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A Mercapto Analogue of 5′-Noraristeromycin

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Abstract—5′-Noraristeromycin (**1**) and its enantiomer (**2**) have been found to possess a wide range of antiviral effects. In the search for analogues of **1** and **2** with improved activity, the synthesis of both enantiomers of 5′-mercapto-5′-deoxy-5′-noraristeromycin (**6** and **7**) has been accomplished. While (+)-**7** was inactive, (−)-**6** did show marginal activity against vaccinia virus, but not any other virus.

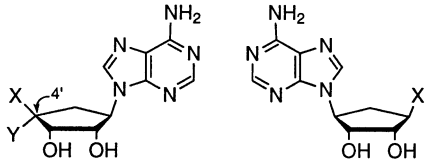
Introduction

Carbocyclic nucleosides and nucleotides have found a meaningful niche in the ongoing search for new medicinal agents.[1] Their success can be traced to their metabolic stability and their substrate compatibility with many enzymes relevant to nucleoside bio-conversions.[2] Several years ago, we began[3] a systematic study of carbocyclic nucleosides (carbanucleosides) lacking the 5′-methylene appendage (5′-norcarbanucleosides). From that effort, both enantiomers of the adenine system (**1** and **2**) were found to have significant biological properties.[3b,4] In the search for compounds related to **1** and **2** that could improve upon their effectiveness, the amino (**3**),[5] epimeric (**4**),[6,7] and fluoro (**5**)[6] analogues and their enantiomers[8] were investigated. To continue the series of varying the C-4′ substituent, the mercapto derivatives (**6** and **7**) have been prepared and their antiviral effects evaluated (Fig. 1).

Chemistry

In designing a reasonable approach to **6** (and, in turn, **7**) formation of the C–S bond at the 4′-position was initially considered via the palladium catalyzed coupling of the allylic acetate **8**[5] with potassium thioacetate[9] (Scheme 1). The resultant allylic thioacetate **9**, availed the sulfur in a deactivated form[10] and protected it from the subsequent oxidation under glycolization conditions.[11] In that regard, subjecting **9** to osmium tetroxide/*N*-methylmorpholine *N*-oxide (NMO) dihydroxylation provided the glycol **10**. Basic conditions, expected to deprotect **10** to yield the target **6**, proved to be too drastic, leading to decomposition. In an effort to avoid these harsh conditions, attempts to prepare debenzoylated **9** were sought. However, its preparation via the palladium-catalyzed coupling of potassium thioacetate with **8** lacking the protecting benzoyl group was unsuccessful and no other methods were attempted.

In seeking another approach to **6** (and **7**), two variations were considered: (i) having the 2′,3′-dihydroxyl groups in place prior to sulfur introduction, and (ii) avoiding the benzoyl protecting group. The chiral cyclopentenone **11**[12] (Scheme 2) provided the essential features for addressing i, and allowed for further elaboration to **6** by the Michael reaction of a thio nucleophile to its C-3



1, X = OH; Y = H
3, X = NH_2; Y = H
4, X = H; Y = OH
5, X = F; Y = H
6, X = SH; Y = H

2, X = OH
7, X = SH

Figure 1.

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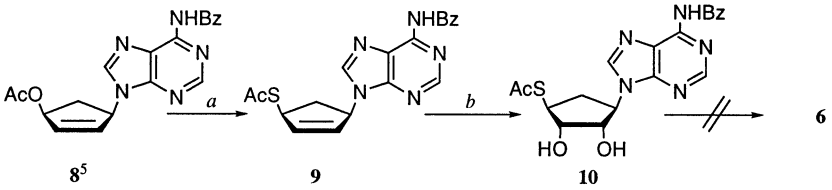
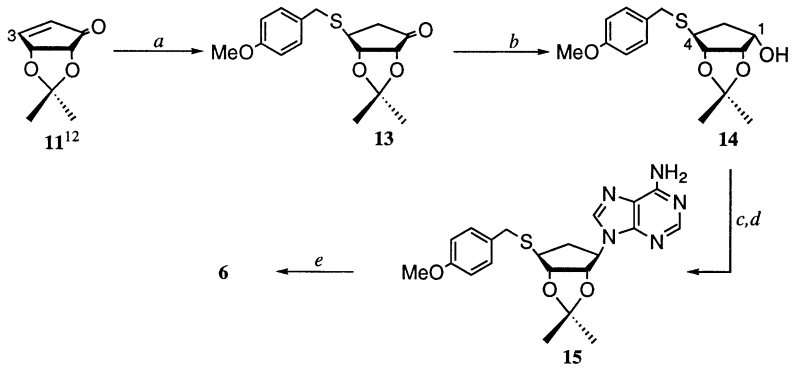


Scheme 1. Reaction conditions. (a) KSAc, 5 mol% $Pd(Ph_3P)_4$, 15 mol% Ph_3P, THF/DMSO (76%); (b) OsO_4, NMO, THF/H_2O (18%).



Scheme 2. Reaction conditions. (a) 4-methoxy-α-toluenethiol, K_2CO_3, THF (99%); (b) BH_3•THF (60%); (c) DIAD, Ph_3P, 6-chloropurine, THF; (d) NH_3, MeOH, 110 °C (71% from steps c and d); (e) TFA, PhOH, reflux (75%).

atom and manipulation of its C-1 carbonyl center for creating the linkage to the purine base (6-chloropurine).

Thus, 4-methoxy-α-toluenethiol (*p*-methoxybenzylmercaptan) was seen as a pro-thiol source and underwent a Michael addition to the chiral cyclopentenone **11**[12] to furnish the product **13**. Reduction of **13** with borane-THF[12] afforded the alcohol **14**. The stereochemistry of **13** and **14** was confirmed by correlating their NMR spectral properties with compounds prepared in an identical way.[3c,12] The coupling of 6-chloropurine to the alcohol **14**, under Mitsunobu conditions, followed by treatment with methanolic ammonia produced **15**. Deprotection of the isopropylidene group as well as the removal of the *p*-methoxybenzyl function[9] of **15** was achieved in one step with trifluoroacetic acid, to provide **6**.

By an analogous route, **7** was obtained from the enantiomer of **11**.[12]

Table 1. Activity of compounds **6** and **7** against different viruses

Virus	Cell[a]	MIC_{50} (μg/mL)[b]	
		6	**7**
HSV-1 (KOS)	E_6SM	> 80	> 80
HSV-2 (G)	E_6SM	240	> 80
HSV-1 TK⁻ B2006	E_6SM	> 80	> 80
HSV-1 TK⁻ VMW1837	E_6SM	> 80	> 80
VV	E_6SM	48	> 80
VSV	E_6SM	> 80	> 80
VSV	HeLa	> 400	> 80
RSV	HeLa	> 400	> 80
Coxsakie B4	HeLa	> 400	> 80
Coxsakie B4	Vero	> 80	> 80
Parainfluenza-3	Vero	> 80	> 80
Reovirus-1	Vero	> 80	> 80
Sindbis	Vero	> 80	> 80
Punta toro	Vero	> 80	> 80
HIV-1	CEM	> 250	> 250
HIV-2	CEM	> 250	> 250
CMV (AD-169)	HEL	> 200	> 50
CMV (Davis)	HEL	> 200	> 200
VZV (OKA)	HEL	> 200	> 200
VZV (YS)	HEL	> 200	> 200

[a]Minimum cyctotoxic concentration required to cause a microscopically detectable alteration of normal E_6SM, HeLa and Vero cell morphology was ≥ 400 μg/mL for **6** and > 400, >80 and ≥ 80, respectively, for **7**; in HEL and CEM cells: > 200 and > 250, respectively, for both **6** and **7**.
[b]Required to reduce virus-induced cytopathicity by 50%.

Antiviral results

Compounds **6** and **7** were evaluated against a wide variety of viruses: herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2), thymidine kinase-deficient (TK^-) HSV-1, vaccinia virus (VV), vesicular stomatitis virus (VSV), respiratory syncytial virus (RSV), cytomegalovirus (CMV), varicella-zoster virus (VZV), human immunodeficiency virus type 1 (HIV-1) and type 2 (HIV-2), and others as indicated in Table 1. The only virus affected was vaccinia virus, by compound **6**, and this only marginally. Since vaccinia virus is sensitive to agents that inhibit *S*-adenosylhomocysteine (AdoHcy) hydrolase, it is plasubile that **6** is acting in the same manner, albeit with much less potency than **1**, which is an inhibitor of AdoHcy hydrolase.[3] In addition to those viruses listed in Table 1, neither compound **6** nor **7** was active when assayed against hepatitis-B virus (HBV).

Conclusions

The limited activity of compounds **6** and **7** suggests that further efforts to improve upon the properties of compound **1** and **2** are not likely to arise following a free 4′-thiol lead. Nevertheless, the activity of compound **6**

towards vaccinia virus corroborates the notion that the 5′-methylene unit of traditional carbocyclic nucleosides is not a structural requirement for molecular recognition and consequent antiviral activity.

Experimental

Chemistry

Melting points were recorded on a Meltemp II melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 250 spectrometer (operated at 250 or 62.5 MHz, respectively). All ^{1}H chemical shifts are reported in δ relative to internal standard tetramethylsilane (TMS, δ 0.00). ^{13}C chemical shifts are reported in δ relative to $CDCl_3$ (center of triplet, δ 77.23) or relative to DMSO-d_6 (center of septet, δ 39.51). The spin multiplicities are indicated by the symbols s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Optical rotations were determined using the sodium-D line on a JASCO DIP-360 polarimeter. Elemental analyses were performed by either M-H-W-Laboratories, Phoenix, Arizona, or Atlantic Microlabs, Atlanta, Georgia. Reactions were monitored by thin-layer chromatography (TLC) using 0.25 mm E. Merck silica gel 60-F_{254} precoated silica gel plates with visualization by irradiation with a Mineralight UVGL-25 lamp or exposure to iodine vapor. Column chromatography was performed on Whatman silica gel (average particle size 5–25 μm, 60 Å) and elution with the indicated solvent system. Yields refer to chromatographically and spectroscopically (^{1}H and ^{13}C NMR) homogeneous materials.

(1′*R*,4′*S*)-*N*-[9-(4′-Acetylthio-2′-cyclopentenyl)-9*H*-purin-6-yl]-benzamide (9). A solution of the allylic acetate **8**[5] (3 g, 8.26 mmol) was stirred with triphenylphosphine (Ph_3P) (0.32 g, 15 mol%) and $Pd(Ph_3P)_4$ (0.5 g, 5 mol%) under N_2 for 30 min. This solution was then added dropwise to a stirred solution of KSAc (1.88 g, 16.5 mmol) in THF/DMSO (1:1, 40 mL). After the addition was completed, the reaction mixture was stirred at 55 °C under N_2 for 16 h. The reaction mixture was then filtered, evaporated under reduced pressure, extracted in CH_2Cl_2 and washed with H_2O. The organic layer was dried (Na_2SO_4), evaporated and purified by column chromatography. Elution with EtOAc/MeOH (25:1) provided **9** (2.4 g, 76%) as a yellow foam: ^{1}H NMR ($CDCl_3$) δ 1.96 (m, 1H), 2.05 (s, 3H), 3.28 (dt, 1H), 4.66 (m, 1H), 5.86 (m, 1H), 6.06 (d, 1H), 6.28 (d, 1H), 7.52-7.68 (m, 5H), 8.02 (m, 1H), 8.80 (s, 1H), 9.19 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 30.6, 39.7, 46.6, 58.8, 128.1, 128.8, 129.0, 130.3, 132.4, 133.8, 138.0, 141.5, 149.7, 151.9, 164.9, 195.0. Anal. calcd for $C_{19}H_{17}N_5O_2S{\cdot}0.25CH_3OH$: C, 59.68; H, 4.68; N, 18.08; S, 8.27. Found: C, 59.40; H, 4.78; N, 17.81; S, 7.90.

(1′*R*,2′*S*,3′*S*,4′*S*)-*N*-[9-(2′,3′-Dihydroxy-4′-*S*-acetylthiocyclopentyl)-9*H*-purin-6-yl]benzamide (10). To a solution of **9** (1.0 g, 2.6 mmol) in THF/H_2O (1:1, 80 mL), was added a 60% aqueous solution of NMO (1.08 g, 5.5 mol) and OsO_4 (15 mg). The reaction mixture was stirred at room temperature for 5 days. Sodium bisulfite (1 g) was added to the reaction mixture and stirring continued for 10 min. The contents of the flask were then filtered, evaporated and the residue purified by column chromatography. Elution with EtOAc/MeOH (5:1) provided **10** (200 mg, 18%) as a white solid: mp >60 °C (dec.); ^{1}H NMR (DMSO-d_6) δ 2.12 (m, 1H), 2.37 (s, 3H), 2.73 (m, 1H), 3.70 (m, 1H), 3.95 (br, 1H), 4.51 (br, 1H), 4.87 (dd, 1H), 5.25 (d, 1H), 5.37 (d, 1H), 7.51-7.67 (m, 5H), 8.03 (d, 1H), 8.53 (s, 1H), 8.73 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 30.4, 32.4, 44.0, 59.3, 73.8, 74.9, 126.1, 128.4, 132.3, 133.4, 144.2, 150.2, 151.1, 152.4, 165.5, 195.2. Anal. calcd for $C_{19}H_{19}N_5O_4S$: C, 55.20; H, 4.63; N, 16.94; S, 7.75. Found: C, 54.98; H, 5.04; N, 16.71; S, 7.53.

(2*R*,3*S*,4*S*)-4-*S*-(*p*-Methoxybenzyl)thio-2,3-(isopropylidenedioxy)-1-cyclo-pentanone (13). Potassium carbonate (5.6 g, 40.6 mmol) was added to a solution of the cyclopentenone **11**[12] (5 g, 32.5 mmol) in dry THF (150 mL), followed by 90% 4-methoxy-α-toluenethiol (6.3 mL, 40.6 mmol). The reaction mixture was stirred under N_2 at room temperature for 3 h, then filtered and evaporated to dryness. The residual oil was purified by column chromatography (elution 8:1, hexane/EtOAc) to afford **13** (9.9 g, 99%) as a white crystalline solid: mp. 120–122 °C; ^{1}H NMR ($CDCl_3$) δ 1.34 (s, 3H), 1.41 (s, 3H), 2.24 (d, 1H), 3.00 (q, 1H), 3.34 (d, 1H), 3.77 (s, 2H), 3.80 (s, 3H), 4.36 (d, 1H), 4.68 (d, 1H), 6.86 (d, 2H), 7.25 (d, 2H); ^{13}C NMR ($CDCl_3$) δ 25.2, 27.0, 35.4, 39.7, 40.3, 55.5, 78.3, 81.5, 113.2, 114.4, 129.0, 130.2, 159.2, 211.5. Anal. calcd for $C_{16}H_{20}O_4S$: C, 62.32; H, 6.54; S, 10.40. Found: C, 62.21; H, 6.59; S, 10.47.

(1*S*,2*S*,3*S*,4*S*)-4-*S*-(*p*-Methoxybenzyl)thio-2,3-(isopropylidenedioxy)-cyclopentan-1-ol (14). To a solution of **13** (5 g, 16.2 mmol) in dry THF (50 mL) cooled to −20 °C was added 1.0 M $BH_3{\cdot}$THF complex (48.5 mL, 48.5 mmol) under N_2. The reaction mixture was then stirred at room temperature for 3 h, cooled in an ice bath and the reaction quenched with H_2O (10 mL) added dropwise. The reaction mixture was then evaporated, extracted in CH_2Cl_2, washed with 10% NaOH (3 × 50 mL), brine (2 × 50 mL), dried (Na_2SO_4) and evaporated. The residual oil was purified by column chromatography (25:1, CH_2Cl_2/EtOAc) to furnish **14** (3.0 g, 60%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.34 (s, 3H), 1.47 (s, 3H), 1.72 (br, 1H), 1.96 (m, 2H), 2.37 (d, 1H), 3.03 (m, 1H), 3.65 (s, 2H), 3.79 (s, 3H), 4.22 (m, 1H), 4.54 (m, 1H), 6.85 (d, 2H), 7.23 (d, 2H); ^{13}C NMR ($CDCl_3$) δ 24.5, 26.2, 35.8, 36.9, 44.6, 55.5, 72.0, 78.9, 85.0, 111.7, 114.2, 129.7, 130.2, 159.0. Anal. calcd for $C_{16}H_{22}O_4S$: C, 61.91; H, 7.14; S, 10.33. Found: C, 62.03; H, 7.13; S, 10.15.

9-[(1′*R*,2′*S*,3′*S*,4′*S*)-4′-*S*-(*p*-Methoxybenzyl)thio-2′,3′-(isopropylidenedioxy)-cyclopentan-1′-yl]-adenine (15). A solution of diisopropyl azodicarboxylate (3.76 g, 17.7 mmol) in dry THF (30 mL) was added dropwise to a solution of Ph_3P (4.69 g, 17.7 mmol) in dry THF (50 mL). This was followed by stirring at room temperature under N_2 for 30 min. To this mixture was added 6-chloropurine (2.51 g, 16.1 mmol). The mixture was stir-

red for 30 min followed by the dropwise addition of a solution of **14** (2.5 g, 16.1 mmol) in dry THF (30 mL). The reaction mixture was stirred under N_2 for 20 h. The solvent was then evaporated and the residue purified by column chromatography. Elution with 5:2 hexane/EtOAc yielded *9*-[(1′*R*,2′*S*,3′*S*,4′*S*)-4′-*S*-(*p*-methoxybenzyl)thio-2′,3′-(isopropylidenedioxy)cyclopentan-1′-yl]-6-chloropurine as a pale yellow solid that was used directly in the next step.

The obtained 9-[(1′*R*,2′*S*,3′*S*,4′*S*)-4′-*S*-(*p*-methoxybenzyl)thio-2′,3′-(iso-propylidenedioxy)cyclopentan-1′-yl]-6-chloropurine was added to a saturated methanolic NH_3 solution (80 mL), which was sealed in a stainless steel pressure vessel and heated at 110 °C for 20 h. After cooling to 0 °C, the reaction vessel was opened and the contents evaporated to dryness to obtain a white solid residue, which was purified by column chromatography; elution with 9:1 EtOAc/MeOH furnished **15** as a pale yellow solid (2.45 g, 71% two steps): mp > 160 °C (dec); ^{1}H NMR ($CDCl_3$) δ 1.29 (s, 3H), 1.55 (s, 3H), 2.08 (br, 1H), 2.44–2.61 (m, 1H), 3.16 (m, 1H), 3.76 (s, 3H), 3.80 (s, 2H), 4.77 (m, 2H), 5.11 (m, 1H), 5.82 (s, 2H), 6.86 (d, 2H), 7.29 (d, 2H), 7.87 (s, 1H), 8.34 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 25.3, 27.5, 35.8, 37.4, 46.7, 55.5,61.3, 84.3, 87.0, 114.0, 114.2, 120.4, 130.1, 130.4, 139.8, 150.3, 153.1, 155.7, 159.0. Anal. calcd for $C_{21}H_{25}N_5O_3S$: C, 59.00; H, 5.89; N, 16.38; S, 7.50. Found: C, 58.92; H, 5.90; N, 16.27; S, 7.41.

(−)-(1*R*,2*S* 3*S*,4*S*)-4-Mercapto-1-(6-amino-9*H*-purin-9-yl)cyclopentan-2,3-diol (6). Compound **15** (600 mg, 1.4 mmol) and phenol (190 mg, 2.1 mmol) were dissolved in trifluoroacetic acid (6 mL), and this solution was stirred and heated under reflux for 2 h. The solution was evaporated, the residue re-dissolved in EtOH (10 mL) and evaporated again. Column chromatography on the residue (elution: 2:1, EtOAc/MeOH) furnished **6** (280 mg, 74.5%) as a white solid: mp > 210 °C (dec.); $[\alpha]_D^{25}$ −12.90° (*c* 0.71, DMSO); ^{1}H NMR (DMSO-d_6) δ 2.03 (m, 1H), 1.8 (m, 1H), 2.64 (m, 1H), 3.06 (br, 1H), 3.89 (m, 1H), 4.54 (m, 1H), 4.66 (m, 1H), 5.10 (d, 1H), 5.20 (d, 1H), 7.22 (s, 2H), 8.13 (s, 1H), 8.19 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 36.7, 58.6, 59.5, 73.7, 78.9, 119.3, 140.3, 149.3, 152.1, 156.0. Anal. calcd for $C_{10}H_{13}N_5O_2S$: C, 44.93; H, 4.90; N, 26.20; S, 11.99. Found: C, 45.06; H, 5.03; N, 25.91; S, 11.80.

(+)-(1*S*,2*R*,3*R*,4*R*)-4-Mercapto-1-(6-amino-9*H*-purin-9-yl)cyclopentan-2,3-diol (7). This was prepared from the enantiomer of **11**[12] via a route analogous to that described for **6**. Physical data for **7**: mp > 210 °C (dec.); $[\alpha]_D^{25}$ +14.20° (*c* 0.63, DMSO); ^{1}H NMR (DMSO-d_6) δ 2.03 (m, 1H), 1.82 (m, 1H), 2.65 (m, 1H), 3.06 (m, 1H), 3.16 (d, 1H), 3.88 (m, 1H), 4.54 (m, 1H), 4.66 (m, 1H), 5.10 (d, 1H) 5.20 (d, 1H), 7.22 (s, 2H), 8.12 (s, 1H), 8.19 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 36.7, 58.5, 59.6, 73.7, 79.0, 119.3, 140.4, 149.4, 152.1, 155.9. Anal. calcd for $C_{10}H_{13}N_5O_2S$: C, 44.93; H, 4.90; N, 26.20; S, 11.99. Found: C, 44.96; H, 4.91; N, 26.09; N, 11.93.

Antiviral activity assays. The antiviral activity assays, other than the anti-HBV assays, were based on the inhibition of virus induced cytopathicity in either E_6SM, HeLa, Vero, CEM, or HEL cell cultures, following previously established procedures.[3b] The anti-HBV assays were performed as described previously.[4]

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