Syntheses of 6-Deaminosinefungin and (S)-6-Methyl-6-deaminosinefungin

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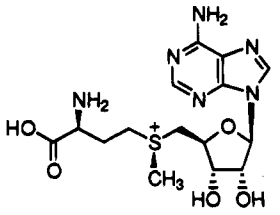
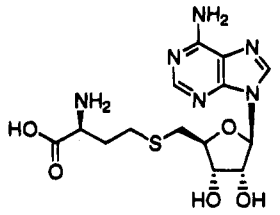
The nucleosides *S*-adenosylmethionine (SAM, AdoMet) and *S*-adenosylhomocysteine (SAH, AdoHcy) are involved in a number of important enzyme systems. The direct or indirect inhibition of these enzymes is currently of high interest, particularly in the areas of antiviral and cell proliferation research. We report here the first chirospecific syntheses of 6(*S*)-methyl-6-deaminosinefungin (**4**) and 6-deaminosinefungin (**5**) which are analogues of SAM (**1**), SAH (**2**), and sinefungin (**3**). From ketone **6** (*tert*-butyl [methyl 2,3-*O*-isopropylidene-5,7,8,9-tetradeoxy-9(*S*)-[(*p*-toluenesulfonyl)amino]-β-D-*ribo*-deculofuranosid]uronate), an intermediate in the sinefungin synthesis, the methylene derivative was prepared by using the tosylhydrazone–hydroboration method. Nucleoside formation with adenine and deprotection then led to 6-deaminosinefungin. For the synthesis of (*S*)-6-methyl-6-deaminosinefungin (**4**), ketone **6** was converted in four steps into the 6(*S*)-methyl derivative using a cuprate reagent. After the adenine was attached, an appropriate deprotection sequence yielded **4**. Thus, **4** was synthesized in 11 steps from ketone **6** in an overall yield of 13%.

Introduction

The nucleosides *S*-adenosylmethionine (SAM, AdoMet) (**1**) and *S*-adenosylhomocysteine (SAH, AdoHcy) (**2**) are involved in a number of important enzyme systems. The direct or indirect inhibition of these enzymes is currently of high interest, particularly in the areas of antiviral and cell proliferation research.



1
S-Adenosylmethionine (SAM)
AdoMet



2
S-Adenosylhomocysteine (SAH)
AdoHcy

One approach to the design of potential antiviral compounds involves the direct or indirect inhibition of SAM-dependent methyl transferase enzymes. Methyl transferase activity is necessary for viral replication since 5′-methyl capping of viral *m*-RNA's is required for their proper functioning.[1] Based on the enzymes involved in this process, different approaches to inhibit SAM-dependent methylation have been considered. One approach concentrates on the direct inhibition of the SAM-dependent methyl transferase enzyme itself; another approach focuses on an indirect effect by inhibition of SAH-hydrolase (AdoHcyase). The SAH (**2**)—released after SAM donates its methyl group—functions as a strong feedback inhibitor of the methyl transferase and must therefore be metabolized rapidly, a task which is performed by SAH-hydrolase. The intracellular ratio of SAH to SAM required for antiviral activity is well below cytotoxic levels, suggesting that viral methyl transferases may be more sensitive to this ratio than cellular enzymes. Selectivity of this sort is essential if effective antivirals are to be obtained by methyl transferase inhibition.

Another aspect of SAM's biological function is its role in polyamine biosynthesis. Polyamines are essential in the proliferation and development of mammalian cells.[2] Disorders in polyamine metabolism are considered to be an important factor in carcinogenesis. When SAM is decarboxylated by SAM-decarboxylase (SAMDC or AdoMetDC), it no longer can function for methyl transfer reactions. Instead, decarboxylated SAM serves as an aminopropyl donor for the synthesis of polyamines and is converted to 5′-(methylthio)adenosine (MTA) in this process. AdoMetDC is a rate-limiting enzyme in polyamine biosynthesis and controls the conversion of the diamine putrescine to the higher polyamines spermidine and spermine. Currently, two classes of inhibitors of AdoMetDC are being studied preclinically as potential antitumor agents:[3] analogues of methylglyoxal bis(guanylhydrazone) (MGBG), which are competitive enzyme inhibitors, as well as analogues of SAM, which are irreversible enzyme inhibitors binding covalently to the pyruvate residue at the active site of AdoMetDC.[4]

In addition to the importance of SAM and SAH in the design of antiviral agents or in the control of cell proliferation, there are indications of SAH-hydrolase inhibitors as immunomodulators. It was recently reported that a potent inhibitor of SAH hydrolase, MDL 28,842 ((*Z*)-5′-fluoro-4′,5′-didehydro-5′-deoxyadenosine), selectively inhibited T-cell activation in mice.[5] The immune response of T-cells is the basis for transplant rejection.

The antibiotic sinefungin (**3**), isolated from various *Streptomyces*,[6] is a structural analogue of SAM and SAH

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(1) Pugh, Ch. S. G.; Borchardt, R. T. *Biochemistry* **1982**, *21*, 1535 and references cited therein. Wolfe, M. S.; Borchardt, R. T. *J. Med. Chem.* **1991**, 1521.

(2) Pegg, Anthony E. *Cancer Res.* **1988**, *48*, 759.

(3) Stanek, J.; Caravatti, G.; Frei, J.; Furet, P.; Mett, H.; Schneider, P.; Regenass, U. *J. Med. Chem.* **1993**, *36*, 2168.

(4) (a) Casara, P.; Marchal, P.; Wagner, J.; Danzin, C. *J. Am. Chem. Soc.* **1989**, *111*, 9111. (b) Wu, Y.; Woster, P. M. *J. Med. Chem.* **1992**, *35*, 3196.

(5) Wolos, J. A.; Frondorf, K. A.; Babcock, G. F.; Stripp, S. A.; Bowlin, T. L. *Cell. Immunol.* **1993**, *149*, 402.

(6) (a) Hamill, R. L.; Hoehn, M. M. *J. Antibiot.* **1973**, *26*, 463. (b) Florent, J.; Lunel, J.; Mancy, D. U.S. Patent 4 189 349, 1980.

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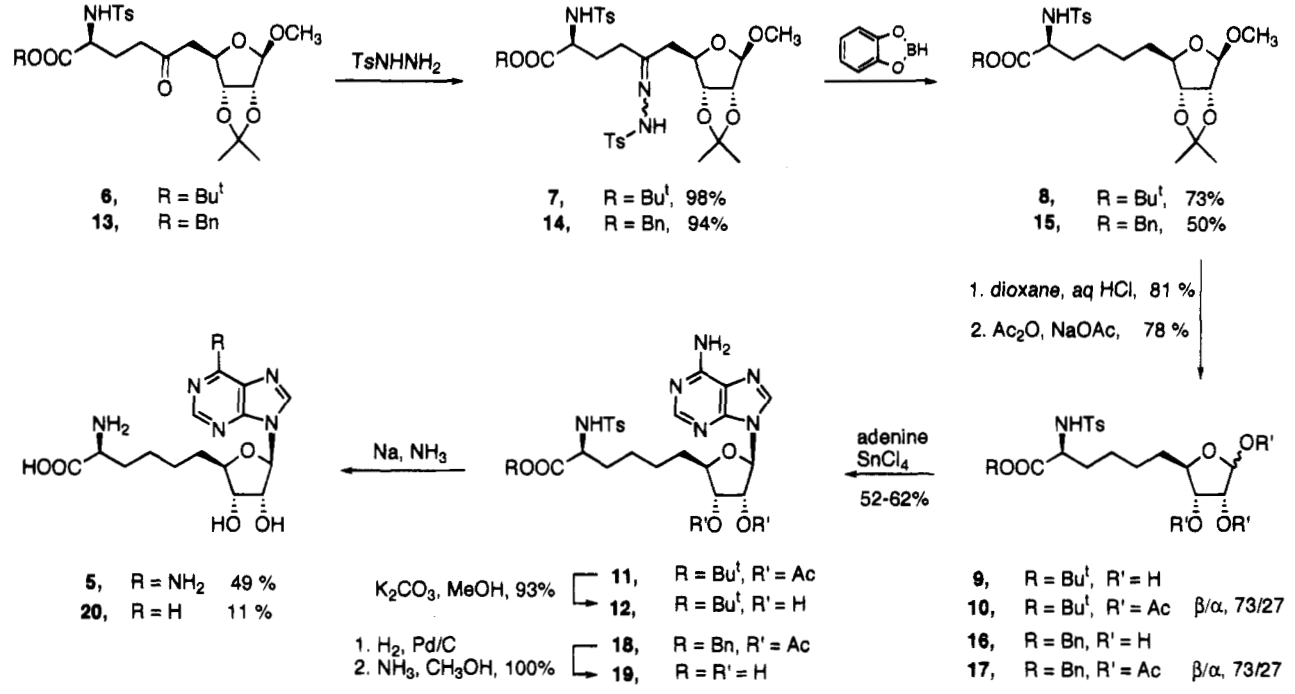
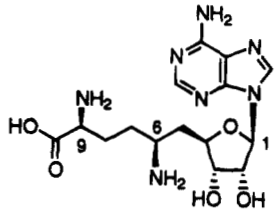
Scheme 1. Synthesis of 6-Deaminosinefungin from Ketone 6



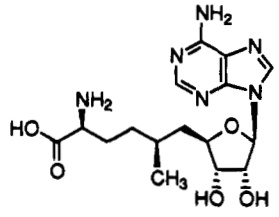
and has shown a variety of biological effects including antiviral,[1] antifungal,[6b] and antiparasitic[7] activities. We



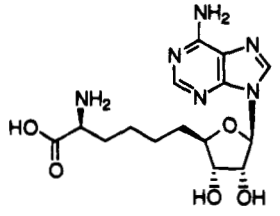
3
Sinefungin

recently reported the first stereospecific synthesis of sinefungin.[8] Considering the importance of SAM and its metabolism in various systems, and cognizant of the potency of sinefungin, our goal has been to design analogues of SAM and/or SAH based on the structure of sinefungin (**3**). Those analogues could be valuable lead compounds in the search of SAM/SAH inhibitors.

We now report the syntheses of (*S*)-6-methyl-6-deaminosinefungin (**4**) and 6-deaminosinefungin (**5**), two carbon analogues of SAM and SAH, respectively. The structural similarity of **4** to SAM and of **5** to SAH might allow for binding to and inhibition of various enzymes including SAM-transferase, SAM-decarboxylase, and SAH-hydrolase. Also, **4** and **5** could clarify the question about the role of the C-6 stereocenter.



4
(*S*)-6-Methyl-6-deaminosinefungin



5
6-Deaminosinefungin

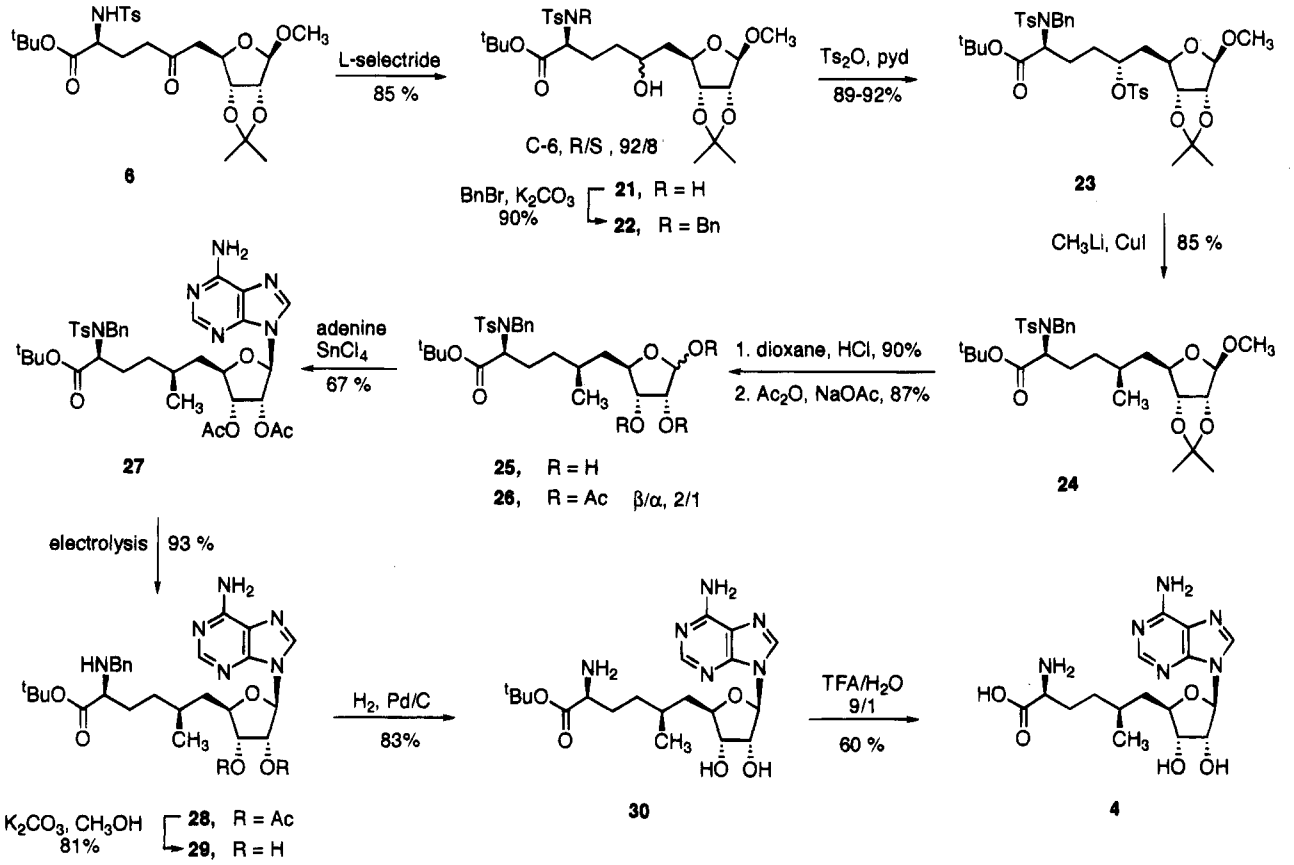
Results and Discussion

The C-6-ketone **6** (Scheme 1), an intermediate in the sinefungin synthesis, was chosen as an appropriate starting point for the synthesis of both target compounds **4** and **5**. Ketone **6** is readily prepared from L-ornithine and D-ribose as reported earlier.[8]

Reduction of ketone **6** to give methylene analogue **8** was expected to be followed by a smooth transformation to **5**. The deoxygenation procedure was required to be quite mild since **6** has proven to be sensitive to both acidic and alkaline conditions. Conversion of **6** to **8** was accomplished in two steps using the tosylhydrazone–hydroboration method.[9] Thus, condensation of **6** with *p*-toluenesulfonohydrazide catalyzed by oxalic acid gave the hydrazone **7** in 98% yield (Scheme 1). Reduction of **7** using catecholborane then gave **8** in 73% yield. In preparation for C-1-adenosylation, the sugar protecting groups of **8** were exchanged by treatment with aqueous dioxane/HCl, which cleaved the methyl glycoside and isopropylidene groups to form triol **9**, followed by acetylation with acetic anhydride and sodium acetate. This gave a 73/27 ratio of triacetates **10β/10α** (estimated by integration of H-C-1 in the ^{1}H NMR) in a yield of 81%. This mixture of **10β** and **10α** was easily separated by chromatography and reaction of **10β** with adenine, catalyzed by $SnCl_4$[10] afforded a 52% yield of nucleoside **11**. Removal of the acetate groups of **11** by treatment with potassium carbonate in MeOH proceeded in 93% yield to give diol nucleoside **12**. Further deprotection of **12** could not be achieved in satisfactory yield despite a variety of attempts. The major problem is the instability of the C-1-*N*-glycoside bond to the acidic conditions necessary for the cleavage of the *tert*-butyl ester. This

(7) Trager, W.; Tershakovec, M. *Exp. Parasitol.* **1980**, *50*, 83.
(8) Maguire, M. P.; Feldman, P. L.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 948.
(9) Kabalka, G. W.; Baker, J. D., Jr. *J. Org. Chem.* **1975**, *40*, 1834.
(10) Saneyoski, M.; Satoh, E. *Chem. Pharm. Bull.* **1979**, *27*, 2518.

Scheme 2. Stereoselective Synthesis of (*S*)-6-Methyldeaminosinefungin from Ketone 6



was in contrast to the stability to trifluoroacetic acid of the *N*-glycosidic bond of similar C-6-NH_2 compounds[8] in which the presence of a positively charged primary amine inhibited N-glycoside cleavage.

Clearly our synthesis needed to be modified to include an ester protecting group that could be removed by nonacidic means. This was provided by the benzyl ester which can be removed by hydrogenolysis and also is sufficiently stable to survive the synthetic sequence. Thus, the ester protecting group was changed from *tert*-butyl to benzyl early in the sequence before joining the ornithine and ribose moieties (see supplementary material) and benzyl ester–ketone **13** was prepared[8] analogously to *tert*-butyl ester–ketone **6**. Conversion of ketone **13** to ester nucleoside **18** was accomplished in the sequence used for the conversion of ketone **6** to nucleoside **11** with minor changes in the experimental procedures.

Condensation of ketone **13** with *p*-toluenesulfonohydrazide gave hydrazone **14** in 94% yield which was in turn reduced with catecholborane to give methylene analogue **15** in 50% yield. Cleavage of the sugar protecting groups of **15** (as with **8**) gave triol **16** which was acetylated to obtain **17**β/**17**α in a ratio of 76/24 and in 78% yield from **15**. Adenosylation of glycosyl ester **17**β catalyzed by $SnCl_4$ gave nucleoside **18** in 62% yield. Use of the benzyl protecting group allowed for facile removal of three of the four protecting groups. Hydrogenolysis of **18** over 10% Pd/C in MeOH followed by addition of methanolic ammonia gave **19** in almost quantitative yield. The *N*-tosyl group of **19** was removed by brief exposure (1 min) to sodium in liquid ammonia at −78 °C which gave a mixture of **5** (49% yield from **18**) and deaminated product **20** (11% yield from **18**). The mixture of **5** and **20** was separated and purified by reversed-phase HPLC. Thus, 6-deaminosinefungin (**5**) was synthesized in eight steps from ketone **13** in 9% overall yield.

Our synthetic plan for the 6-methylsinefungin analogue **4** is outlined in Scheme 2. It is known[8] that ketone **6** is reduced stereoselectively to alcohols **21** using excess L-Selectride (Aldrich) in 85% yield, with a ratio of 92/8, *R*/*S*, at C-6. Alcohol **21** was further protected with an *N*-benzyl group to give **22** in 90% yield. This additional protection of the sulfonamide was necessary to avoid lactam formation in the later methylation step, in which a strong nucleophilic base would be used. The secondary alcohol **22** was then transformed into tosylates **23** using *p*-toluenesulfonic anhydride (Ts_2O) in pyridine.[11] Separation of the epimeric tosylates **23** could be achieved by chromatography, and diastereomerically pure **23** was obtained in 89–92% yield. Tosylate **23** was shown to be diastereomerically pure by ^1H NMR and HPLC, and the configuration at C-6 has been shown[8] to be *R*.

To obtain the C-6 methyl compound **24**, the methyl function at C-6 was introduced using cuprates, formed in situ from cuprous iodide and methyllithium[12] in ether.[13] Since introduction of the methyl group into **23** takes place with inversion[14] at C-6, methyl compound **24**, obtained in 85% yield, has the *S*-configuration at C-6. Introduction of the methyl group under these basic

(11) Bonner, R. M.; Rapoport, H. *J. Am. Chem. Soc.* **1951**, *73*, 2872.
(12) Johnson, C. R.; Dutra, G. A. *J. Am. Chem. Soc.* **1973**, *95*, 7777.
(13) It was important to monitor the formation of the cuprate. When the first equivalent of methyllithium was added to the suspension of cuprous iodide in ether, a bright orange color appeared, indicating the formation of the mono complex. When the second equivalent of methyllithium was added, the orange color disappeared, leaving behind an almost colorless, clear solution. An excess of methyllithium is not advisable; strongly basic conditions lead to a loss of the benzyl group and subsequent formation of a pyrrolidine.
(14) Johnson, C. R.; Dutra, G. A. *J. Am. Chem. Soc.* **1973**, *95*, 7783.

conditons carries the potential of racemization at the α carbon (C-9) of **24**. We found no signs of racemization in the ^1H NMR or in an HPLC chromatogram; however, to prove diastereomeric purity, we deliberately racemized **24**. Thus, a sample of diastereomerically pure **24** was dissolved in THF and treated at −78 °C with 100 mol % of potassium hexamethyldisilazane (KHMDS). After 10 min the mixture was warmed to 0 °C, quenched with saturated NH_4Cl, and stirred for 1 h. After isolation the expected racemization at C-9 was confirmed by ^1H NMR and HPLC and provided a control sample.

In preparation for C-1-adenosylation, the sugar protecting groups of **24** were exchanged by treatment with aqueous dioxane/HCl (→ **25**, 90% yield) followed by acetylation with acetic anhydride and sodium acetate. Triacetate **26** was obtained in 87% yield with a 2/1 ratio of β/α. The anomeric mixture can be separated; however, separation was not necessary.[15] Transformation of the mixture**26** into nucleoside **27** was effected by reaction with adenine/$SnCl_4$[10] in acetonitrile.[16] As anticipated, the β-anomer of **27** was obtained in 65−67% yield by reacting either the α or the β anomer of **26**. The fully protected nucleoside **27** was obtained as a white solid in 67% yield.

We now faced the task of removing four different protecting groups from nucleoside **27**. Essential was to find an appropriate deprotection sequence which would not cleave the *N*-glycosidic bond during the acidic *tert*-butyl ester cleavage. Our plan was to remove the *p*-toluenesulfonyl group first, on the hypothesis that a preexisting positive charge on the secondary amine would inhibit *N*-glycoside cleavage. To remove the tosyl group we used electrolysis,[17] which is much milder and more specific than dissolving metal[18] and provided secondary amine **28** in a clean reaction with excellent yields of 90−93%. The acetyl groups of **28** were removed with potassium carbonate in MeOH at 0 °C[19] to obtain diol **29** in 81% yield. The *N*-benzyl group of diol **29** was removed by hydrogenolysis using 10% Pd/C in MeOH to provide primary amine **30** in 83% yield. Finally, amine **30** was treated with TFA/H_2O (9/1) at 0 °C. After chromatography, we obtained (*S*)-6-methyl-6-deaminosinefungin (**4**) in 60% yield as a zwitterion. Thus, **4** was synthesized in 11 steps from ketone **6** in an overall yield of 13%.

Conclusion

We report the first chirospecific syntheses of (*S*)-6-methyl-6-deaminosinefungin (**4**) and 6-deaminosinefungin (**5**) which are analogues of SAM (**1**), SAH (**2**) and sinefungin (**3**). Compound **4** in which the methyl group is attached stereospecifically, is a direct mimic of SAM (**1**) and may be a competitive inhibitor since it is incapable of methyl transfer. The synthesis of (*S*)-6-methyl-6-deaminosinefungin (**4**) required stereospecific methylation at C-6 and removal of the *N*-(*p*-toluenesulfonyl) group which was achieved by electrolysis. Developing an appropriate deprotection sequence allowed use of the *tert*-butyl ester protecting group. The methods developed for our syntheses should be applicable for the preparation of a variety of other analogues of sinefungin, SAM and SAH.

Experimental Section

General. Ether and THF were distilled from Na/benzophenone; CH_3CN and 1,2-dichloroethane were distilled from CaH_2; CH_3OH was distilled from Mg; dioxane was distilled from sodium. Reactions were conducted under an atmosphere of dry nitrogen unless otherwise noted, and final organic solutions in the isolation process were dried over $MgSO_4$, unless otherwise noted, before rotary evaportion at reduced pressure. Melting points were determined with an open capillary apparatus and are uncorrected. NMR spectra were taken in $CDCl_3$ unless otherwise noted; chemical shifts are reported in ppm (δ unit) downfield of internal TMS with coupling constants in hertz. Elemental analyses were performed by the Analytical Laboratory, College of Chemistry, University of California, Berkeley, CA. HPLC was performed on an Altex system using a reversed-phase Whatman Partisil 10 ODS-3 column. Low-pressure chromatography (LPC) was carried out using 230−400-mesh silica gel. Analytical TLC was done with aluminum-backed silica plates (E. Merck), products were visualized by UV absorption, I_2, or by spraying with a solution of ninhydrin (400 mg of ninhydrin in 200 mL of absolute EtOH).

***tert*-Butyl [Methyl 2,3-*O*-(isopropylidene)-5,7,8,9-tetradeoxy-9(*S*)-[(*p*-toluenesulfonyl)amino]-β-D-*ribo*-deculofuranosid]uronate (6).** Using the same procedures as described,[8] ketone **6** was prepared from the corresponding oxime: ^{13}C NMR δ 21.4, 24.9, 26.4, 26.7, 27.5, 38.2, 47.6, 54.9, 55.3, 82.5, 82.6, 84.0, 85.2, 109.5, 112.4, 127.3, 129.2, 136.3, 143.6, 170.4, 207.0.

***tert*-Butyl [Methyl 2,3-*O*-(isopropylidene)-5,6,7,8,9-pentadeoxy-9(*S*)-[(*p*-toluenesulfonyl)amino]-6-[(*p*-toluenesulfonyl)hydrazono]-β-D-*ribo*-decofuranosid]-uronate (7).** A solution of ketone **6** (822 mg, 1.56 mmol), toluenesulfonohydrazide (640 mg, 3.44 mmol), and anhydrous oxalic acid (915 mg, 10.2 mmol) in absolute EtOH (20 mL) was stirred at 22 °C for 9 h. The reaction mixture was partitioned between CH_2Cl_2/H_2O, 100/50 mL, and the separated organic layer was washed with saturated $NaHCO_3$ (50 mL) and brine (30 mL), dried ($MgSO_4$), and evaporated to give 1.37 g of a white foam. This foam was dissolved in CH_2Cl_2, (80 mL), and succinic anhydride (1.2 g, 12 mmol) and dry pyridine (1 mL) were added. The mixture was stirred for 14 h, and then MeOH (10 mL), containing 3 mL of concentrated ammonium hydroxide, was added. The mixture was stirred for 10 min, diluted with CH_2Cl_2 (50 mL), washed with H_2O (50 mL), 1 M citric acid (50 mL), saturated $NaHCO_3$ (50 mL), and brine (40 mL), dried, and evaporated to give 1.06 g (98%) of crude **7** which was used directly in the next step.

***tert*-Butyl [Methyl 2,3-*O*-(isopropylidene)-5,6,7,8,9-pentadeoxy-9(*S*)-[(*p*-toluenesulfonyl)amino]-β-D-*ribo*-decofuranosid]uronate (8).** To a solution of catechol (949 mg, 8.62 mmol) in ethanol-free $CHCl_3$ (27 mL) at 0 °C was added dropwise 1 M BH_3/THF (8.62 mL). The solution was warmed to 22 °C over 30 min and cooled to 0 °C, and then a solution of tosylhydrazone **7** (913 mg, 1.31 mmol) in $CHCl_3$ (18 mL) was injected dropwise over a 30-min period and the reaction mixture was stirred at 2 °C for 26 h. Sodium acetate trihydrate (3.45 g, 25.4 mmol) was added, and the mixture was diluted with $CHCl_3$ (90 mL), heated at reflux for 14 h, and then partitioned between ether/H_2O, 500/200 mL. The separated organic layer was washed with 1 M citric acid (200 mL), saturated $NaHCO_3$ (200 mL), and brine (100 mL) and dried. Evaporation gave 1.55 g of a residue which on LPC (eluting with 0.5% MeOH in $CHCl_3$) gave 491 mg (73%) of **8**; after recrystallization from hexane/EtOAc, mp 106−108 °C: $[\alpha]^{24}_D$ +8.5° (*c* 2.6, $CHCl_3$); IR (KBr) 3215, 1730, 1345, 1158, 1095 cm^{-1}; ^1H NMR δ 1.12−1.80 (m, 8 H), 1.24 (s, 9 H), 1.32 (s, 3 H), 1.48 (s, 3 H), 2.40 (s, 3 H), 3.33 (s, 3 H), 3.76 (m, 1 H), 4.10 (m, 1 H), 4.50 (d, J = 6.0, 1 H), 4.59 (d, J = 6.0, 1 H),

(15) Vorbrüggen, H.; Krolikiewicz, K; Bennua, B. *Chem. Ber.* **1981**, *114*, 1234.

(16) Saneyoski and Satoh[10] used a large excess of adenine and $SnCl_4$ (1000 mol %). We found that this reaction can be done with a smaller excess of both (500 mol %), still providing the same yield.

(17) Roemmele, R. C.; Rapoport, H. *J. Org. Chem.* **1988**, *53*, 2367. Civitello, E. R.; Rapoport, H. *J. Org. Chem.* **1992**, *57*, 834.

(18) Partial loss of the 6-amine of adenine occurs when using Na/liquid NH_3 for the detosylation in the preparation of **5**, leading to a small amount of **20**.

(19) Plattner, J. J.; Gless, R. D.; Rapoport, H. *J. Am. Chem. Soc.* **1972**, *94*, 8613.

4.93 (s, 1 H), 5.13 (d, J = 9.3, 1 H), 7.28 (d, J = 8.3, 2 H), 7.72 (d, J = 8.3, 2 H). Anal. Calcd for $C_{25}H_{39}NO_8S$: C, 58.5; H, 7.7; N, 2.7. Found: C, 58.4; H, 7.9; N, 2.7.

***tert*-Butyl [5,6,7,8,9-Pentadeoxy-9(*S*)-[(*p*-toluenesulfonyl)amino]-1,2,3-tri-*O*-acetyl]-β-D-*ribo*-decofuranuronate (10β) and its C-1 Epimer 10α.** To a solution of methylene compound **8** (410 mg, 0.799 mmol) in dioxane (100 mL) was added 4 M HCl (33 mL), and the biphasic mixture was stirred at 22 °C for 40 h and then partitioned between EtOAc/0.25 M Na_2HPO_4, 200/200 mL. The aqueous layer was back-extracted with EtOAc (3 × 100 mL), and the combined organic phase was washed with brine (100 mL), dried, and evaporated to give 400 mg of an off-white solid **crude ribose analogue 9**. This solid was dissolved in acetic anhydride (50 mL), anhydrous sodium acetate (0.77 g, 9.4 mmol) was added, the mixture was stirred at 50 °C for 5 h, and then the solvent was evaporated. The residue was coevaporated with *p*-xylene twice and partitioned between EtOAc/H_2O, 100/50 mL, and then the separated organic layer was washed with saturated $NaHCO_3$ (50 mL) and brine (25 mL), dried, and evaporated to give 700 mg of an oil. Chromatography (eluting with 30% EtOAc/hexane) gave 228 mg (49%) of **10β** (containing 1% of an unidentified impurity) and 110 mg (21%) of a mixture of **10β/10α** (84/16). After recrystallization from hexane/ether pure **10β** was obtained, mp 106–108 °C: $[\alpha]^{24}_D$ +21° (*c* 0.8, $CHCl_3$); IR (KBr) 3280, 1750, 1728, 1350, 1215 cm^{-1}; ^1H NMR δ 1.23 (s, 9 H), 1.29–1.70 (m, 8 H), 2.07 (s, 3 H), 2.09 (s, 3 H), 2.12 (s, 3 H), 2.40 (s, 3 H), 3.72 (m, 1 H), 4.14 (m, 1 H), 5.18 (m, 2 H); 5.31 (d, J = 4.7, 1 H), 6.12 (d, J = 0.6, 1 H), 7.28 (d, J = 8.2, 2 H), 7.71 (d, J = 8.2, 2 H). Anal. Calcd for $C_{27}H_{39}NO_{11}S$: C, 55.4; H, 6.7; N, 2.4. Found: C, 55.4; H, 6.8; N, 2.4.

***tert*-Butyl [1-(9-Adenyl)-2,3-di-*O*-acetyl-1,5,6,7,8,9-hexadeoxy-9(*S*)-[(*p*-toluenesulfonyl)amino]]-β-D-*ribo*-decofuranuronate (11).** Into a suspension of adenine (429 mg, 3.47 mmol) in CH_3CN (18 mL), distilled from P_2O_5, then from CaH_2) was injected a solution of $SnCl_4$ (3.75 mL, 0.985 M in 1,2-dichloroethane, 3.69 mmol). This mixture was stirred at 22 °C for 15 min, and then a solution of triacetate **11β** (223 mg, 0.38 mmol) in CH_3CN (7 mL) was injected. After being stirred at 22 °C for 4.5 h the mixture was partitioned between EtOAc/0.25 M Na_2HPO_4, 200/200 mL. The organic layer was washed with brine (100 mL), dried, and evaporated to give 240 mg of a white solid. Chromatography (eluting with EtOAc) gave 145 mg (52%) of crude **11** as a white foam, used directely in the next step: ^1H NMR δ 1.21 (s, 9 H), 1.25–2.00 (m, 8 H), 2.07 (s, 3 H), 2.14 (s, 3 H), 2.40 (s, 3 H), 3.75 (m, 1 H), 4.17 (m, 1 H), 5.45 (t, J = 5.3, 1 H), 5.80 (d, J = 9.2, 1 H), 5.87 (br s, 2 H), 5.92 (t, J = 5.5, 1 H), 6.09 (d, J = 5.3, 1 H), 7.26 (d, J = 8.3, 2 H), 7.71 (d, J = 8.3, 2 H), 7.94 (s, 1 H), 8.36 (s, 1 H).

***tert*-Butyl [1-(9-Adenyl)-1,5,6,7,8,9-hexadeoxy-9(*S*)-[(*p*-toluenesulfonyl)amino]]-β-D-*ribo*-decofuranuronate (12).** To a solution of crude **11** (115 mg, 0.17 mmol) in MeOH (15 mL) was added anhydrous K_2CO_3 (150 mg). The mixture was stirred at 22 °C for 45 min, filtered, adjusted to pH 7 with AcOH, and partitioned between EtOAc/H_2O, 40/20 mL. The aqueous layer was back-extracted with EtOAc (2 × 20 mL), and the combined organics were washed with brine and dried. Evaporation gave 93 mg (93%) of **12** as an amorphous solid: ^1H NMR δ 1.03–1.80 (br m, 8 H), 1.19 (s, 9H), 2.36 (s, 3 H), 3.79 (br m, 1 H), 4.10 (br m, 2 H), 4.63 (br m, 1 H), 5.96 (d, J = 4.8, 1 H), 6.56–6.85 (br m, 3 H), 7.24 (d, J = 8.2, 2 H), 7.71 (d, J = 8.2, 2 H), 8.01 (s, 1 H), 8.17 (s, 1 H). Anal. Calcd for $C_{26}H_{36}N_6O_7S$: C, 54.2; H, 6.3; N, 14.6. Found: C, 54.0; H, 6.4; N, 14.3.

The corresponding **benzyl ester–ketone 13** was prepared from the same intermediates and by the same procedures[8] as used to prepare ***tert*-butyl ester–ketone 6.** Thus, ***tert*-butyl (*S*)-2-[(*p*-toluenesulfonyl)amino]-5-nitropentanoate** was hydrolyzed to the **(*S*)-2-[(*p*-toluenesulfonyl)amino]-5-nitropentanoic acid** with trifluoroacetic acid in CH_2Cl_2. This acid was converted to **benzyl (*S*)-2-[(*p*-toluenesulfonyl)amino]-5-nitropentanoate** by treatment with *O*-benzyl-*N*,*N*'-diisopropylisourea. Aldol condensation, catalyzed by fluoride ion, with the 5-aldehyde derived from ribose gave the corresponding diastereomeric mixture of nitro alcohols, **benzyl [methyl 6-nitro-6,7,8,9-tetradeoxy-9(*S*)-[(*p*-toluenesulfonyl)amino]-2,3-*O*-isopropylidene-β-D-*ribo*-furanosid]uronates.** These were dehydrated to a mixture of **nitrovinyl isomers** which were reduced to the oximes **benzyl [methyl 6-(hydroxyimino)-5,6,7,8,9-pentadeoxy-9(*S*)-[(*p*-toluenesulfonyl)amino]-2,3-*O*-isopropylidene-β-D-*ribo*-decofuranosid]uronates.** Oxidation with ceric ammonium nitrate then gave **benzyl ester–ketone 13.** These procedures are described in the supplementary material.

Benzyl [Methyl 2,3-*O*-isopropylidene-5,6,7,8,9-pentadeoxy-9(*S*)-[(*p*-toluenesulfonyl)amino]-6-(*p*-toluenesulfonylhydrazono)-β-D-*ribo*-decofuranosid]uronate (14). A solution of ketone **13** (2.52 g, 4.49 mmol), *p*-toluenesulfonohydrazide (1.26 g, 6.61 mmol), and anhydrous oxalic acid (1.22 g, 13.6 mmol) in absolute EtOH (35 mL) was stirred at 22 °C for 24 h. The solution was then partitioned between CH_2Cl_2/H_2O, 150/75 mL, and the separated organic layer was washed with saturated $NaHCO_3$ (75 mL) and brine (50 mL), dried, and evaporated. Chromatography (eluting with 40% EtOAc/petroleum ether, applied to the column in CH_2Cl_2) gave 3.07 g (94%) of **14** and allowed for partial separation of the hydrazone isomers **14a** and **14b**. For the higher R_f hydrazone: partial ^1H NMR δ 1.30 (s, 3 H), 1.48 (s, 3 H), 2.39 (s, 3 H), 2.40 (s, 3 H), 5.71 (d, J = 8.5,1 H), 7.10–7.36 (m, 9 H), 7.66 (d, J = 8.3, 2 H), 8.10 (s, 1 H). For the lower R_f hydrazone: partial ^1H NMR δ 1.31 (s, 3 H), 1.44 (s, 3 H), 2.34 (s, 3 H), 2.38 (s, 3 H), 3.49 (s, 3 H), 5.37 (d, J = 9.2, 1 H), 7.08–7.40 (d, J = 8.5, 2 H), 7.71 (d, J = 8.6, 2 H), 9.20 (s, 1 H).

Benzyl [Methyl 2,3-*O*-isopropylidene-5,6,7,8,9-pentadeoxy-9(*S*)-[(*p*-toluenesulfonyl)amino]-β-D-*ribo*-decofuranosid]uronate (15). To a stirred solution of tosylhydrazone **14** (1.42 g, 1.95 mmol) in ethanol-free $CHCl_3$ (20 mL) at 0 °C was added dropwise catecholborane (6.40 mL, 1.53 M solution in THF, 9.79 mmol). The resulting solution was stirred at 0 °C for 24 h, sodium acetate trihydrate (5.14 g, 37.8 mmol) and $CHCl_3$ (50 mL) were added, and the mixture was heated to reflux for 18 h and then partitioned between ether/H_2O, 500/150 mL. The separated organic phase was washed with 1 M citric acid (150 mL), saturated $NaHCO_3$ (150 mL), and brine (100 mL), dried, and evaporated. Chromatography of the crude residue (eluting with 0.5% MeOH/$CHCl_3$ to remove catechol) gave 780 mg of an impure colorless oil. LPC (eluting with 30% EtOAc/petroleum ether; applied to the column in CH_2Cl_2) gave 529 mg (50%) of semicrystalline **15**. The **15** thus obtained was further purified by recrystallization from hexane/EtOAc then from ether, which gave 493 mg, 47% yield, of methylene compound **15**, mp 86–87 °C: $[\alpha]^{20}_D$ +7.6° (*c* 1.1, $CHCl_3$); ^1H NMR δ 1.20–1.80 (m, 8 H), 1.31 (s, 3 H), 1.48 (s, 3 H), 2.40 (s, 3 H), 3.31 (s, 3 H), 3.95 (m, 1 H), 4.06 (m, 1 H), 4.47 (d, J = 5.9, 1 H), 4.58 (d, J = 5.9, 1 H), 4.90 (s, 2 H), 4.92 (s, 1 H), 5.18 (d, J = 9.3, 1 H), 7.14–7.38 (m, 7 H), 7.69 (d, J = 8.3, 2 H). Anal. Calcd for $C_{28}H_{37}NO_8S$: C, 61.4; H, 6.8; N, 2.6. Found: C, 61.2; H, 6.9; N, 2.5.

Benzyl [5,6,7,8,9-Pentadeoxy-9(*S*)-[(*p*-toluenesulfonyl)amino]-1,2,3-tri-*O*-acetyl]-β-D-*ribo*-decofuranuronate (17β) and its C-1 Epimer 17α. To a solution of methylene compound **15** (1.15 g, 2.10 mmol) in dioxane (210 mL) was added 4 M HCl (70 mL), the biphasic mixture was stirred at 22 °C for 44 h, and then the mixture was partitioned between EtOAc/0.25 M Na_2HPO_4, 560/750 mL. The aqueous layer was back-extracted with EtOAc (3 × 250 mL), and the combined organics were washed with brine (350 mL), dried, and evaporated to give 1.04 g of crude triol **16** as an off-white solid. This solid was dissolved in acetic anhydride (100 mL), anhydrous sodium acetate (2.20 g, 26.8 mmol) was added, the mixture was stirred at 50 °C for 5 h, and then the solvent was evaporated. The residue was coevaporated with *p*-xylene twice and partitioned between EtOAc/H_2O, 100/40 mL, and the separated organic layer was washed with saturated $NaHCO_3$ (40 mL) and brine (20 mL), dried, and evaporated to yield 1.26 g of an oil. Chromatography (eluting with 30% EtOAc/petroleum ether, applied to column in CH_2Cl_2) gave 758 mg (58%) of **17β** (containing 2% of an unidentified impurity) and 264 mg (20%) of a mixture of **17β/17α** (84/16). For **17β** (oil): $[\alpha]^{20}_D$ +16° (*c* 1.3, $CHCl_3$); ^1H NMR δ 1.22–1.82 (m, 8 H), 2.07 (s, 6 H), 2.12 (s, 3 H), 2.40 (s, 3 H), 3.92 (m, 1 H), 4.89 (s, 2 H),

5.13 (dd, J = 4.9, 6.8, 1 H), 5.29 (m, 2 H), 6.11 (s, 1 H), 7.14–7.40 (m, 7 H), 7.68 (d, J = 8.2, 2 H). Anal. Calcd for $C_{30}H_{37}NO_{11}S$: C, 58.1; H, 6.0; N, 2.3. Found: C, 57.7; H, 6.0; N, 2.2. For **17α** (oil): ^{1}H NMR δ 1.20–1.80 (m, 8 H), 2.07 (s, 3 H), 2.12 (s, 3 H), 2.40 (s, 3 H), 3.93 (m, 1 H), 4.16 (m, 1 H), 4.90 (s, 2 H), 5.00 (dd, J = 3.6, 6.8, 1 H), 5.17 (m, 1 H), 5.28 (d, J = 9.1, 1 H), 6.35 (d, J = 4.6, 1 H), 7.12–7.38 (m, 7 H), 7.69 (d, J = 8.2, 2 H).

Benzyl [1-(9-Adenyl)-2,3,-di-*O*-acetyl-1,5,6,7,8,9-hexadeoxy-9(*S*)-[(*p*-toluenesulfonyl)amino]]-β-D-*ribo*-decofuranuronate (18). Using the same procedure as for the preparation of *tert*-butyl ester **11**, from 706 mg (1.14 mmol) of triacetate **17β**, there was obtained 480 mg, 61% yield, of **18** as an amorphous foam: $[\alpha]^{20}_D$ +15° (*c* 1.7, $CHCl_3$); ^{1}H NMR δ 1.22–1.95 (br m, 8 H), 2.07 (s, 3 H), 2.14 (s, 3 H), 2.38 (s, 3 H), 3.95 (m, 1 H), 4.15 (m, 1 H); 4.84 (d, J = 12.0, 1 H), 4.89 (d, J = 12.0, 1 H), 5.43 (t, J = 5.2, 1 H), 5.88 (m, 3 H), 6.07 (d, J = 5.3, 1 H), 6.15 (br d, J = 9.5, 1 H), 7.11–7.39 (m, 7 H), 7.68 (d, J = 8.3, 2 H), 7.92 (s, 1 H), 8.35 (s, 1 H); HRMS calcd for $C_{33}H_{39}N_6O_9S$ (MH^+) 695.2501, found 695.2483.

1-(9-Adenyl)-1,5,6,7,8,9-hexadeoxy-9(*S*)-[(*p*-toluenesulfonyl)amino]-β-D-*ribo*-decofuranoic acid (19). A solution of nucleoside **18** (460 mg, 0.66 mmol) in MeOH (30 mL) and 10% Pd/C (50 mg) was stirred at 22 °C under a H_2 atmosphere (balloon) for 24 h. An additional 55 mg of 10% of Pd/C was added and the hydrogenolysis continued for 24 h, and then a saturated solution of methanolic ammonia (30 mL, saturated at 0 °C) was added. The mixture was stirred at 22 °C for 3 h, filtered through Celite, and evaporated to give 363 mg of the ammonium salt **19** as an off-white foam: ^{1}H NMR (CD_3OD) δ 1.28–1.82 (br m, 8 H), 2.37 (s, 3 H), 3.58 (m, 1 H), 3.98 (m, 1 H), 4.10 (br t, J = 4.9, 1 H), 5.95 (d, J = 5.1, 1 H), 7.30 (d, J = 8.0, 2 H), 7.71 (d, J = 8.0, 2 H), 8.21 (s, 1 H), 8.24 (s, 1 H); HRMS calcd for $C_{22}H_{29}N_6O_7S$ (MH^+) 521.1821, found 521.1811.

6-Deaminosinefungin (5) and 9(*S*)-Amino-1,5,6,7,8,9-hexadeoxy-1-(9*H*-purin-9-yl)-β-D-*ribo*-decofuranoic acid (20). To a vigorously stirred (mechanical stirrer with glass paddle) solution of diol **19** (88 mg, 0.16 mmol) in liquid ammonia (30 mL, distilled from sodium) at −78 °C was added sodium (147 mg) in small chunks over a period of 15 s. After the addition was completed the solution was stirred for another 60 s, and then the reaction was quenched by addition of NH_4Cl (385 mg) and the ammonia was evaporated under a stream of N_2. The residue was dissolved in H_2O, the mixture was filtered, and the filtrate was purified by reversed-phase HPLC (eluting with 4% CH_3CN/H_2O) to give 29 mg (49%) of **5** and 6 mg (11%) of **20**. For **5**: mp 188 °C (softens) >195 °C dec; $[\alpha]^{20}_D$ −11° (*c* 2.9, H_2O); ^{1}H NMR (D_2O, δ relative to dioxane, 3.53 ppm, as an internal standard) δ 1.23 (m, 4 H), 1.56 (m, 2 H), 1.56 (m, 2 H), 1.67 (m, 2 H), 3.51 (t, J = 5.8, 1 H), 3.90 (m, 1 H), 4.00 (t, J = 4.9, 1 H), 4.99 (t, J =5.3, 1 H), 5.75 (d, J = 5.4, 1 H), 7.89 (s, 1 H), 7.99 (s, 1 H); ^{13}C NMR (D_2O, δ relative to dioxane, 66.5 ppm, as an internal standard) δ 24.2, 24.5, 30.5, 32.4, 54.8, 73.0, 73.5, 84.4, 87.1, 118.6, 139.7, 148.7, 152.7, 155.4, 175.4; HRMS calcd for $C_{15}H_{23}N_6O_5$ (MH^+) 367.1732, found 367.1713. Anal. Calcd for $C_{15}H_{23}N_6O_5{\cdot}2H_2O$: C, 44.8; H, 6.5; N, 20.9. Found: C, 45.1; H, 5.9; N, 20.7. For **20**: ^{1}H NMR (D_2O, δ relative to dioxane, 3.53 ppm, as an internal standard) δ 1.23 (m, 4 H), 1.61 (m, 4 H), 3.48 (m, 1 H), 3.91 (m, 1 H), 4.08 (t, J = 4.9, 1 H), 4.65 (t, J = 5.3, 1 H), 5.92 (d, J = 5.2, 1 H), 8.40 (s, 1 H), 8.68 (s, 1 H); 8.87 (s, 1 H); ^{13}C NMR (D_2O, δ relative to dioxane, 66.5 ppm, as an internal standard) δ 24.2, 24.5, 30.5, 32.3, 54.8, 73.1, 73.5, 84.7, 87.6, 133.5, 145.4, 147.9, 150.7, 152.1, 175.4; HRMS calcd for $C_{15}H_{22}N_5O_5$ (MH^+) 352.1622, found 352.1614. Anal. Calcd for $C_{15}H_{21}N_5O_5{\cdot}H_2O$: C, 48.8; H, 6.3, N, 19.0. Found: C, 48.5; H, 6.4; N, 18.7.

***tert*-Butyl [Methyl 2,3-*O*-isopropylidene-5,7,8,9-tetradeoxy-9(*S*)-[(*p*-toluenesulfonyl)amino]-β-D-*allo*-decofuranosid]uronate (21).** Using the same procedures as described previously, alcohol **21** was prepared from the corresponding ketone **6** in a yield of 85%. By integration of the C1-H in the ^{1}H NMR the ratio of the epimeric alcohols was determined to be 92/8: ^{13}C NMR δ 21.3, 24.9, 26.4, 27.5, 29.7, 32.8, 41.7, 55.3, 56.2, 70.1, 82.2, 84.2, 85.0, 86.4, 109.9, 112.4, 127.2, 129.5, 136.8, 143.3, 170.0.

***tert*-Butyl [Methyl 2,3-*O*-isopropylidene-5,7,8,9-tetradeoxy-9(*S*)-[*N*-benzyl-*N*-(*p*-toluenesulfonyl)amino]-β-D-*allo*-decofuranosid]uronate (22).** To a solution of alcohols **21** (1.40 g, 2.65 mmol) in CH_3CN (12 mL) was added calcined K_2CO_3 (1.282 g, 9.3 mmol) and benzyl bromide (385 μL, 3.18 mmol) via syringe. The resulting heterogenous mixture was stirred at 35 °C until no more starting material was detected by TLC (65 h); the reaction mixture then was diluted with CH_2Cl_2 (430 mL), washed with H_2O (2×) and brine, dried, and evaporated. Chromatography (eluting with 50% EtOAc/hexane) gave 1.47 g (90%) of benzyl-protected compound **22** as a clear oil which crystallizes into a white solid at 4 °C. Separation of the two epimeric compounds was not achieved: R_f 0.32, 50% EtOAc/hexane; mp 87 °C; ^{1}H NMR δ 1.19 (s, 9 H), 1.25 (s, 3 H), 1.41 (s, 3 H), 1.3–1.4 (m, 4 H), 1.78–1.83 (m, 2 H), 2.33 (s, 3 H), 2.46 (d, J = 2.8, 1 H), 3.01 (m, 1 H), 3.26 (s, 3 H), 4.10 (dd, J = 4.1; 5.2, 1 H), 4.30–4.36 (m, 3 H), 4.50 (d, J = 7.2, 1 H), 4.76 (d, J = 16.2, 1 H), 4.86 (s, 1 H), 7.19 (m, 5 H), 7.39 (d, J = 8.2, 2 H), 7.63 (d, J = 8.2, 2 H); ^{13}C NMR δ 21.4, 24.9, 26.5, 27.3, 27.7, 33.8, 41.5, 49.1, 55.3, 60.7, 70.4, 81.8, 84.2, 85.0, 86.6, 109.9, 112.3, 127.38, 127.44, 128.2, 128.6, 129.4, 137.2, 138.2, 143.2, 169.8. Anal. Calcd for $C_{32}H_{45}NO_9S$: C, 62.0; H, 7.3; N, 2.3. Found: C, 61.7; H, 7.3; N, 2.2.

***tert*-Butyl [Methyl 9(*S*)-[*N*-benzyl-*N*-(*p*-toluenesulfonyl)amino]-2,3-*O*-isopropylidene-5,7,8,9-tetradeoxy-6-*O*-(*p*-toluenesulfonyl)-β-D-*allo*-decofuranosid]uronate (23).** A solution of *N*-benzyl alcohol **22** (1.03 g, 1.66 mmol) in pyridine (16.6 mL) was cooled to 0 °C, and *p*-toluenesulfonic anhydride (1.36 g, 4.16 mmol) was added. The solution was stirred at 0 °C for 1 h and then diluted with EtOAc (600 mL), washed with 1 M citric acid (4 × 130 mL), saturated $NaHCO_3$, and brine, and dried. After evaporation, the residue was applied to silica gel to separate the epimeric tosylates. After LPC (eluting with 30% EtOAc/hexane), 1.14 g (89%) of diasteromerically pure **23** was obtained as a fluffy, white foam: R_f 0.28, 30% EtOAc/hexane for major diastereomer; R_f 0.17 for minor diastereomer. **23** (major): mp 45 °C: $[\alpha]^{20}_D$ −31.6° (*c* 1.00, $CHCl_3$); ^{1}H NMR δ 1.20 (s, 9 H), 1.24 (s, 3 H), 1.40 (s, 3 H), 1.36–1.76 (m, 6 H), 2.33 (s, 3 H), 2.35 (s, 3 H), 3.27 (s, 3 H), 3.96 (d, J = 6.0; 5.9, 1 H), 4.0–4.05 (m, 1 H), 4.17 (dd, J = 4.9; 4.9, 1 H), 4.24 (d, J = 16.1, 1 H), 4.31 (d, J = 5.9, 1 H), 4.47 (d, J = 5.9, 1 H), 4.67 (d, J = 16.3, 1 H), 4.82 (s, 1 H), 7.18–7.22 (m, 9 H), 7.60 (m, 4 H); ^{13}C NMR δ 21.4, 21.6, 24.9, 26.4, 26.8, 27.7, 30.6, 39.6, 49.2, 55.4, 60.4, 81.0, 82.0, 82.8, 84.2, 85.3, 109.8, 112.3, 127.4, 127.5, 127.6, 128.4, 128.5, 129.5, 129.7, 134.2, 137.1, 137.8, 143.3, 144.5, 169.3. Anal. Calcd for $C_{39}H_{51}NO_{11}S_2$: C, 60.5; H, 6.6; N, 1.8. Found: C, 60.4; H, 6.6; N, 1.7.

***p*-Toluenesulfonic Anhydride.** To *p*-toluenesulfonic acid monohydrate (41.6 g, 240 mmol) suspended in benzene (100 mL) was added thionyl chloride (56 mL, 767 mmol). The mixture was refluxed for 1 h at which time the heterogenous reaction became a homogenous yellow solution. The excess $SOCl_2$ was distilled off, and to the remaining cooled concentrate 160 mL of ether was added. After the solution was cooled at 0 °C for 1 h, the precipitated white crystals of *p*-toluenesulfonic anhydride were collected, washed with ether, and dried at high vacuum. The anhydride was stored under an argon atmosphere: yield, 28.5 g (96 mmol, 80%); mp 124–126 °C (lit.[20] 124–126 °C).

***tert*-Butyl [Methyl 9(*S*)-[*N*-Benzyl-*N*-(*p*-toluenesulfonyl)amino]-2,3-*O*-isopropylidene-6(*S*)-methyl-5,6,7,8,9-pentadeoxy-β-D-*allo*-decofuranosid]uronate (24).** To a suspension of CuI (1.653 g, 8.68 mmol) in ether (20 mL) at 0 °C was added dropwise CH_3Li (12.4 mL, 1.4 M in ether, 17.36 mmol) over 15 min, and the mixture was stirred for an additional 5 min at 0 °C. The reagent vessel was cooled to −50 °C (bath), and a solution of tosylate **23** (1.12 g, 1.44 mmol) in ether (20 mL) was added dropwise over 25 min maintaining the internal temperature at ≤−40 °C. The mixture was stirred at −40 °C (bath) for 60 min and then diluted with EtOAc/saturated NH_4Cl, 1000/400 mL, and stirred at room temperature for 20 min. The separated organic layer was washed with

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brine (2×), dried, and evaporated. Chromatography (eluting with 30% EtOAc/hexane) gave 755 mg (85%) of the methyl compound **24** as a slightly yellow oil which solidified at 4 °C: mp 78–80 °C; R_f 0.40, 30% EtOAc/hexane; $[\alpha]^{20}_D$ −42.1° (*c* 1.13, $CHCl_3$); ^1H NMR δ 0.60 (d, *J* = 6.5, 3 H), 1.26 (s, 9 H), 1.29 (s, 3 H), 1.45 (s, 3 H), 0.97–1.65 (m, 7 H), 2.40 (s, 3 H), 3.23 (s, 3 H), 4.14 (dd, *J* = 10.5; 4.6, 1 H), 4.35 (m, 2 H), 4.41 (d, *J* = 6.0, 1 H), 4.55 (d, *J* = 6.0, 1 H), 4.76 (d, *J* = 11.0, 1 H), 4.87 (s, 1 H), 7.22–7.28 (m, 5 H), 7.40 (d, *J* = 7.3, 2 H), 7.69 (d, *J* = 8.2, 2 H); ^{13}C NMR δ 18.2, 21.4, 24.9, 26.5, 27.7, 28.5, 29.4, 34.1, 41.8, 49.2, 55.0, 61.1, 81.8, 84.7, 85.0, 85.5, 109.6, 111.8, 127.4, 127.5, 128.3, 129.5, 136.8, 138.0, 143.4, 169.9. Anal. Calcd for $C_{33}H_{47}NO_8S$: C, 64.2; H, 7.7; N, 2.3. Found: C, 64.2; H, 7.4; N, 2.1.

***tert*-Butyl [9(*S*)-[*N*-Benzyl-*N*-(*p*-toluenesulfonyl)amino]-6(*S*)-methyl-5,6,7,8,9-pentadeoxy-1,2,3-tri-*O*-acetyl]-β-D-*ribo*-decofuranuronate (26β) and its C-1 Epimer, 26α.** To a solution of methyl compound **24** (650 mg, 1.05 mmol) in dioxane (135 mL) was added 4 M HCl (45 mL), and the biphasic mixture was stirred at room temperature for 20 h. The resulting homogenous solution was partitioned between EtOAc/0.5 M Na_2HPO_4, 650/325 mL, and the aqueous layer was back-extracted with EtOAc. The combined organic extracts were washed with brine, dried, and evaporated. Chromatography (eluting with EtOAc) gave 535 mg (0.95 mmol, 90%) of **25** as an off-white solid. After the absence of the isopropylidene and the methoxy protecting groups was established (^1H NMR), **25** was used directly in the next step: R_f 0.35, EtOAc). To a solution of triol **25** (525 mg, 0.932 mmol) in acetic anhydride (50 mL) was added anhydrous sodium acetate (934 mg, 11.37 mmol), the mixture was stirred at 55 °C (bath) for 16 h, and then the solvent was evaporated. The residue was coevaporated with *p*-xylene twice and partitioned between EtOAc/H_2O, 200/150 mL. The organic layer was washed with saturated $NaHCO_3$ and brine, dried, and evaporated. Chromatography (eluting with 50% EtOAc/hexane) gave 650 mg of triacetate **26** as an anomeric mixture. By LPC (eluting with 30% EtOAc/hexane) the anomers were separated into 365 mg (57%) of **26β** and 183 mg (29%) of **26α**: R_f 0.18, 30% EtOAc/hexane for **26β**; R_f 0.13 for **26α**.

26β: ^1H NMR δ 0.59 (d, *J* = 6.4, 3 H), 1.07 (m, 1 H), 1.19–1.44 (m, 4 H), 1.27 (s, 9 H), 1.60 (m, 2 H), 2.05 (s, 3 H), 2.06 (s, 3 H), 2.10 (s, 3 H), 2.40 (s, 3 H), 4.11 (m, 1 H), 4.33 (m, 1 H), 4.37 (d, *J* = 16.3, 1 H), 4.77 (d, *J* = 16.2, 1 H), 5.06 (m, 1 H), 5.29 (d, *J* = 4.8, 1 H), 6.09 (s, 1 H), 7.24–7.28 (m, 5 H), 7.42 (d, *J* = 7.1, 2 H), 7.70 (d, *J* = 8.2, 2 H); ^{13}C NMR δ 17.9, 20.17, 20.22, 20.8, 21.1, 27.4, 28.0, 28.6, 33.5, 41.0, 49.0, 60.7, 74.1, 74.3, 79.3, 81.5, 98.0, 127.2, 128.0, 128.1, 129.2, 137.1, 137.8, 142.9, 168.9, 169.1, 169.51, 169.53.

26α: ^1H NMR δ 0.59 (d, *J* = 6.5, 3 H), 1.07 (m, 1 H), 1.19–1.55 (m, 4 H), 1.27 (s, 9 H), 1.59 (m, 2 H), 2.05 (s, 3 H), 2.10 (s, 3 H), 2.11 (s, 3 H), 2.40 (s, 3 H), 4.18 (m, 1 H), 4.32 (m, 1 H), 4.39 (d, *J* = 16.3, 1 H), 4.79 (d, *J* = 16.3, 1 H), 4.92 (m, 1 H), 5.19 (m, 1 H), 6.33 (d, *J* = 4.6, 1 H), 7.25–7.30 (m, 5 H), 7.43 (d, *J* = 7.1, 2 H), 7.70 (d, *J* = 8.3, 2 H); ^{13}C NMR δ 18.1, 20.2, 20.5, 20.9, 21.3, 27.6, 28.2, 28.5, 33.7, 40.2, 49.1, 60.8, 69.6, 72.8, 81.1, 81.7, 93.7, 127.3, 127.4, 128.2, 128.3, 129.4, 137.3, 138.0, 143.1, 169.2, 169.5, 169.7, 169.9. Anal. Calcd for $C_{35}H_{47}NO_{11}S$ (mixture of α and β): C, 60.9; H, 6.9; N 2.0. Found: C, 61.0; H, 6.9; N, 2.2.

***tert*-Butyl 1-(9-Adenyl-)-9(*S*)-[*N*-Benzyl-*N*-(*p*-toluenesulfonyl)amino]-2,3-di-*O*-acetyl-1,5,6,7,8,9-hexadeoxy-6(*S*)-methyl-β-D-*ribo*-decofuranuronate (27).** To a solution of adenine (331 mg, 2.5 mmol) in CH_3CN (10 mL) was added $SnCl_4$ (2.5 mL, 1 M solution in 1,2-dichloroethane). After the solution was stirred at room temperature for 15 min, triacetate **26β** (340 mg, 0.49 mmol) in CH_3CN (10 mL) was added via syringe, and the solution was stirred at room temperature for 17 h and then partitioned between EtOAc/0.25 M Na_2HPO_4 170/170 mL. The aqueous layer was back-extracted with EtOAc (85 mL), and the combined organic extracts were washed with brine, dried, and evaporated. Chromatography (eluting with EtOAc) gave 250 mg (67%) of nucleoside **27** as a white solid: R_f 0.20, EtOAc; mp softening at 33 °C, molten at 135 °C: $[\alpha]^{20}_D$ −26.5° (*c* 0.98, $CHCl_3$); ^1H NMR δ 0.61 (d, *J* = 5.9, 3 H), 1.05–1.66 (m, 7 H), 1.26 (s, 9 H), 2.06 (s, 3 H), 2.14 (s, 3 H), 2.40 (s, 3 H), 4.17 (m, 1 H), 4.35 (m, 1 H), 4.35 (d, *J* = 16.2, 1 H), 4.78 (d, *J* = 16.2, 1 H), 5.32 (m, 1 H), 5.89 (m, 3 H), 6.09 (d, *J* = 5.6, 1 H), 7.25 (m, 5 H), 7.39 (d, *J* = 6.1, 2 H), 7.70 (d, *J* = 8.3, 2 H), 7.90 (s, 1 H), 8.36 (s, 1 H); ^{13}C NMR δ 18.0, 20.3, 20.5, 21.3, 27.7, 28.1, 28.5, 33.6, 39.9, 49.1, 60.8, 73.0, 73.9, 80.1, 81.7, 85.8, 127.3, 127.4, 128.1, 128.3, 129.4, 137.3, 137.9, 138.9, 143.1, 149.6, 153.2, 155.7, 169.3, 169.6, 169.8. Anal. Calcd for $C_{38}H_{48}N_6O_9S$: C, 59.7; H, 6.3; N, 10.9. Found: C, 59.6; H, 6.5; N, 10.5.

***tert*-Butyl 1-(9-Adenyl)-9(*S*)-(benzylamino)-2,3-di-*O*-acetyl-1,5,6,7,8,9-hexadeoxy-6(*S*)-methyl-β-D-*ribo*-decofuranuronate (28).** Using the procedure previously described,[17] the electrolytic apparatus was preelectrolyzed at −1.925 V to a background current of 0.9 mA. Phenol (40 mg, 0.42 mmol, distilled under vacuum) was added to the cathode chamber, and again the apparatus was preelectrolyzed at −1.925 V to a background current of 1.0–1.2 mA. The potential of the cell was then turned off, nucleoside **27** (94 mg, 0.123 mmol) in CH_3CN (1.2 mL) was added to the cathode chamber, and the eletrolysis was carried out at −1.825 V. Detosylation was monitored by TLC and stopped when no more starting material was detected (2 h 20 min). The solution in the cathode chamber was collected and evaporated, the residue was partitioned between EtOAc/phosphate buffer, 50/50mL [buffer: 1 M KH_2PO_4, pH adjusted to 7.0 with 2.0 M KOH], and the organic layer was dried and evaporated. The residue consisted of compound **28**, plus a few percent of monoacetylated material and phenol. Chromatography (eluting with 7% MeOH/CH_2Cl_2) gave 68 mg (90%) of **28** as a white solid, containing 4% of monoacetylated byproduct; it was used directly in the next reaction. **28**: R_f 0.36, 10% MeOH/CH_2Cl_2; $[\alpha]^{20}_D$ −23.0° (*c* 1.25, $CHCl_3$); ^1H NMR δ 0.91, (d, *J* = 6.5, 3 H), 1.26–1.74 (m, 6 H), 1.46 (s, 9 H), 1.86–1.92 (m, 1 H), 2.07 (s, 3 H), 2.13 (s, 3 H), 3.08 (t, *J* = 6.5, 1 H), 3.59 (d, *J* = 12.8, 1 H), 3.78 (d, *J* = 12.8, 1 H), 4.26 (m, 1 H), 5.40 (t, *J* = 5.2, 1 H), 5.59 (s br, 2 H), 5.91 (t, *J* = 5.4, 1 H), 6.08 (d, *J* = 5.3, 1 H), 7.30 (m, 5 H), 7.88 (s, 1 H), 8.37 (s, 1 H); ^{13}C NMR δ 18.7, 20.4, 20.6, 28.1, 29.3, 30.6, 33.0, 40.3, 52.0, 61.3, 73.2, 73.8, 80.2, 81.1, 86.2, 119.9, 127.0, 128.3, 129.5, 138.9, 139.6, 153.1, 155.4, 156.4, 169.5, 169.7, 174.6.

***tert*-Butyl 1-(9-Adenyl)-9(*S*)-(benzylamino)-1,5,6,7,8,9-hexadeoxy-6(*S*)-methyl-β-D-*ribo*-decofuranuronate (29).** Detosylated nucleoside **28** (174 mg, 0.285 mmol) was dissolved in MeOH (5 mL), the solution was cooled to 0 °C, K_2CO_3 (95 mg, 0.69 mmol) in H_2O (2 mL) was added, and the reaction mixture was stirred at 0 °C. After 2 h the pH was adjusted to 7.0 with 1 M H_3PO_4, and the MeOH was evaporated. The residue was diluted with H_2O and extracted with EtOAc (3×), and the combined organic extracts were dried and evaporated. Chromatography (eluting with 10% MeOH/CH_2Cl_2) gave 122 mg (81%) of **29** as a white solid: R_f 0.14, 10% MeOH/CH_2Cl_2; R_f 0.80, 3/6/1, MeOH/CH_3Cl/NH_4OH; mp softens at 30 °C, molten at 75 °C: $[\alpha]^{20}_D$ −20.0° (*c* 0.55, $CHCl_3$); ^1H NMR δ 0.96 (d, *J* = 6.5, 3 H), 1.25–1.75 (m, 6 H), 1.48 (s, 9 H), 1.88 (m, 1 H), 3.12 (t, *J* = 6.5, 1 H), 3.59 (d, *J* = 12.7, 1 H), 3.78 (d, *J* = 12.7, 1 H), 4.13 (m, 1 H), 4.33 (m, 1 H), 4.47 (m, 1 H), 5.80 (s br, 2 H), 5.85 (d, *J* = 5.7, 1 H), 6.3–6.4 (s br, 1 H), 7.29 (m, 5 H), 7.96 (s, 1 H), 8.29 (s, 1 H); ^{13}C NMR δ 19.0, 28.1, 29.5, 30.5, 32.8, 40.9, 52.0, 61.2, 74.5, 74.8, 81.1, 83.3, 89.5, 115.5, 127.1, 128.3, 128.4, 129.5, 138.8, 139.2, 149.0, 152.5, 155.5, 174.4. Anal. Calcd for $C_{27}H_{38}N_6O_5$: C, 61.6; H, 7.3; N 16.0. Found: C, 61.3; H, 7.2; N, 15.6.

***tert*-Butyl 1-(9-Adenyl)-9(*S*)-amino-1,5,6,7,8,9-hexadeoxy-6(*S*)-methyl-β-D-*ribo*-decofuranuronate (30).** A solution of diol **29** (136 mg, 0.26 mmol) in MeOH (7 mL) and 10% Pd/C (28 mg) was stirred at room temperature under H_2 at 1 atmosphere for 24 h. After filtration over Celite, an additional 28 mg of 10% of Pd/C was added, and the hydrogenolysis was continued for 24 h. The mixture was filtered through Celite, the filtrate was evaporated, and 94 mg (83%) of amine **30** was obtained: R_f 0.72, 3/6/1, MeOH/CH_3Cl/NH_4OH; $[\alpha]^{20}_D$ +4.7° (*c* 0.75, CH_3OH); ^1H NMR δ 0.97 (d, *J* = 6.4, 3 H), 1.21–1.84 (m, 7 H), 1.46 (s, 9 H), 3.80 (m, 1 H), 4.09 (m, 1 H), 4.15 (m, 1 H), 4.73 (m, 1 H), 5.93 (d, *J* = 4.3, 1 H), 8.19 (s, 1 H), 8.21 (s, 1 H); ^{13}C NMR (CD_3OD) δ 19.5, 28.3, 28.4, 30.9, 34.0, 41.9, 55.7, 75.1, 75.6, 82.1, 83.7, 90.3, 120.6, 141.4, 150.6, 153.9,

157.3, 176.1. Anal. Calcd for $C_{20}H_{32}N_6O_5 \cdot 1H_2O$: C, 52.9; H, 7.5; N 18.5. Found: C, 53.0; H, 7.4; N, 18.7.

6-(*S*)-Methyl-6-deaminosinefungin (4). Amine **30** (64 mg, 0.146 mmol) was dissolved in trifluoroacetic acid/H_2O (9/1, 10 mL). The mixture was stirred at 0 °C, and after 50 min, the solvent was evaporated at room temperature under high vacuum and the residue was coevaporated with toluene (3×). Chromatography (eluting with 3/6/1, MeOH/$CHCl_3$/NH_4OH) gave 33 mg (60%) of 6(*S*)-methyldeaminosinefungin (**4**): R_f 0.17, 3/6/1, MeOH/CH_3Cl/NH_4OH; $[\alpha]^{20}_D$ +7.2° (*c* 0.53, H_2O); ^1H NMR (D_2O, δ relative to dioxane, 3.53 ppm) δ 0.72 (d, J = 5.9, 3 H), 1.04 (m, 1 H), 1.24 (m, 1 H), 1.40 (m, 2 H), 1.62 (m, 3 H), 3.49 (t, J = 5.7, 1 H), 4.00 (m, 1 H), 4.04 (m, 1 H), 4.59 (t, J = 5.2, 1 H), 5.81 (d, J = 5.2, 1 H), 8.02 (s, 1 H), 8.06 (s 1 H); ^{13}C NMR (D_2O, δ relative to dioxane, 66.5 ppm) δ 17.8, 27.8, 28.9, 31.8, 39.8, 54.9, 73.4, 73.7, 82.6, 87.5, 120.0, 140.3, 148.8, 151.9, 155.0, 174.8; HPLC analysis 4.6 mm × 250 mm, IBM ODS 8635 308 (reversed-phase, 5 μm), eluting with 4% CH_3CN/H_2O, flow rate 2.0 mL/min, t_R 12.5 min, monitored at 254 nm; HRMS calcd for $C_{16}H_{25}N_6O_5$ (MH^+) 381.1886, found 381.1883.

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Supplementary Material Available: Experimental procedures for the preparation of benyzl ester–ketone **13** (3 pages). This material is contained in libraries on microfiche, immediately follows this article on the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.