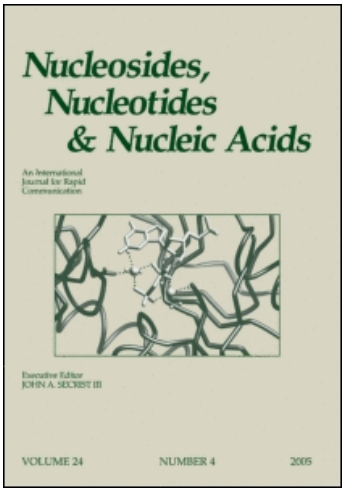

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FACILE SYNTHESIS OF 8,2'-*S*-CYCLOPURINE NUCLEOSIDE

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ABSTRACT: This paper describes the synthesis of 8,2'-anhydro-8-mercapto-9-(β-D-arabinofuranosyl)purine (8,2'-*S*-cyclopurinenucleoside, **1**) *via* the shorter route from 3',5'-di-*O*-acectyl-8,2'-*S*-cycloadenosine (**6**) and by direct reductive deamination with *n*-pentyl nitrite in tetrahydrofuran (THF) and deacetylation. The preparation of 8,2'-*S*-cycloadenosine (**2**) was achieved in good yield by the cyclization of the protected 8-mercaptoadenosine with triphenylphosphine and diethyl azodicarboxylate (DEAD) in THF at room temperature, under Mitsunobu reaction conditions.

9-β-D-Ribofuranosylpurine (nebularine, Pu),[1] a naturally occurring nucleoside antibiotic, is of special interest as the simplest member of the purine nucleosides and because of its biological activity against viruses and bacteria.[2] Based on these facts, it seemed possible that a purine cyclonucleoside with a fixed high anti conformation, due to the anhydro linkage between the base and the sugar moiety, might also have biological activity.

In a previous paper,[3] we reported the synthesis of 8,2'-*S*-cyclopurinenucleoside (**1**) from 8,2'-*S*-cycloadenosine (**2**), but it involved a rather lengthy six step pathway and seemed unsuitable for practical use. In this study, we report the new synthetic method of **2** and the facile synthesis of **1**. Compound **2** is usually prepared by reaction of 2'-*O*-aryl-sulfonyl-8-bromoadenosine with thiourea in 1-propanol or sodium hydrosulfide in *N,N*-dimethylformamide (DMF).[4] Furthermore, synthetic routes of compound **2** by the cyclocarbonate method were reported.[5] Recently, Chern *et al.* reported that 8,2'-*S*-cyclo-

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guanosine was synthesized by the cyclization of 3',5'-*O*-(tetraisopropyldisiloxane-1,3-diyl)-8-mercaptoguanosine with triphenylphosphine (PPh_3) and diethyl azodicarboxylate (DEAD) in DMF, under Mitsunobu reaction conditions, in a 71% yield.[6] According to the method, the synthesis of **2** was achieved by treatment of 3',5'-*O*-(tetraisopropyldisiloxane-1,3-diyl)-8-mercaptoadenosine (**4**) with PPh_3 and DEAD in THF at room temperature for 48 h, by the proper choice of a solvent among DMF, dioxane, toluene and ether, and reaction conditions, and thus compound **5** was obtained in a 75% yield as shown in TABLE 1. Subsequent treatment of **5** with tetrabutylammonium fluoride (TBAF) afforded 8,2'-*S*- cycloadenosine (**2**) in a 91% yield.

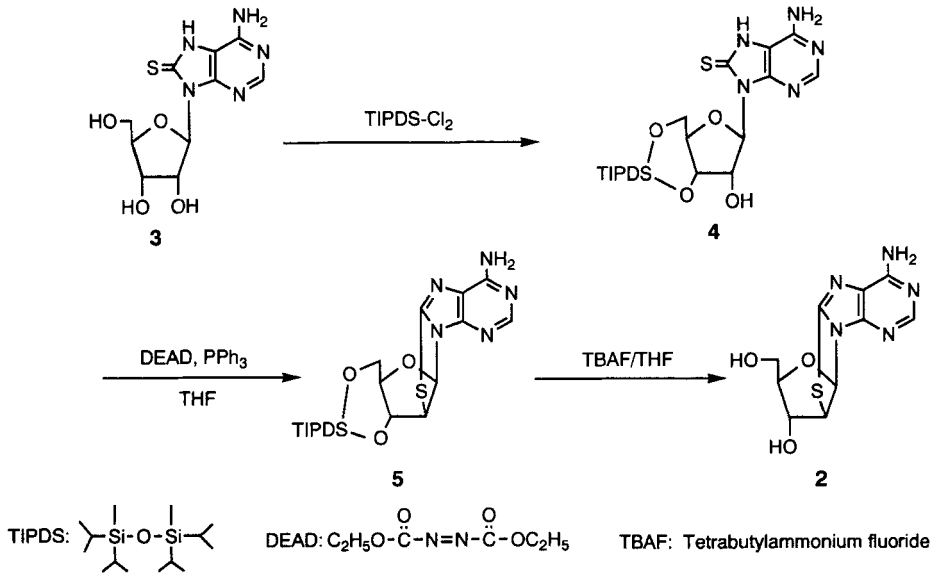
Compound **1** was synthesized by direct reductive deamination of 3',5'-di-*O*-acetyl-8,2'-*S*-cycloadenosine (**6**),[7] obtained by a short synthesis, with *n*-pentyl nitrite in THF at 50 °C for two days under a nitrogen atmosphere using Nairs' method,[8] followed by deacetylation with ammonia in ethanol at room temperature for two days, in a 64% yield from **6**.

In conclusion, the successful preparation of 8,2'-*S*-cyclopurinenucleoside by a shorter route has been performed.

EXPERIMENTAL

The UV spectra were recorded on a Hitachi 340 spectrometer. The mass spectra were recorded on a JEOL JMX-DX300 spectrometer. The ^1H NMR spectra were recorded on a Bruker AMX-400 spectrometer. The TLC was performed on silica gel plates (Merck 60 HF_{245}). The column chromatography was performed using silica gel (Merck 60H). Melting points were determined with a Yazawa micromelting point apparatus, type BY-1, and are uncorrected.

3',5'-*O*-(Tetraisopropyldisiloxane-1,3-diyl)-8-mercaptoadenosine (4). 8-Mercaptoadenosine (**3**)[9] (299 mg, 1 mmole) was dried by evaporation with pyridine solution and was dissolved in dry pyridine (10 ml), and then 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (0.32 ml, 1 mmole) was added dropwise at 0 °C. The mixture was stirred at room temperature for 1 h and was evaporated. The residue was poured into a mixture of ice water and AcOEt (1 : 1). The organic layer was washed successively with 1 M HCl, water, saturated $NaHCO_3$, and saturated NaCl, and then was dried with Na_2SO_4. The solvent was removed by evaporation. The residue was purified by silica gel column chromatography using MeOH in CH_2Cl_2 (0 - 2%). The yield of **4** was 357 mg (66%) as colorless, fine needles, mp 131-134 °C (from 50% EtOH); UV: (50% EtOH): λmax 228 nm, 302, 308; (H^+): λmax 226 nm, 302, 308; (OH^-): λmax 298 nm; ^1H NMR (DMSO-d_6): δ 12.56 (br s, 1H, NH), 7.96 (s, 1H, H-2), 6.99 (br s, 2H, NH_2), 6.25 (d, 1H, H-



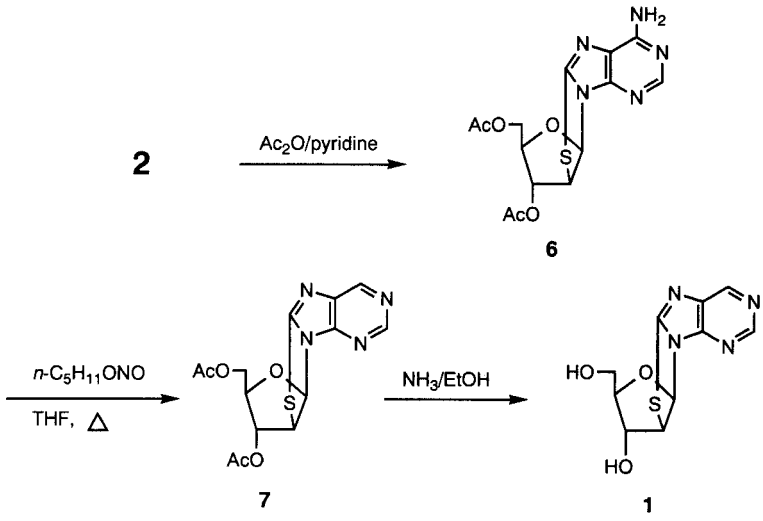
SCHEME 1

TABLE 1. The Cyclization of **4** under Mitsunobu Reaction Conditions

Molar ratio of **4** : PPh_3 : DEAD	Solv.	Conditions Temp.	Time	Yield **5** (%)
1 : 1 : 1	DMF	rt	5 min	0
1 : 1 : 1	dioxane	rt	5 min	0
1 : 1 : 1	toluene	rt	5 min	0
1 : 1 : 1	ether	rt	5 min	0
1 : 1 : 1	THF	rt	5 min	18
1 : 1 : 1	THF	rt	48 h	75

1', J = 7.8 Hz), 5.26-5.21 (m, 2H, 2'-OH, H-3'), 4.71 (d, 1H, H-2'), 4.07-3.80 (m, 3H, H-4', 5'a, 5'b), 1.11-0.94 (m, 28H, isopropyl x 4); MS: (FD) *m/z* 542 (M^+). *Anal.* Calcd. for $C_{22}H_{39}N_5O_5SSi_2 \cdot 1/2CH_3OH$: C, 48.90; H, 7.49; N, 12.39. Found: C, 48.52; H, 7.30; N, 12.00.

8,2'-Anhydro-3',5'-*O*-(tetraisopropyldisiloxane-1,3-diyl)-8-mercapto-adenosine (5). Compound **4** (271 mg, 0.5 mmole) and PPh_3 (135 mg, 0.5 mmole) were dissolved in dry THF (5.1 ml). After DEAD (0.078 ml, 0.5 mmole) was added to the



SCHEME 2

solution at -10 - -20 °C, the mixture was stirred at room temperature for 48 h. The solvent was evaporated, and the residue was purified by silica gel column chromatography using MeOH in CH_2Cl_2 (0 - 5%), TLC (CH_2Cl_2 : MeOH = 19 : 1) Rf = 0.66. The yield was 197 mg (75%) as colorless, fine needles, mp 238-242 °C (from MeOH); UV: (50% EtOH): λmax 224 nm, 278; (H^+): λmax 277 nm; (OH^-): λmax 277 nm; ^{1}H NMR (DMSO-d_6): δ 8.05 (s, 1H, H-2), 7.14 (br s, 2H, NH_2), 6.47 (d, 1H, H-1', J = 7.0 Hz), 4.95 (t, 1H, H-2'), 4.53 (t, 1H, H-3'), 4.07 (q, 1H, H-4'), 3.76-3.66 (m, 2H, H-5'a, 5'b), 1.23-0.71 (m, 28H, isopropyl x 4); high resolution MS: *m/z* 523.20879 (M^+ for $C_{22}H_{37}N_5O_4SSi_2$; Calcd. 523.21039). *Anal.* Calcd. for $C_{22}H_{39}N_5O_4SSi_2$: C, 50.44; H, 7.12; N, 13.37. Found: C, 49.94; H, 7.01; N, 13.15.

8,2'-Anhydro-8-mercaptoadenosine (2).[4] Compound **5** (105 mg, 0.2 mmole) was dissolved in dry THF (7.2 ml) and was stirred with 1 M TBAF (0.2 ml) at room temperature for 1 h. The solvent was removed by evaporation and the residue was recrystallized from water. The yield of **2** was 51 mg (91%) as colorless needles, and it was identified by comparison to an authentic sample by mp, TLC Rf value, and UV and ^{1}H NMR spectra. mp 133-136 °C; UV: (pH 7): λmax 275.5 (ε 20300) nm; (pH 2): λmax 277 (ε 20100) nm; (pH 13): λmax 276 (ε 20300) nm; ^{1}H NMR (D_2O): δ 8.23 (s, 1H, H-2), 6.72 (d, 1H, H-1', J = 6.8 Hz), 5.03 (q, 1H, H-2'), 4.63 (t, 1H, H-3'), 4.33 (m, 1H, H-4'), 3.69 (q, 1H, H-5'a), 3.57 (q, 1H, H-5'b). *Anal.* Calcd. for $C_{10}H_{11}N_5O_3S$: C, 41.63; H, 3.82; N, 24.28. Found: C, 41.51; H, 4.07; N, 24.05.

8,2'-Anhydro-8-mercapto-9-(3',5'-di-*O*-acetyl-β-D-arabinofuranosyl)-purine (7). To a solution of 8,2'-anhydro-8-mercapto-9-(3',5'-di-*O*-acetyl-β-D-arabinofuranosyl)adenine (**6**)[7] (84 mg, 0.23 mmole) in dry THF was added dry *n*-pentyl nitrite (0.46 ml, 3.4 mmole), and the mixture was stirred at 50 °C for 45 h under a nitrogen atmosphere. An additional aliquot of *n*-pentyl nitrite (0.23 ml) was added, and the solution was stirred at 50 °C for another 48 h. The solvent was then removed by evaporation and the oily residue was purified by silica gel column chromatography using MeOH in CH_2Cl_2 (0 - 5%), TLC (CH_2Cl_2 : MeOH = 9 : 1) Rf = 0.67. The yield of **7** was 73 mg (90%) as colorless, fine needles, mp 192-196 °C (from EtOH); UV: (50% EtOH): λmax 250 nm, 284; (H^+): λmax 285.5 nm; (OH^-): λmax 285 nm; ^{1}H NMR (DMSO-d_6): δ 8.93 (s, 1H, H-2), 8.81 (s, 1H, H-6), 6.75 (d, 1H, H-1', J = 6.8 Hz), 5.26-5.21 (m, 2H, H-2', 3'), 4.56 (q, 1H, H-4'), 4.10 (d, 2H, H-5'a, 5'b), 2.12 (s, 3H, 3'-CH_3COO), 1.83 (s, 3H, 5'-CH_3COO). *Anal.* Calcd. for $C_{14}H_{14}N_4O_5S$: C, 47.99; H, 4.03; N, 15.99. Found: C, 47.86; H, 4.34; N, 15.50.

8,2'-Anhydro-8-mercapto-9-(β-D-arabinofuranosyl)purine (1).[3] Absolute EtOH (400 ml) was cooled to ice/salt bath temperature, and was saturated with NH_3 over a period of 0.5 h. Acetylated purinecyclonucleoside (**7**) (310 mg, 0.89 mmole) was then dissolved in a minimum amount of absolute EtOH and was added to the saturated solution. After standing for one day at room temperature, the mixture was resaturated with NH_3 and was allowed to react for one more day. The solvent was removed by evaporation and the residue was recrystallized from MeOH. The yield of **1** was 169 mg (72%) as colorless plates, mp 208 °C (lit.[3] 210-212 °C); UV: (H_2O): λmax 252 nm, 285.5; (H^+): λmax 230.5 nm, 295; (OH^-): λmax 252 nm, 286; MS: (FD): *m/z* 266 (M^+); ^{1}H NMR (D_2O): δ 8.80 (s, 1H, H-2), 8.78 (s, 1H, H-6), 6.83 (d, 1H, H-1', J = 6.8 Hz), 5.08 (q, 1H, H-2'), 4.67 (t, 1H, H-3'), 4.36 (q, 1H, H-4'), 3.70 (q, 1H, H-5'a), 3.58 (q, 1H, H-5'b). *Anal.* Calcd. for $C_{16}H_{10}N_4O_3S$: C, 45.10; H, 3.79; N, 21.10. Found: C, 45.01; H, 3.89; N, 20.85.

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