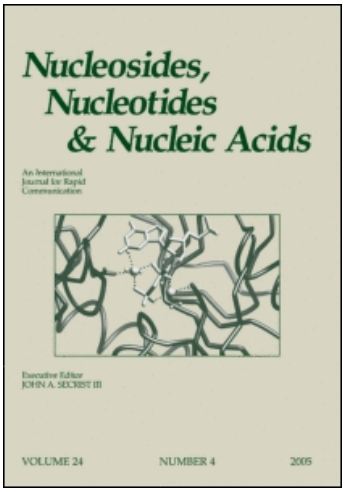

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Triaryl(Oxy)Phosphine Dibromide- A Convenient Reagent for the Preparation of S-Arylthioinosines and N^6, 5'-Disubstituted Adenosine Derivatives from Inosine

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To cite this Article Bridges, Alexander J.(1988) 'Triaryl(Oxy)Phosphine Dibromide- A Convenient Reagent for the Preparation of S-Arylthioinosines and N^6, 5'-Disubstituted Adenosine Derivatives from Inosine', Nucleosides, Nucleotides and Nucleic Acids, 7: 3, 375 — 383
To link to this Article: DOI: 10.1080/07328318808068717
URL: http://dx.doi.org/10.1080/07328318808068717

NUCLEOSIDES & NUCLEOTIDES, 7(3), 375-383 (1988)

TRIARYL(OXY)PHOSPHINE DIBROMIDE. A CONVENIENT REAGENT FOR THE PREPARATION OF S-ARYLTHIOINOSINES AND N^6,5'-DISUBSTITUTED ADENOSINE DERIVATIVES FROM INOSINE.

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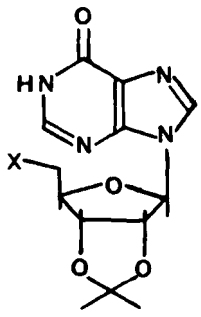
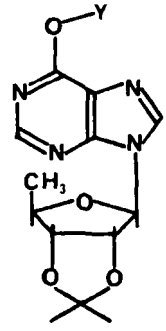
Abstract. Inosine isopropylidene 1 reacts with triphenylphosphine/phosphite dibromide and thiophenol to give 5'-bromo-S-phenylthioinosine 5 which is a versatile precursor for 5',N^6-disubstituted adenosine derivatives.

In connection with an investigation of adenosine agonists, we were interested in synthetic procedures which would allow us easy access to 5'-modified adenosine derivatives, where we could introduce a variety of substituents at the N^6-position. Two major synthetic approaches can be envisioned for this. In one approach the desired 5'-modification is carried out on a suitable ribose derivative which is then coupled to an appropriate adenine moiety[1]. In the second approach both of the required modifications are carried out on a nucleoside precursor. As this latter approach avoids the problematical step of making the nucleosidic bond, with its potential for producing a mixture of both regio and stereo-isomers, we decided to investigate such routes.





1 X = OH
2 X = H

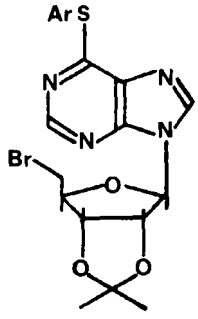
3 Y = Ph_3P^+
4 Y = $P(=O)(OEt)_2$

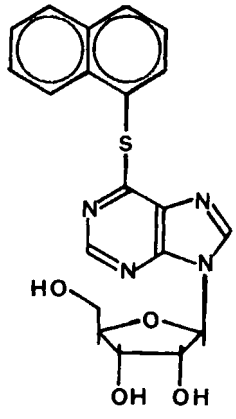
A very attractive precursor for the doubly modified adenosines appeared to be the commercially available inosine isopropylidene **1** [2]. Compound **1** is a nucleoside with only the two sites to be modified left unprotected. Initially, two approaches to the activation of both sites, conversion of **1** to the C6,5'-dichloride with $POCl_3$ and initial conversion to the 5'-deoxy-5'-iodo derivative with methyltriphenoxyphosphonium iodide[3], were examined. Although both routes led to some of the desired

intermediates, neither proved very satisfactory for our purposes, so we initiated a search for novel ways of doing this activation.

Whilst examining Mitsunobu reactions[4] between an inosine derivative **2** and primary amines, we had results which were suggestive that the desired C6-oxyphosphonium species **3** was being formed, but was decomposing via attack of the amine at phosphorus rather than by displacement at C6. The likelihood of this being the problem was reinforced by the behaviour of the corresponding, isolable, C6 phosphate ester **4**, which was cleaved back to the inosine **2** on treatment with primary amines. In order to find out whether a group, which was more nucleophilic and less phosphophilic than nitrogen, could be made to attack at C6, we substituted arylthiols for the amine. No S-arylthioinosine derivative was obtained when **4**, or the putative intermediate **3**, generated via the Mitsunobu conditions, were treated with thiophenol. However, when **1** was reacted with triphenylphosphine dibromide[5] in pyridine (but not dioxan) as the source of electrophilic phosphorus, the 5'-bromo derivative was formed rapidly, followed slowly by a second intermediate which was much more polar than **1**, and may be a C6-oxyphosphonium species. Once formation of this intermediate was complete, addition of thiophenol led to rapid formation of the desired 5'-bromo-S-phenylthioinosine **5**, in 57-71% isolated yields after chromatography. Similarly the corresponding S-naphthylthioinosine **6** was obtained in 65% yield. Inosine triacetate formed the corresponding S-naphthylthioinosine, but this could not be separated from the Ph_3PO byproduct until the acetates were deprotected giving S-naphth-1-ylthioinosine **7** in 54% yield over 2 steps. It was also found that triphenylphosphite dibromide[6] could be used in this reaction without apparent detriment. However the reaction did not give identifiable products when guanosine-2',3',5'-tri-O-acetate or inosine-5'-uronic acid isopropylidene were used as substrates.

For our purposes, the most interesting result was the easy preparation of **5**, because the product is a 5'-bromonucleoside with the C6-oxo group replaced by a potential leaving group, which is clearly a potential intermediate for 5',N^6-disubstituted adenosine synthesis. Oxidation of the sulfur atom of **5** with two equivalents of mCPBA went smoothly to give the bromosulfone **8** in 90-96% yield. The C6-sulfone proved to be a good leaving group, being cleanly displaced by cyclopentylamine in chloroform

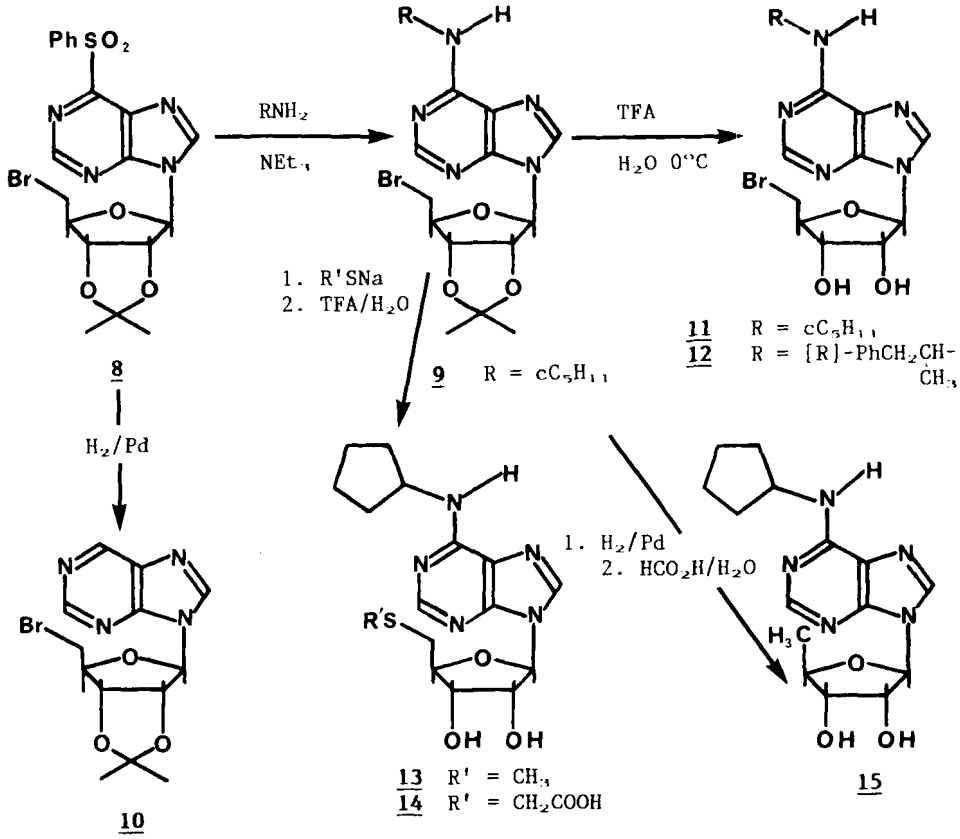




5 Ar = Ph
6 Ar = 1-Naphthyl

7

at 25°C in 0.5-12h to form a protected disubstituted adenosine **9** in 82-89% isolated yields. In fact, when **8** was subjected to hydrogenolysis over Pd/C for 4 hours to remove the bromine, the desulfonylated bromide **10** was obtained instead in 45% purified yield. Bromide **10** was also produced when sulfide **5** was subjected to hydrogenolysis, but in this case a lower yield (24%) and 14% of unreacted starting material were obtained after 40h and two extra additions of catalyst. This demonstrated the greater reactivity of the C6 position, and is suggestive that the catalyst was poisoned by the sulfur byproducts before the halogen could be subsequently removed. Adenosine **9** proved to be quite a versatile intermediate. Simple acid hydrolysis gave N^6-cyclopentyl-5'-bromo-5'-deoxyadenosine **11** in 45% yield. Similarly **8** was converted into 5'-bromo-5'-deoxy-N^6-([R]-1-methyl-2-phenylethyl) adenosine **12** in 46% yield. Reaction of **9** with methiolate, or the dianion of thioglycolic acid, followed by deprotection gave the adenosine 5'-thioethers **13**[7] and **14** in 66% and 30% yields respectively. Catalytic hydrogenolysis of **9** with Pd on C followed by deprotection with aqueous formic acid at 50°C gave N^6-cyclopentyl-5'-deoxy adenosine **15**[7] in 19% yield.



Scheme 1. Synthesis of 5'-Modified Adenosines from Bromosulfone 8.

Throughout this work no N3-5' cyclonucleosides were isolated and we kept to nonpolar solvents as much as possible to suppress this tendency. The hydrogenolyses of **5** and **8** show that these compounds are quite stable in methanol, 14% of **5** being recovered unchanged after 40h at 25°C. To investigate this further, NMR studies of the stability of **8**, **9** and **10** were carried out in DMSO at 25°C[8] . The electron deficient sulfonyl purine **8** was the most stable of the three, showing less than 5% loss of starting material in 48h. The parent purine **10** appeared to decompose to three different products with a halflife of 7-8 days, whereas the more electron rich adenosine **9** decomposed to a single major product, presumably the corresponding cyclonucleoside, with a halflife of slightly over 1h. From this it was concluded that these systems have less tendency than might be expected to form cyclonucleosides, and that, with caution, this problem can be avoided in most reactions.

In summary this paper describes a new reagent for the activation of the C6-oxo and 5'-hydroxy groups of inosine derivatives. This gives ready access to S-arylthio inosines, which can be converted on to doubly modified adenosines in a few straightforward steps in reasonable overall yields.

Experimental

6-(1-Naphthalenylthio)-9-β-D-ribofuranosyl-9H-purine 7.
Inosine-2',3',5'-tri-O-acetate (0.39g, 1.0 mmol) and triphenylphosphine dibromide, formed in situ from triphenylphosphine (0.39g, 1.5 mmol) and bromine (0.24g, 1.5 mmol), were stirred in pyridine (5 mL) under N_2 at 25°C. After 1h 1-naphthylthiol (0.32g, 1.5 mmol) was added, and after a further 20 min the reaction mixture was poured onto dilute HCl (0.5M, 100 mL) and extracted with $CHCl_3$ (3X20 mL). The combined extracts were washed with dilute HCl (0.5M, 50 mL), water (25 mL), dilute NaOH soln. (0.2M, 25 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residual gum was unsuccessfully flash and thin layer chromatographed. The residual gum was stirred in MeOH (10 mL) and concentrated aqueous ammonia (2 mL) under N_2 at 25°C for 6h. The volatiles were removed under reduced pressure. Water (25 mL) was added and the residual oil was extracted with EtOAc (2X25 mL). The organic phase was washed with water (2X25 mL), saturated brine (25 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residual gum was recrystallised from $CHCl_3$/MeOH to give the **thioinosine 7** (0.22g, 54%) as white crystals mp 197.5-200°C. $C_{20}H_{18}N_4O_4S$ requires: C, 58.54; H, 4.39; N, 13.66; S, 7.80%. Found: C, 58.44: H, 4.54; N, 13.51; S, 7.99%. IR (KBr) 3520, 1572, 1564, 1440, 1414, 1335, 1205, 1166, 1124, 1084, 1070, 1062, 1054, 936, 798, 769 cm^{-1}. NMR (DMSO) 8.81, 8.40 (1H, 1H, 2s), 8.16-7.94 (4H, m), 7.65-7.51 (3H, m), 6.01 (1H, d, J = 5.5 Hz), 5.55 (1H, d, J = 5.9 Hz), 5.25 (1H, d, J = 5.0 Hz), 5.12 (1H, t, J = 5.5 Hz), 4.62 (1H, q, J ◻ 5.5 Hz), 4.19 (1H, approx q, J = 4.5 Hz), 3.98 (1H, approx q, J ◻ 4 Hz), 3.50-3.80 (2H, ABq of d of ds). CMR (DMSO) δ1.25, 70.29, 85.76, 87.91, 123.95, 125.31, 126.07, 126.57, 127.48, 128.77, 130.73, 131.23, 133.92, 134.54, 136.16, 143.88, 148.67, 151.66, 159.30. Mass spectrum. M^+ 410 (15), 160 (100).

9-[5-Bromo-5-deoxy-2,3-di-O-(1-methylethylidene)-β-D-ribofuranosyl]-6-(1-naphthalenylthio)-9H-purine 6.
Inosine-2',3'-di-O-isopropylidene (0.31g, 1 mmol) and triphenylphosphine dibromide (1.09g, 2.5 mmol) were stirred in pyridine (5 mL) under N_2 at 25°C for 1h. 1-Naphthylthiol (0.24g, 1.5mmol) was added, and after 20 min the reaction mixture was poured onto dilute HCl (0.5M, 150 mL) and

extracted with $CHCl_3$ (3X20 mL). The organic phase was washed with water (25 mL), dilute NaOH soln. (0.2M, 25 mL), water (25 mL), saturated brine (25 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residual oil was purified by preparative tlc on silica eluting with 3% MeOH in $CHCl_3$ to give the **thioether 6** (0.41g, 65%) as a pale yellow gummy monochloroform adduct. Analytical sample dried in vacuo. $C_{23}H_{21}BrN_4O_3S$ requires: C, 53.80; H, 4.09; N, 10.92; Br, 15.59; S, 6.24%. Found: C, 53.41; H, 4.08; N, 10.76; Br, 14.43; S 5.69%. IR (KBr) 1564, 1384, 1333, 1205, 1090, 800, 773 cm^{-1}. NMR ($CDCl_3$) 8.43 (1H, s), 8.26 (1H, d of ds, J = 7.3, 1.8 Hz), 8.17 (1H, s), 7.90-8.05 (3H, m), 7.60-7.25(3H, m), 6.17 (1H, d, J = 2.3 Hz), 5.45 (1H, d of ds, J = 2.3, 6.3 Hz), 5.11 (1H, d of ds, J = 6.3, 3.0 Hz), 4.51 (1H, d of ds of ds, J = 3.0, 7.4, 5.2 Hz), 3.60, 3.44 (2H, ABq of ds, J_{AB} = 10.5 Hz, J_d = 7.4, 5.2 Hz), 1.61, 1.38 (3H, 3H, 2s). Mass spectrum. (FAB) 515 (28, $^{81}BrMH^+$), 514 (100, $^{81}BrM^+$), 513 (60, $^{81}BrM\text{-}H^+$, $^{79}BrMH^+$), 512 (97, $^{79}MH^+$), 511 (34, $^{79}BrM\text{-}H^+$).

9-[5-Bromo-5-deoxy-2,3-di-O-(1-methylethylidene)-β-D-ribofuranosyl]-6-(phenylthio)-9H-purine 5.

Bromine (8.0g, 50 mmol) was added dropwise over 5 min to a solution of triphenylphosphite (15.5g, 50 mmol) in pyridine (100 mL) stirred under N_2 on a 25°C bath. Inosine-2',3'-di-O-isopropylidene (6.16g, 20 mmol) in pyridine (100 mL) was added dropwise over 15 min. After 5 min thiophenol (3.3g, 30 mmol) was added over 10 min. The mixture was concentrated under reduced pressure at 40°C. The residue was dissolved in $CHCl_3$ (200 mL) and was washed with water (200 mL), dilute HCl (1 M, 300 mL) and saturated brine (100 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residual oil was subjected to flash chromatography on silica (225 g), eluting with 3:1 then 2:1 hexane/EtOAc (2L, 1L). Removal of the solvent under reduced pressure at 45°C gave the **5'-bromothioinosine 5** (6.59g, 71%) as a white solid foam. $C_{19}H_{19}N_4BrO3S$ requires: C, 49.24; H, 4.10; N, 12.10; Br, 17.28; S, 6.91%. Found: C, 49.30; H, 3.96; N, 11.74; Br, 16.44; S, 6.78%. IR (KBr) 1565, 1483, 1445, 1438, 1384, 1375, 1371, 1205, 1159, 1142, 1088, 935, 863, 840, 748, 690 cm^{-1}. NMR ($CDCl_3$) 8.62, 8.16 (1H, 1H, 2s), 7.66 (2H, d of ds, J ◘ 6, 3 Hz), 7.53-7.45 (3H, m), 6.18 (1H, d, J = 2.5 Hz), 5.47 (1H, d of ds, J = 2.5, 6.4 Hz), 5.15 (1H, d, J = 6.4, 3.1 Hz), 4.54 (1H, d of d of ds, J = 3.1, 7.5 5.5 Hz), 3.61, 3.46 (2H, ABq of ds, J_{AB} ◘ 10.5 Hz, J_d = 7.5, 5.5 Hz), 1.63, 1.40 (3H, 3H, 2s). CMR ($CDCl_3$) 25.32, 27.07, 31.70, 83.37, 84.17, 86.48, 91.24, 114.79, 126.94, 129.35, 129.71, 131.44, 135.67, 142.48, 147.93, 152.40, 161.59. Mass spectrum. 464 (18, $^{81}BrM^+$), 462 (18, $^{79}BrM^+$), 227 (100).

9-[5-Bromo-5-deoxy-2,3-di-O-(1-methylethylidene)-β-D-ribofuranosyl)-6-(phenylsulfonyl)-9H-purine 8.

m-Chloroperoxybenzoic acid (85%, 6.0g, 30 mmol) and $NaHCO_3$ (2.5g, 30 mmol) were added in one portion to a solution of 5'-bromothioinosine 5 (5.28g, 11.4 mmol) in CH_2Cl_2 (100 mL) stirred under N_2 at 25°C. After 6h the reaction mixture was vacuum filtered, and the residue rinsed with CH_2Cl_2. The combined filtrates were washed with NaOH solution (0.25 M, 100 mL), water (100 mL), saturated brine (100 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure at 40°C to give **5'-bromoinosine 8** (5.34g, 95%) as a pale yellow solid foam mp 73-9°C. $C_{19}H_{19}N_4Br O_5S$ requires: C, 46.06; H, 3.84; N, 11.31; Br, 16.16; S, 6.46%. Found C, 46.16; H, 3.76; N, 11.80; Br, 14.30; S, 5.54%. IR (KBr) 1564, 1334, 1209, 1160, 1084, 729, 583, 567 cm^{-1}. NMR ($CDCl_3$) 9.10, 8.57 (1H, 1H, 2s), 8.28 (2H, d of d, J = 6.5, 1.5 Hz), 7.8-7.53 (3H, m), 6.26 (1H, d, J = 2.7 Hz), 5.35 (1H, d of d, J = 2.7, 6.4 Hz), 5.07 (1H, d of d, J = 6.4, 3.1 Hz), 4.56 (1H, m), 3.63, 3.52 (1H, 1H, ABq of ds, J_{AB} = 11 Hz, J_d =

6.2, 5.0 Hz), 1.63, 1.39 (3H, 3H, 2s). CMR ($CDCl_3$) 25.22, 27.08, 31.85, 82.98, 84.18, 85.70, 91.06, 115.28, 129.19, 129.57, 130.53, 134.45, 138.30, 146.78, 151.93, 153.67. Mass spectrum 496 (0.3, $^{81}BrM^+$), 494 (0.3, $^{79}BrM^+$), 77 (100).

5'-Bromo-N^6-cyclopentyl-5'-deoxy-2,'3'-di-O-(1-methylethylidene)adenosine 9.

A solution of the 5'-bromosulfone **8** (1.97g, 4 mmol), cyclopentylamine (0.68g, 8 mmol) and triethylamine (0.81g, 8 mmol) in $CHCl_3$ (40 mL) was stirred under N_2 at 25°C for 14h. The reaction mixture was washed with dilute NaH_2PO_4 solution (0.4M, 50 mL), water (2X25 mL), saturated brine and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the desired **adenosine 9** containing 50 mol% $CHCl_3$ (1.78g, 89%) as a yellow solid foam. NMR ($CDCl_3$) 8.35, 7.84 (1H, 1H, 2s), 6.06 (1H, d, J ◻ 2.5 Hz), 5.87 (1H, br d, J ◻ 8 Hz), 5.48 (1H, d of d, J = 2.5, 6 Hz), 5.14 (1H, d of d, J ◻ 6, 3 Hz), 4.7-4.3 (2H, m), 3.62, 3.40 (1H, 1H, ABq of ds, J_{AB} = 10.5 Hz, J_d ◻ 6, 7 Hz), 2.3-1.9 (2H, m), 1.8-1.2 (12H, m plus s at 1.63, 1.41).

5'-Bromo-N6-cyclopentyl-5'-deoxyadenosine 11.

A solution of 5'-bromo-N^6-cyclopentyl-5'-deoxy-2,'3'-di-O-(1-methylethylidene)adenosine **9** (1.64g, 3.4 mmol) in TFA (9mL) containing water (1mL) and EtOH (3mL) was stirred under N_2 at 0°C for 4h. The reaction mixture was poured onto cold Na_2CO_3 solution (1M, 50 mL, Gas evolution!) and extracted with $CHCl_3$ (2X50 mL). The organic phase was washed with saturated Na_2CO_3 solution (50 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica, eluting with 5% MeOH in $CHCl_3$. Removal of the solvent under reduced pressure gave the desired **5'-bromoadenosine 11** (0.68g, 45%) as an offwhite crystalline solid mp 65-81°C. $C_{15}H_{20}BrN_5O_3 \cdot H_2O.0.2CHCl_3$ requires: C, 41.45; H, 5.00; N, 15.91; Br, 18.18; Cl, 5.05%. Found: C, 41.59; H, 4.54; N, 15.88; Br, 18.06; Cl, 4.84%. IR (KBr) 1623, 1580, 1478, 1336, 1295, 1231, 1120, 1050, 796, 648 cm^{-1}. NMR (DMSO) 8.37, 8.23 (1H, 1H, 2s), 7.75 (1H, d, J = 7.7 Hz), 5.96 (1H, d, J = 5.7 Hz), 5.61 (1H, d, J ◻ 6.0 Hz), 5.49 (1H, d, J = 5.1 Hz), 4.79 (1H, q, J = 5.8 Hz), 4.7-4.4 (1H, br s), 4.23 (1H, approx q, J = 4.6 Hz), 4.12 (1H, approx q, J = 6 Hz), 3.84, 3.72 (1H, 1H, ABq of ds, J_{AB} = 10.5 Hz, J_d ◻ 5.6, 6.6 Hz), 2.05-1.85 (2H, m), 1.8-1.55 (6H, m). Mass spectrum 399 (0.7, $^{81}BrM^+$), 397 (0.6, $^{79}BrM^+$), 135 (100).

9-[5-Bromo-5-deoxy-2,3-di-O-(1-methylethylidene)- β -D-ribofuranosyl]-9H-purine 10.

A solution of the bromosulfone **8** (0.99g, 2 mmol) and triethylamine (0.3 mL) in MeOH (75 mL), containing 20% Pd on C (0.3g), was hydrogenated at 50 psi at 25°C until gas uptake ceased (3h 40min). The mixture was celite filtered, and the solvent was removed under reduced pressure. The residue was added to dilute Na_2CO_3 solution (100 mL), and was extracted with $CHCl_3$ (2X25 mL). The organic phase was washed with water (2X25 mL), saturated brine (25 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by preparative tlc on silica eluting once with 5% MeOH in $CHCl_3$ to give the **glycosylated purine 10** (0.32g, 45%) as a light yellow glass mp 114-9°C. IR (KBr) 1599, 1570, 1499, 1202, 1102, 1093, 1065, 872, 795, 642 cm^{-1}. NMR $CDCl_3$) 9.20 (1H, s), 9.04 (1H, s), 8.29 (1H, s), 6.24 (1H, d, J = 2.4 Hz), 5.49 (1H, d of d, J = 2.4, 6.2 Hz), 5.17 (1H, d of d, J = 6.2, 3.0 Hz), 4.50-4.60 (1H, m), 3.66, 3.51 (1H, 1H, ABq of ds, J_{AB} = 10.6 Hz, J_d = 7.1, 5.2 Hz), 1.66, 1.42 (3H, 3H, 2s). CMR ($CDCl_3$) 25.3, 27.1, 31.7, 83.3, 84.1, 86.1, 90.9, 114.9, 134.7, 144.5, 149.2, 150.4, 152.7. Mass Spectrum (FAB) 357 (100, $^{81}BrMH+$), 355 (100, $^{79}BrMH+$).

(R)-5'-Bromo-5'-deoxy-N⁶-(1-methyl-2-phenylethyl)adenosine 12.
A solution of [R]-1-phenylprop-2-ylamine (0.54g, 4 mmol), the bromosulfone 8 (0.99g, 2 mmol) and triethylamine (0.40g, 4 mmol) in CH_2Cl_2 (15 mL) was stirred under N_2 at 25°C for 40h. The reaction mixture was poured onto NaH_2PO_4 solution (0.2 M, 50 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2X25 mL). The organic extracts were washed with water (25 mL), saturated brine (25 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was stirred in 10% aqueous TFA (5 mL) under N_2 at 0°C for 2h. The reaction mixture was poured onto EtOAc (50 mL), and was washed with NaOH solution (1N, 50 mL), dilute Na_2CO_3 solution (50 mL), saturated brine (25 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by preparative tlc on silica eluting with 10% in $CHCl_3$ to give the **5'-bromoadenosine 12** (0.42g, 46%) as a pale yellow foam mp 76-87°C. $C_{19}H_{22}N_5BrO_3.0.33H_2O$ requires: C, 50.22; H, 4.99; N, 15.42%. Found: C, 50.02; H, 4.97; N, 15.16%. IR (KBr) 1619, 1580, 1476, 1335, 1295, 1233, 1126, 1052, 747, 702 cm^{-1}. NMR ($CDCl_3$) 8.37, 8.22 (1H, 1H, 2s), 7.73 (1H, d, J = 8 Hz), 7.3-7.1 (5H, m), 5.94 (1H, d, J = 5.6 Hz), 5.61 (1H, brs), 5.50 (1H, brs), 4.79 (1H, brs), 4.63 (1H, brs), 4.23 (1H, brs), 1H (1H, approx q, J = 4 Hz), 3.84, 3.72 (1H, 1H, ABq of ds, J_{AB} = 10.7 Hz, J_d = 5.2, 6.7 Hz), 3.02 2.76 (1H, 1H, ABq of ds, J_{AB} = 13.4 Hz, J_d = 7.4, 6.5 Hz), 1.19 (3H, d, J = 6.4 Hz). Mass Spectrum (FAB) 451 (16, $^{81}Br^{13}CMH^+$) 450 (50, $^{81}BrMH^+$) 449 (16, $^{81}BrM^+$, $^{79}Br^{13}CMH^+$) 448 (54, $^{79}BrMH^+$) 447 (2, $^{79}BrM^+$) 254 (100).

N⁶-Cyclopentyl-5'-deoxy-5'-(methylthio)adenosine 13.
A solution of sodium methiolate (0.35g, 5 mmol) and 5'-bromo-N_6-cyclopentyl-5'-deoxy-2,'3'-di-O-(1-methylethylidene)adenosine 9 (1.78g, 3.6 mmol) in DMSO (10 mL) was stirred under N_2 at 25°C for 90 min. The reaction was poured onto NaOH solution (0.2M, 50 mL) and was extracted with EtOAc (3X25 mL). The extracts were washed with water (2X25 mL), saturated brine (25 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was stirred in aqueous TFA (10 mL, 1:9) and EtOH (3 ml), stirred under N_2 at 0°C for 2h. The mixture was poured onto Na_2CO_3 solution (1M, 100 mL) and extracted with EtOAc (3X25 mL). The organic phase was washed with water (2X25 mL), saturated brine (25 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residual gum was purified by preparative tlc eluting once with 10% MeOH in $CHCl_3$ to give, after removal of the solvent under reduced pressure the **5'-methylthioadenosine 13**[7] (0.87g, 66%) as a tan solid foam mp 50-60°C. $C_{16}H_{23}N_5O_3S.0.2CHCl_3$ requires: C, 49.97; H, 5.96; N, 17.99%. Found: C, 49.82; H, 5.95; N, 17.99%. IR (KBr) 1621, 1582, 1478, 1051 cm^{-1}. NMR (DMSO) 8.37, 8.23 (1H, 1H, 2s), 7.72 (1H, d, J = 7.9 Hz), 5.92 (1H, d, J = 5.8 Hz), 5.52 (1H, d, J = 6.2 Hz), 5.35 (1H, d, J = 5 Hz), 4.76 (1H, q, J = 6 Hz), 4.65-4.4 (1H, m), 4.17 (1H, approx q, J = 4.5 Hz), 4.04 (1H, approx q, J = 3 Hz), 2.88, 2.80 (1H, 1H, ABq of ds, J_{AB} = 14 Hz, Jd = 5.9, 7 Hz), 2.06 (3H, s), 2.05-1.9 (2H, m), 1.85-1.45 (6H, m). CMR (DMSO) 15.66, 23.55, 32.22, 36.12, 51.50, 72.58 (2' and 3'), 83.65, 87.30, 119.30, 139.28, 148.40, 152.37, 154.12. Mass spectrum 365 (5, M^+), 232 (100).

N⁶-Cyclopentyl-5'-deoxy-5'-((S,2-hydroxy-2-oxoethyl)thio))cyclopentyl adenosine 14
Thioglycollic acid (0.37g, 4 mmol) in DMSO (5 mL) was added dropwise to a slurry of hexane-washed NaH (60% oil suspension, 0.32g, 8 mmol) in DMSO 10 mL) stirred under N_2 at 25°C. After 10 min 5'-bromo-N^6-cyclopentyl-5'-deoxy-2,'3'-di-O-(1-methylethylidene)adenosine 9 (1.50g, 3 mmol) was added and the mixture was stirred for a further 15 min. The reaction

mixture was poured onto NaOH solution (0.2M, 50mL) and washed with $CHCl_3$ (3X25 mL). The aqueous layer was acidified to pH2 and extracted with EtOAc (3X25 mL). The extracts were washed with water (25 mL), saturated brine (25 mL), dried ($MgSO_4$) and the solvent was removed under reduced pressure and the residue was stirred in aqueous TFA (10 mL, 1:9) and EtOH (3 mL) for 100 min under N_2 at 0°C. The reaction mixture was poured onto cold, vigourously stirred, Na_2CO_3 solution (1M, 50 mL). The pH of the aqueous layer was adjusted to 2 with TFA, and the precipitate was collected by vacuum filtration and recrystallised from EtOH to give the desired **adenosine 14** (0.37g, 30%) as an offwhite crystalline solid mp 191-3°C. $C_{17}H_{23}N_5O_5S.2H_2O$ requires: C, 45.84; H, 6.07; N, 15.73; S, 7.19%. Found: C, 45.80; H, 5.52; N, 15.67; S, 7.33%. IR (KBr) 3300, 1708, 1634, 1588, 1485, 1320, 1129, 1096, 1050 cm^{-1}. NMR (DMSO) 12.5 (1H, s), 8.34, 8.22 (1H, 1H, 2s), 7.71 (1H, d, J = 7.7 Hz), 5.90 (1H, d, J = 5.7 Hz), 5.51 (1H, d, J = 5.9 Hz), 5.34 (1H, d, J = 4.8 Hz), 4.73 (1H, approx q, J = 5.5 Hz), 4.7-4.4 (1H, m), 4.15 (1H, approx q, J = 4.4 Hz), 4.04 (1H, approx q, J = 5.3 Hz), 3.28 (2H, s), 3.00, 2.92 (1H, 1H, ABq of ds, J_{AB} ◻ 14 Hz, J_d = 6.0, 7.5 Hz), 2.05-1.85 (2H, m), 1.8-1.5 (6H, m). Mass Spectrum (FAB) 410 (100, MH^+) 409 (6, M^+).

N^6-Cyclopentyl-5'-deoxyadenosine 15.
5'-Bromo-N^6-cyclopentyl-5'-deoxy-2,3'-di-O-(1-methylethylidene)adenosine 9 (0.77g, 1.7 mmol) was hydrogenated in MeOH (100 mL) containing triethylamine (0.3 mL) and Pd/C (20%, 0.2g) at 50 psi at 25°C for 26h. The catalyst was removed by filtration, the solvent by evaporation under reduced pressure, and the residual gum was added to water (25 mL) and extracted with EtOAc (2X25 mL). The extracts were washed with water (25 mL), saturated brine (25 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was heated in 50% aqueous formic acid, stirring under N_2 at 50°C for 4h. The volatiles were removed under reduced pressure, and the residual gum was purified by two preparative tlcs, eluting with 10% MeOH in $CHCl_3$ and then 5% MeOH in EtOAc to give the **5'-deoxyadenosine 15**[7] (0.10g, 19%) as a light yellow gum. IR (KBr) 3500, 1620, 1583, 1477, 1094, 1055 cm^{-1}. NMR (DMSO) 8.34, 8.23 (1H, 1H, 2s), 7.72 (1H, d, J = 7.7 Hz), 5.87 (1H, d, J = 4.9 Hz), 5.45 (1H, d, J = 5.7 Hz), 5.18 (1H, d, J ◻ 5.4 Hz), 4.67 (1H, approx q, J = 5 Hz), 4.7-4.45 (1H, brs), 4.10-3.95 (2H, m), 2.05-1.9 (2H, m), 1.8-1.45 (6H, m), 1.31 (3H, d, J = 6.1 Hz). CMR (DMSO) 18.95, 23.28, 32.17, 52.04, 72.97, 74.46, 79.46, 87.83, 139.14, 139.16, 152.27, 154.23. Mass Spectrum 319 (14, M^+), 135 (100).

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8. We thank a referee for suggesting this experiment.

Received September 15, 1987