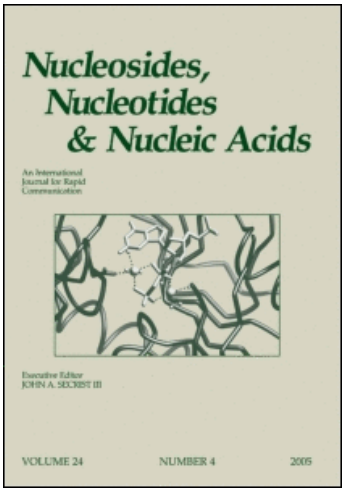

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Enantiospecific Synthesis of 5'-Noraristeromycin and its 7-Deaza Derivative and A Formal Synthesis of (-)-5'-Homoaristeromycin

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ENANTIOSPECIFIC SYNTHESIS OF 5'-NORARISTEROMYCIN AND ITS 7-DEAZA DERIVATIVE AND A FORMAL SYNTHESIS OF (-)-5'-HOMOARISTEROMYCIN

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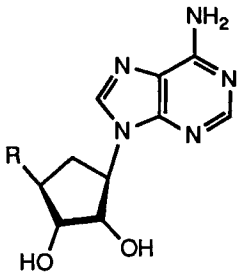
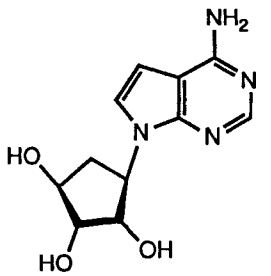
Abstract. Beginning with the treatment of the diacetate of *cis*-3,5-cyclopentenediol (**5**) with *Pseudomonas cepacia* lipase, (-)-5'-noraristeromycin (**1**) and (-)-7-deaza 5'-noraristeromycin (**3**) have been prepared. Subjecting **5** to treatment with porcine liver esterase led to an efficient preparation of a substituted cyclopentane precursor which, following literature precedence, can be converted into (-)-5'-homoaristeromycin (**4**).

As part of a program that is focusing on carbocyclic nucleosides as the basis for antiviral drug design[1-4] (±)-5'-noraristeromycin ((±)-**1**) emerged as a potent broad spectrum antiviral agent with a particularly selective effect towards human cytomegalovirus (HCMV).[4] These properties were attributed[4] to inhibition of S-adenosyl-L-homocysteine (AdoHcy) hydrolase by (±)-**1**. To analyze this lead further for anti-HCMV drug development, a synthesis of the enantiomer of **1** corresponding to the configuration of the parent aristeromycin (**2**) was desired. At the same time this goal was established, enantiospecific routes into (i) 7-deaza 5'-noraristeromycin (**3**) and (ii) 5'-homoaristeromycin (**4**) were also desired: because, in the former case (**3**), of the anti-HCMV properties of 7-deazapurines[5] and, in the latter case (**4**), to enhance the hydrophobicity[6] of the aristeromycin C-5' side chain by the presence of an additional methylene moiety. These syntheses are described herein.



1, R=OH
2, R=CH_2OH
4, R=CH_2CH_2OH



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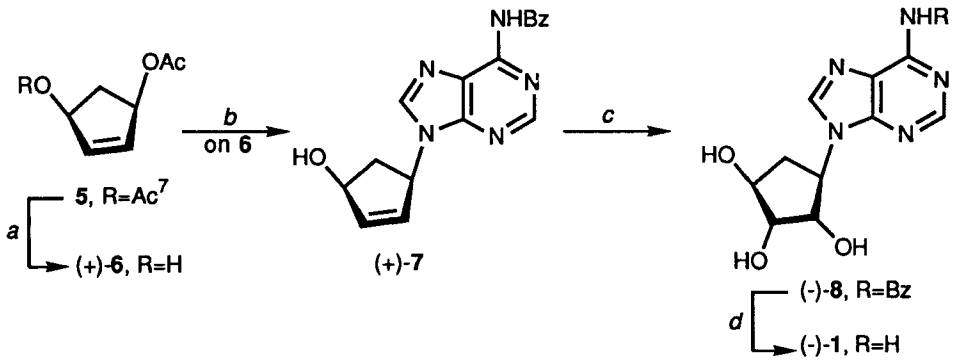


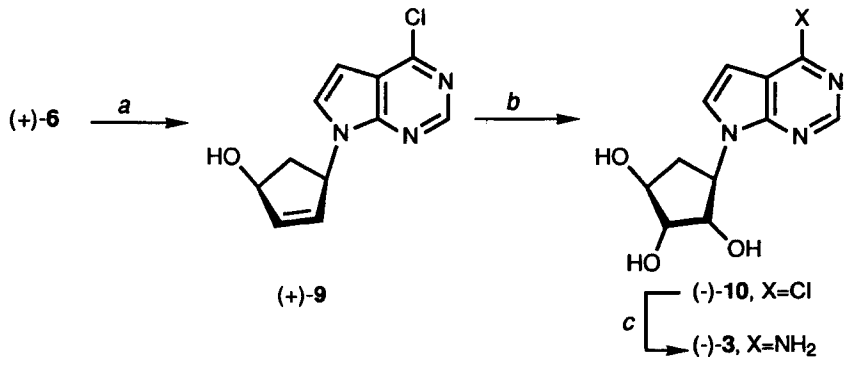
Reaction conditions: a, Pseudomonas cepacia lipase, phosphate buffer, pH 7, 25 °C; *b*, catalytic $Pd(PPh_3)_4$, PPh_3, N^6-benzoyladenine, NaH, DMSO-THF, 50 °C; *c*, OsO_4, N-methylmorpholine N-oxide, THF-H_2O; *d*, NH_3/MeOH, 100 °C.

Scheme 1

In this direction (Scheme 1), treatment of the diacetate of *cis*-3,5-cyclopentenediol ((±)-**5**)[7] with *Pseudomonas cepacia* lipase (PCL)[3] yielded (+)-(1*R*, 4*S*)-4-hydroxy-2-cyclopentenyl-1-acetate ((+)-**6**).[8] (It should be noted that use of PCL,[10] which displays a pro-*R*-hydrolytic preference,[3,10a] was expected to provide (-)-**6** from **5**.) Using a procedure that has been employed to couple cyclopentyl allylic acetates with nucleophiles in the presence of Pd(0) catalysis to give *cis* oriented products,[11] reaction of (+)-**6** with N^6-benzoyladenine gave (+)-**7**. Standard *vicinal* glycolization of (+)-**7** to (-)-**8** was followed by deblocking in ammonia to give the desired (-)-**1** that was found to possess an $[\alpha]_{25}^{D}$ value of -45.3 and to have nmr spectral properties identical to (±)-**1**,[4] which has been prepared unambiguously in the "β-configuration" with the cyclopentyl group at the N-9 position.

Similar to the preparation of (-)-**1**, treating (+)-**6** with 4-chloropyrrolo[2,3-*d*]pyrimidine[12] (Scheme 2) (to (+)-**9**) followed by, first, glycolization to (-)-**10** and, then, ammonolysis yielded (-)-**3**.

A preparation of **4** has been described by Jones and Roberts,[13] who also reported it to be inactive towards HSV-1 and HSV-2, possibly,[13] due to its failure to be phosphorylated, a suggestion that is relevant[14] to its role as a potential AdoHcy hydrolase inhibitor. There was no indication,[13] however, of the action of **4** towards HCMV or viruses affected by AdoHcy hydrolase inhibition.



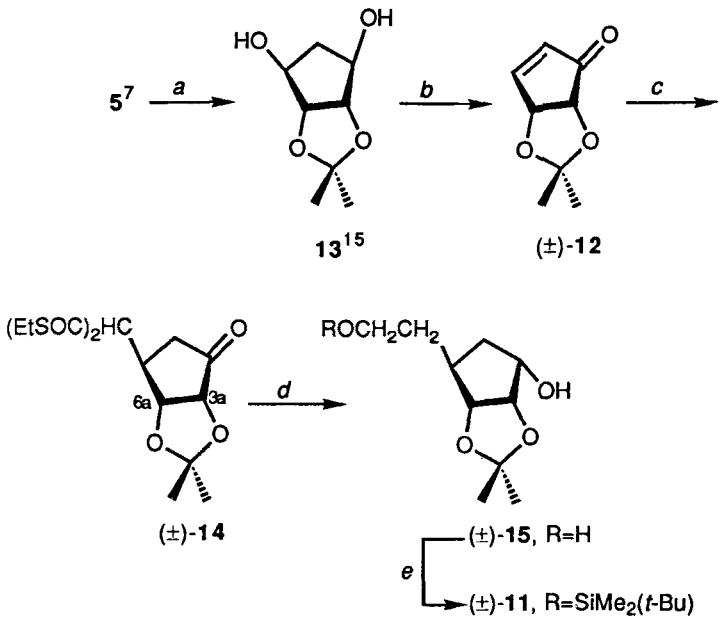
Reaction conditions: a, catalytic $Pd(PPh_3)_4$, PPh_3,4-chloropyrrolo[2,3-*d*]pyrimidine,[12] NaH, DMSO/THF, 55 °C; *b*, OsO_4, N-methylmorpholine N-oxide, THF-H_2O, rt; *c*, NH_3/MeOH, 120 °C, 24 h

Scheme 2

The final three steps in the Jones and Roberts[13] route to **4** involved coupling of the triflate of (-)-**11** with 6-chloropurine followed by deprotection and ammonolysis. To employ this pathway to **4**, we desired a synthesis of (-)-**11** that would not utilize L-ribonic-γ-lactone, which was the starting material for the reported[13] preparation of (-)-**11** but is expensive and not synthetically readily available. For this purpose, we focused on the work of Johnson and his collaborators,[15,16] which suggested that a 1,4-conjugate addition reaction to the appropriate stereoisomer of cyclopentenone **12** would be a fruitful approach.

This idea was evaluated by, first, using (±)-**12** (Scheme 3), which was subjected to the conjugate addition of *S,S'*-diethyl dithiomalonate[19] in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) to give (±)-**14**. Assurance that the Michael addition to (±)-**12** had occurred from the top face was achieved by reference to the work of Borchardt and his colleagues,[20] who used nmr studies to confirm that a related nucleophilic attack occurred from the less hindered side of a similar cyclopentenone. Treatment of (±)-**14** with Raney nickel resulted in diol (±)-**15**. Reaction of (±)-**15** with *t*-butyldimethylsilyl chloride under standard conditions produced (±)-**11**, whose nmr data agreed with that reported[13] for the (-)-enantiomer.

To adapt Scheme 3 for the preparation of (-)-**11** for the purposes of preparing **4**, an enantiospecific synthesis of the stereoisomer (-)-**12**, which was more amenable to scale-up than literature methods,[15,21,22] was sought. The route chosen involved the oxidation of the alcohol functionality of (+)-**16** (Scheme 4) with concomitant elimination of acetic acid.[18]



Reaction conditions: a, reference 15; *b,* PCC[17,18] pyridine and celite in CH_2Cl_2, rt, 24 h; *c,* $CH_2(COSEt)_2$/DABCO in 1,2-dimethoxyethane, rt, 5 h; *d,* Raney Ni W-2 in toluene, rt, 1 h; *e,* *t*-$BuMe_2SiCl$/pyridine/DMAP in CH_2Cl_2, rt, 20 h

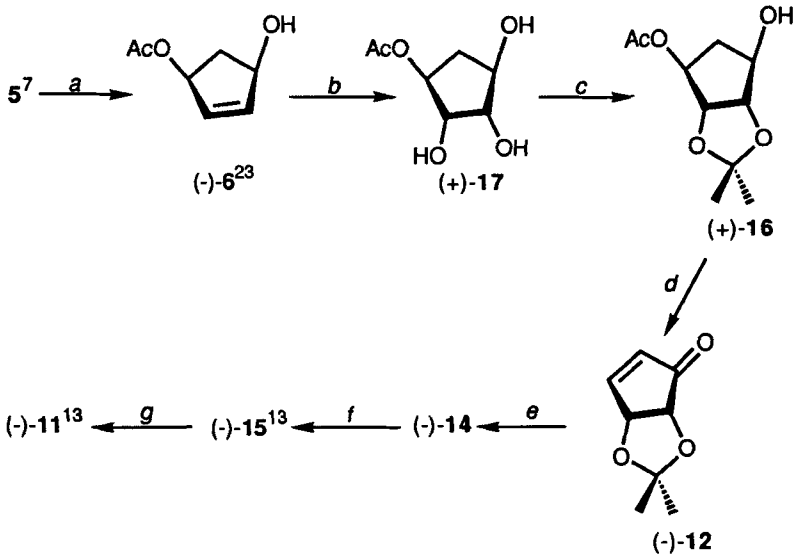
Scheme 3

Achieving the desired (+)-**16** began with the enzymatic hydrolysis of **5** to (-)-**6** employing porcine liver esterase.[23] Treatment of (-)-**6** with N-methylmorpholine N-oxide and osmium tetroxide gave (+)-**17**.[25] Using standard conditions, compound (+)-**17** was transformed into the desired (+)-**16**,[25] which, upon pyridinium chlorochromate oxidation, resulted in (-)-**12**.[25] Following procedures for the (±)-**12** to (±)-**11** process of Scheme 3, enone (-)-**12** was converted to (-)-**11**, whose physical data agreed with the literature.[13] With this synthesis of (-)-**11**, a formal preparation of **4** was in hand.[13]

The complete study of antiviral properties of (-)-**1**, (-)-**3**, and (-)-**4** will be reported in the future.

Experimental Section

Unless otherwise noted, the reactions were carried out using freshly distilled solvents under anhydrous conditions in an argon atmosphere. The glassware was dried overnight in an oven at 100 °C. All reactions were monitored by thin-layer chromatography



Reaction conditions: *a*, PLE,[23] rt; *b*, OsO_4/NMO; *c*, acetone and $Me_2C(OMe)_2$/*p*-TsOH; *d*, PCC[18] in CH_2Cl_2; *e*, $CH_2(COSEt)_2$/DABCO in 1,2-dimethoxyethane, rt, 5 h; *f*, Raney Ni W-2 in toluene, rt, 1 h; *g*, *t*-$BuMe_2SiCl$/pyridine/DMAP in CH_2Cl_2, rt, 20 h

Scheme 4

(TLC) using 0.25-mm E. Merck silica gel 60-F_{254} precoated silica gel glass plates with visualization by irradiation with a Mineralight UVGL-25 lamp, exposure to iodine vapor, or spraying with 3% phenol in 5% ethanolic H_2SO_4 and subsequent heating at 200 °C. The column chromatography purifications were performed on Aldrich flash chromatography silica gel 60 (particle size 0.035-0.07 mm; 220-440 mesh ASTM) by eluting with the indicated solvent system. The ^1H nmr and ^{13}C nmr spectra were recorded on either a JEOL FX90Q or Bruker AMX-360 spectrometer in $CDCl_3$ referenced to internal tetramethylsilane (TMS) at 0.0 ppm. As a convenience with the carbocyclic nucleoside analogues, the ^1H nmr assignments are made using standard nucleoside designations, which may not always conform with the compound name given. Melting points were obtained using a Mel-Temp capillary melting point apparatus and are uncorrected. Optical rotations were recorded on Perkin-Elmer 241MC polarimeter. The microanalysis was performed by M-H-W Laboratories, Phoenix, AZ.

(+)-(1*R*, 4*S*)-4-Hydroxy-2-cyclopentenyl Acetate ((+)-6). Compound **5**[7] (56.0 g, 353.26 mmol) was suspended in 0.1 M phosphate buffer (200 mL) and the pH was adjusted to 7 by the addition of 1 N NaOH. To the stirred mixture *Pseudomonas cepacia* lipase (5 g, 165000 units, PS-30, Amano) was added and the pH was kept constant, during the hydrolysis, by the continuous addition of 1 N NaOH solution. After consumption of 352.5 mL (1.0 equivalent) of 1 N NaOH (2.5 h), the reaction mixture was extracted with AcOEt (3 x 150 mL). The combined organic phases were dried ($MgSO_4$) and evaporated to dryness using a rotary evaporator. The residue was then chromatographed on silica gel (AcOEt-hexane, 1:1) and the product containing fractions (by tlc) were evaporated to dryness. The residual oil was distilled (80-85 °C/0.2 mm). The distillate solidified and was then recrystallized twice from pentane-ether (1:1) to give (+)-**6** as colorless needles (43.8 g, 87%): mp 45-46 °C; $[\alpha]_D^{25}$ +67.3° (*c* 0.27 $CHCl_3$) (lit.[9] mp 46-48.5 °C, $[\alpha]_D$ +66.3°). The nmr spectral data of this compound agreed with the literature.[23b] In a substantial scale-up of this reaction, it was found that, due to the cost of the enzyme, the proportions of PCL to **5** (3 g of PCL to 200 g of **5**, 8.5 h hydrolysis time) could be reduced without loss of optical purity and chemical yield.

(1*R*, 4*S*)-N-[9-(4-Hydroxy-2-cyclopentenyl)-9*H*-purin-6-yl]benzamide ((+)-7). To a solution of N^6-benzoyladenine (8.7 g, 36.40 mmol) in dry DMSO (50 mL) was added sodium hydride (80% suspension in mineral oil, 1.2 g, 40.00 mmol). The reaction mixture was stirred at the room temperature for 30 min, followed by the addition of tetrakis(triphenylphosphine)palladium (2.6 g, 2.25 mmol), triphenylphosphine (1 g, 3.81 mmol) and a solution of (+)-**6** (5.16 g, 36.34 mmol) in dry THF (50 mL). This mixture was stirred at 50 °C for 20 h. The volatiles were removed by rotary evaporation *in vacuo* at 18 mm and 50 °C. The residue was slurried in CH_2Cl_2 (250 mL) and filtered to remove insoluble solids. The filtrate that resulted was washed with brine (2 x 200 mL), dried ($MgSO_4$) and evaporated to dryness. The residual oil was purified by flash chromatography on silica gel by eluting first with AcOEt to remove the non-polar impurities and then with AcOEt-MeOH (9:1). The product containing fractions were evaporated to dryness and the residue recrystallized from AcOEt-hexane-CH_2Cl_2 (1:1:1) to give (+)-**7** as an off-white solid (9.4 g, 81%): mp 159-161 °C; $[\alpha]_D^{25}$ +70.27° (*c* 0.555, MeOH); ^1H nmr (DMSO-d_6) δ 1.97 (dt, J_1=15 Hz, J_2=4 Hz, 1 H, H-5'), 2.96 (dt, J_1=15.5 Hz, J_2=7.6 Hz, 1 H, H-5'), 4.78 (m, 1 H, H-1'), 5.24 (d, 1 H, OH, D_2O exchangeable), 5.65 (m, 1 H, H-4'), 6.09 (m, 1 H, H-2'), 6.28 (m. 1 H, H-3'), 7.58 (m, 3 H, Ph), 8.08 (m, 2 H, Ph), 8.37 (s, 1 H, H-8), 8.71 (s, 1 H, H-2), 11.05 (br, 1 H, NH); ^{13}C nmr (DMSO-d_6) δ 41.39, 57.64, 73.89, 128.55, 128.56 (three carbons), 132.40, 133.86, 139.98, 143.02, 150.38, 151.36, 166.10 (C=O). ^1H nmr experiments with the chiral shift reagent

(+)-Eu(tfc)$_3$ did not show any visible enantiomeric contamination. Anal. Calcd. for $C_{17}H_{15}N_5O_2$: C, 63.54; H, 4.71; N, 21.79. Found: C, 63.63; H, 4.80; N, 21.59.

(1*S*, 2*R*, 3*S*, 4*R*)-4-(6-Amino-9*H*-purin-9-yl)cyclopentane-1,2,3-triol ((-)-1). To a solution of (+)-**7** (6 g, 18.69) in THF-H_2O (10:1, 100 mL) was added a 60% aqueous solution of N-methylmorpholine N-oxide (6 mL, 30.73 mmol) and then osmium tetroxide (110 mg). The reaction mixture was stirred at room temperature for 24 h. The solvent was removed by rotary evaporation and the residue was co-evaporated with EtOH (3 x 50 mL) to give a gummy material. This residue was triturated with hot H_2O to give (1*S* 2*R*, 3*S*, 4*R*)-N-[9-(2,3,4-trihydroxycyclopentyl)-9*H*-purin-6-yl]benzamide ((-)-**8**) as a tan solid (6.56 g, 99%): mp 150 °C (dec.); $[\alpha]_D^{25}$ -31.7° (*c* 0.5, MeOH); ^{1}H nmr (DMSO-d_6) δ 1.62-2.7 (m, 2 H, H-5'), 3.26 (m, 3 H, OH), 3.65 (m, 1 H, H-1'), 4.58 (m, 3 H, H-2', H-3' and H-4'), 7.34 (m, 3 H, Ph), 7.78 (m, 2 H, Ph), 8.29 (s, 1 H, H-2), 8.48 (s, 1 H, H-8), 11.28 (br, 1 H, NH); ^{13}C nmr (DMSO-d_6) δ 37.92, 58.94, 73.95, 75.58, 76.93, 128.78 (three carbons), 132.73, 133.82, 144.38, 150.45, 151.42, 152.84, 166.05 (C=O). This material was used in the next step without further purification.

A solution of (-)-**8** (450 mg, 1.27 mmol) in MeOH-NH_4OH (1:1, 20 mL) was heated, in a sealed tube, at 100 °C for 20 h. After cooling to room temperature, the reaction mixture was evaporated to dryness. The residue was triturated with a small amount of MeOH to give a white solid, which was filtered and purified by silica gel chromatography (eluent CH_2Cl_2-MeOH, 8:2) to give (-)-**1** (280 mg, 88%) as an off-white solid: mp 227 °C (dec.); $[\alpha]_D^{25}$ -45.3 (*c* 1.0, DMF); ^{1}H nmr (DMSO-d_6) δ 1.77-1.90 (m, 1 H, H-5'), 2.50-2.60 (m, 1 H, H-5'), 3.75 (m, 1 H, H-2'), 3.89 (m, 1 H, H-1'), 4.40-4.52 (m, 1 H, H-3'), 4.62-4.81 (m, 1 H, H-4'), 4.87 (d, 1 H, *J*=3.6 Hz, OH), 5.01 (d, 1 H, *J*=6.6 Hz, OH), 5.36 (d, 1 H, *J*=4.8 Hz, OH), 7.22 (s, 2 H, NH_2), 8.11 (s, 1 H, H-8), 8.15 (s, 1 H, H-2); ^{13}C nmr (DMSO-d_6) δ 36.50, 58.81, 73.40, 75.56, 76.44, 118.32, 142.47, 145,42, 148.73, 150.60. This spectral data agrees with that previously reported for (±)-**1**.[4] Anal. Calcd. for $C_{10}H_{13}N_5O_3 \cdot 0.25\ H_2O$: C, 46.96; H, 5.32; N, 27.38. Found: C, 46.83; H, 5.21; N, 27.06.

(1*S*, 4*R*)-4-(4-Chloropyrrolo[2,3-*d*]pyrimidin-7-yl)cyclopent-2-en-1-ol ((+)-9). To a solution of 4-chloropyrrolo[2,3-*d*]pyrimidine[12] (4 g, 26.14 mmol) in dry DMSO (50 mL) was added NaH (60% dispersion in mineral oil, 1.05 g, 26.14 mmol). The reaction mixture was stirred at room temperature for 30 min, followed by the addition of tetrakis(triphenylphosphine)palladium (2.0 g, 1.73 mmol), triphenylphosphine (1 g, 3.81 mmol) and a solution of (+)-**6** (4 g, 28.17 mmol) in dry THF (100 mL). This mixture was stirred at 55 °C for 24 h. The volatiles were removed by rotary evaporation *in vacuo* at 18 mm and 50 °C. The residue was slurried in CH_2Cl_2 (250 mL), filtered to

remove insoluble solids, and the filtrate washed with brine (2 x 200 mL), dried ($MgSO_4$) and evaporated to dryness. The material remaining was triturated with Et_2O and the insoluble solids were removed by filtration. The new filtrate was evaporated to dryness and the residue was purified by flash column chromatography on silica gel. Elution first with hexane to remove nonpolar impurities and then AcOEt-hexane (1:1) gave **9** as white solid (2.42 g, 79% based upon recovered 4-chloropyrrolo[2,3-*d*]pyrimidine (2 g)): mp 112-114 °C; $[\alpha]_D^{25}$ +60.49° (*c* 0.324, CH_2Cl_2); ^1H nmr ($CDCl_3$) δ 2.15 (dt, J_1=15.2 Hz, J_2=8.50 Hz, 1 H, H-5'), 3.05 (dt, J_1=15.24 Hz, J_2=8.50 Hz, 1 H, H-5'), 5.03 (m, 1 H, H-1'), 5.48 (m, 1 H, OH), 5.57 (d, *J*=5.87 Hz, 1 H, H-4'), 5.99 (dd, J_1=5.57 Hz, J_2=2.32 Hz, 1 H, H-2'), 6.36 (d, *J*=5.57 Hz, 1 H, H-3'), 6.64 (d, *J*=3.52 Hz, 1 H, H-5), 7.44 (d, *J*=3.52 Hz, 1 H, H-6), 8.61 (s, 1 H, H-2); ^{13}C nmr ($CDCl_3$) δ 39.13, 58.70, 73.64, 98.13, 117.20, 127.54, 129.77, 137.57, 148.35, 149.80, 152.30. Anal. Calcd. for $C_{11}H_{10}ClN_3O$: C, 56.06; H, 4.28; N, 17.83. Found: C, 55.90; H, 4.53; N, 17.65.

(1*S*, 2*R*, 3*S*, 4*R*)-4-(4-Chloropyrrolo[2,3-*d*]pyrimidin-7-yl)cyclopentane-1,2,3-triol ((-)-10). To a solution of (+)-**9** (1.8 g, 7.66 mmol) and 60% aqueous N-methylmorpholine N-oxide (2.5 g, 12.80 mmol) in THF (80 mL) was added osmium tetroxide (100 mg). The reaction mixture was stirred at room temperature for 4 h. To this mixture was added sodium bisulfite (2 g) and the stirring continued at room temperature for 15 min. The solvent was removed by rotary evaporation and the residue was subjected to column chromatography on silica gel. The product containing fractions eluted with AcOEt, which, upon evaporation to dryness, provided (-)-**10** (1.45 g, 70%) as a white solid: mp 97-99 °C; $[\alpha]_D^{25}$ -21.36° (*c* 0.206, DMF); ^1H nmr (DMSO-d_6) δ 1.51-1.86 (m, 1 H, H-5'), 2.49-2.70 (m, 1 H, H-5'), 3.80 (m, 3 H, H-1', H-2', and H-3'), 4.48 (m, 1 H, H-4'), 4.89 (s, 1 H, OH), 5.05 (d, *J*=7.04 Hz, 1 H, OH), 5.16 (d, *J*=3.81 Hz, 1 H, OH), 6.72 (d, *J*=3.81 Hz, 1 H, H-5), 7.86 (d, *J*=3.52 Hz, 1 H, H-6), 8.63 (s, 1 H, H-2); ^{13}C nmr (DMSO-d_6) δ 37.06, 58.56, 73.52, 76.28, 76.71, 99.09, 116,91, 128.99, 149.92, 150.06, 151.04. Anal. Calcd. for $C_{11}H_{12}ClN_3O_3 \cdot 0.25\ H_2O$: C, 48.19; H, 4.60; N, 15.33. Found: C, 48.38; H, 4.96; N, 14.92.

(1*S*, 2*R*, 3*S*, 4*R*)-4-(4-Aminopyrrolo[2,3-*d*]pyrimidin-7-yl)cyclopentane-1,2,3-triol ((-)-3). To a suspension of (-)-**10** (1 g, 3.72 mmol) in MeOH (20 mL) was added liquid ammonia (20 mL). The mixture was sealed in a stainless steel tube and heated at 120 °C for 24 h. After cooling to -20 °C, the sealed tube was opened and the solvent removed by rotary evaporation. The residue was purified by silica gel column chromatography. The column was first eluted with CH_2Cl_2-MeOH (9:1) to remove nonpolar impurities and then with CH_2Cl_2-MeOH-NH_4OH (5:4:1). The product containing fractions were evaporated to dryness and the residue treated with decolorizing carbon in hot H_2O, which was removed by filtration and the filtrate evaporated to dryness.

After washing the solid with acetone-absolute EtOH (9:1), it was dried over P_2O_5 *in vacuo* to give (-)-**3** (910 mg, 98%) as a white solid: mp 204-206 °C; $[\alpha]_D^{25}$ -34.91° (*c* 0.212, DMF); ^{1}H nmr (DMSO-d_6) δ 1.64 (m, 1 H, H-5'), 2.50 (m, 1 H, H-5'), 3.78 (m, 3 H, H-1', H-2', and H-3'), 4.39 (m, 2 H, H-4' and OH), 4.82 (m, 2 H, 2 x OH), 6.69 (d, 1 H, *J* = 2.93 Hz, H-5), 7.27 (brs, 3 H, H-6 and NH_2), 8.07 (s, 1 H, H-2); ^{13}C nmr (DMSO-d_6) δ 37.38, 58.41, 73.79, 76.34, 77.15, 99.58, 102.72, 122.93, 149.85, 149.89, 156.63. Anal. Calcd. for $C_{11}H_{14}N_4O_3 \cdot 1.0\ H_2O$: C, 49.25; H, 6.01; N, 20.88. Found: C, 49.53; H, 6.21; N, 20.46.

(±)-2,2-Dimethyl-6-[*bis*(thioethoxycarbonyl)methyl]-3aβ,5,6α,6aβ-tetrahydro-4*H*-cyclopenta-1,3-dioxol-4-one (14).[26] Compound **13**[15] (39.5 g, 0.227 mmol) was dissolved in dry CH_2Cl_2 (1 L) and dry pyridine (300 mL). Pyridinium chlorochromate (218.03 g, 1.01 mol, freshly dried over P_2O_5) and celite (50 g) were added to the mixture and the mixture was stirred at room temperature for 24 h. After concentration *in vacuo* at room temperature to remove the CH_2Cl_2, the resultant black tar was triturated with Et_2O (1 L) and filtered. The black residue was also washed thoroughly with Et_2O (6 x 500 mL) and AcOEt (3 x 500 mL). The combined organic phases were evaporated to dryness on a rotary evaporator. The residual brown oil was co-evaporated with toluene (3 x 300 mL) to remove pyridine and the new residue chromatographed over silica gel (400 g) (hexane-AcOEt, 8.5:1.5) to give (±)-2,2-dimethyl-3aβ,6aβ-dihydro-4*H*-cyclopenta-1,3-dioxol-4-one) ((±)-**12**) as a colorless oil, which crystallized in the freezer and was recrystallized (18 g, 51.5%) from pentane: mp 35-37 °C (lit.[15] 37.5-38.5 °C). The nmr spectral data for this compound agreed with the literature data for **12**.[15]

A solution of (±)-**12** (500 mg, 3.25 mmol), *S,S'*-diethyl dithiomalonate[19] (733 mg, 3.81 mmol) and 1,4-diazabicyclo[2.2.2]octane (436 mg, 3.88 mmol) in 1,2-dimethoxyethane (10 mL) was stirred under Ar for 5 h. The reaction mixture was acidified with ice cold 2 N HCl (20 mL) and then extracted with CH_2Cl_2 (3 x 10 mL). Drying ($MgSO_4$), filtration, and concentration of the combined extracts yielded crude product, which, upon chromatography using silica gel (hexane-AcOEt, 1:1), gave pure (±)-**14** as a yellow oil (810 mg, 72%): ^{1}H nmr ($CDCl_3$) δ 1.34 (s, 3 H, Me), 1.35 (t, 6 H, $C\underline{H}_3CH_2S$), 1.43 (s, 3 H, Me), 1.89 (m, 1 H, H-6), 2.75 (m, 2 H, H-5), 2.90 (m, 5 H, $CH_3C\underline{H}_2S$ and C<u>H</u>CO), 4.25 (d, *J*=22 Hz, 1 H, H-6a), 4.76 (d, *J*=22 Hz, 1 H, H-3a); ^{13}C nmr ($CDCl_3$) δ 14.48 ($\underline{C}H_3CH_2S$), 24.48 (Me), 24.86 (Me), 26.92, 38.08, 39.38, 69.29, 78.98, 80.18, 112.35 ($\underline{C}Me_2$), 193.39 (thioester C=O), 211.82 (ketone C=O) Anal. Calcd. for $C_{15}H_{22}O_5S_2$: C, 52.00; H, 6.40. Found: C, 52.21; H, 6.54.

(±)-2,2-Dimethyl-6-[2-(*t*-butyldimethylsiloxy)ethyl]-3aβ,5,6α,6aβ-tetrahydro-4*H*-cyclopenta-1,3-dioxol-4α-ol ((±)-11).[26] To a suspension of modified W-2 Raney nickel (5 mL settled volume, pre-washed 4 x with distilled H_2O, 3 x

with 10% aqueous AcOH, 2 x with 2-propanol and 3 x with toluene) in toluene (20 mL) was added a solution of (±)-**14** (610 mg, 1.76 mmol) in toluene (10 mL). After stirring at room temperature under Ar for 1 h, the reaction mixture was filtered through celite and the residue thoroughly washed with MeOH. Concentration of the combined organic phases followed by column chromatography of the crude product on silica gel (hexane-AcOEt, 1:1) yielded (±)-2,2-dimethyl-6-(2-hydroxyethyl)-3aβ,5,6α,6aβ-tetrahydro-4*H*-cyclopenta-1,3-dioxol-4α-ol ((±)-**15**) as an oil (230 mg, 65%).

A solution of (±)-**15** (200 mg, 0.99 mmol), *t*-butyldimethylsilyl chloride (170 mg, 1.13 mmol), 4-dimethylaminopyridine (121 mg, 0.99 mmol) and dry pyridine (156 mg, 1.97 mmol) in dry CH_2Cl_2 (10 mL) was stirred under Ar for 20 h. The reaction mixture was washed with 0.5 N HCl (2 x 10 mL), dried ($MgSO_4$) and evaporated to dryness using a rotary evaporator. The residue was chromatographed on silica gel (hexane-AcOEt, 5:1) to give (±)-**11** (234 mg, 75%). The nmr spectral data for this compound agreed with the literature data for (-)-**11**.[13]

(-)-(3a*R*,6a*R*)-2,2-Dimethyl-3a,6a-dihydro-4*H*-cyclopenta-1,3-dioxol-4-one ((-)-12). By adapting a literature procedure,[23b] compound **5**[7] (12.9 g, 70.12 mmol) was treated with 30 mg (6000 units) of porcine liver esterase (Sigma) at room temperature.[24] After the consumption of one equivalent of 1 N NaOH (52 h), the reaction mixture was worked up as described[23b] to give, after distillation and recrystallization five times from pentane-ether (1:1), (-)-(1*S*,4*R*)-4-hydroxy-2-cyclopentenyl acetate ((-)-**6**) (4.2 g, 42%): mp 44-46 °C; $[\alpha]_D^{25}$ -67.8° (*c* 0.27 $CHCl_3$) (lit.[23b] mp 40-40.5 °C, $[\alpha]_D^{20}$ -68.0°).

A solution of (-)-**6** (3.0 g, 21.12 mmol) was treated with OsO_4 as described in the literature for its optical antipode[18] to yield 3.5 g (95%) of (+)-(1*S*,2*S*,3*S*,4*R*)-1-acetoxy-2,3,4-trihydroxycyclopentane ((+)-**17**): $[\alpha]_D^{25}$ +44.6° (*c* 1.29 MeOH) (lit.[18] for (-)-**17** $[\alpha]_D^{25}$ -44.3° (*c* 1.30 MeOH). Due to the instability of (+)-**17**, it was used immediately in the next step without further characterization.

Triol (+)-**17** (3.0 g, 17.04 mmol) was converted to acetonide (+)-**16** (2.7 g, 75%) as described in the literature for its optical antipode[18]: $[\alpha]_D^{25}$ +11.5° (*c* 2.6 $CHCl_3$) (lit.[18] for (-)-**16** $[\alpha]_D^{23}$ -10.3° (*c* 2.62 $CHCl_3$).

A solution of (+)-**16** (2.5 g, 11.57 mmol) in dry CH_2Cl_2 (25 mL) was treated with pyridinium chlorochromate as described in the literature for its optical antipode[18] to produce (-)-**12** (1.4 g, 79%): mp 68-69 °C, $[\alpha]_D^{25}$ -71.3 (*c* 1.0 $CHCl_3$) (lit.[21] mp 66-67 °C, $[\alpha]_D$ -70.7 (*c* 1.0 $CHCl_3$)). The nmr data of this compound agreed the literature.[21]

(-)-(3a*R*,6*R*,6a*R*)-2,2-Dimethyl-6-[*bis*(thioethoxycarbonyl)methyl]-3a,5,6,6a-tetrahydro-4*H*-cyclopenta-1,3-dioxol-4-one ((-)-14). Treating (-)-**12** (500 mg, 325 mmol) with *S,S'*-diethyl dithiomalonate[19] (733 mg, 3.81 mmol), as

described for achieving (±)-**14**, resulted (-)-**14** (811 mg, 73%): $[\alpha]_D^{25}$ -17.3° (*c* 1.0 $CHCl_3$). The nmr data of this compound agreed with (±)-**14**.

(-)-(3a*S*,4*S*,6*S*,6a*R*)-2,2-Dimethyl-6-[2-(*t*-butyldimethylsiloxy)-ethyl]-3a,5,6,6a-tetrahydro-4*H*-cyclopenta-1,3-dioxol-4-ol ((-)-11). Compound (-)-**14** (610 mg, 1.76 mmol) was converted into (-)-**15** (228 mg, 64%) upon reaction with W-2 Raney nickel as described for preparing (±)-**15**. This was followed by treatment of a solution of (-)-**15** (200 mg, 0.99 mmol) with *t*-butyldimethylsilyl chloride (170 mg, 1.13 mmol) as reported herein for obtaining (±)-**11**. In this way, (-)-**11** (235 mg, 75%), $[\alpha]_D^{25}$ -9.8° (*c* 1.97 $CHCl_3$) (lit.[13] $[\alpha]_D$ -10.0° (*c* 1.97 $CHCl_3$)) was obtained. The nmr data for this compound agrees with the literature.[13]

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(25) The antipodal forms of (+)-**17**,[18] (+)-**16**,[15,18] and (-)-**12**[15,18] have been reported in the literature.

(26) This nomenclature is based on that used in reference 15 for similarly functionalized cyclopentanes.

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