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Synthesis of Novel 3′,6′-Dideoxy-3′,6′-Epithio and 2′,6′-Dideoxy-2′,6′-Epithio Nucleosides

Ryan L. Marshall, N. Kent Dalley, Paul B. Savage*

Department of Chemistry and Biochemistry, Brigham Young University, Provo, UT 84602

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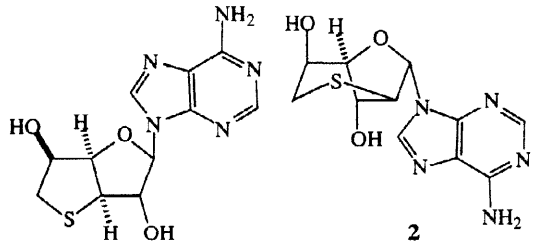
Abstract: New 3′,6′-dideoxy-3′,6′-epithio and 2′,6′-dideoxy-2′,6′-epithionucleosides were prepared from 3′,6′-dideoxy-3′,6′-epithioglucofuranose derivatives, which were obtained from 3-trifluoromethanesulfonyl diacetone allose.

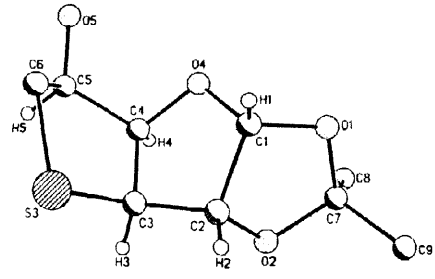
Sulfur substitution for oxygen in the carbohydrate moiety of nucleosides has provided compounds that have found use in antisense gene therapy[1-3] and as enzyme inhibitors.[4-8] In addition, nucleos(t)ides containing bicyclic carbohydrate groups (e.g., griseolic acid[9] and the octosyl acids[10]) display significant biological activity. Bicyclic carbohydrates have also been used in attempts to predispose furanoses to adopt conformations found in RNA and/or DNA.[11-15] For example, Zuo et al.[15] prepared a nucleoside bearing a 3′,6′-anhydroglucose group and incorporated it into an oligonucleotide in an effort to enhance the affinity of the oligonucleotide for RNA and/or DNA. However, their oligonucleotide displayed poorer affinity for complementary ssRNA than controls lacking the bicyclic structure. They suggested that the 5,5 ring system may be too rigid and that a more flexible bicyclic structure might provide better affinity. Decreasing the rigidity, while restricting conformation, might be achieved by incorporation of sulfur into the bicyclic system.

Figure 1. Structures of nucleosides **1** and **2**.



We now report the preparation of nucleosides in which sulfur has been incorporated into bicyclic carbohydrates (e.g., **1** and **2**, Figure 1). Treatment of triflated diacetone allose (**3**)[16] with potassium thioacetate in DMF provided thioacetate **4** in high yield (Scheme 1). Heating thioacetate **4** with sodium butoxide in butanol resulted in rapid formation of 3,6-dideoxy-3,6-epithioglucose **5** in good yield (70%). The structure of **5** was confirmed by X-ray crystallography (Figure 2). Its formation presumably occurs due to proximity of the C-3 thiolate to C-6 of **4**. Compound **5** was first reported by Owen and coworkers[17] and was prepared by treatment of the C-6 tosylate of 3-deoxy-3-thioglucofuranose with base.

Figure 2. Crystal structure of **5**. (Selected hydrogen atoms have been omitted for clarity.)



We have now investigated the preparation of nucleoside analogs of **5**. In preparation for nucleoside formation, we synthesized **6** as a mixture of anomers (Scheme 1). Reaction of **6** and N^6-benzoyladenine with tin tetrachloride in acetonitrile[18,19] gave analog **7** (Scheme 2). Deprotection using ammonia saturated methanol[18] provided nucleoside **1**, whose stereochemistry was confirmed via X-

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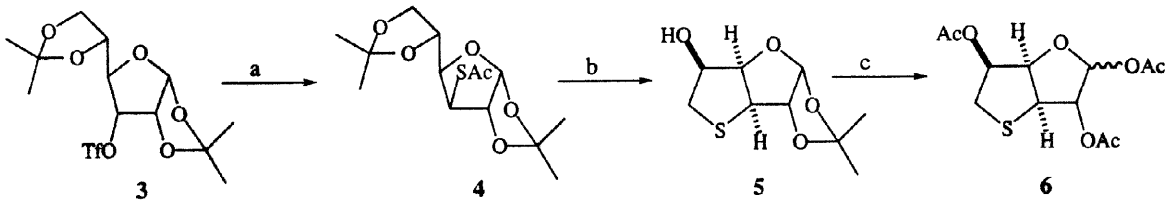
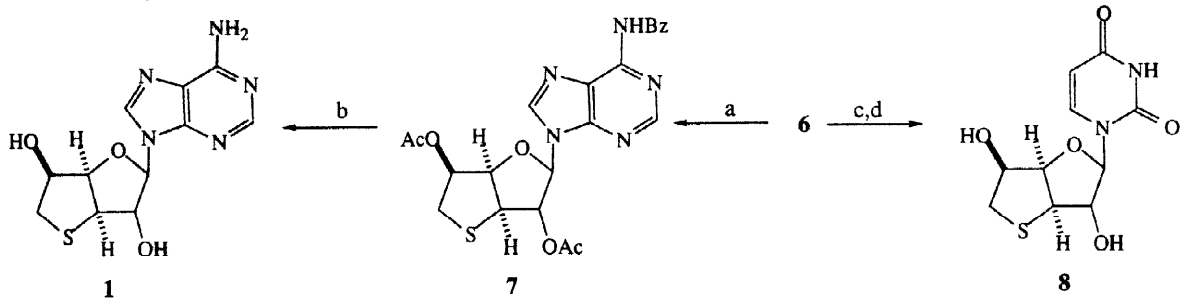
Scheme 1. Preparation of 3,6-dideoxy-3,6-epithioglucofuranosyl acetates **6**.



Reagents: a) potassium thioacetate, DMF (98%). b) sodium butoxide, butanol (reflux) (70%). c) 80% aqueous acetic acid (reflux); acetic anhydride, pyridine (89%).

Scheme 2. Preparation of nucleosides **1** and **8**.



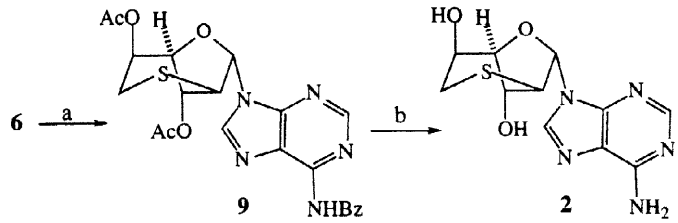
Reagents: a) N^6-benzoyladenine, tin tetrachloride, acetonitrile (98%). b) NH_3, MeOH (88%). c) uracil, chlorotrimethylsilane, hexamethyldisilizane, trimethysilyltriflate, acetonitrile (48%). d) sodium methoxide, methanol (24%).

ray crystallography (Figure 3). Uracil analog **8** was also prepared from **6** using hexamethyldisilazane, trimethylsilyl chloride and trimethylsilyl triflate in acetonitrile (Scheme 2).[19]

In one attempt to prepare **1**, we inadvertently used a sample of tin tetrachloride that had been exposed to moisture. Rather than recover **7**, we obtained rearranged product **9** with an *altro* configuration (Scheme 3). Compound **9** was deprotected to give **2**, whose structure was confirmed using X-ray crystallography (Figure 3).

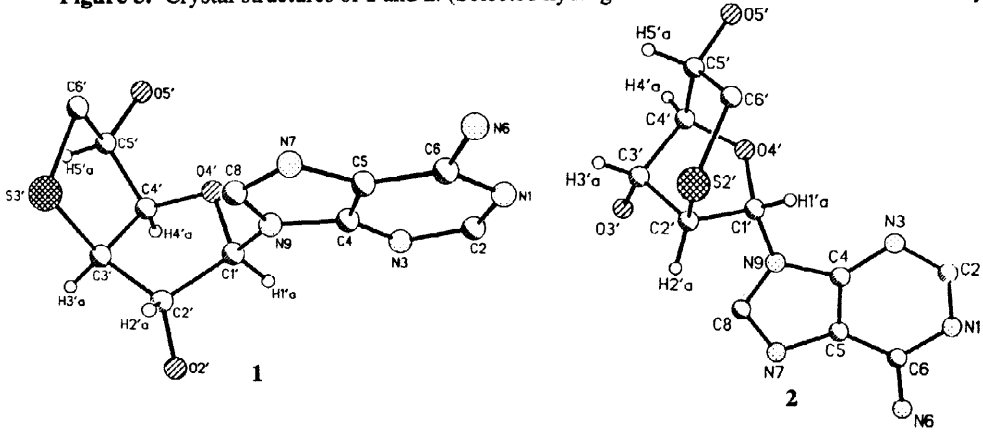
A possible mechanism by which **9** is formed from **6** (Scheme 4) involves participation of the thioether at C-3 in displacing acetate from

Scheme 3. Preparation of adenosine analog **2**.



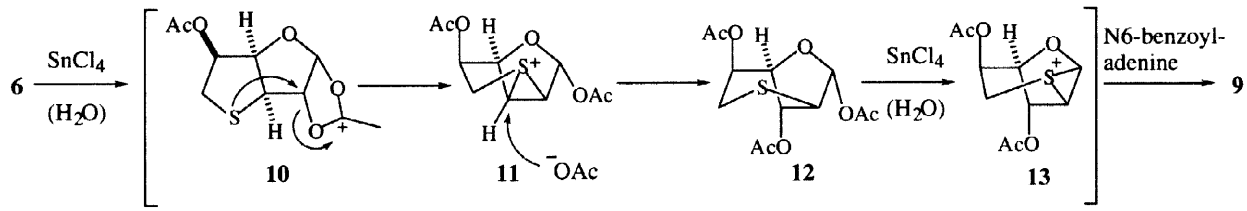
reagents: a) N6-benzoyladenine, tin tetrachloride, water (1 eq.) (70%). b) NH_3, MeOH (88%).

Figure 3. Crystal structures of **1** and **2**. (Selected hydrogen atoms have been omitted for clarity.)



C-2 to give episulfonium ion **11**. Attack of acetate at C-3 gives 2,6-epithio intermediate **12**. Sulfur migration from C-3′ to C-2′ in nucleosides has been observed and proposed to occur via an episulfonium intermediate.[20] Following the migration of sulfur, the anomeric position is activated by tin. Sulfur again provides anchimeric assistance (**13**) and directs the attack of adenine to give α anomer **9** (no β anomer was detected). Directing effects of sulfur at C-2 have been used to control stereochemistry in the formation of nucleosides.[21]

Scheme 4. Potential mechanism for formation of **9** from **6**.



The different isomers obtained from reactions using dry or water-contaminated tin tetrachloride (compounds **7** and **9**, respectively) apparently result from HCl formed when water reacts with tin tetrachloride. Treatment of **6** with N^6-benzoyladenine, tin tetrachloride, and dry HCl in acetonitrile gave **9**. However, HCl alone does not catalyze the reaction of **6** with N^6-benzoyladenine.

In summary, two new nucleoside analogs (**1** and **2**) have been prepared using rearrangement reactions giving **5** and **9**. Formation of **5** involved displacement of an acetonide oxygen by thiolate, and **9** involved migration of sulfur from C-3 to C-2 in a furanose ring.

Crystal experimental data for 1, 2 and 5:

Atomic coordinates, bond lengths and angles have been deposited with the Cambridge Crystallographic Data Center. Structures solved, refined and displayed using SHELXTL-PLUS program package. All nonhydrogen atoms were refined anisotropically. Hydrogen atom positions for hydrogens bonded to carbon atoms were calculated. Hydrogen atoms bonded to oxygen and nitrogen atoms were found in the difference map (except for one hydrogen bonded to N-6 in **1**). Hydrogens were refined using the riding model. X-ray source was graphite monochromated MoKα radiation, λ = 0.71073 Å.

1: $C_{11}H_{13}N_5O_3S$-(0.5)CH_3OH, MW 311.3, monoclinic, C2, a = 15.603 (8), b = 11.959 (8), c = 7.931 (4) Å, β = 102.47 (4)°, V = 1442 $Å^3$, 959 observed reflections, R = 0.077, R_W = 0.082.

2: $C_{11}H_{13}N_5O_3S$-2CH_3OH, MW 331.4, monoclinic, $P2_1$, a = 9.795 (4), b = 6.812 (2), c = 10.704 (4) Å, β = 95.92 (4)°, V = 710.4 $Å^3$, 1351 observed reflections, R = 0.055, R_W = 0.043.

5: $C_9H_{14}O_4S$, MW 218.3, orthorhombic, $P2_12_12_1$, a = 6.4750 (10), b = 9.073 (2), c = 17.875 (3) Å, V = 1050.0 $Å^3$, 1222 observed reflections, R = 0.035, R_W = 0.046.

Characterization of 1, 2 and 8:

1: m.p. 243° C; IR (neat) 3332, 3061, 2985, 1747, 1732, 1506 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 8.42 (s, 1 H) 8.17 (s, 1 H), 7.34 (s, 2 H), 6.05 (d, *J* = 5.1 Hz, 1 H), 5.94 (d, *J* = 4.4 Hz, 1 H), 5.52 (d, *J* = 6.1 Hz, 1 H), 4.75 (dd, *J* = 7.8, 4.6 Hz, 1 H), 4.70 (dd, *J* = 5.9, 3.7 Hz, 1 H), 4.18 (m, 1 H), 3.67 (dd, *J* = 5.9, 2.9 Hz, 1 H), 2.86 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.0, 152.8, 149.6, 139.1, 118.8, 90.7, 84.6, 82.0, 75.4, 52.0, 34.2; HRFAB-MS (thioglycerol matrix) *m/e:* ($[M + H]^+$) 296.0803 (100%), cacld. 296.0817.

2: m.p. 167° C; IR (neat) 3331, 1647, 1022 cm^{-1}; ^1H NMR (CD_3OD, 300 MHz) δ 8.42 (s, 1 H), 8.12 (s, 1 H), 6.52 (s, 1 H), 4.65 (s, 1 H), 4.31 (s, 1 H), 3.91 (dd, *J* = 6.3, 3.4 Hz, 1 H), 3.52 (s, 1 H), 2.86 (m,

2 H); ^{13}C NMR (CD_3OD, 75 MHz) δ 157.2, 153.9, 150.2, 141.9, 120.0, 92.3, 91.5, 79.1, 72.6, 50.3, 29.2; HRCI-MS *m/e*: ($[M + H]^+$) 296.0811 (100%); cacld. 296.0817.

8: m.p. 124-126° C; IR (neat) 3319, 2926, 1693, 1681, 1468, 1392, 1103 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.99 (d, J = 8.1 Hz, 1 H), 6.00 (d, J = 3.9 Hz, 1 H), 5.78 (d, J = 8.06 Hz, 1 H), 4.70 (dd, J = 5.1, 3.5 Hz, 1 H), 4.33 (m, 2 H), 3.63, (dd, J = 5.1, 2.12 Hz, 1 H), 2.95 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.2, 152.6, 142.9, 103.6, 94.4, 86.3, 84.2, 77.6, 53.8, 35.1; HRCI-MS *m/e*: ($[M + H]^+$) 273.0530 (100%), cacld. 273.0545.

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