Nucleic Acid Related Compounds. 105. Synthesis of 2′,3′-Didehydro-2′,3′-dideoxynucleosides from Ribonucleoside Cyclic 2′,3′-(Sulfates or Phosphates) or 2′,3′-Dimesylates via Reductive Elimination with Sodium Naphthalenide[1]

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Treatment of purine ribonucleosides with thionyl fluoride resulted in formation of cyclic 2′,3′-sulfite esters. Acetylation of the 5′-hydroxy group and Sharpless oxidation ($NaIO_4/RuCl_3$) gave the cyclic 2′,3′-sulfate ester derivatives. Treatment of 5′-*O*-silyl-protected ribonucleosides with thionyl chloride followed by oxidation gave an alternative route to the cyclic 2′,3′-sulfates. Reductive elimination with sodium naphthalenide (THF/−50 °C) gave the 2′,3′-unsaturated nucleosides. Parallel treatment of adenosine cyclic 2′,3′-phosphate gave the 2′,3′-olefin. The adenine, hypoxanthine, and 2-amino-6-methoxypurine 2′,3′-didehydro-2′,3′-dideoxynucleosides were prepared efficiently (40−60% overall yields of crystalline, analytically pure products; 3−5 steps, some combined into one-flask procedures) by treatment of 5′-*O*-protected 2′,3′-di-*O*-mesylribonucleosides with sodium naphthalenide. Reactions were performed at or below ambient temperature with readily available reagents and standard laboratory conditions.

Introduction

Various 2′,3′-dideoxy- and 2′,3′-didehydro-2′,3′-dideoxynucleosides inhibit replication of human immunodeficiency viruses (HIV), and some have become therapeutic agents for the treatment of AIDS.[2] Their inhibition of replication of hepatitis B viruses (HBV) also has been demonstrated.[3] Chemistry and activity associated with dideoxynucleosides have been reviewed.[4−6] Methods for the synthesis of 2′,3′-didehydro-2′,3′-dideoxynucleosides from ribonucleosides include Corey−Winter treatment of cyclic 2′,3′-thionocarbonates,[7,8] Barton−McCombie fragmentation of vicinal bis(xanthates),[8] and reductive elimination (zinc−copper couple) of 2′,3′-bromohydrin acetates.[6] Stereoselective coupling to give dideoxynucleosides from 2-phenylseleno sugars has been employed,[9] and coupling syntheses of L enantiomers are of recent interest because some have potent activity against HIV and HBV and lower toxicity to host cells.[10]

We considered that readily available[11] 2′,3′-*O*-sulfinylnucleosides could serve as starting materials for 2′,3′-unsaturated nucleosides. Our preliminary studies indicated that 2′,3′-sulfite esters failed to undergo reductive elimination to give 2′,3′-didehydro-2′,3′-dideoxynucleosides with several reagent systems. The more reactive cyclic 2′,3′-sulfates,[12] potentially available by Sharpless oxidation[13] of the sulfites, were then examined. During the course of this work, sugar cyclic sulfates[14] and 2′,3′-di-*O*-mesylnucleosides[5b−d] were reported to undergo reductive elimination with telluride dianions[5b,14] and lithium areneselenoates,[5c] and hydrogenolysis with palladium catalysts.[5d] Treatment of sugar cyclic sulfates with potassium selenocyanate followed by sodium borohydride also gave olefins.[15] We now report syntheses of purine

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(1) For Part 104, see: Maeba, I.; Morishita, N.; Francom, P.; Robins, M. J. *J. Org. Chem.*, in press.

(2) (a) Mitsuya, H.; Broder, S. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 1911. (b) Balzarini, J.; Kang, G.-J.; Dalal, M.; Herdewijn, P.; De Clercq, E.; Broder, S.; Johns, D. G. *Mol. Pharmacol.* **1987**, *32*, 162.

(3) (a) Suzuki, S.; Lee, B.; Luo, W.; Tovell, D.; Robins, M. J.; Tyrrell, D. L. J. *Biochem. Biophys. Res. Commun.* **1988**, *156*, 1144. (b) Lee, B.; Luo, W.; Suzuki, A.; Robins, M. J.; Tyrrell, D. L. J. *Antimicrob. Agents Chemother.* **1989**, *33*, 336. (c) Howe, A. Y. M.; Robins, M. J.; Wilson, J. S.; Tyrrell, D. L. J. *Hepatology* **1996**, *23*, 87. (d) Robins, M. J.; Wilson, J. S.; Madej, D.; Lindmark, R. J.; Wnuk, S. F.; Gati, W. P.; Tyrrell, D. L. J. Unpublished data.

(4) For comprehensive reviews, see: (a) Huryn, D. M.; Okabe, M. *Chem. Rev.* **1992**, *92*, 1745. (b) Herdewijn, P.; Balzarini, J.; De Clercq, E. *Advances in Antiviral Drug Design*; JAI Press: Greenwich, CT, 1993; Vol. 1, pp 233−318. (c) Wnuk, S. F. *Tetrahedron* **1993**, *49*, 9877.

(5) For recent reports, see: (a) Luzzio, F. A.; Menes, M. E. *J. Org. Chem.* **1994**, *59*, 7267. (b) Clive, D. L. J.; Wickens, P. L.; Sgarbi, P. W. M. *J. Org. Chem.* **1996**, *61*, 7426. (c) Clive, D. L. J.; Sgarbi, P. W. M.; Wickens, P. L. *J. Org. Chem.* **1997**, *62*, 3751. (d) Antonov, K. V.; Konstantinova, I. D.; Miroshnikov, A. I. *Nucleosides Nucleotides* **1998**, *17*, 153 and references therein.

(6) (a) Robins, M. J.; Hansske, F.; Low, N. H.; Park. J. I. *Tetrahedron Lett.* **1984**, *25*, 367. (b) Robins, M. J.; Madej, D.; Low, N. H.; Hansske, F.; Zou, R. In *Nucleic Acid Chemistry. Improved and New Synthetic Procedures, Methods, and Techniques;* Townsend, L. B., Tipson, R. S., Eds.; Wiley: New York, 1991; Vol. 4, pp 211−219. (c) Robins, M. J.; Wilson, J. S.; Madej, D.; Low, N. H.; Hansske, F.; Wnuk, S. F. *J. Org. Chem.* **1995**, *60*, 7902 and references therein.

(7) Dudycz, L. W. *Nucleosides Nucleotides* **1989**, *8*, 35.

(8) Chu, C. K.; Bhadti, V. S.; Doboszewski, B.; Gu, Z. P.; Kosugi, Y.; Pullaiah, K. C.; Van Roey, P. V. *J. Org. Chem.* **1989**, *54*, 2217.

(9) Beach, J. W.; Kim, H. O.; Jeong, L. S.; Nampalli, S.; Islam, Q.; Ahn, S. K.; Babu, J. R.; Chu, C. K. *J. Org. Chem.* **1992**, *57*, 3887.

(10) (a) Lin, T.-S.; Luo, M.-Z.; Liu, M.-C.; Pai, S. B.; Dutschman, G. E.; Cheng, Y.-C. *J. Med. Chem.* **1994**, *37*, 798. (b) Bolon, P. J.; Wang, P.; Chu, C. K.; Gosselin, G.; Boudou, V.; Pierra, C.; Mathé, C.; Imbach, J.-L.; Faraj, A.; el Alaoui, A.; Sommadossi, J.-P.; Pai, S. B.; Zhu, Y.-L.; Lin, J.-S.; Cheng, Y.-C.; Shinazi, R. F. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1657. (c) Rassu, G.; Zanardi, F.; Battistini, L.; Gaetani, E.; Casiraghi, G. *J. Med. Chem.* **1997**, *40*, 168.

(11) Robins, M. J.; Hansske, F.; Wnuk, S. F.; Kanai, T. *Can. J. Chem.* **1991**, *69*, 1468.

(12) (a) Berridge, M. S.; Franceschini, M. P.; Rosenfeld, E.; Tewson, T. J. *J. Org. Chem.* **1990**, *55*, 1211. (b) Lohray, B. B. *Synthesis* **1992**, 1035.

(13) Gao, Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 7538.

(14) Chao, B.; McNulty, K. C.; Dittmer, D. C. *Tetrahedron Lett.* **1995**, *36*, 7209.

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2′,3′-didehydro-2′,3′-dideoxynucleosides via reductive elimination of cyclic 2′,3′-(sulfate or phosphate) esters of ribonucleosides, or more efficiently (40−60% overall yields of analytically pure products) of 2′,3′-di-*O*-mesyl derivatives, with sodium naphthalenide. All reactions are conducted at ambient or lower temperatures and utilize readily available reagents and standard laboratory conditions.

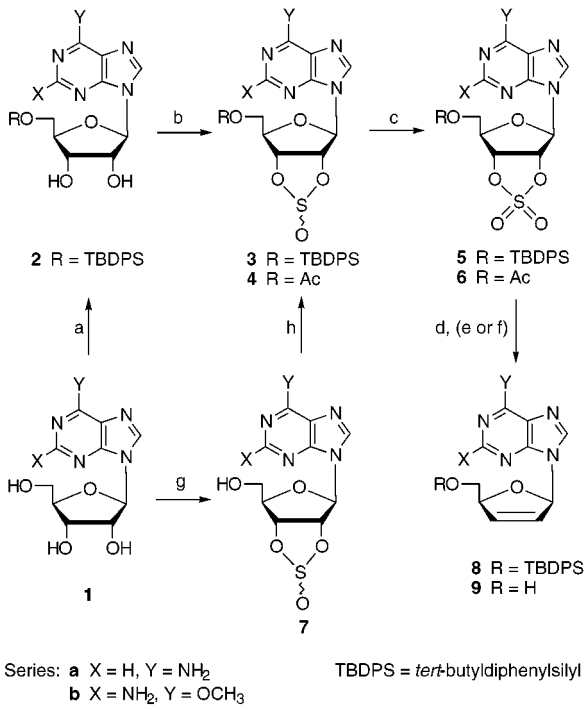
Results and Discussion

We used 5′-chloro-5′-deoxy-2′,3′-*O*-sulfinyladenosine[11] in our initial studies. None of the reductive systems investigated caused significant 2′,3′ elimination. Sharpless oxidation[13] ($NaIO_4/RuCl_3$) gave 5′-chloro-5′-deoxy-2′,3′-*O*-sulfonyladenosine (55%), although others had reported problems with this oxidation.[5b] Several reductive systems [e.g., Bu_3SnH/AIBN,[8] $Na_2S_2O_4$/viologen,[16] Zn−Cu couple/DMF,[6] sodium naphthalenide,[17,18] and lithium 4,4′-di-*tert*-butylbiphenyl[19]] failed to give 2′,3′-unsaturated products, produced uninviting mixtures, or both. The cyclic 2′,3′-sulfate was refluxed with sodium iodide in acetone, and precipitation of the presumed 9-(5-chloro-3,5-dideoxy-3-iodo-β-D-xylofuranosyl)adenine 2′-sulfate sodium salt (∼70%) occurred. This product was treated with Zn−Cu/DMF to give 5′-chloro-2′,3′-didehydro-2′,3′,5′-trideoxyadenosine[3d] (48%).

Treatment of adenosine with $SOCl_2$[11] under modified conditions failed to effect selective introduction of the 2′,3′-*O*-sulfinyl moiety without replacement of the 5′-hydroxyl group by chloride, in contrast with pyrimidine nucleosides.[11,20] Treatment of adenosine (**1a**, Scheme 1) with the less reactive thionyl fluoride (generated in situ[21]) gave 2′,3′-*O*-sulfinyladenosine (**7a**, exo/endo ∼2:1, 72%). Acetylation of **7a** and oxidation[13] of the resulting **4a** gave the cyclic 2′,3′-sulfate **6a** (67% from **7a**), which was stable at ∼4 °C in the crystalline form for at least 1 year. However, it decomposed at elevated temperatures or in solution in DMSO. Of the reagents noted above, sodium naphthalenide[17,18] gave the best conversions of **6a** to 2′,3′-didehydro-2′,3′-dideoxyadenosine (**9a**). Purification [Dowex (OH^-) resin, H_2O] and recrystallization gave **9a** (48%). The use of SOF_2 allowed selective introduction of the 2′,3′-*O*-sulfinyl function and subsequent acetylation of O5′.

Protection of O5′ of adenosine (**1a**) with *tert*-butyldiphenylsilyl (TBDPS) chloride gave **2a**. Treatment of **2a** with $SOCl_2$/MeCN gave the 2′,3′-*O*-sulfinyl derivative **3a** (63% from **1a**). Oxidation of **3a** gave the 2′,3′-sulfate **5a** (90%) which underwent smooth reductive elimination with sodium naphthalenide (−50 °C, ∼10 min) to give **8a**. Desilylation (TBAF/THF or NH_4F/MeOH[22]) and purification [Dowex 1 × 2 (OH^-)] gave **9a** (54% from **5a**). The overall sequence (**1a** → **9a**, 63%) was performed without isolation of intermediates (**2a**, **3a**, **5a**, **8a**) with aqueous partition workups and final purification of **9a** on Dowex (OH^-) resin. This 5-step (some consecutive one-flask) sequence uses readily available reagents and mild conditions and is one of the most efficient methodologies for the synthesis of dideoxynucleosides.[4−8] In contrast, our exploratory reaction of 2′,3′-sulfate **5a** with sodium telluride[14] gave olefin **8a** in low yield (<20%). The presence of unresolved impurities in 2′,3′-unsaturated nucleosides prepared by reductive eliminations with lithium telluride and lithium areneselenoates has been noted.[5b,c]

Scheme 1[a]



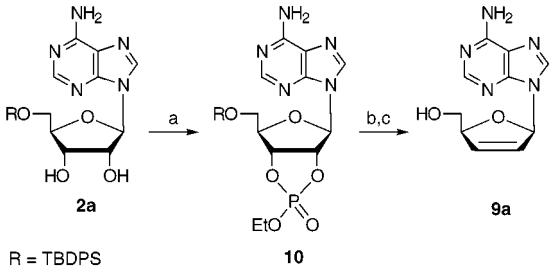
[a] (a) TBDPSCl/pyridine; (b) $SOCl_2$/MeCN; (c) $NaIO_4/RuCl_3 \cdot 3H_2O$/MeCN/$H_2O$; (d) $[C_{10}H_8]^{\bullet-}Na^+$/THF/−50 °C; (e) TBAF/THF; (f) NH_3/MeOH; (g) SOF_2/MeCN; (h) Ac_2O/pyridine.

Other procedures for oxidation of cyclic sulfites to sulfates [e.g., $KMnO_4$, $Ca(MnO_4)_2$][12] gave lower yields. However, we developed one modification (Oxone/$RuCl_3$) of the Sharpless oxidation[13] that gave **5a** (60%) from **3a**. Application of this cyclic sulfate methodology for the synthesis of pyrimidine 2′,3′-unsaturated nucleosides has an inherent flaw: oxidation of 2′,3′-*O*-sulfinyluridine[11,20] resulted in the formation of the 2,2′-anhydroarabino product (cyclonucleoside) via intramolecular displacement of sulfate from C2′ by O2.

Our sequence was successful for the synthesis of the anti-HBV agent 2-amino-9-(2,3-dideoxy-β-D-*glycero*-pentofuranosyl)-6-methoxypurine[3d] precursor **9b**. Guanosine was converted[23] into its 2-amino-6-methoxypurine analogue[23a] **1b**. Silylation (O5′) of **1b**, treatment of **2b** with $SOCl_2$, and oxidation of **3b** gave the 2′,3′-sulfate **5b**. Treatment of **5b** with sodium naphthalenide and deprotection of **8b** gave 2-amino-9-(2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)-6-methoxypurine (**9b**; 20% from **1b** with purification of intermediates). Treatment of **1b** with SOF_2, acetylation, oxidation, and reductive elimination

(15) Calvo-Flores, F. G.; Garcia-Mendoza, P.; Hernandez-Mateo, F.; Isac-Garcia, J.; Santoyo-González, F. *J. Org. Chem.* **1997**, *62*, 3944.
(16) (a) Amino, Y.; Iwagami, H. *Chem. Pharm. Bull.* **1991**, *39*, 622. (b) Park, K. K.; Lee, C. W.; Choi, S. Y. *J. Chem. Soc., Perkin Trans. 1* **1992**, 601.
(17) (a) Beels, C. M. D.; Coleman, M. J.; Taylor, R. J. K. *Synlett* **1990**, 479. (b) Guijarro, D.; Mancheno, B.; Yus, M. *Tetrahedron Lett.* **1992**, *33*, 5597.
(18) (a) Garst, J. F. *Acc. Chem. Res.* **1971**, *4*, 400. (b) Molander, G. A.; Harris, C. R. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: New York, 1995; Vol. 7, pp 4602−4604.
(19) Rawson, D. J.; Meyers, A. I. *Tetrahedron Lett.* **1991**, *32*, 2095.
(20) Sowa, T.; Tsunoda, K. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 505.
(21) Tullock, C. W.; Coffman, D. D. *J. Org. Chem.* **1960**, *25*, 2016.
(22) Zhang, W.; Robins, M. J. *Tetrahedron Lett.* **1992**, *33*, 1177.
(23) (a) Gerster, J. F.; Jones, J. W.; Robins, R. K. *J. Org. Chem.* **1963**, *28*, 945. (b) Robins, M. J.; Uznanski, B. *Can. J. Chem.* **1981**, *59*, 2601.

Scheme 2[a]



[a] (a) NaH/THF/$EtOPOCl_2$; (b) $[C_{10}H_8]^{\bullet-}Na^+$/THF/−50 °C; (c) TBAF/THF.

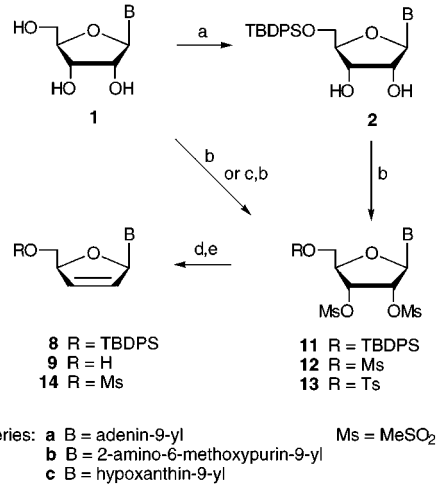
(**7b** → **4b** → **6b** → **9b**) gave **9b** [48%, after Dowex (OH^-) purification].

We briefly explored the use of cyclic 2′,3′-phosphates as substrates[24] for this sequence, but their preparation has been problematic.[25−27] Treatment of 5′-*O*-TBDPS-adenosine (**2a**, Scheme 2) with NaH/THF and then ethyl dichlorophosphate generated triester **10**. Treatment of **10** with sodium naphthalenide, deprotection, and purification [Dowex (OH^-)] gave 2′,3′-didehydro-2′,3′-dideoxyadenosine (**9a**; 27% from **2a**).

These reductive eliminations presumably involve single electron transfer (SET) from sodium naphthalenide to the sulfate or phosphate moieties,[24] followed by homolysis of the 2′ or 3′ carbon−oxygen bond. A second SET to the carbon radical would produce a carbanion with a good leaving group on the vicinal C2′ or C3′. Departure of the 2′- or 3′-(sulfate or phosphate) would produce the olefin, and a similar mechanism has been suggested[28a] for the conversion of vicinal dimesylates into alkenes. The possibility of consecutive SET-mediated homolytic cleavage of each carbon−oxygen bond also was considered.[24] Treatment of vicinal dimesylates with sodium naphthalenide has been used for the synthesis of alkenes.[18b,28] However, analogous treatment of ditosylates gave diols,[28a] presumably via competitive sulfur−oxygen bond cleavage.[29] We recently noted efficient removal of *O*-tosyl groups from the sugar[30,31] and halogens from the heterocycle[31] of purine nucleosides with sodium naphthalenide.

Treatment of 5′-*O*-TBDPS-adenosine (**2a**) with methanesulfonyl chloride gave the crystalline vicinal dimesylate **11a** (67% from **1a**, Scheme 3). The 2′,3′-unsaturated derivative **8a** was formed rapidly upon treatment of **11a** with sodium naphthalenide (∼5 min, −50 °C). Deprotection of **8a** (TBAF) and purification [Dowex (OH^-)] gave

Scheme 3[a]



[a] (a) TBDPSCl/pyridine; (b) $MeSO_2Cl$/pyridine; (c) TsCl/pyridine; (d) $[C_{10}H_8]^{\bullet-}Na^+$/THF/−50 °C; (e) TBAF/THF.

2′,3′-didehydro-2′,3′-dideoxyadenosine (**9a**, 79% from **11a**). This four-step procedure (**1a** → **9a**, 43%) eliminates the Sharpless oxidation step[13] and uses no noxious[5b,c,8] reagents. The 2-amino-6-methoxypurine **9b** (55% from **2b**) and hypoxanthine **9c** (69% from **2c**) analogues were prepared analogously.

Mesylation of 5′-*O*-TBDPS-inosine (**2c**) gave a separable mixture of 5′-*O*-TBDPS-2′,3′-di-*O*-mesylinosine (**11c**, 67%) and 5′-*O*-TBDPS-2′,3′,6-tri-*O*-mesylinosine (22%). Sulfonylation of O6 of guanosine analogues is well-known.[32] Treatment of **11c** with sodium naphthalenide and desilylation of **8c** gave 2′,3′-didehydro-2′,3′-dideoxyinosine (**9c**, 74% from **11c** after chromatography and recrystallization). Analogous treatment of the crude mixture (**11c**/trimesylate, ∼3:1) also gave clean **8c** (76%). Apparently, SET to the 6-*O*-mesyl group resulted in sulfur−oxygen bond cleavage owing to the higher energy of an aryl (sp^2) radical (but the usual carbon−oxygen bond homolysis occurred at the sugar sp^3 carbon). Pyrimidine nucleoside 2′,3′-dimesylate derivatives underwent SET also to the heterocyclic base.[31] Very slow addition of stoichiometric quantities of sodium naphthalenide produced uracil 2′,3′-unsaturated nucleoside products, but ^1H NMR and HRMS peaks indicated the presence of 5,6-dihydrouracil byproducts.

Treatment of 2′,3′,5′-tri-*O*-mesyladenosine[33] (**12a**) with sodium naphthalenide (−50 °C) gave the 5′-*O*-mesyl olefin **14a** (63%). The desired **9a**, with a free 5′-hydroxyl group, was not detected. Excess sodium naphthalenide, longer reaction times, or higher temperatures (∼−20 °C) resulted in loss of adenine. Because our mild conditions had converted 5′-*O*-tosyl- or 2′,3′,5′-tri-*O*-tosyladenosine into adenosine,[31] we prepared 2′,3′-di-*O*-mesyl-5′-*O*-tosyladenosine (**13a**) from 5′-*O*-tosyladenosine.[34] As expected, treatment of **13a** under our standard conditions gave **9a** (55%). However, the preparation of **13a** involved separation of its 5′-*O*-tosyl precursor (42%) from a mixture of tosylates.[34]

(24) Marshall, J. A.; Lewellyn, M. E. *J. Org. Chem.* **1977**, *42*, 1311.
(25) (a) Holy, A.; Sorm, F. *Collect. Czech. Chem. Commun.* **1969**, *34*, 3383. (b) van Boom, J. H.; de Rooy, J. F. M.; Reese, C. B. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2513. (c) Shimidzu, T.; Yamana, K.; Kanda, N.; Kitagawa, S. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3483.
(26) Hutchinson, D. W. In *Chemistry of Nucleosides and Nucleotides*; Townsend, L. B., Ed.; Plenum Press: New York, 1991; Vol. 2, pp 81−160.
(27) Chen, X.; Zhang, N.-J.; Li, Y.-M.; Jiang, Y.; Zhang, X.; Zhao, Y.-F. *Tetrahedron Lett.* **1997**, *38*, 1615.
(28) (a) Carnahan, J. C., Jr.; Closson, W. D. *Tetrahedron Lett.* **1972**, *33*, 3447. (b) Hrovat, D. A.; Miyake, F.; Trammell, G.; Gilbert, K. E.; Mitchell, J.; Clardy, J.; Borden, W. T. *J. Am. Chem. Soc.* **1987**, *109*, 5524.
(29) (a) Closson, W. D.; Wriede, P.; Bank, S. *J. Am. Chem. Soc.* **1966**, *88*, 1581. (b) Ganson, J. R.; Schulenberg, S.; Closson, W. D. *Tetrahedron Lett.* **1970**, 4397. (c) Closson, W. D.; Ganson, J. R.; Rhee, S. W.; Quaal, K. S. *J. Org. Chem.* **1982**, *47*, 2476.
(30) Jarrell, H. C.; Ritchie, R. G. S.; Szarek, W. A.; Jones, J. K. N. *Can. J. Chem.* **1973**, *51*, 1767−1770.
(31) Lewandowska, E.; Neschadimenko, V.; Wnuk, S. F.; Robins, M. J. *Tetrahedron* **1997**, *53*, 6295−6302.
(32) (a) Daskalov, H. P.; Sekine, M.; Hata, T. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3076. (b) Bridson, P. K.; Markiewicz, W. T.; Reese, C. B. *J. Chem. Soc., Chem. Commun.* **1977**, 791. (c) Stimac, A.; Muhic, D.; Kobe, J. *Nucleosides Nucleotides* **1994**, *13*, 625.
(33) Sasaki, T.; Minamoto, K.; Tanizawa, S. *J. Org. Chem.* **1973**, *38*, 2896.
(34) Herdewijn, P. *Tetrahedron* **1989**, *45*, 6563.

Table 1. ^{1}H NMR Spectral Data[a,b]

compound	H1′[c] ($J_{1'-2'}$)	H2′[d] ($J_{2'-3'}$)	H3′[d] ($J_{3'-4'}$)	H4′[e] ($J_{4'-5'}$)	H5′[d] ($J_{5'-5''}$)	H5″[d] ($J_{5''-4'}$)	H2[f]	H8[f]	NH_2[g] or NH[g]	others[f]
2b[h]	5.84 (5.1)	4.50[i]	4.27[i]	4.01−3.94[i]	3.88 (11.2)	3.73 (4.5)		7.99	6.48	3.97 (OMe)
3a[j,k]	6.43 (2.5)	6.35 (6.1)	5.98 (4.0)	4.41[i]	3.85[i,l]		8.09	8.34	7.42	
3b[j,k]	6.35 (1.5)	6.18[i]	6.18[i]	4.36[i]	3.86[i,l]			8.06	6.62	3.98 (OMe)
4a[k]	6.38[i]	6.38[i]	5.95 (3.7)	4.56 (4.1)	4.26[i] (12.1)	(6.0)	8.21	8.35	7.43	1.98 (Ac)
4a[m]	6.62 (3.0)	6.25 (7.5)	5.82 (4.0)	4.81[i]	4.26[i] (12.1)	(6.0)	8.21	8.41	7.43	1.98 (Ac)
4b[k]	6.33[f]	6.20[i]	6.20[i]	4.43[i]	4.34 (12.0)	4.17 (4.5)		8.05	6.69	2.00(Ac) 3.98 (OMe)
4b[m]	6.54 (1.6)	6.08[i]	6.08[i]	4.74[i]	4.34 (12.0)	4.17 (4.5)		8.11	6.69	2.00(Ac) 3.98 (OMe)
5a[j]	6.64 (2.3)	6.52 (7.0)	6.08 (4.3)	4.65[i]	3.88[i,l] (11.4)	(5.4)	8.04	8.33	7.41	
5b[j]	6.58 (1.4)	6.40[i]	6.40[i]	4.62[i]	3.85[i,l]			8.03	6.66	3.97 (OMe)
6a	6.63 (2.8)	6.53 (7.0)	6.11 (4.0)	4.76[i]	4.41 (12.0)	4.22 (6.2)	8.20	8.34	7.47	1.96 (Ac)
6b	6.57[f]	6.43[i]	6.43[i]	4.69[i]	4.36 (12.0)	4.18 (4.7)		8.02	6.75	2.00 (Ac) 3.98 (OMe)
7a[k]	6.30[i]	6.25 (5.7)	5.80 (3.0)	4.38 (4.6)	3.64[i,l]		8.19	8.38	7.43	5.41[n] (5.6,[o] OH5′)
7a[m]	6.58 (3.4)	6.17 (7.5)	5.71 (3.7)	4.58[i]	3.64[i,l]		8.19	8.43	7.43	5.31[n] (5.6,[o] OH5′)
7b[k]	6.20[i]	6.20[i]	5.94 (3.7)	4.28[i]	3.63[i,l]			8.08	6.64	5.20[n] (5.2,[o] OH5′) 3.97 (OMe)
7b[m]	6.48 (3.0)	6.07 (7.1)	5.80 (4.2)	4.55[i]	3.63[i,l]			8.13	6.64	5.20[n](5.2,[o] OH5′) 3.97 (OMe)
8b[j]	6.82[i]	6.21[i]	6.51[i,p]	4.98[i]	3.80 (12.0)	3.73 (4.5)		7.71	6.51[p]	3.98 (OMe)
8c[j]	6.95[i] (1.5)	6.24 (5.8)	6.55 (1.5)	5.04−5.10[i] (5.0)	3.84 (11.0)	3.78 (5.9)	7.87	8.05	12.30	
9a	6.95[i]	6.15[e]	6.48[e]	4.90[i]	3.60[c] (4.0)		8.16	8.17	7.25	5.05[g] (OH5′)
9b	6.80[i]	6.10 (6.0)	6.44 (1.7)	4.86[i]	3.54[l]			7.89	6.50	3.96 (OMe) 5.12[g] (OH5′)
11a[j]	6.38 (4.5)	6.21 (5.3)	5.87 (5.0)	4.42−4.48[i]	3.88−4.06[i]		8.04	8.33	7.40	3.32, 3.41 (Ms)
11b[j]	6.23 (5.1)	5.98 (5.2)	5.71 (4.4)	4.39−4.43[i]	3.97−4.05[i]			8.04	6.47	3.32, 3.41 (Ms) 3.98 (OMe)
11c[j]	6.36 (4.6)	6.05 (5.3)	5.77 (5.2)	4.04−4.46[i] (5.0)	4.03 (11.8)	3.94 (4.2)	7.92	8.30	12.31	3.33, 3.40 (Ms)
14a	7.00[d,q] (1.7)	6.30[e,r] (5.9)	6.53[e] (1.7)	5.12−5.19 (3.9)	4.42[c]		8.08	8.19	7.32	3.09 (Ms)

[a] Chemical shifts (δ, 200 MHz, Me_2SO-d_6). [b] Apparent first-order coupling constants (in parentheses). [c] Doublet unless otherwise noted. [d] Doublet of doublets unless otherwise noted. [e] Doublet of doublets of doublets unless otherwise noted. [f] Singlet. [g] Broad singlet. [h] Peaks for TBDPS at δ 0.99[f] and 7.40−7.85.[i] [i] Multiplet. [j] Peaks for TBDPS similar to those in footnote *h*. [k] Sulfite exo diastereomer. [l] Collapsed singlet for H5′,5″. [m] Sulfite endo diastereomer. [n] Triplet. [o] $J_{OH5'-CH_2}$. [p] Collapsed singlet for H3′, NH_2. [q] $J_{1'-3'} = 3.2$ Hz. [r] $J_{2'-4'} = 3.8$ Hz.

In summary, we have developed mild and efficient procedures (~50% overall yields; 3−5 steps, some combined into one-flask sequences) for conversion of purine ribonucleosides into crystalline, analytically pure 2′,3′-didehydro-2′,3′-dideoxynucleosides. Cyclic 2′,3′-(sulfates or phosphates) or 2′,3′-dimesylates undergo reductive elimination upon treatment with sodium naphthalenide (THF/−50 °C) to give the 2′,3′-unsaturated products. All reactions proceed at or below ambient temperature with readily available reagents under standard laboratory conditions.

Experimental Section

Uncorrected melting points were determined on a microstage block. UV spectra were determined with solutions in MeOH. NMR spectra (Tables 1 and 2) were determined with solutions in Me_4Si/Me_2SO-d_6 at 200 MHz (^{1}H) or 50 MHz (^{13}C). Low-resolution mass spectra were determined at 20 eV. Reagent grade chemicals were used, and solvents and thionyl chloride were distilled before use. Thionyl fluoride was prepared as described[21] (0.4 M NaF and 0.1 M $SOCl_2$ in MeCN) and distilled at −20 °C into the reaction flask. Pyridine and MeCN were dried by reflux over and distillation from CaH_2. THF was refluxed over and distilled first from $LiAlH_4$ and then from potassium benzophenone ketyl. Sodium naphthalenide was prepared as a 0.5 M stock solution from sodium and naphthalene in dried THF under argon with ultrasound irradiation.[35] TLC was performed with Merck Kieselgel sheets with visualization under 254 nm light: S_1 [$CHCl_3$/MeOH (4:1)] or S_2 [EtOAc/*i*-PrOH/H_2O (4:1:2, upper layer)]. Merck Kieselgel 60 (230−400 mesh) or Dowex 1 × 2 (OH^-) resin was used for column chromatography. "Diffusion crystallization" was performed with the noted solvent combinations as described.[36] Solid products were dried in vacuo over P_4O_{10} at elevated temperatures. The composition of crystalline analytical samples containing solvent was verified by integration of EtOAc ^{1}H NMR peaks. Procedures A−D are illustrated with

(35) Azuma, T.; Yanagida, S.; Sakurai, H. *Synth. Commun.* **1982**, *12*, 137.

(36) Robins, M. J.; Mengel, R.; Jones, R. A.; Fouron, Y. *J. Am. Chem. Soc.* **1976**, *98*, 8204.

Table 2. ^{13}C NMR Spectral Data[a,b]

compound	C2	C4	C5	C6	C8	C1′	C2′	C3′	C4′	C5′
2b[c,d]	160.19	154.46	114.17	160.93	137.62	86.72	84.38	73.58	70.19	64.29
3a[e,f]	153.05	148.99	119.32	156.46	140.13	87.42	86.22	84.82[g]	84.82[g]	63.30
3b[e,f,h]	160.13	153.35	114.12	161.12	138.78	87.02	86.73	86.04	85.19	63.98
4a[f,i,j]	153.16	149.14	119.26	156.46	139.92	87.63	86.06	84.82	82.14	63.26
4a[i,k,l]	153.16	148.96	119.26	156.46	140.04	89.42	89.40	87.44	84.23	63.64
4b[f,h,k]	160.17	153.40	114.24	161.16	138.78	87.17	86.68	85.09	83.10	63.54
5a[e]	153.02	148.76	119.23	156.47	140.17	87.04	85.75	84.24	84.02	63.05
5b[e,h]	160.10	152.98	114.08	161.15	138.69	86.75	86.67	85.52	84.61	63.81
6a[k]	153.10	148.91	119.18	157.14	140.02	87.22	85.56	84.59	81.75	62.97
6b[h,k]	160.18	153.08	113.99	161.20	138.66	86.72	84.37	82.72	79.43	63.36
7a[f,i]	153.08	149.15	119.23	156.46	139.85	88.08	85.97	85.43	84.99	61.17
7a[i,l]	153.08	149.15	119.23	156.48	139.85	89.38	89.30	88.30	87.27	61.43
7b[f,h]	160.20	153.08	113.99	161.18	138.53	87.24	86.34	85.56[g]	85.56[g]	61.32
8b[e,h]	160.26	154.15	115.68	160.96	137.25	87.56	126.09	134.01	84.61	66.29
8c[e]	146.13	148.29	125.82	156.88	138.35	88.51	124.63	134.12	87.99	66.11
9b[h]	160.05	153.95	113.96	160.96	138.09	88.05	128.59	134.64	87.68	62.94
11a[e,l]	152.92	149.25	119.52	156.40	140.28	85.80	81.96	76.74	74.93	62.18
11b[e,h,m]	160.24	154.02	114.16	161.16	137.76	84.43	82.05	76.68	75.52	62.53
11c[e,m]	146.36	148.11	125.16	156.64	139.54	85.83	82.15	77.00	74.69	62.23
14a[n]	153.10	149.53	119.02	156.35	139.00	88.07	127.03	132.58	84.41	70.49

[a] Chemical shifts (δ, 50 MHz, Me_2SO-d_6). [b] Proton-decoupled singlets. [c] Peaks for TBDPS at δ 135.38, 135.29, 133.06, 132.89, 130.16, 128.16, 26.93, 19.07. [d] Peak for OMe at δ 53.46. [e] Peaks for TBDPS similar to those in footnote *c*. [f] Sulfite exo diastereomer. [g] Peaks not resolved. [h] Peak for OMe similar to that in footnote *d* (δ 53.45−53.96). [i] Assignments from a spectrum of the diastereomeric mixture. [j] Peaks also at δ 170.24, 20.67 (Ac). [k] Peaks for Ac similar to those in footnote *j*. [l] Sulfite endo diastereomer. [m] Peaks for Ms at δ 38.23−38.30. [n] Peak for Ms at δ 36.84

specific examples but are general (with indicated modifications for individual cases).

5′-*O*-(*tert*-Butyldiphenylsilyl)adenosine (2a). TBDPSCl (0.28 mL, 0.302 g, 1.1 mmol) was added to a suspension of adenosine (**1a**; 0.267 g, 1 mmol) in dried pyridine and was stirred for 24 h at ambient temperature. Volatiles were evaporated in vacuo, and toluene was added and evaporated (3 × 10 mL). The residue was partitioned (EtOAc/H_2O), and the organic phase was washed (H_2O, brine), dried (Na_2SO_4), and filtered. Volatiles were evaporated, and the residue was triturated with Et_2O to give the known[37] **2a** (0.404 g, 80%) as a white solid (mp 185−186 °C): MS *m*/*z* 505 (8, M^+), 448 (100, M − 57), 136 (90, BH_2).

2-Amino-9-[5-*O*-(*tert*-butyldiphenylsilyl)-β-D-ribofuranosyl]-6-methoxypurine (2b). Silylation of **1b**[23a] (0.53 g, 1.78 mmol) as described for **2a** and column chromatography of the product (2% MeOH/$CHCl_3$) gave **2b** (0.65 g, 68%) as a colorless solid (mp 185−187 °C, softening at 110 °C): UV max 251, 282 nm (ε 10 000, 9000), min 233, 262 nm (ε 5800, 5300); MS *m*/*z* 535 (2, M^+), 478 (100, M − 57), 199 (60). Anal. Calcd for $C_{27}H_{33}N_5O_5Si$: C, 60.54; H, 6.21; N, 13.07. Found: C, 60.31; H, 6.37; N, 12.89.

5′-*O*-(*tert*-Butyldiphenylsilyl)-2′,3′-*O*-sulfinyladenosine (3a). $SOCl_2$ (0.33 mL, 0.535 g, 4.5 mmol) was added to a cooled (ice/H_2O) suspension of **2a** (0.757 g, 1.5 mmol) in MeCN (15 mL) and was stirred for 2 h at ambient temperature. The reaction mixture was cooled (ice/H_2O), H_2O (10 mL) was added, and the solution was neutralized to pH 5−6 (solid $NaHCO_3$) and extracted (EtOAc, 3 × 20 mL). The combined organic phase was washed [cold $NaHCO_3$/H_2O (20 mL), H_2O (20 mL), and brine (20 mL)] and dried (Na_2SO_4). The white solid that precipitated during flash evaporation was filtered and dried to give **3a** (0.553 g, 67%). Volatiles were evaporated from the mother liquor, and the residue was recrystallized (EtOAc/hexanes) to give **3a** (91 mg, 11%, total yield 78%, exo/endo >15:1, mp 178−181 °C): UV max 259 nm (ε 14 600), min 234 nm (ε 3900); MS *m*/*z* 494 (100, M − 57), 135 (40, BH). Anal. Calcd for $C_{26}H_{29}N_5O_5SSi$: C, 56.60; H, 5.30; N, 12.69. Found: C, 56.45; H, 5.46; N, 12.57.

2-Amino-9-[5-*O*-(*tert*-butyldiphenylsilyl)-2,3-*O*-sulfinyl-β-D-ribofuranosyl]-6-methoxypurine (3b). Treatment of **2b** (0.26 g, 0.49 mmol) with $SOCl_2$ (as described for **3a**) gave crude **3b** (0.26 g, 92%, exo/endo >15:1). Diffusion crystallization (EtOAc/hexane) gave white crystals (mp 190−191 °C): UV max 250, 282 nm (ε 10 600, 9000), min 233, 263 nm (ε 6000, 6000); MS *m*/*z* 581 (8, M^+), 524 (62, M − 57), 199 (100). Anal. Calcd for $C_{27}H_{31}N_5O_6SSi$: C, 55.75; H, 5.37; N, 12.04. Found: C, 55.68; H, 5.20; N, 11.95.

5′-*O*-Acetyl-2′,3′-*O*-sulfinyladenosine (4a). Ac_2O (0.07 mL, 0.061 g, 0.6 mmol) was added to a solution of **7a** (0.156 g, 0.5 mmol) in pyridine (5 mL) at ∼0 °C (ice/H_2O) and was stirred for 6 h at ∼0 °C, and MeOH (5 mL) was added. Stirring was continued for 30 min, volatiles were evaporated in vacuo, and toluene was added and evaporated (3 × 5 mL). The white residue was dissolved (EtOAc, 20 mL), the solution was washed [cold $NaHCO_3$/H_2O (10 mL), H_2O (10 mL), and brine (10 mL)] and dried (Na_2SO_4), and volatiles were evaporated to give a white solid. Recrystallization (MeCN/hexanes) gave **4a** (0.143 g, 81%, exo/endo ∼2:1, mp 184−185 °C): UV max 258 nm (ε 14 100), min 226 nm (ε 1900); MS *m*/*z* 355 (100, M^+), 136 (40, BH_2), 135 (40, BH). Anal. Calcd for $C_{12}H_{13}N_5O_6S$: C, 40.56; H, 3.69; N, 19.71. Found: C, 40.64; H, 4.00; N, 19.59.

9-(5-*O*-Acetyl-2,3-*O*-sulfinyl-β-D-ribofuranosyl)-2-amino-6-methoxypurine (4b). Acetylation of **7b** (0.21 g, 0.61 mmol, as described for **4a**) gave **4b** (0.224 g, 95%, exo/endo ∼2:1) as a white solid. A sample was diffusion crystallized (EtOAc/hexanes) to give **4b** (mp 97−99 °C): UV max 250, 282 nm (ε 10 700, 9200), min 225, 264 nm (ε 3000, 5200); MS *m*/*z* 385 (80, M^+), 165 (100, BH). Anal. Calcd for $C_{13}H_{15}N_5O_7S$: C, 40.52; H, 3.92; N, 18.17. Found: C, 40.33; H, 3.72; N, 18.11.

***Procedure A.* 5′-*O*-(*tert*-Butyldiphenylsilyl)-2′,3′-*O*-sulfonyladenosine (5a).** $NaIO_4$ (0.160 g, 1.5 mmol), $RuCl_3 \cdot 3H_2O$ (∼1 mg, ∼0.004 mmol), and then H_2O (1.0 mL) were added to a solution of **3a** (0.276 g, 0.5 mmol) in MeCN (7 mL) under N_2 at ∼0 °C (ice/H_2O) and was stirred for 10 min at 0 °C and then 1 h at ambient temperature. EtOAc (20 mL) and brine (10 mL) were added, and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic phase was washed [H_2O (15 mL), $NaHCO_3$/H_2O (15 mL), and brine (2 × 15 mL)], dried (Na_2SO_4), and filtered with a Celite pad (to remove green ruthenium species). The filtrate was evaporated in vacuo to give gray crystalline **5a** (0.255 g, 90%) of sufficient purity for the reductive elimination step. A sample was flash chromatographed (2% MeOH/EtOAc) and recrystallized (EtOAc/hexanes) to give **5a** (mp ∼260 °C dec): UV max 259 nm (ε 14 900), min 234 nm (ε 4200); MS *m*/*z* 567 (90, M^+), 136 (100, BH_2). Anal. Calcd for $C_{26}H_{29}N_5O_6SSi$: C, 55.01; H, 5.15; N, 12.34. Found: C, 54.86; H, 5.42; N, 12.09.

(37) Beaton, G.; Jones, A. S.; Walker, R. T. *Tetrahedron* **1988**, *44*, 6419.

An analogous oxidation of **3a** (0.057 g, 0.1 mmol) with Oxone (0.20 g, 0.325 mmol) replacing $NaIO_4$ gave colorless crystalline **5a** (0.035 g, 60%).

2-Amino-9-[5-*O*-(*tert*-butyldiphenylsilyl)-2,3-*O*-sulfonyl-*β*-D-ribofuranosyl]-6-methoxypurine (5b). Oxidation of **3b** (0.30 g, 0.52 mmol) by procedure A gave **5b** (0.265 g, 86%) as a gray solid. Chromatography and crystallization (procedure A) gave **5b** (mp 95−97 °C): UV max 249, 282 nm (ϵ 10 700, 9100), min 230, 263 nm (ϵ 3700, 5500); MS *m*/*z* 597 (20, M^+), 540 (100, M − 57). Anal. Calcd for $C_{27}H_{31}N_5O_7SSi$: C, 54.26; H, 5.23; N, 11.72. Found: C, 54.36; H, 5.46; N, 11.49.

5′-*O*-Acetyl-2′,3′-*O*-sulfonyladenosine (6a). Oxidation of **4a** (0.355 g, 1 mmol) by procedure A gave **6a** (0.308 g, 83%) as gray crystals. Chromatography (procedure A) and crystallization (EtOAc) gave **6a** (mp 208−210 °C dec): UV max 258 nm (ϵ 15 000), min 225 nm (ϵ 1800); MS *m*/*z* 371 (10, M^+), 164 (100), 135 (24, BH). Anal. Calcd for $C_{12}H_{13}N_5O_7S\cdot 0.3EtOAc$: C, 39.96; H, 3.66; N, 17.65. Found: C, 40.14; H, 4.02; N, 17.32.

9-(5-*O*-Acetyl-2,3-*O*-sulfonyl-*β*-D-ribofuranosyl)-2-amino-6-methoxypurine (6b). Oxidation of **4b** (0.32 g, 0.83 mmol) by procedure A gave **6b** (0.30 g, 90%) as a gray solid. Chromatography and crystallization (procedure A) gave **6b** (mp 148−150 °C): UV max 249, 282 nm (ϵ 10 700, 9000), min 225, 264 nm (ϵ 3000, 5400); MS *m*/*z* 401 (50, M^+), 165 (44, BH), 83 (100). Anal. Calcd for $C_{13}H_{15}N_5O_8S$: C, 38.90; H, 3.77; N, 17.45. Found: C, 39.12; H, 3.87; N, 17.18.

2′,3′-*O*-Sulfinyladenosine (7a). SOF_2[21] was distilled (−20 °C) into a low-pressure jar cooled at −70 °C. Cold (−20 °C) MeCN (20 mL) and adenosine (**1a**; 0.267 g, 1 mmol) were added slowly, the jar was sealed, and the contents were stirred for 24 h at ambient temperature. The mixture was cooled (ice/H_2O), H_2O (10 mL) was added, and the solution was concentrated (∼10 mL) in vacuo. EtOAc (30 mL) was added with cooling (ice/H_2O), and the solution was neutralized (to pH 5.0−5.5, solid $NaHCO_3$). The organic layer was separated, and the aqueous phase was extracted (EtOAc, 3 × 20 mL). The combined organic phase was washed [cold $NaHCO_3/H_2O$ (20 mL), H_2O (20 mL), and brine (20 mL)] and dried (Na_2SO_4), and volatiles were evaporated to give **7a** (0.225 g, 72%, exo/endo ∼2:1) as a white solid. A sample was recrystallized (EtOAc/hexanes) to give **7a** (mp 198−200 °C dec): UV max 259 nm (ϵ 14 300), min 226 nm (ϵ 1900); MS *m*/*z* 313 (40, M^+), 164 (100), 135 (90, BH). Anal. Calcd for $C_{10}H_{11}N_5O_5S$: C, 38.34; H, 3.54; N, 22.35. Found: C, 38.12; H, 3.74; N, 22.13.

2-Amino-6-methoxy-9-(2,3-*O*-sulfinyl-*β*-D-ribofuranosyl)-purine (7b). Treatment of **1b**[23a] (0.295 g, 1 mmol) with SOF_2 as described for **7a** [with addition of pyridine (0.16 mL, 2 mmol) to the reaction mixture] gave **7b** (0.314 g, 92%, exo/endo ∼2:1). A sample was diffusion crystallized (EtOAc/hexanes) to give **7b** (mp 188−189 °C): UV max 250, 282 nm (ϵ 10 200, 9000), min 225, 263 nm (ϵ 3400, 5000); MS *m*/*z* 343 (80, M^+), 165 (100, BH). Anal. Calcd for $C_{11}H_{13}N_5O_6S$: C, 38.48; H, 3.82; N, 20.40. Found: C, 38.26; H, 3.93; N, 20.16.

***Procedure B.* 9-[5-*O*-(*tert*-Butyldiphenylsilyl)-2,3-dideoxy-*β*-D-*glycero*-pent-2-enofuranosyl]adenine (8a).** Sodium naphthalenide[35] in dried THF (0.5 M) was added slowly (double-ended cannula) to a stirred solution of **5a** (0.120 g, 0.21 mmol) in dried, deoxygenated (Ar, 30 min) THF (8 mL) at −50 °C (under Ar) until the green color of the radical anion persisted [TLC (S_2) after 5 min indicated complete conversion of **5a** to a more polar product]. Saturated NH_4Cl/H_2O was added (pH 5.5−6.5), volatiles were evaporated in vacuo, and EtOAc (20 mL) and H_2O (10 mL) were added. The aqueous phase was extracted [EtOAc (15 mL)], and the combined organic phase was dried (Na_2SO_4). Volatiles were evaporated, and the residue was chromatographed (1% MeOH/$CHCl_3$) to give colorless **8a** (0.058 g, 59%, mp 154−156 °C, lit.[9] mp 155−157 °C): UV max 260 nm; MS *m*/*z* 471 (2, M^+), 414 (100, M − 57).

2-Amino-9-[5-*O*-(*tert*-butyldiphenylsilyl)-2,3-dideoxy-*β*-D-*glycero*-pent-2-enofuranosyl]-6-methoxypurine (8b). Treatment of **5b** (0.13 g, 0.22 mmol) by procedure B gave solid **8b** (46 mg, 42%). A sample was purified [RP-HPLC: C_{18} column, H_2O/MeCN (70:30 → 0:100), 120 min (t_R 110 min)] to give **8b** (mp 75−80 °C): UV max 249, 281 nm (ϵ 11 100, 10 200), min 225, 263 nm (ϵ 6900, 5800); MS *m*/*z* 501 (20, M^+), 165 (100, BH). Anal. Calcd for $C_{27}H_{31}N_5O_3Si$: C, 64.64; H, 6.23; N, 13.96. Found: C, 64.80; H, 6.07; N, 13.57.

9-[5-*O*-(*tert*-Butyldiphenylsilyl)-2,3-dideoxy-*β*-D-*glycero*-pent-2-enofuranosyl]hypoxanthine (8c). Treatment of **11c** (0.13 g, 0.17 mmol) by procedure B and crystallization (EtOAc) gave **8c** (29 mg). Chromatography of the mother liquor (1% MeOH/EtOAc) and crystallization (EtOAc) gave additional **8c** (48 mg, 79% total, mp 89−91 °C): UV max 250 nm (ϵ 14 900), min 233 nm (ϵ 6500); MS *m*/*z* 415 (10, M − 57), 136 (100, BH). Anal. Calcd for $C_{26}H_{28}N_4O_3Si\cdot 0.5EtOAc$: C, 65.09; H, 6.24; N, 10.84. Found: C, 64.91; H, 6.55; N, 10.84.

Parallel treatment of the crude mesylate mixture (**11c**/trimesylate ∼3:1, 0.136 g, ∼0.20 mmol) gave colorless crystalline **8c** (78 mg, 76%) with identical physical and spectral properties.

***Procedure C.* 9-(2,3-Dideoxy-*β*-D-*glycero*-pent-2-enofuranosyl)adenine (9a). Method A.** TBAF/THF (1 M, 0.32 mL, 0.32 mmol) was added to a solution of **8a** (0.15 g, 0.318 mmol) in THF (5 mL) and was stirred for 2 h at ambient temperature. Volatiles were evaporated, and the residue was dissolved (H_2O) and chromatographed [Dowex 1 × 2 (OH^-), H_2O] to give colorless crystalline **9a** (0.068 g, 92%, mp 194−195 °C, lit.[9] mp 188−190 °C): UV max 259 nm (ϵ 13 200), min 226 nm (ϵ 1900); MS *m*/*z* 233 (10, M^+), 135 (100, BH).

Treatment of **8a** (0.12 g, 0.254 mmol) with NH_4F (0.10 g, 2.7 mmol) in MeOH (10 mL) for 5 h at 60 °C gave **9a** (0.052 g, 88%) after purification [Dowex 1 × 2 (OH^-), H_2O].

Method B. Treatment of **6a** (0.185 g, 0.5 mmol) by procedure B (to the point of evaporation of volatiles) gave a more polar product [TLC (S_1)]. Et_2O (20 mL) and H_2O (10 mL) were added, and the organic layer was extracted (H_2O, 5 mL). The combined aqueous phase was concentrated and chromatographed [Dowex 1 × 2 (OH^-), H_2O]. The white solid was diffusion crystallized (MeOH/Et_2O) to give **9a** (0.056 g, 48%).

Method C. NaH (0.06 g, 1.25 mmol, 50% dispersion in mineral oil) was washed (dried THF, 3 × 5 mL) and suspended in dried THF (10 mL) under argon. A solution of **2a** (0.2 g, 0.4 mmol) in dried THF (10 mL) was added and was stirred at ambient temperature until evolution of H_2 ceased. A solution of ethyl dichlorophosphate (0.048 mL, 0.065 g, 0.4 mmol) in dried THF (5 mL) was added dropwise, and after 1 h, TLC (S_1) indicated conversion of almost all starting material to a less polar product. The reaction mixture was cooled (−50 °C) and subjected to procedure B, and a more polar product was formed [TLC (S_1)]. Saturated NH_4Cl/H_2O was added, volatiles were evaporated in vacuo, and EtOAc (20 mL) and H_2O (10 mL) were added. The aqueous layer was extracted (EtOAc, 10 mL), and the combined organic phase was dried (Na_2SO_4). Volatiles were evaporated, and the residue was dissolved (THF, 10 mL). The mixture was deprotected and chromatographed (procedure C) to give colorless crystalline **9a** (0.025 g, 27%). Further elution of the Dowex 1 × 2 (OH^-) column with MeOH gave **1a** (0.013 g, 12%).

Method D. Treatment of **11a** (0.13 g, 0.20 mmol) by procedure B (−50 °C, ∼10 min) and crude **8a** by procedure C [aqueous layer washed (Et_2O) before purification on the Dowex column)] gave **9a** (0.036 g, 79%, mp 194−195 °C): UV max 259 nm (ϵ 13 400), min 226 nm (ϵ 2000).

Method E. Treatment of 5′-*O*-tosyladenosine[34] (0.505 g, 1.2 mmol) by procedure D [back-extraction of the combined aqueous layers ($CHCl_3$, 3×), no column chromatography] and crystallization (MeOH) gave **13a** (415 mg, 60%, mp 163−166 °C dec): ^1H NMR δ 2.36 (s, 3, Me), 3.30, 3.40 (2 × s, 2 × 3, 2 × Ms), 4.46−4.59 (m, 3, H4′,5′,5″), 5.72 (dd, $J_{3'-4'}$ = 4.0 Hz, $J_{3'-2'}$ = 5.3 Hz, 1, H3′), 6.10 (t, J = 5.1 Hz, 1, H2′), 6.29 (d, $J_{1'-2'}$ = 4.9 Hz, 1, H1′), 7.31 (d, J = 8.0 Hz, 2, arom), 7.45 (br s, 2, NH_2), 7.68 (d, J = 8.0 Hz, 2, arom), 8.05 (s, 1, H2), 8.26 (s, 1, H8); HRMS (CI) *m*/*z* 578.0693 (60, MH^+ [$C_{19}H_{24}N_5O_{10}S_3$] = 578.0685). Treatment of **13a** (0.072 g, 0.125 mmol) by procedure B (as modified in method B) gave **9a** (0.016 g, 55%).

2-Amino-9-(2,3-dideoxy-*β*-D-*glycero*-pent-2-enofuranosyl)-6-methoxypurine (9b). Method A. Treatment of **6b** (0.12 g, 0.3 mmol) by procedure B and workup [as described for **9a** (method B)] gave **9b** (0.048 g, 61%) as a white solid

(mp 108−109 °C): UV max 247, 282 nm (ϵ 9700, 9100), min 225, 262 nm (ϵ 3800, 4600); MS *m*/*z* 263 (18, M^+), 165 (100, BH). Anal. Calcd for $C_{11}H_{13}N_5O_3$: C, 50.19; H, 4.98; N, 26.60. Found: C, 49.96; H, 5.19; N, 26.69.

Method B. Deprotection of **8b** (0.11 g, 0.22 mmol) by procedure C gave **9b** (0.048 g, 86%) with identical physical and spectral properties.

Method C. Treatment of **11b** (0.14 g, 0.20 mmol) by procedure B and deprotection of the crude **8b** by procedure C gave **9b** (0.038 g, 72%) with identical physical and spectral properties.

9-(2,3-Dideoxy-*β*-D-*glycero*-pent-2-enofuranosyl)hypoxanthine (9c). Method A. Treatment of **11c** (0.12 g, 0.157 mmol) by procedure B and then **8c** by procedure C [chromatography (3 → 7% MeOH/$CHCl_3$) and recrystallization (MeOH)] gave **9c** (0.028 g, 76%, mp >300 °C, lit.[8] mp >310 °C): UV max 249 nm (ϵ 14 000), min 221 nm (ϵ 3400).

Method B. Deprotection of **8c** (0.14 g, 0.296 mmol) by procedure C [silica gel column chromatography (3 → 7% MeOH/$CHCl_3$)] gave **9c** (0.065 g, 94%).

***Procedure D.* 5′-*O*-(*tert*-Butyldiphenylsilyl)-2′,3′-di-*O*-methanesulfonyladenosine (11a).** $MeSO_2Cl$ (0.12 mL, 0.18 g, 1.6 mmol) in dried pyridine (12 mL) was added dropwise to a cooled (ice/H_2O) solution of **2a** (0.3 g, 0.59 mmol) in dried pyridine (15 mL) and was stirred for 5 h [starting material was converted into a less polar product, TLC (S_1)]. Volatiles were evaporated, toluene was added and evaporated (2 × 5 mL), and the residue was dissolved ($CHCl_3$, 30 mL). The solution was washed [$NaHCO_3$/H_2O (2 × 15 mL), H_2O (10 mL), and brine (10 mL)] and dried (Na_2SO_4), volatiles were evaporated, and the residue was chromatographed (2% MeOH/$CHCl_3$) to give colorless crystalline **11a** (0.33 g, 84%, mp 153−155 °C): UV max 258 nm (ϵ 14 800), min 234 nm (ϵ 4100); MS *m*/*z* 604 (100, M − 57), 135 (20, BH). Anal. Calcd for $C_{28}H_{35}N_5O_8S_2Si$: C, 50.81; H, 5.33; N, 10.58. Found: C, 50.89; H, 5.37; N, 10.44.

2-Amino-9-[5-*O*-(*tert*-butyldiphenylsilyl)-2,3-di-*O*-methanesulfonyl-*β*-D-ribofuranosyl]-6-methoxypurine (11b). Treatment of **2b** (0.13 g, 0.243 mmol) by procedure D and chromatography (1% MeOH/$CHCl_3$) gave **11b** (0.128 g, 76% mp 85−87 °C): UV max 251, 281 nm (ϵ 11 600, 8800), min 233, 267 nm (ϵ 6400, 6900); MS *m*/*z* 634 (20, M − 57), 166 (100, BH). Anal. Calcd for $C_{29}H_{37}N_5O_9S_2Si$: C, 50.35; H, 5.39; N, 10.12. Found: C, 50.41; H, 5.46; N, 10.01.

5′-*O*-(*tert*-Butyldiphenylsilyl)-2′,3′-di-*O*-methanesulfonylinosine (11c). Treatment of **2c**[37] [0.25 g, 0.494 mmol; prepared from inosine (61%) as described for **2a**] by procedure D gave **11c** and its 6-*O*-mesyl derivative (∼3:1, 0.32 g, ∼96%). Chromatography (1% MeOH/$CHCl_3$) gave the 6-*O*-mesyl byproduct (0.08 g, 22%): ^{1}H NMR *δ* 0.94 (s, 9, *t*-Bu), 3.35, 3.36, 3.85 (3 × s, 3 × 3, 3 × Ms), 3.89−4.01 (m, 2, H5′,5″), 4.80−4.98 (m, 1, H4′), 5.74 (dd, $J_{3'-4'}$ = 5.3 Hz, $J_{3'-2'}$ = 5.4 Hz, 1, H3′), 5.98 (dd, $J_{2'-1'}$ = 4.6 Hz, 1, H2′), 6.43 (d, 1, H1′), 7.32−7.74 (m, 10, arom), 8.49 (s, 1, H8), 8.52 (s, 1, H2). This was followed by **11c** (0.22 g, 67%, mp 110−115 °C): UV max 250 nm (ϵ 14 000), min 232 nm (ϵ 8300); MS *m*/*z* 605 (10, M − 57), 136 (100, BH). Anal. Calcd for $C_{28}H_{34}N_4O_9S_2Si$: C, 50.74; H, 5.17; N, 8.45. Found: C, 50.90; H, 5.13; N, 8.25.

2′,3′,5′-Tri-*O*-methanesulfonyladenosine (12a). Treatment of **1a** (1.34 g, 5 mmol) with $MeSO_2Cl$ as reported[33] gave **12a** (88%, mp 184−186 °C dec, lit.[33] 185−195 dec): UV max 260 nm (ϵ 13 800); ^{1}H NMR *δ* 3.15, 3.33, 3.47 (3 × s, 3 × 3, 3 × Ms), 4.65 (br s, 3, H4′,5′,5″), 5.70−5.80 (m, 1, H3′), 6.13 (dd, $J_{2'-3'}$ = 5.5 Hz, $J_{2'-1'}$ = 5.4 Hz, 1, H2′), 6.38 (d, 1, H1′), 7.48 (br s, 2, NH_2), 8.20 (s, 1, H2), 8.39 (1, H8).

9-(2,3-Dideoxy-5-*O*-methanesulfonyl-*β*-D-*glycero*-pent-2-enofuranosyl)adenine (14a). Treatment of a solution of **12a** (0.1 g, 0.2 mmol) in DMF/THF (1:7, 8 mL) by procedure B and chromatography (3 → 7% MeOH/EtOAc) gave **14a** (0.039 g, 63%) as off-white crystals (mp 131−132 °C) UV max 259 nm (ϵ 15 000), min 226 nm (ϵ 2000). Anal. Calcd for $C_{11}H_{13}N_5O_4S$·0.1EtOAc: C, 42.77; H, 4.35; N, 21.88. Found: C, 42.98; H, 4.52; N, 21.55.

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