70 (s, 2 H, $OCH_2O$), 5.36 (br.s, 1 H, NCH), 5.59 (br.s, 1 H, –CH=), 5.82 (d, 1 H, *J* 7.5 Hz, NCH=C*H*), and 7.07 (d, 1 H, *J* 7.5 Hz, NC*H*=CH–); e.i.m.s.: *m/z* 323 ($M^+$), 308 ($M^+$ − Me) 262, 204, 155, and 149.

*Anal.* Calc. for $C_{15}H_{21}N_3O_5 \cdot 0.5\ H_2O$: C, 54.21; H, 6.67; N, 12.64. Found: C, 54.66; H, 6.83; N, 12.49.

*4-Amino-1-[(1R, 2S, 3R)-2,3-dihydroxy-4-hydroxymethyl-4-cyclopenten-1-yl]-2(1H)-pyrimidinone* (**18**). — *From* **17**. A solution of **17** (43 mg) in methanol (1 mL) and 2M HCl (2 mL) was stirred for 16 h at 30–35°. Methanol was removed under reduced pressure and the residual solution applied onto a column of Amberlite CG-120 ($H^+$) cation-exchange resin. After washing with water until neutral, elution with 0.07M $NH_4OH$ and evaporation under reduced pressure gave **18** (30 mg, 94% yield), amorphous powder, $[\alpha]_D^{20}$ −67.5° (*c* 1.84, methanol), $R_F$ (3:1:1 ethyl acetate–ethanol–water) 0.19; $\lambda_{max}^{MeOH}$ 279, $\lambda_{min}^{MeOH}$ 259 nm; $\nu_{max}^{film}$ 3350, 3200, 1645, 1605, 1500, 1400, 1285, and 1120 $cm^{-1}$; $^1$H-n.m.r. ($CD_3OD$, $CDCl_3$; $Me_4Si$): 4.04 (t, 1 H, *J* 5 Hz, OCH), 4.28 (s, 2 H, C$H_2$OH), 4.55 (d, 1 H, *J* 5 Hz, OCH), 5.48 (br.s, 1 H, NCH), 5.69 (s, 1 H, –CH=), 5.88 (d, 1 H, *J* 7.5 Hz, NCH=CH–), and 7.39 (d, 1 H, *J* 7.5 Hz, NC*H*=); e.i.m.s.: *m/z* 239 ($M^+$), 222 ($M^+$ − OH), 203, 192, 112 (C + 2), 111 (C + 1), and 110 (C).

*From* **21**. To a solution of **21** (2.04 g) in methanol (30 mL) and water (6 mL) was added iodomethane (0.3 mL), followed by dropwise addition of M NaOH (5.5 mL) under stirring in an ice bath. After the mixture had been stirred for 30 min at the same temperature, acetic acid was added until neutrality, and the mixture evaporated to dryness under reduced pressure. A solution of the residue in methanol (10 mL) was saturated with $NH_3$ at −78° in a stainless-steel tube, and kept for 16 h at 80–90°. The solvent was evaporated under reduced pressure, and the residue dissolved in water and applied onto a column of Amberlite IR-120 ($H^+$) cation-exchange resin. Elution with 2% $NH_4OH$ and evaporation of the eluent under reduced pressure gave **18** (1.20 g, 94% yield), crystallized from aqueous ethanol (810 mg), m.p. 208–212° (dec.), $[\alpha]_D^{22}$ −94.5° (*c* 0.55, water); other spectroscopic data identical with those of the compound obtained from **17**.

*Anal.* Calc. for $C_{10}H_{13}N_3O_4 \cdot 0.5\ H_2O$: C, 48.38; H, 5.68; N, 16.93. Found: C, 48.57; H, 5.57; N, 16.92.

*1-[(1R, 2S, 3R)-2,3-Diacetoxy-4-acetoxymethyl-4-cyclopenten-1-yl]-2,4(1H, 3H)-pyrimidinedione* (**20**). — A mixture of **14** (6.07 g) and acetic anhydride (40 mL) in dry pyridine (80 mL) was stirred for 5 h at room temperature. The reaction was quenched by addition of methanol under ice cooling and the solvent removed under reduced pressure. The residual syrup was chromatographed in a column of silica gel with 3:1 ethyl acetate–hexane to give **20** (8.46 g, 91% yield), colorless, m.p. 149–150°; $[\alpha]_D^{24}$ −70° (*c* 0.32, methanol); $R_F$ (ethyl acetate) 0.51; $\nu_{max}^{film}$ 1740–1690, 1460, 1380, and 1240 $cm^{-1}$; $^1$H-n.m.r. ($CDCl_3$; $Me_4Si$): δ 2.06 (s, 3 H, OAc), 2.12 (s, 6 H, 2 OAc), 4.68 (br.s, 2 H, $-CH_2OAc$), 5.20 (t, 1 H, *J* 6.7 Hz, OCH), 5.70–5.94 (br, 4 H, OCH, NCH, −CH=, −COCH=), 7.04 (d, 1 H, *J* 8 Hz, N–CH=), and 9.12 (br.s, 1 H, CONHCO).

*Anal.* Calc. for $C_{16}H_{18}N_2O_8$: C, 52.46; H, 4.95; N, 7.65. Found: C, 52.45; H, 4.83; N, 7.62.

In addition, the $N^3$,2′,3′,6′-tetraacetate was obtained (670 mg, 7% yield), syrup, $\nu_{max}^{film}$ 1790, 1745, 1710, 1670, 1445, 1380, and 1240 $cm^{-1}$; $^1$H-n.m.r. ($CDCl_3$; $Me_4Si$): δ 2.04, 2.10, 2.12 (3 s, 9 H, 3 OAc) 2.54 (s, 3 H, NAc), 4.70 (br.s, 2 H, $CH_2OAc$), 5.21 (t, 1 H, *J* 6 Hz, OCH), 5.68–5.96 (m, 4 H, OCH, NCH, COCH=, −CH=), and 7.09 (d, 1 H, *J* 8 Hz, N–CH=); e.i.m.s.: *m/z* 408 ($M^+$), 366 ($M^+$ − OAC), 350, 349, 307, and 204.

*1-[(1R, 2S, 3R)-2,3-Diacetoxy-4-acetoxymethyl-4-cyclopenten-1-yl]-4-thio-2(1H, 3H)-pyrimidinone* (**21**). — A mixture of **20** (1.5 g) and $P_2S_5$ (3.3 g) in dry pyridine (18 mL) was stirred for 5 h at 100–110°, and then poured into ice–water. The precipitate was collected by filtration, washed with cold ethanol, and was purified by silica gel column chromatography with 1:1 chloroform–ethyl acetate to give **21** (1.3 g, 83% yield) yellow crystals, m.p. 214–215°, $[\alpha]_D^{23}$ −84.5° (*c* 0.31, 9:1 chloroform–methanol), $R_F$ (1:1 ethyl acetate–hexane; 0.26; $\lambda_{max}$ 333, (9:1 $CHCl_3$–$CH_3OH$) $\lambda_{min}$; 278 nm; $\nu_{max}^{KBr}$ 1740, 1690, 1625, 1465, 1380, and 1375 $cm^{-1}$; $^1$H-n.m.r. [$(CD_3)SO$; $Me_4Si$] δ 1.99, 2.04, 2.06 (3 s, 9 H, 3 OAc), 4.64 (br.s, 2 H, $CH_2OAc$), 5.32 (t, 1 H, *J* 6 Hz, OCH), 5.52 (br.s, 1 H, NCH), 5.79 (d, 1 H, *J* 6 Hz, OCH), 6.05

(s, 1 H, -CH=), 6.30 (d, *J* 8 Hz, 1 H, CSCH=), and 7.38 (d, *J* 8 Hz, 1 H, N-CH=); e.i.m.s.: *m/z* 382 ($M^+$), 322 ($M^+$ - AcOH), 262, 255, 220, and 153.

*Anal.* Calc. for $C_{16}H_{18}N_2O_7S$: C, 50.26; H, 4.74; N, 7.33. Found: C, 50.24; H, 4.90; N, 7.37.

*1-[(1R, 2S, 3R)-2,3-Dihydroxy-4-hydroxymethyl-4-cyclopenten-1-yl]-2-oxo-4-thiopyrimidine* (**22**). — Compound **21** (1.70 g) was treated with saturated methanolic $NH_3$ for 1 day at room temperature. The solvent was then evaporated off under reduced pressure and the residue chromatographed in a column of silica gel with 4:1 chloroform–methanol to give **22** (950 mg, 83% yield), yellow foam, $[\alpha]_D^{21}$ −96.5° (*c* 0.19, methanol), $R_F$ (3:1:1 ethyl acetate–ethanol–water) 0.68; $\lambda_{max}^{MeOH}$ 336, 249 nm; $\nu_{max}^{KBr}$ 3350, 1690, 1610, 1460, 1260, and 1180 $cm^{-1}$; $^1$H-n.m.r. ($D_2O$; DSS): δ 4.18 (t, *J* 5.5 Hz, 1 H, OCH), 4.30 (br.s, 2 H, $CH_2OH$), 4.63 (d, 1 H, *J* 5.5 Hz, OCH), 5.46 (br.s, 1 H, NCH), 5.81 (s, 1 H, CH=), 6.50 (d, 1 H, *J* 8 Hz, -CSCH=), and 7.33 (d, 1 H, *J* 8 Hz, N-CH=); e.i.m.s.: *m/z* 258 ($M^+$ + 2), 256 ($M^+$), 149, 129 (4-thioU + 1), and 128.

*(1R, 2S, 3R)-2,3-Isopropylidenedioxy-1-[N-(3-methoxy-2-methylacryloyl) ureido]-4-methoxymethyloxymethyl-4-cyclopentene* (**23**). — A solution of **3** (2.29 g) in dry *N,N*-dimethylformamide (50 mL) was cooled to −45 to −50° in a dry ice–acetone bath. A solution of 3-methoxy-2-methylacryloyl isocyanate [prepared from 3-methoxy-2-methylacryloyl chloride (1.35 g) and AgNCO (3.00 g) in dry benzene by heating] was added dropwise under an Ar atmosphere. The mixture was stirred for 30 min at the same temperature and then for 1 h at room temperature, poured into ice-cold, satd. $NaHCO_3$ with vigorous stirring, and extracted with ethyl acetate several times. The combined organic layer was washed with water, dried ($MgSO_4$), and evaporated to dryness under reduced pressure. The residue was chromatographed in a column of silica gel with 2:1 ethyl acetate–hexane to give **23** (3.22 g, 87% yield), colorless syrup, $R_F$ (1:1 ethyl acetate–hexane) 0.15; $\nu_{max}^{film}$ 3250, 2940, 1680, 1610, 1530, 1470, 1370, and 1300 $cm^{-1}$; $^1$H-n.m.r. ($CDCl_3$; $Me_4Si$): δ 1.32 and 1.38 [2 s, 6 H, $C(CH_3)_2$], 1.76 (d, *J* 1.2 Hz, 3 H, $CH_3C$), 3.37 (s, 3 H, OMe), 3.86 (s, 3 H, *Me*O–CH=), 4.17 (s, 2 H, $CH_2O$), 4.55 and 5.12 (2 d, 2 H, *J* 5.6 Hz, 2 OCH), 4.67 (s, 2 H, $OCH_2O$), 4.77 (m, 1 H, NCH), 5.67 (br.s, 1 H, -CH=), 7.38 (d, 1 H, *J* 1.2 Hz, MeO–C*H*=), 8.36 (br.s, 1 H, CONHCO), and 8.65 (br.d, 1 H, CHN*H*CO); f.a.b.m.s.: *m/z* 371 ($MH^+$).
CHN*H*CO); f.a.b.m.s.: *m/z* 371 ($MH^+$).

*1-[(1R, 2S, 3R)-2,3-Isopropylidenedioxy-4-methoxymethyloxymethyl-4-cyclopenten-1-yl]-5-methyl-2,4(1H, 3H)-pyrimidinedione* (**24**). — To a solution of **23** (3.0 g) in acetone (75 mL) was added 2.8% $NH_4OH$ (225 mL), and the mixture stirred with reflux for 15 h. The reaction was monitored by t.l.c. (1:1 ethyl acetate–hexane). After being cooled to room temperature, the mixture was evaporated under reduced pressure and the residue coevaporated to dryness with ethanol under reduced pressure several times. The residual syrup was chromatographed in a column of silica gel with 4:1 ethyl acetate–hexane to give **24** (2.17 g, 80% yield), colorless crystals, recrystallized from 1:1 ethyl acetate–ether, m.p. 139–140.5°, $[\alpha]_D^{24}$

$-77.5°$ (*c* 1.37, chloroform); $\lambda_{max}^{MeOH}$ 270 nm; $\nu_{max}^{KBr}$ 3170, 3050, 1690, 1650, 1480, 1460, 1380, 1370, and 1250 $cm^{-1}$; $^1$H-n.m.r. ($CDCl_3$; $Me_4Si$) 1.35 and 1.44 [2 s, 6 H, $C(CH_3)_2$], 1.90 (d, 3 H, *J* 1.2 Hz, $CH_3$–C=), 3.41 (s, 3 H, OMe), 4.30 (s, 2 H, $CH_2O$), 4.59 (d, 1 H, *J* 5.6 Hz, OCH), 4.72 (s, 2 H, $OCH_2O$), 5.24 (d, 1 H, *J* 5.6 Hz, OCH), 5.38 (s, 1 H, NCH), 5.60 (br.d, 1 H, –CH=), 6.84 (d, 1 H, *J* 1.2 Hz, NCH=), and 9.00 (br, 1 H, CONHCO); f.a.b.m.s.: *m/z* 339 ($MH^+$).

*Anal.* Calc. for $C_{16}H_{22}N_2O_6$: C, 56.79; H, 6.55; N, 8.28. Found: C, 57.17; H, 7.10; N, 8.71.

*1-[(1*R*, 2*S*, 3*R*)-2,3-Dihydroxy-4-hydroxymethyl-4-cyclopenten-1-yl]-5-methyl-2,4(1*H*, 3*H*)-pyrimidinone* (**25**). — A solution of **24** (4.55 g) in trifluoroacetic acid (45 mL) and water (45 mL) was stirred for 3 h at 60°, and then for 13 h at room temperature. The mixture was evaporated and coevaporated to dryness with ethanol under reduced pressure several times. The residue was dissolved in a minimum amount of methanol, the solution mixed with silica gel (20 g), and the mixture dried under reduced pressure and placed on top of a column of silica gel which was developed with 5:1 chloroform–methanol. Evaporation of the eluate under reduced pressure afforded **25** (2.55 g, 75%), crystals recrystallized from aqueous ethanol, m.p. 210–211.5° (dec.); $[\alpha]_D^{24}$ $-108°$ (*c* 0.65, methanol); $R_F$ (5:1 chloroform–methanol) 0.17; $\lambda_{max}^{H_2O}$ 273 nm; $\nu_{max}^{KBr}$ 3400, 3050, 1680, 1480, 1400, and 1270 $cm^{-1}$; $^1$H-n.m.r. [$(CD_3)_2SO$–$D_2O$; $Me_4Si$]: $\delta$ 1.76 (d, 3 H, *J* 1.0 Hz, $CH_3$–C=), 3.89 (d, *J* 5.6 Hz, OCH), 4.07 (s, 2 H, $CH_2OH$), 4.31 (d, 1 H, *J* 5.6 Hz, OCH), 5.33 (m, 1 H, NCH), 5.48 (d, 1 H, *J* 1.71 Hz, –CH=), 7.16 (d, 1 H, *J* 1.0 Hz, NCH=), and 11.21 (br.s, 1 H, CONHCO); f.a.b.m.s.: *m/z* 255 ($MH^+$).

*Anal.* Calc. for $C_{11}H_{14}N_2O_5$: C, 51.96; H, 5.55; N, 11.02. Found: C, 51.47; H, 5.80; N, 11.06.

*9-[(1*R*, 2*S*, 3*R*)-2-Hydroxy-3,6-O-(tetraisopropyldisiloxane-1,3-diyl)-4-cyclopenten-1-yl]guanine* (**26**). — To a solution of **9** (20.3 mg) and imidazole (22 mg) in dry *N,N*-dimethylformamide (1 mL) was added 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (25 $\mu$L) under cooling in an ice bath. After the mixture had been stirred for 1 h at room temperature, water was added for quenching the reaction. The precipitate was collected by filtration and partitioned between chloroform and water. The organic layer was evaporated to dryness under reduced pressure and the residue chromatographed in a silica gel column with 30:1 chloroform–methanol to give **26** (22 mg, 58% yield), colorless solid, $[\alpha]_D^{24}$ $-57.5°$ (*c* 0.45, methanol), $R_F$ (5:1 chloroform–methanol) 0.57; $\nu_{max}^{KBr}$ 2950, 2870, 1690, 1630, 1600, 1470, 1370, and 1090 $cm^{-1}$; $^1$H-n.m.r. [$(CD_3)_2SO$; $Me_4Si$]: $\delta$ 1.1 (br.s, 28 H, 4 $C(CH_3)_2$], 4.20 (m, 1 H, OCH), 4.43 (br.s, 2 H, $CH_2O$), 4.77 (d, 1 H, *J* 5.0 Hz, OCH), 5.16 (d, 1 H, *J* 6.0 Hz, NCH), 5.78 (br.s, 1 H, –CH=), 6.36 (br, 2 H, $NH_2$), and 7.62 (s, 1 H, NCH=); f.a.b.m.s.: *m/z* 522 ($MH^+$).

*9-[(1*R*, 3*R*)-3,6-O-(Tetraisopropyldisiloxane-1,3-diyl)-4-cyclopenten-1-yl]guanine* (**28**). — To a solution of **26** (246 mg) in dry acetonitrile (150 mL) was added *N,N'*-thiocarbonyldiimidazole (130 mg). The mixture was stirred with reflux for 6 h under an Ar atmosphere, and then evaporated to dryness. To the residue, dissolved in dry benzene (150 mL), were added tributyltin hydride (0.5 mL) and a catalytic

amount of azo(isobutyronitrile), and the mixture was refluxed for 5 h under an Ar atmosphere. Evaporation under reduced pressure gave a syrup, which was chromatographed in a silica gel column with 20:1 chloroform–methanol to give **28** (95 mg, 40% yield), amorphous solid, $[\alpha]_D^{24}$ −74° (*c* 0.32, methanol), $R_F$ (10:1 chloroform–methanol) 0.33; $\nu_{max}^{KBr}$ 2850, 2880, 1700, 1630, 1600, 1470, 1370, and 1100 $cm^{-1}$; $^1$H-n.m.r. [$CDCl_3$–$(CD_3)_2SO$; $Me_4Si$]: δ 1.1 [br.s, 28 H, 4 $C(CH_3)_2$], 2.32 (m, 2 H, $CH_2$), 4.46 (br.s, 2 H, $CH_2O$), 5.20–5.50 (m, 2 H, NCH, OCH), 5.79 (br.s, 1 H, –CH=), 6.03 (br, 2 H, $NH_2$), 7.73 (s, 1 H, NCH=), and 10.53 (br, 1 H, CONH); e.i.m.s.: *m/z* 506 ($MH^+$).

*9-[(1R, 3R)-3-Hydroxy-4-hydroxymethyl-4-cyclopenten-1-yl]guanine* (**29**). — To a solution of **28** (80 mg) in oxolane (20 mL) was added M tetrabutylammonium fluoride in oxolane (0.4 mL). The mixture was stirred for 10 min at room temperature and evaporated under reduced pressure. A solution of the residue in methanol was applied to silica gel plates which were developed in 3:1:1 ethyl acetate–ethanol–water. Elution of the main band with 1:1 chloroform–methanol gave **29** (35 mg, 85% yield) as crystals, recrystallized from methanol, m.p. >250° (dec.); $[\alpha]_D^{24}$ −65° (*c* 0.05, methanol); $R_F$ (3:1:1 ethyl acetate–ethanol–water) 0.47; $\lambda_{max}^{H_2O}$ 253, $\lambda_{min}^{H_2O}$ 227 nm; $^1$H-n.m.r. $(CD_3)_2SO$; $Me_4Si$): δ 2.0–2.3 (m, 2 H, $CH_2$), 4.14 (s, 2 H, $CH_2OH$), 4.7–5.1 (m, 3 H, OCH, 2 OH), 5.39 (m, 1 H, NCH), 5.70 (d, 1 H, *J* 1.0 Hz, –CH=), 6.44 (br, 2 H, $NH_2$), 7.49 (s, 1 H, NCH=), and 10.57 (br, 1 H, CONH); c.i.m.s.: *m/z* 264 ($MH^+$).

*1-[(1R, 2S, 3R)-2-Hydroxy-3,6-O-(tetraisopropyldisiloxane-1,3-diyl)-4-cyclopenten-1-yl]-2,4(1H, 3H)-pyrimidinedione* (**30**). — To a solution of **12** (4.1 g) and imidazole (5.0 g) in dry *N,N*-dimethylformamide (77 mL) was added 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (4.0 mL) under cooling in an ice bath. After the mixture had been stirred for 30 min at the same temperature, additional 1,3-dichloro-1,1,3,3,-tetraisopropyldisiloxane (1.2 mL) was added. The mixture was stirred for 1 h at room temperature, and then poured into ice–water with vigorous stirring and extracted with chloroform several times. The organic layer was separated, washed with water, dried ($MgSO_4$), and evaporated under reduced pressure. The residue was purified by chromatography in a silica gel column with 3:1 chloroform–ethyl acetate to give **30** (5.85 g, 71% yield), foam, $R_F$ (2:1 ethyl acetate–chloroform) 0.37; $^1$H-n.m.r. ($CDCl_3$; $Me_4Si$): δ 1.09 [br.s, 28 H, 4 $C(CH_3)_2$], 4.07 (m, 1 H, OCH), 4.46 (br.s, 2 H, $CH_2OH$), 5.01 (d, 1 H, *J* 5.8 Hz, OCH), 5.43 (br.s, 1 H, NCH), 5.58 (br.s, 1 H, –CH=), 5.71 (d, 1 H, *J* 8.1 Hz, COCH=), 7.08 (d, 1 H, *J* 8.1 Hz, NCH=), and 8.74 (br, 1 H, CONHCO); f.a.b.m.s.: *m/z* 483 ($MH^+$).

*1-[(1R, 2S, 3R)-2-Hydroxy-5-methyl-3,6-O-(tetraisopropyldisiloxane-1,3-diyl)-4-cyclopenten-1-yl]-2,4(1H, 3H)-pyrimidinedione* (**31**). — To a solution of **25** (1.03 g) and imidazole (1.74 g) in dry *N,N*-dimethylformamide (25 mL) was added 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (1.85 g) in dry *N,N*-dimethylformamide (5 mL) with exclusion of moisture under cooling in an ice bath. The mixture was stirred for 1 h at room temperature. After quenching of the reaction by addition of water, the supernatant was removed by decantation. The residue was partitioned

between chloroform and water, and the organic layer was dried (Whatman 1PS filter paper) and evaporated under reduced pressure. The residue was purified by chromatography in a silica gel column with 4:1 chloroform–ethyl acetate to give **31** (1.35 g, 68% yield), syrup which crystallized from ethanol, m.p. 206–209°, $[\alpha]_D^{24}$ −14.5° (*c* 0.45, chloroform), $R_F$ (2:1 chloroform–ethyl acetate) 0.33; $\nu_{max}^{KBr}$ 3450, 2950, 2880, 1700, 1470, 1390, 1380, 1260, 1100, and 1040 $cm^{-1}$; $^1$H-n.m.r. ($CDCl_3$; $Me_4Si$): δ 1.07 [br.s, 28 H, 4 $C(CH_3)_2$], 1.90 (d, 3 H, *J* 1.2 Hz, $CH_3C=$), 4.06 (m, 1 H, OCH), 4.47 (br.s, 2 H, $CH_2O$), 5.01 (d, 1 H, *J* 5.4 Hz, OCH), 5.45 (m, 1 H, NCH), 5.58 (br.s, 1 H, $-CH=$), 6.88 (d, 1 H, *J* 1.2 Hz, $NCH=$), and 8.72 (br., 1 H, CONHCO); c.i.m.s.: *m/z* 497 ($MH^+$).

*Anal.* Calc. for $C_{23}H_{40}N_2O_6Si_2$: C, 55.61; H, 8.12; N, 5.64. Found: C, 55.74; H, 8.22; N, 5.29.

*1-[(1*R*, 3*R*)-3,6-*O*-(Tetraisopropyldisiloxane-1,3-diyl)-4-cyclopenten-1-yl]-2,4(1*H*, 3*H*)-pyrimidinedione (**34**) and 1-[(1*R*, 2*R*, 3*R*)-2-2'-anhydro-3,6-O-(tetraisopropyldisiloxane-1,3-diyl)-4-cyclopenten-1-yl]-4(1*H*)-pyrimidinone* (**38**). — (*a*). A mixture of **31** (2.13 g) and *N,N'*-thiocarbonyldiimidazole (1.73 g, 1.1 equiv.) in dry acetonitrile (50 mL) was refluxed for 3 h under an Ar atmosphere. Tributyltin hydride (9.51 mL, 4 equiv.) and a catalytic amount of azo(isobutyronitrile) were added, and the mixture refluxed for 1 h. The reaction was monitored by t.l.c. with 2:1 chloroform–ethyl acetate. The mixture was evaporated under reduced pressure and the residue chromatographed in a column of silica gel, developed with 4:1 hexane–ethyl acetate to afford **34** (920 mg, 44.7% yield), colorless syrup which crystallized from ethanol, m.p. 160–163°, $[\alpha]_D^{22}$ −92° (*c* 0.08, chloroform), $R_F$ (2:1 ethyl acetate–chloroform) 0.5; $\lambda_{max}^{MeOH}$ 267, $\lambda_{min}^{MeOH}$ 233 nm; $\nu_{max}^{KBr}$ 2950, 2870, 1693, 1620, 1465, and 1380 $cm^{-1}$; $^1$H-n.m.r. ($CDCl_3$; $Me_4Si$): δ 1.06 [br.s, 28 H, 4 $C(CH_3)_2$], 2.06 and 2.44 (ddd, 1 H, *J* 4,7,14 Hz; ddd, 1 H, *J* 4,8,14 Hz, $CH_2$), 4.44 (br.s, 2 H, $CH_2O$), 5.20 (br, 1 H, HCOSi), 5.56 (s, 1 H, $-CH=$), 5.70 (dd, 1 H, *J* 1.8 Hz, $COCH=$), 5.80 (br, 1 H, NCH), 7.09 (d, 1 H, *J* 8 Hz, $NCH=$), and 9.60 (br, 1 H, CONHCO); e.i.m.s.: *m/z* 466 ($M^+$), 426, 425, 424, and 423 [$M^+ - C(CH_3)_2$].

*Anal.* Calc. for $C_{22}H_{38}N_2O_5Si_2$: C, 56.62; H, 8.21; N, 6.00. Found: C, 56.51; H, 8.07; N, 6.06.

Further elution with 30:1 chloroform–methanol gave **37** (607 mg, 30% yield), m.p. 201–203°, $[\alpha]_D^{24}$ −226° (*c* 0.36, chloroform), $R_F$ (2:1 chloroform–ethyl acetate) 0.07; $\lambda_{max}^{MeOH}$ 256, 227 nm; 3450, 2950, 2880, 1660, 1530, 1480, 1260, 1110, and 1040 $cm^{-1}$; $^1$H-n.m.r. ($CDCl_3$; $Me_4Si$): δ 1.12 [br.s, 28 H, 4 $C(CH_3)_2$], 4.42 (br.s, 2 H, $CH_2O$), 5.21–5.42 (m, 3 H, NCH, 2 OCH), 5.82 (br.s, 1 H, $-CH=$), 6.02 (d, 1 H, *J* 7.6 Hz, $COCH=$), and 7.29 (d, 1 H, *J* 7.6 Hz, $NCH=$); f.a.b.m.s.: *m/z* 465 ($MH^+$).

(*b*). A mixture of **30** (508 mg) and *N,N'*-thiocarbonyldiimidazole (188 mg) in dry acetonitrile (30 mL) was refluxed for 2 h under an Ar atmosphere. Additional *N,N'*-thiocarbonyldiimidazole (188 mg) was added, and refluxing was continued for 3 h. The mixture was cooled to ambient temperature, the solvent removed by evaporation under reduced pressure with exclusion of moisture, and the residue

dissolved in dry benzene (40 mL). Butyltin hydride (2.84 mL) and a catalytic amount of azo(isobutyronitrile) were added at 80°, the mixture was stirred for 1 h at 80°, and the solvent removed under reduced pressure. Compound **34** (387 mg, 79% yield) was obtained by chromatography of the residue in a column of silica gel with 6:1 chloroform–ethyl acetate.

*5-Methyl-1-[(1*R*, 3*R*)-3,6-O-(tetraisopropyldisiloxane-1,3-diyl)-4-cyclopenten-1-yl]-2,4(1*H*, 3*H*)-pyrimidinedione* (**35**). — A solution of **31** (1.90 g) and *N,N'*-thiocarbonyldimidazole (818 mg, 1.2 equiv.) in dry acetonitrile (50 mL) was refluxed for 3 h under an Ar atmosphere. Additional *N,N'*-thiocarbonyldiimidazole (545 mg, 0.8 equiv.) was added and refluxing continued for 3 h. The mixture was evaporated to dryness under reduced pressure with exclusion of moisture, and the residue dissolved in dry benzene (150 mL). Butyltin hydride (9.80 mL) and a catalytic amount of azo(isobutyronitrile) were added at 80°, the mixture stirred for 1.5 h at the same temperature, and the solvent removed under reduced pressure. The residue was chromatographed in a column of silica gel with 6:1 chloroform–ethyl acetate to give **35** (1.40 g, 77% yield), syrup which crystallized from ethanol, m.p. 162–164°, $[\alpha]_D^{24}$ +5.2° (*c* 0.27, chloroform), $R_F$ (2:1 chloroform–ethyl acetate) 0.26; $\nu_{max}^{KBr}$ 3440, 2950, 2870, 1690, 1470, 1380, 1260, 1100, and 1030 $cm^{-1}$; $^1$H-n.m.r. ($CDCl_3$;$Me_4Si$): $\delta$ 1.07 [br.s, 28 H, 4 $C(CH_3)_2$], 1.89 (d, 1 H, *J* 1.2 Hz, $CH_3C=$), 2.12 and 2.35 (2 m, 2 H, $CH_2$), 4.46 (br.s, 2 H, $CH_2O$), 5.21 (m, 1 H, OCH), 5.57 (br.s, 1 H, –CH=), 5.76 (m, 1 H, NCH), 6.89 (d, *J* 1.2 Hz, 1 H, NCH=), and 8.98 (br.s, 1 H, CONHCO); c.i.m.s.: *m/z*.

*Anal.* Calc. for $C_{23}H_{40}N_2O_5Si_2$: C, 57.46; H, 8.39; N, 5.83. Found: C, 57.39; H, 8.46; N, 5.49.

*1-[(1*R*, 3*R*)-3-Hydroxy-4-hydroxymethyl-4-cyclopenten-1-yl]-2,4(1*H*, 3*H*)-pyrimidinedione* (**36**). — To a solution of **34** (985 mg) in oxolane (35 mL) was added M tetrabutylammonium fluoride (5.1 mL) in oxolane. The mixture was stirred for 30 min at room temperature and then evaporated under reduced pressure. The residue was partitioned between chloroform and water. The aqueous layer was separated and evaporated under reduced pressure. A chromatographic purification in a column of silica gel with 10:1 chloroform–methanol afforded **36** (353 mg, 71% yield), foam which was crystallized from ethanol, m.p. 147–149°, $[\alpha]_D^{24}$ −46° (*c* 0.36, methanol, $R_F$ (5:1 chloroform–methanol) 0.23; $\lambda_{max}^{H_2O}$ 268 nm; $\nu_{max}^{KBr}$ 3400, 3170, 1700, 1470, 1420, 1400, 1280, and 1250 $cm^{-1}$; $^1$H-n.m.r. [$(CD_3)SO$; $Me_4Si$]: $\delta$ 1.80–2.29 (m, 2 H, $CH_2$), 4.12 (d, *J* 4.0 Hz, $CH_2OH$), 4.65–4.88 (m, 3 H, OCH, 2 OH), 5.49–5.57 (m, 3 H, NCH, –CH=, COCH=), 7.20 (d, 1 H, *J* 7.8 Hz, NCH=), and 11.04 (br, 1 H, CONHCO); c.i.m.s.: *m/z* 225 ($MH^+$).

*Anal.* Calc. for $C_{10}H_{12}N_2O_4$: C, 53.57; H, 5.39; N, 12.50. Found: C, 53.33; H, 5.68; N, 12.81.

*1-[(1*R*, 3*R*)-3-Hydroxy-4-hydroxymethyl-4-cyclopenten-1-yl]-5-methyl-2,4-(1*H*, 3*H*)-pyrimidinedione* (**37**). — A mixture of **35** (97 mg) and M tetrabutylammonium fluoride in oxolane (0.42 mL) was treated in a manner similar to that just described. A chromatographic purification by preparative t.l.c. with 5:1 chloro-

form–methanol gave **37** (44 mg, 92% yield) as colorless crystals which were recrystallized from aqueous ethanol, m.p. >210° (dec.), $[\alpha]_D^{24}$ −31° (*c* 0.42, methanol), $R_F$ (5:1 chloroform–methanol) 0.33; $\lambda_{max}^{H_2O}$ 272, $\lambda_{max}^{H^+}$ 272, $\lambda_{max}^{OH^-}$ 270 nm; $\nu_{max}^{KBr}$ 3380, 3170, 3030, 1680, 1480, 1290, and 1260 $cm^{-1}$; $^1$H-n.m.r. [$(CD_3)SO$; $Me_4Si$]: δ 1.75 (d, 3 H, *J* 1.2 Hz, MeC=), 1.9–2.1 (m, 2 H, $CH_2$), 4.11 (d, 2 H, *J* 5.0 Hz, C$H_2$OH), 4.75 (m, 1 H, OCH), 5.53 (m, 2 H, NCH, –CH=), and 7.07 (d, 1 H, *J* 1.2 Hz, NCH=); c.i.m.s.: *m/z* 239 ($MH^+$).

*Anal.* Calc. for $C_{11}H_{14}N_2O_4 \cdot 2/3H_2O$: C, 52.58; H, 6.55; N, 11.15. Found: C, 52.78; H, 6.00; N, 11.39.

*1-[(1*R*, 2*R*, 3*R*)-2,2'-Anhydro-3-hydroxy-4-hydroxymethyl-4-cyclopenten-1-yl]-4(1*H*)-pyrimidinone* (**39**). — Treatment of **38** (460 mg) as just described gave **39** (224 mg, quantitative yield), $[\alpha]_D^{24}$ −171° (*c* 0.23, methanol), $R_F$ (5:1 chloroform–methanol) 0.10; $\lambda_{max}^{H_2O}$ 257, 225 nm; $\nu_{max}^{KBr}$ 3400, 3220, 1650, 1620, 1520, 1480, 1250, 1230, and 1100 $cm^{-1}$; $^1$H-n.m.r. [$(CD_3)SO$; $Me_4Si$]: δ 4.09 (br.s, 2 H, $CH_2O$), 4.72 (br.s, 1 H, OCH), 5.12 (d, 1 H, *J* 7.1 Hz, OCH), 5.76 (d, 1 H, *J* 7.3 Hz, COCH=), 5.87 (d, 1 H, *J* 1.0 Hz, –CH=), and 7.76 (d, *J* 7.3 Hz, NCH=); c.i.m.s.: *m/z* 223 ($MH^+$).

*1-[(1*R*, 3*R*)-3-Acetoxy-4-acetoxymethyl-4-cyclopenten-1-yl]-2,4(1*H*, 3*H*)-pyrimidinedione* (**40**). — A mixture of **36** (1.44 g) and acetic anhydride (15 mL) in dry pyridine (30 mL) was stirred for 16 h at ambient temperature. After quenching of the reaction by addition of methanol under cooling in an ice bath, the solvent was removed under reduced pressure. The residue was partitioned between chloroform and water, and the organic layer separated, dried (Whatman 1PS filter paper), and concentrated under reduced pressure. The residue was purified by chromatography in a silica gel column with ethyl acetate–hexane, and then ethyl acetate to give **40** (1.74 g, 88% yield), colorless foam, $[\alpha]_D^{22}$ −54° (*c* 0.24, methanol), $R_F$ (ethyl acetate) 0.42; $\lambda_{max}^{MeOH}$ 267, $\lambda_{min}^{MeOH}$ 232.5 nm; $\nu_{max}^{KBr}$ 1740, 1690, 1460, 1375, and 1235 $cm^{-1}$; $^1$H-n.m.r. ($CDCl_3$/$Me_4Si$): δ 2.08 and 2.12 (2 s, 6 H, 2 OAc), 2.20 and 2.52 (m, 2 H, $CH_2$), 4.73 (br.s, 2 H, C$H_2$OAc), 5.76 (d, 1 H, *J* 8 Hz, COCH=), 5.90 (br, 3 H, C*H*OAc, NCH, –CH=), 7.05 (d, 1 H, *J* 8 Hz, NCH=), and 9.76 (br, 1 H, CONHCO); e.i.m.s.: *m/z* 309 ($M^+ + 1$), 308 ($M^+$), 249 ($M^+ - OAc$), 248 ($M^+ -$ AcOH), 206, and 205.

*1-[(1*R*, 3*R*)-3-Acetoxy-4-acetoxymethyl-4-cyclopenten-1-yl]-2-oxo-4-thiopyrimidine* (**41**). — To a solution of **40** (1.70 g) in pyridine (20 mL) was added $P_2S_5$ (4.40 g), and the mixture stirred for 5 h at 100–110°. Compound **42** (1.55 g, 87% yield) was obtained in the same manner as described before for **20** from **21**, pale yellow foam, $[\alpha]_D^{22}$ −36° (*c* 0.22, methanol); $R_F$ (1:1 ethyl acetate–hexane) 0.39; $\lambda_{max}^{MeOH}$ 335, $\lambda_{min}^{MeOH}$ 277.5 nm; $\nu_{max}^{KBr}$ 1740, 1710, 1615, 1455, 1370, 1235, and 1135 $cm^{-1}$; $^1$H-n.m.r. ($CDCl_3$; $Me_4Si$): δ 2.08 and 2.12 (2 s, 6 H, 2 OAc), 2.22 and 2.54 (m, 2 H, $CH_2$), 4.72 (br.s, 2 H, C$H_2$OAc), 5.88 (br, 3 H, NCH, OCH, –CH=), 6.40 (dd, 1 H, *J* 2.8 Hz, CSCH=), 6.86 (d, 1 H, *J* 8 Hz, NCH=), and 10.10 (br.s, 1 H, CONHCS); e.i.m.s.; *m/z* 326 ($M^+ + 2$), 324 ($M^+$), 204 ($M^+ - 2$ AcOH), 197, 137, and 95.

*4-Amino-1-[(1*R*, 3*R*)-3-hydroxy-4-hydroxymethyl-4-cyclopenten-1-yl]-2(1*H*)-*

*pyrimidinone* (**42**). — To a solution of **41** (1.35 g) in methanol (20 mL) and water (5 mL) was added iodomethane (2 mL), and M NaOH (4.5 mL) was added dropwise under cooling in an ice bath. The mixture was stirred for 1 h at the same temperature, and then made neutral with 10% acetic acid in methanol. The solvent was removed under reduced pressure, the residue dissolved in methanol (5 mL), and liquid ammonia (15 mL) added under cooling at −78°. The mixture was kept, in a stainless steel tube, for 5 h at 90°, and then 16 h at 65°, evaporated under reduced pressure, and the residue treated with activated charcoal in methanol. The solvent was removed under reduced pressure and the residue, dissolved in dilute HCl, was applied onto a column of Amberlite CG-120 ($H^+$) cation-exchange resin. After washing with water, elution with 70 mM $NH_4OH$ gave **42** (850 mg, 92% yield), slightly yellow foam which crystallized from ethanol, m.p. 188–191° (dec.), $[\alpha]_D^{22}$ −12.5° (*c* 0.22, methanol), $R_F$ (3:1:1 ethyl acetate–ethanol–water) 0.35; $\lambda_{max}^{MeOH}$ 276, $\lambda_{min}^{MeOH}$ 260 nm. $\nu_{max}^{KBr}$ 3325, 3200, 1640, 1607, 1530, 1485, and 1395 $cm^{-1}$; $^1H$-n.m.r. [$(CD_3)SO$; $Me_4Si$]: δ 1.82 and 2.12 (m, 2 H, $CH_2$), 4.08 (br.s, 2 H, C*H*$_2$OH), 4.68 (br.s, 1 H, *CH*OH), 5.49 (br.s, 2 H, –CH=C), NCH), 5.64 (d, 1 H, *J* 8 Hz, –C*H*=CH–N), and 7.18 (d, 1 H, *J* 8 Hz, –CH=C*H*N); e.i.m.s.: *m/z* 206 ($M^+$ − OH), 205 ($M^+$ − $H_2O$), 188, 187, 116, 114, 113, and 112.

*Anal.* Calc. for $C_{10}H_{13}N_3O_2$: C, 53.81; H, 5.87; N, 18.82. Found: C, 53.40; H, 5.77; N, 18.75.

*1-[(1*R*, 3*R*)-3-Hydroxy-4-hydroxymethyl-4-cyclopenten-1-yl]-2-oxo-4-thiopyrimidine* (**43**). — A solution of **42** (110 mg) in methanol (3 mL) was saturated with $NH_3$ under cooling in an ice bath. The mixture was kept in a stoppered container for 16 h at room temperature, the solvent removed under reduced pressure, and the residue purified by chromatography in a column of silica gel with 5:1 chloroform–methanol to give **43** (81 mg, quantitative yield), yellow oil, $[\alpha]_D^{22}$ −1.6° (*c* 0.8, methanol; $R_F$ (3:1:1 ethyl acetate–ethanol–water) 0.76; $\lambda_{max}^{MeOH}$ 336, $\lambda_{min}^{MeOH}$ 278 nm; $\nu_{max}^{film}$ 3375, 1690, 1610, 1460, 1250, 1135, and 1070 $cm^{-1}$; $^1H$-n.m.r [$(CD_3)_2SO$; $Me_4Si$]: δ 2.24 (m, 2 H, $CH_2$), 4.28 (br.s, 2 H, C*H*$_2$OH), 4.80–4.90 (br, 1 H, OCH), 5.68 (br.s, 2 H, NCH, –CH=), 6.30 (d, 1 H, *J* 8 Hz, –CSCH=), and 7.13 (d, 1 H, *J* 8 Hz, NCH=); e.i.m.s.: *m/z* 241 ($M^+$ + 1), 240 ($M^+$), 149, 129, and 128.

*1-[(1*R*, 2*R*, 3*R*)-2,2'-Anhydro-3,6-O-(tetraisopropyldisiloxane-1,3-diyl)-4-cyclopenten-1-yl]-4(1*H*)-pyrimidinone* (**38**). — To a solution of **30** (900 mg) and 4-dimethylaminopyridine (235 mg) in dry pyridine (5 mL) were added triethylamine (0.27 mL) and then trifluoromethanesulfonyl chloride (0.22 mL). The mixture was stirred for 2 h at room temperature, and then poured into ice–water and extracted with chloroform several times. The combined organic layer was washed with water, dried (Whatman 1PS filter paper), and evaporated under reduced pressure. The residue was chromatographed in a column of silica gel with 50:1 chloroform–methanol to give **38** (460 mg, 53% yield), identical in all respects with that obtained from **32**.

*1-[(1*R*, 2*R*, 3*R*)-2,3-Diacetoxy-4-acetoxymethyl-4-cyclopenten-1-yl]-2,4(1*H*, 3*H*)-pyrimidinedione* (**45**). — A solution of **39** (220 mg) in water (1 mL) and M

NaOH (0.5 mL) was stirred for one day at room temperature, and then for one day at 60°. After neutralization with 2M acetic acid, the solvent was removed under reduced pressure. The remaining solvent was codistilled several times with dry pyridine to afford crude **44**, which was dissolved in dry pyridine (5 mL) and acetic anhydride (0.5 mL). The mixture was stirred for 5 h at room temperature, the reaction quenched by addition of methanol, and the solvent removed under reduced pressure. The residue was partitioned between chloroform and water. The organic layer was separated, dried (Whatman 1PS), and evaporated to dryness under reduced pressure. The residue was purified by chromatography in a silica gel column with 40:1 chloroform–methanol to give **45** (355 mg, 98% yield), syrup, $[\alpha]_D^{24}$ −24.5° (*c* 0.40, methanol), $R_F$ (20:1 chloroform–methanol) 0.27; $^1$H-n.m.r. ($CDCl_3$; $Me_4Si$): δ 1.99, 2.12 and 2.13 (3 s, 9 H, 3 OAc), 4.71 (br.s, 2 H, $CH_2OAc$), 5,42 (t, 1 H, *J* 3.0,6.0 Hz, OCH), 5.70 (d, 1 H, *J* 8.1 Hz, COCH=), 5.6–6.0 (m, 3 H, NCH, OCH, –CH=C), 7.03 (d, 1 H, *J* 8.1 Hz, NCH=), and 9.30 (br, 1 H, CONHCO); c.i.m.s.: *m/z* 367 ($MH^+$) and 307 ($MH^+$ − AcOH).

*1-[(1R, 2R, 3R)-2,3-Diacetoxy-4-acetoxymethyl-4-cyclopenten-1-yl]-4-thio-2(1H, 3H)-pyrimidinone* (**46**). — To a solution of **45** (350 mg) in dry pyridine (7 mL) was added $P_2S_5$ (770 mg). The mixture was stirred for 4 h at 100–110°, and then poured into ice–water and extracted with chloroform several times. The combined organic layer was dried (Whatman 1PS) and evaporated under reduced pressure, and the residue chromatographed in a column of silica gel with 50:1 chloroform–methanol to give **46** (329 mg, 90% yield), pale-yellow amorphous powder, characterized only by $^1$H-n.m.r. and used without further purification; $R_F$ (20:1 chloroform–methanol) 0.49; $^1$H-n.m.r. ($CDCl_3$; $Me_4Si$): δ 1.98 (s, 3 H, OAc), 2.10 (s, 6 H, 2 OAc), 4.70 (br.s, 2 H, $CH_2OAc$), 5.47 (dd, 1 H, *J* 3.0,6.0 Hz, CHOAc), 5.7–6.0 (m, 3 H, NCH, CHOAc, –CH=C), 6.37 (d, 1 H, *J* 7.0 Hz, CSCH=), and 6.87 (d, 1 H, *J* 7.0 Hz, NCH=).

*4-Amino-1-[(1R, 2R, 3R)-2,3-dihydroxy-4-hydroxymethyl-4-cyclopenten-1-yl]-2(1H)-pyrimidinone* (**48**). — To a mixture of **46** (320 mg) and iodomethane (0.12 mL) in methanol (15 mL) and water (3 mL) was added dropwise M NaOH (1.1 mL). After the mixture had been stirred for 1 h at room temperature, 10% acetic acid was added to the reaction mixture to neutrality. The solvent was evaporated to dryness under reduced pressure to afford crude **47**. A solution of **47** in methanol (20 mL) was saturated with $NH_3$ at −78° in a stainless-steel tube and kept for 9 h at 90°. It was concentrated under reduced pressure, and the residue applied to preparative silica gel plates which were developed in 1:1 chloroform–methanol. The major band was separated and eluted with 1:1 chloroform–methanol to give **48** (85 mg, 43% yield), which crystallized from methanol, m.p. >262° (dec.), $[\alpha]_D^{24}$ +49° (*c* 0.23, water), $R_F$ (10:6:3:4 butyl acetate–acetic acid–acetone–water) 0.17; $\nu_{max}^{KBr}$ 3400, 3330, 3210, 1650, 1490, 1400, 1290, 1210, and 1030 $cm^{-1}$; $^1$H-n.m.r. [$(CH_3)_2SO$–$D_2O$; $Me_4Si$]: δ 4.07 (m, 3 H, CHOH, $CH_2OH$), 4.30 (dd, 1 H, *J* 1.0, 5.4 Hz, CHOH), 5.50 (m, 2 H, NCH, –CH=C), 5.59 (d, *J* 7.3 Hz, –CH=CH–N), 6.90 (br, 2 H, $NH_2$), and 7.10 (d, *J* 7.3 Hz, 1 H, NCH=); c.i.m.s.: *m/z* 240 ($MH^+$).

*Anal.* Calc. for $C_{10}H_{13}N_3O_4$: C, 50.20; H, 5.48; N, 17.57. Found: C, 49.92; H, 5.50; N, 17.39.

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