Asymmetric Synthesis of Nucleosides via Molybdenum-Catalyzed Alkynol Cycloisomerization Coupled with Stereoselective Glycosylations of Deoxyfuranose Glycals and 3-Amidofuranose Glycals

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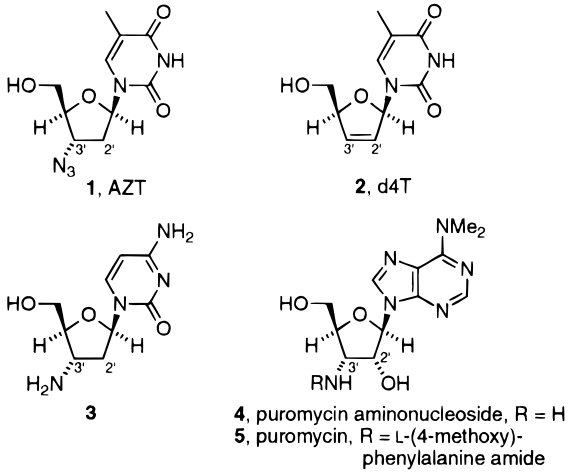
Abstract: Deoxygenated furanose glycals were efficiently prepared by molybdenum pentacarbonyl-catalyzed cycloisomerization of alkynyl alcohols, which were easily prepared in chiral nonracemic form by short synthetic sequences featuring asymmetric epoxidations of commercially available allylic alcohols. The cycloisomerization reaction was demonstrated to be compatible with ester and amide functional groups. A 2,3-dideoxyfuranose glycal was stereoselectively converted into the anti-AIDS β-nucleoside stavudine (2′,3′-didehydro-2′,3′-dideoxythymidine, d4T) and the antiviral 3′-deoxy-β-nucleoside cordycepin. The anchimeric and hydrogen-bond-directing effects of 3-amido-2,3-dideoxyfuranose glycals were exploited in a novel and highly stereoselective synthesis strategy for a variety of biologically active 3′-amino-2′,3′-dideoxy- and 3′-amino-3′-deoxy-β-nucleosides, including puromycin aminonucleoside. In addition, the mechanism of the molybdenum-catalyzed alkynol cycloisomerization reaction has been studied. Evidence is presented which indicates that cyclic molybdenum carbene anions are catalytic intermediates in these cyclizations.

Introduction

The recent resurgence of interest in deoxynucleoside chemistry has been fueled by the discovery of antiviral and antitumor activities of these compounds, as well as their potential as components of antisense oligonucleotides. 3′-Azido-2′,3′-dideoxythymidine (AZT, **1**; Scheme 1) was the first drug approved for the treatment of acquired immunodeficiency syndrome (AIDS). More recently 2′,3′-didehydro-2′,3′-dideoxythymidine (d4T, **2**) has shown clinical efficacy, both separately and in combination with AZT.[1] 3′-Amino-2′,3′-dideoxycytidine (**3**) and 3′-amido-3′-deoxynucleosides including puromycin (**5**) exhibit antitumor activity,[2] whereas phosphoramidate-linked 3′-amino-2′,3′-dideoxynucleosides have shown enhanced binding with complementary RNA and DNA strands without loss of discrimination against strands containing mismatched residues.[3]

Several strategies have been successfully employed for the synthesis of deoxynucleosides including compounds **1**−**5**. Functional group interconversion from naturally occurring (but rather expensive) nucleosides is a useful approach for the preparation of many pyrimidine nucleosides, but is generally limited to preparation of one enantiomeric series.[4] The conceptually simple exchange of one heteroatomic substituent for another can involve a rather lengthy synthetic sequence once protective group manipulations and stereochemical issues are considered, especially with purine nucleosides.[5] Alternatives featuring coupling of carbohydrates with pyrimidine/purine moieties permit flexibility in the variety of functional group changes in nucleoside analogs, provided that such couplings are stereoselective. The most flexible approach might involve asymmetric synthesis of the carbohydrate moieties from simple starting materials, particularly for deoxygenated or unusually functionalized carbohydrates.

Scheme 1. Representative Deoxynucleoside Antibiotics



1,2-Glycals have shown considerable promise as glycosyl donors for the preparation of various oxygen-, carbon-, and

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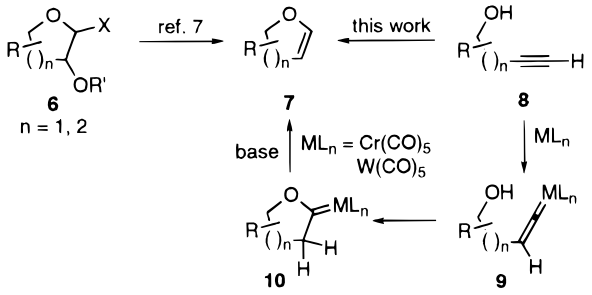
Scheme 2. Preparation of 1,2-Glycals



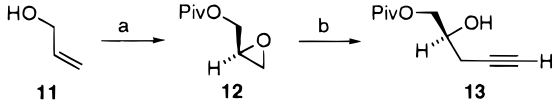
nitrogen-linked glycoconjugates.[6] 1,2-Glycals **7** are generally prepared by reductive elimination of 2-(acyloxy)glycosyl halides **6**, readily available from furanose and pyranose sugars (Scheme 2).[7] At the outset of our studies, we envisioned that deoxygenated glycals and other endocyclic enol ether substances might be prepared by cyclization of the corresponding isomeric alkynyl alcohol **8**. Prior to our work a single-step cyclization reaction of alkynyl alcohols **8** to endocyclic enol ethers **7** was unknown, although the general concept of alkynol cyclization to carbenes **8**−**10** has recently been applied to natural product synthesis.[8] We have previously reported that molybdenum pentacarbonyl−trialkylamine complexes catalyze the cycloisomerization of 1-alkyn-4-ols to substituted 2,3-dihydrofurans.[9]

Herein we discuss mechanistic insights on molybdenum-catalyzed alkynol cyclization reactions, related issues of functional group compatibility, and applications of the dihydrofuran cyclization products to the stereoselective synthesis of a variety of bioactive nucleosides, including **2**−**4**.

Results

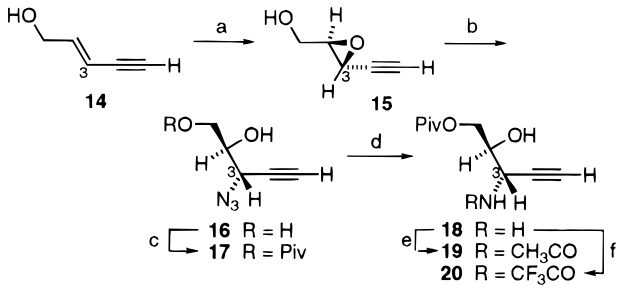
Asymmetric Synthesis of Alkynols. Our general approach to the asymmetric synthesis of alkynols featured hydroxyl-directed asymmetric epoxidation followed by regioselective nucleophilic addition. For instance, the chiral nonracemic alkynol **13** was prepared by asymmetric epoxidation of allyl alcohol (**11**) with *in situ* derivatization[10] as the pivaloate ester **12** (Scheme 3). Regioselective addition of lithium acetylide−boron trifluoride etherate[11] to **12** at low temperature (−78 to −20 °C) provided the homopropargylic secondary alcohol **13**; if this reaction was conducted at higher temperatures or without boron trifluoride, partial migration of the ester group was observed. The enantiomeric purity was determined by forming the Mosher ester[12] of the secondary alcohol **13**; ^{1}H NMR analysis of the diastereomeric methoxy singlets indicated an enantiomeric excess of 89% (±1%, three determinations).

Scheme 3. Asymmetric Synthesis of Alkynol **13**



Reagents and Conditions: (a) 5 mol% Ti(O-*i*-Pr)$_4$, 6 mol% D-DIPT, PhCMe$_2$OOH, 3Å MS, CH_2Cl_2, -20°C; *t*-BuCOCl, Et_3N (37%). (b) LiC≡CH, BF_3-OEt_2, THF, -78°C to -20°C (70%).

Scheme 4. Asymmetric Synthesis of Alkynols Bearing Propargylic Nitrogen Substituents



Reagents and Conditions: (a) 10 mol% Ti(O-*i*-Pr)$_4$, 12 mol% D-DIPT, PhCMe$_2$OOH, 3Å MS, CH_2Cl_2, -5°C (47%). (b) Ti(O-*i*-Pr)$_2$(N_3)$_2$, toluene (77%). (c) *t*-BuCOCl, py., CH_2Cl_2, 0°C to 20°C (79%). (d) $SnCl_2$, CH_3OH. (e) Ac_2O, aq. CH_3OH (87%, two steps). (f) $(CF_3CO)_2O$, py., CH_2Cl_2, then CH_3OH (78%, two steps).

Alkynol substrates bearing heteroatomic propargylic substituents were prepared from (*E*)-2-penten-4-yn-1-ol (**14**) (Scheme 4). Asymmetric epoxidation provided compound **15**, which was followed by titanium-mediated regioselective addition of azide[13] and selective protection of the primary alcohol of azido diol **16**. Mosher ester analysis of the secondary alcohol of **17** indicated an enantiomeric excess of 92 ± 1%. Reduction of the azide[14] to the amine **18** and acylation provided the 3-amidoalkynols **19** and **20**.

Molybdenum-Catalyzed Alkynol Cyclizations. Reaction of **13** with molybdenum hexacarbonyl and trimethylamine *N*-oxide in ether/triethylamine at room temperature provided the protected dihydrofuranmethanol **21** in 80% isolated yield (Table 1).[9c] Similar results were observed upon reaction of **13** with photogenerated triethylamine−molybdenum pentacarbonyl.[9b] However, attempts to extend this reaction to the alkynediol substrate **22** resulted in the unexpected formation of the furfuryl alcohol derivative **23**. Reaction with the C3-silyl ether derivative **24** provided only a low yield of dihydrofuran **25** accompanied by furan **23**; reaction of the diastereomer **26** gave exclusively furan **23**. Reaction of the azidoalkynols **16** and **17** as well as the amine **18** also gave the furan products **27** and **28** upon reaction with triethylamine−molybdenum pentacarbonyl, but the corresponding 3-amidoalkynols **19** and **20** provided the cycloisomeric 3-amidoglycals **29** and **30** without evidence of furan formation.

Asymmetric Synthesis of Deoxynucleosides from Deoxyfuranoid Glycals. The efficient preparation of **21** provided a formal asymmetric synthesis of the anti-AIDS compound d4T (**2**) via the known iodonucleoside **31**,[15] obtained by *N*-iodosuccinimide (NIS)-induced addition of bis(trimethylsilyl)thymine to **21** (Scheme 5). Calculation of reagent costs for the d4T synthesis via cycloisomerization methodology revealed that NIS is a rather costly reagent on a per mole basis. We subsequently

(6) For recent reviews, see: (a) (*O*-glycosylation) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503. (b) (*C*-glycosylation) Jaramillo, C.; Knapp, S. *Synthesis* **1994**, 1.

(7) (a) Fischer, E. *Ber.* **1914**, *47*, 196. (b) Roth, W.; Pigman, W. *Methods Carbohydr. Chem.* **1963**, *2*, 405. (c) Shafizadeh, F. *Methods Carbohydr. Chem.* **1963**, *2*, 409. (d) Ireland, R. E.; Wilcox, C. S.; Thaisrivongs, S. *J. Org. Chem.* **1978**, *43*, 786. (e) Cavallaro, C. L.; Schwartz, J. *J. Org. Chem.* **1995**, *60*, 7055.

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(9) (a) McDonald, F. E.; Connolly, C. B.; Gleason, M. M.; Towne, T. B.; Treiber, K. D. *J. Org. Chem.* **1993**, *58*, 6952. (b) McDonald, F. E.; Schultz, C. C. *J. Am. Chem. Soc.* **1994**, *116*, 9363. (c) McDonald, F. E.; Gleason, M. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 350. (d) McDonald, F. E.; Schultz, C. C.; Chatterjee, A. K. *Organometallics* **1995**, *14*, 3628.

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(11) (a) Midland, M. M. *J. Org. Chem.* **1975**, *40*, 2250. (b) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391.

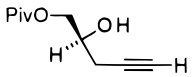
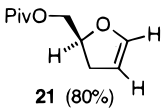
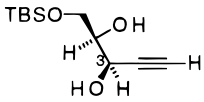
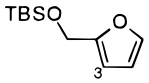
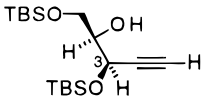
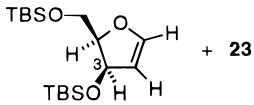
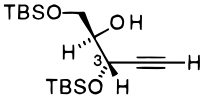
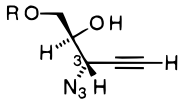
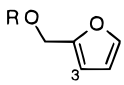
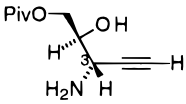
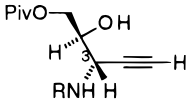
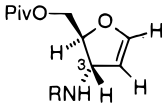
(12) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(13) Caron, M.; Carlier, P. R.; Sharpless, K. B. *J. Org. Chem.* **1988**, *53*, 5185.

(14) Maiti, S. N.; Singh, M. P.; Micetich, R. G. *Tetrahedron Lett.* **1986**, *27*, 1423.

(15) Kim, C. U.; Misco, P. F. *Tetrahedron Lett.* **1992**, *33*, 5733.

Table 1. Cyclization of Alkynols with Trialkylamine−Molybdenum Pentacarbonyl

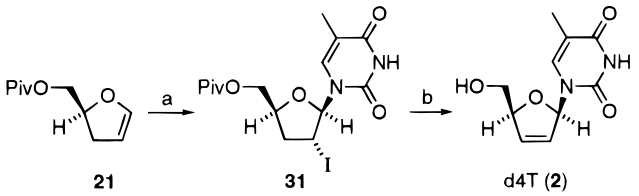
alkynol	products (isolated yield)[b]
 **13**	 **21** (80%)
 **22**[a]	 **23** (58%)
 **24**[a]	 **25** (18%) + **23**
 **26**[a]	**23** (76%)
 **16** R = H **17** R = Piv	 **27** R = H **28** R = Piv
 **18**	**2 8**
 **19** R = CH_3CO **20** R = CF_3CO	 **29** R = CH_3CO (89%) **30** R = CF_3CO (92%)

[a] Synthesis schemes are described in the supporting information. [b] Yields of furan products are unoptimized.

found that iodine (I_2) was equally suitable for the stereoselective, high-yield iodoglycosylation of **21**. The crude iodonucleoside **31** underwent E2 reaction as well as pivaloate methanolysis upon reaction with a large excess of freshly prepared sodium methoxide to give d4T (**2**) in excellent overall yield. d4T produced by our route exhibited an enantiomeric excess of approximately 90%, demonstrating the stereochemical integrity of the secondary alcohol in the novel cycloisomerization synthesis of **21**.

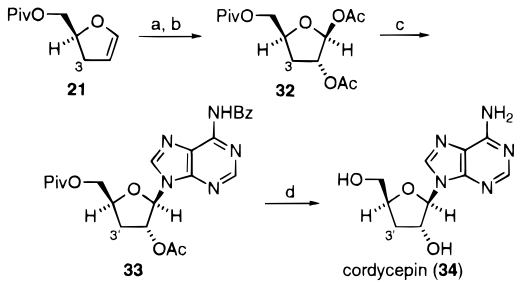
A variety of other methods were evaluated for stereoinduction in reactions with the 3-deoxyfuranoid glycal **21**. Reaction of **21** with triphenylphosphine−hydrogen bromide[16] and bis(trimethylsilyl)thymine directly affords the 2′,3′-dideoxynucleosides, but without significant stereoselectivity as both α and β anomers are formed in a 1.5:1 mixture. Reaction of 2-(phenylsulfonyl)-3-phenyloxaziridine,[17] bis(trimethylsilyl)thymine, and **21** provides three of the four possible 3′-deoxynucleoside products. However, osmium tetroxide-catalyzed dihydroxylation[18] of **21** followed by acylation of the crude diol provides a 13:4:3:1 mixture of diacetylated products favoring **32** (Scheme 6). This stereochemical assignment is clarified after Lewis acid-catalyzed adenine glycosylation[19] to give the β-nucleoside **33** as the major component. Basic methanolysis of acyl groups affords synthetic cordycepin (**34**).

Scheme 5. Asymmetric Synthesis of d4T (**2**)



Reagents and Conditions: (a) I_2, $(Me_3Si)_2$-thymine, CH_2Cl_2 (94%, 7 : 1 mixture). (b) 60 equiv. NaOMe, MeOH (80%).

Scheme 6. Stereoselective Dihydroxylation of **21** and Synthesis of Cordycepin (**34**)



Reagents and Conditions: (a) 1 mol% OsO_4, *N*-methylmorpholine-*N*-oxide, THF / *t*-BuOH / H_2O (67%). (b) Ac_2O, Et_3N, CH_2Cl_2 (90%, 13 : 4 : 3 : 1 mixture). (c) TMSOTf, *N*-benzoyl-*N*, *N*-bis(trimethylsilyl)adenine, $ClCH_2CH_2Cl$, 83°C (65%). (d) NaOMe, MeOH (42%).

A low-yield preparation of a 3-amidofuranose glycal similar to **29** has been previously documented,[20] but glycoconjugate synthesis from these glycals has not been reported. Direct glycosylation of the glycal **29** or **30** with pyrimidine and purine bases[21] under a variety of acidic reaction conditions (Ph_3P−HBr,[16] TMSOTf[22]) was sluggish at room temperature, and generally gave a mixture of α- and β-nucleosides when the glycosylation reaction was carried to high conversion. However, we found that reaction of **29** with trifluoromethanesulfonic acid and silylated thymine at room temperature with acetonitrile[23] as solvent afforded predominantly the β-nucleoside **35T** (Scheme 7, entry 1). Addition of acetic acid to **29** gave a more highly reactive glycosyl donor, **36**, which underwent high-yielding TMSOTf-induced glycosylation with silylated pyrimidine bases in the presence of acetonitrile to afford the desired β-nucleoside **35T,U,C** (entries 2−4). We subsequently found that similar results are more consistently obtained by using trifluoromethanesulfonic acid as the activating agent (entries 5 and 6); possibly trifluoromethanesulfonic acid is also generated by *in situ* hydrolysis of trimethylsilyl trifluoromethanesulfonate. The

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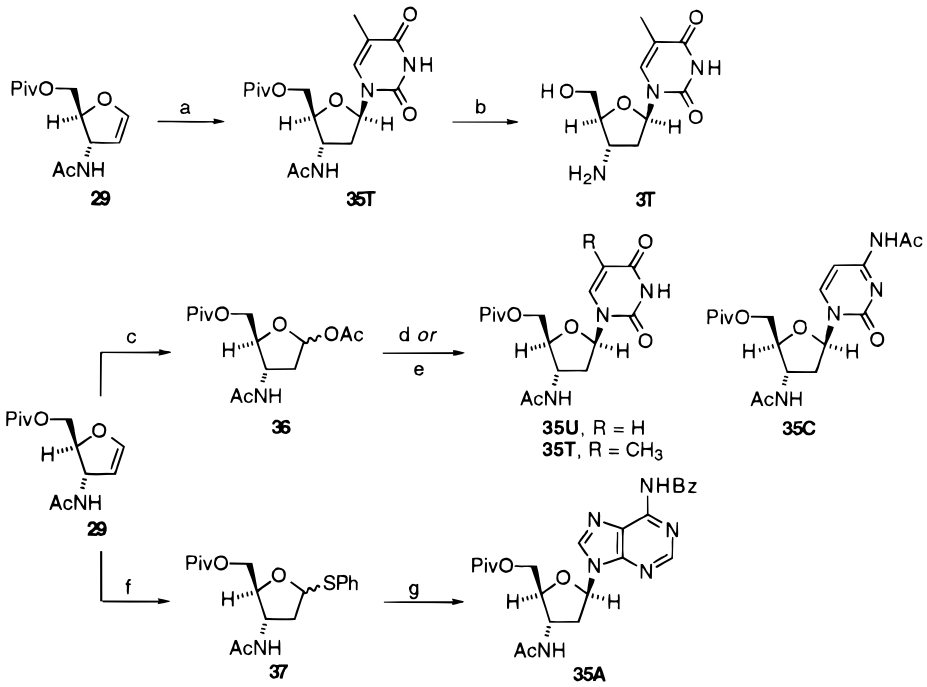
(23) (a) Vankar, Y. D.; Vankar, P. S.; Behrendt, M.; Schmidt, R. R. *Tetrahedron* **1991**, *47*, 9985. (b) Schmidt, R. R. In *Synthetic Oligosaccharides: Indispensable Probes for the Life Sciences*; Kovac, P., Ed.; ACS Symposium Series 560; American Chemical Society: Washington, DC, 1994; pp 276−296.

Scheme 7. Glycosylation of **29** to 3′-Amido-2′,3′-dideoxynucleosides



Reagents and Conditions: (a) CF_3SO_3H, silylated base, 3Å MS, MeCN, 20°C (entry 1); (b) excess NaOMe, MeOH, 65°C (68%); (c) AcOH, Ac_2O, 3Å MS, cat. TsOH (92%); (d) TMSOTf, silylated base, 3Å MS, MeCN, 0°C to 20°C (entries 2-4); (e) CF_3SO_3H, silylated base, 3Å MS, MeCN, 20°C (entry 5-6); (f) thiophenol, CF_3SO_3H, 3Å MS, CH_2Cl_2, 20°C (75%); (g) NIS, TfOH, silylated base, MeCN, -40°C (entry 7).

entry	silylated base	glycosyl donor	conditions	nucleoside, isolated yield (β : α ratio)
1	$(TMS)_2$-thymine	**29**	a	**35T**, 50% (>20 : 1)
2	$(TMS)_2$-thymine	**36**	d	**35T**, 85% (4.7 : 1)
3	$(TMS)_2$-uracil	**36**	d	**35U**, 85% (21 : 1)
4	*N*-Ac$(TMS)_2$-cytosine	**36**	d	**35C**, 77% (8.7 : 1)
5	$(TMS)_2$-thymine	**36**	e	**35T**, 87% (8.4 : 1)
6	*N*-Ac$(TMS)_2$-cytosine	**36**	e	**35C**, 84% (3.3 : 1)
7	*N*-Bz$(TMS)_2$-adenine	**37**	g	**35A**, 42% (>10 : 1)

addition of purine bases is not stereoselective under these conditions, presumably due to acid-catalyzed equilibration. However, the more reactive thioglycoside donor **37** can be activated with *N*-iodosuccinimide and trifluoromethanesulfonic acid[24] at significantly lower temperatures, giving the purine β-nucleoside **35A** with high stereoselectivity (entry 7). The ester and amide protective groups are removed with sodium methoxide in methanol to give the 3′-amino-2′,3′-dideoxynucleosides (cf. **35T** → **3T**).

In the case of guanine glycosylations, the reaction of **37** under kinetic conditions gave primarily the N-7 regioisomer **35G*** as the major nucleoside product (Scheme 8, entry 1).[25] We observed that the proportion of N-9 regioisomer **35G** increased when glycosylation was carried out at room temperature, but under these conditions the α-nucleoside isomers were also observed (entry 2), and were the major product when the glycosylation was conducted in refluxing acetonitrile (entry 3). Observable amounts of glycal **29** were also obtained under these reaction conditions.

The amide functional group of **29** directs epoxidation with peroxyacids[26] from the α-face, and the epoxide intermediate is trapped by the carboxylic acid byproduct to give **38** (Scheme 9). Acylation of the 2-hydroxyl group permits *trans*-glycosylation of **39** under Lewis acid conditions to give purine β-nucleosides including **40**.[27] Basic methanolysis of **40** provides the deprotected puromycin aminonucleoside (**4**). Similar stereoinduction is observed in the peroxyacetic acid epoxidation of the 3-trifluoroacetamide glycal **30**, leading to the diacetate **42** (Scheme 10). Under the thermodynamic conditions of these glycosylations, the naturally occurring N-9 regioisomers **43A**, **43G**, and **43A′** are the major products obtained (entries 1−3).

Dimethyldioxirane epoxidation of **30** is also directed by the amide when epoxidation is conducted in the non-hydrogen-bonding solvent CH_2Cl_2;[28cd] the crude glycal epoxide **44** reacts

(24) Knapp, S.; Shieh, W.-C. *Tetrahedron Lett.* **1991**, *32*, 3627.

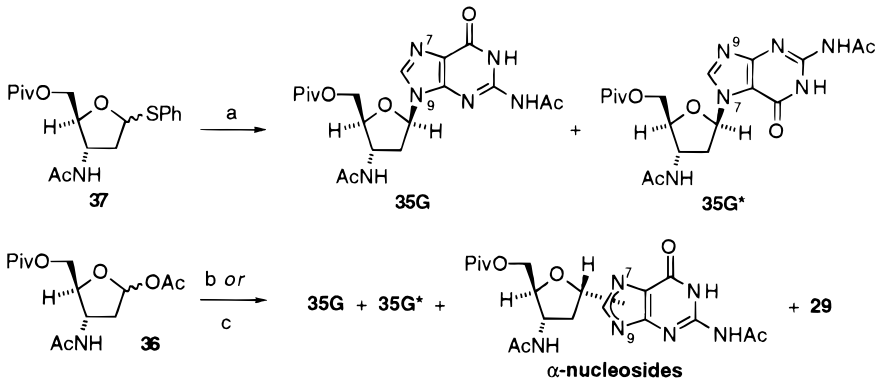
(25) (a) Garner, P.; Ramakanth, S. *J. Org. Chem.* **1988**, *53*, 1294. (b) Imazawa, M.; Eckstein, F. *J. Org. Chem.* **1978**, *43*, 3044.

(26) Goodman, L.; Winstein, S.; Boschan, R. *J. Am. Chem. Soc.* **1958**, *80*, 4312.

(27) (a) Azhayev, A. V.; Ozols, A. M.; Bushnev, A. S.; Dyatkina, N. B.; Kochetkova, S. V.; Victorova, L. S.; Kukhanova, M. K.; Krayevsky, A. A.; Gottikh, B. P. *Nucleic Acids Res.* **1979**, *6*, 625. (b) Vorbrüggen, H.; Krolikiewicz, K.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1234.

(28) (a) Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187. (b) Baertschi, S. W.; Raney, K. D.; Stone, M. P.; Harris, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 7929. (c) For hydroxyl-directed epoxidations with dimethyldioxirane, see: Chow, K.; Danishefsky, S. *J. Org. Chem.* **1990**, *55*, 4211. (d) After our manuscript was submitted, a directed epoxidation of 3-benzamido-1-cyclohexene with dimethyldioxirane was reported: Murray, R. W.; Singh, M.; Williams, B. L.; Moncrieff, H. M. *J. Org. Chem.* **1996**, *61*, 1830.

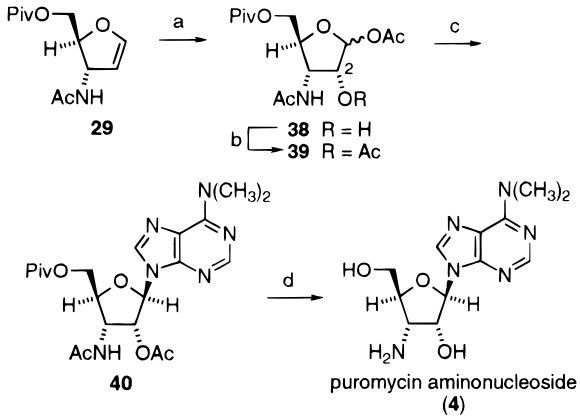
Scheme 8. Glycosylations of **36** and **37** with Guanine



Reagents and Conditions: (a) *N*-Ac(TMS)$_3$-guanine, NIS, TfOH, EtCN, 3Å MS, -78°C to 0°C, 2 h. (entry 1); (b) *N*-Ac(TMS)$_3$-guanine, TMSOTf, MeCN, 3Å MS, 20°C, 3 h. (entry 2); (c) *N*-Ac(TMS)$_3$-guanine, TMSOTf, MeCN, 3Å MS, 81°C, 1.5 h. (entry 3).

entry	glycosyl donor	conditions	nucleosides, combined yield	relative ratio of products **35G** : **35G*** : α-nucleosides : **29**
1	**37**	a	35%	1.0 : 7.3 : 0 : 0
2	**36**	b	38%	3.4 : 1.4 : 1.0 : 0
3	**36**	c	50%	2.2 : 1.0 : 12 : 3.2

Scheme 9. Stereoselective Epoxidation/Glycosylation of **29** and Synthesis of Puromycin Aminonucleoside (**4**)



Reagents and Conditions: (a) 32% CH_3CO_3H, CH_2Cl_2; (b) Ac_2O, py., DMAP (95%; 2 steps); (c) *N,N*-Me$_2$(TMS)adenine, TMSOTf, 3Å MS, $ClCH_2CH_2Cl$, 83°C (73%); (d) excess NaOMe, MeOH, 65°C (61%).

stereospecifically with silylated pyrimidine bases to give **43T,U,C** in good yields (Scheme 10, entries 4−6). However, the effectiveness of the one-pot dioxirane procedure is apparently limited to pyrimidine bases, as benzoyladenine gives a very messy reaction resulting in a low isolated yield of **43A** (entry 7).

Discussion

Mechanism of Molybdenum-Catalyzed Alkynol Cyclizations. We propose that trialkylamine−molybdenum pentacarbonyl-catalyzed alkynol cycloisomerizations proceed by the mechanism shown in Scheme 11. Displacement of the trialkylamine ligand by the terminal alkyne of **45** is followed by isomerization of the η^2-molybdenum−alkyne complex **46** to the vinylidene carbene **47**.[29] At this stage we propose that alcohol deprotonation induces cyclization to give the molybdenum carbene anion **48**. Protonation of the molybdenum−carbon bond then provides the endocyclic enol ether product **49** and regenerates the trialkylamine−molybdenum pentacarbonyl catalyst. In this mechanism the tertiary amine serves as a proton carrier in the conversion of **47** to **49**. The tertiary amine base is required for successful reaction; alkynol substrates are recovered unchanged upon addition to molybdenum pentacarbonyl−ether complex in the absence of triethylamine.

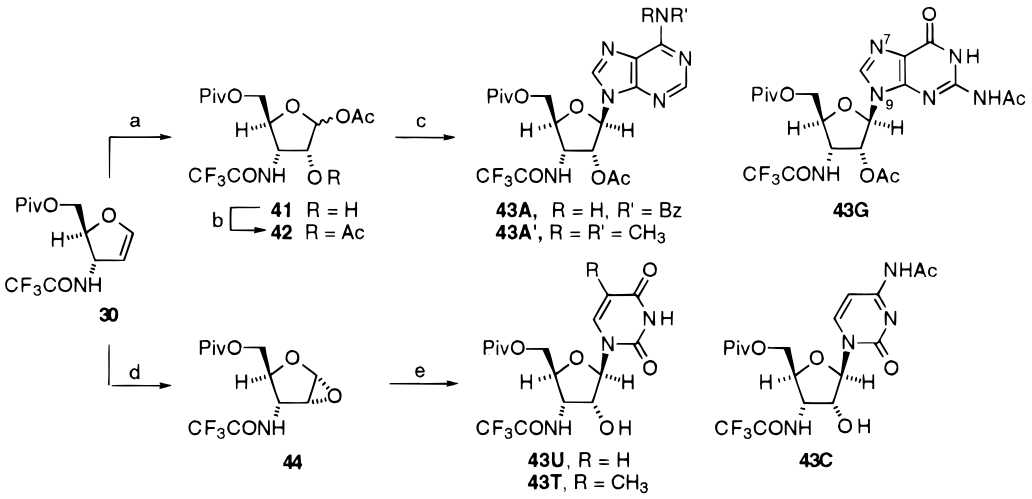
Alkynol substrates bearing good leaving groups at the propargylic position (i.e., 3-azido-1-alkyn-4-ols **16** and **17**) afford furan products resulting from cyclization and elimination (Scheme 12). Basic functional groups such as propargylic amines (compound **18**), hydroxyl groups (substrate **22**), and even silyl ethers (compounds **24** and **26**) are protonated by the trialkylammonium cation (**48** → **50**). These cationic (and therefore electrofugic) groups undergo elimination to give the plausible intermediate molybdenum carbene **51**. Deprotonation of the vinylogously acidified C4-hydrogen and protonation of the furan−molybdenum intermediate **52** affords furan products **53**.

Additional evidence implicating molybdenum carbene anions as mechanistic intermediates for these cyclizations includes reactions with various electrophiles. For instance, reaction of alkynol **54** with 1 equiv of triethylamine−molybdenum pentacarbonyl in the presence of benzaldehyde provides the enol ether **56** along with the molybdenum carbene **57** (Scheme 13).[9b] This structure is consistent with nucleophilic addition of a molybdenum carbene anion, **55-Mo**, to the aldehyde followed by dehydration, as precedented for stoichiometric chromium oxacarbenes.[30] We have also observed that reaction of alkynols such as **54** with catalytic triethylamine−molybdenum carbonyl in the presence of tributyltin triflate gives the endocyclic α-stannyldihydrofuran **58**.[9d] The same product is also obtained from the stoichiometric chromium carbene **59** under basic conditions, further implicating the common intermediacy of carbene anions **55** in these reactions.

(29) (a) Bruce, M. I.; Swincer, A. G. *Adv. Organomet. Chem.* **1983**, *22*, 59. (b) Silvestre, J.; Hoffmann, R. *Helv. Chim. Acta* **1985**, *68*, 1461. (c) Bruce, M. I. *Chem. Rev.* **1991**, *91*, 197.

(30) (a) Casey, C. P.; Brunsvold, W. R. *J. Organomet. Chem.* **1975**, *102*, 175. (b) Wulff, W. D.; Anderson, B. A.; Toole, A. J. *J. Am. Chem. Soc.* **1989**, *111*, 5485.

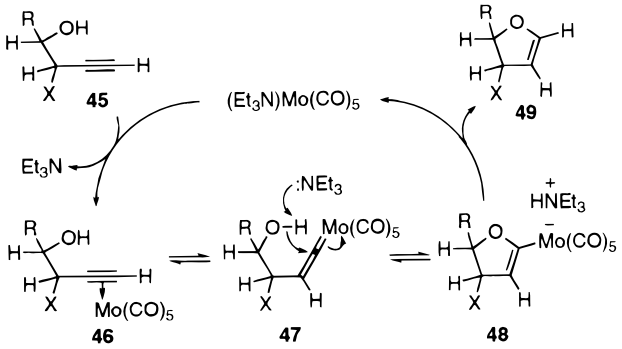
Scheme 10. Epoxidation/Glycosylation of **30** to 3′-Amido-3′-deoxynucleosides



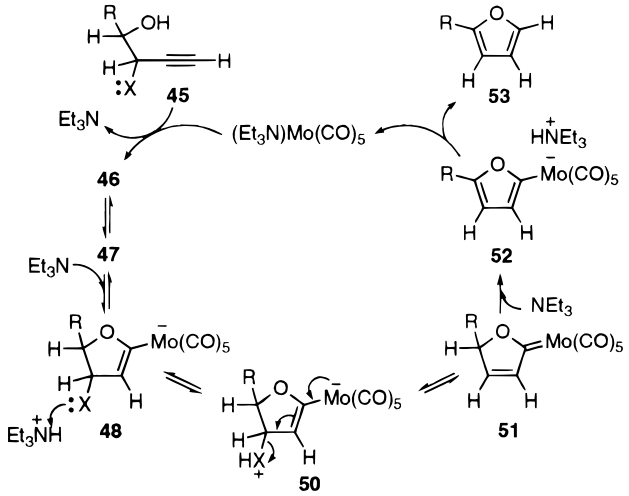
Reagents and Conditions: (a) 32% CH_3CO_3H, CH_2Cl_2; (b) Ac_2O, py., DMAP (97%; 2 steps); (c) silylated base, TMSOTf, 3Å MS, $ClCH_2CH_2Cl$, 83°C (entries 1 - 3); (d) dimethyldioxirane, CH_2Cl_2 / acetone (6/1), 0°C; (e) silylated base, MeCN, 20°C; aq. AcOH / THF workup (entries 4 - 7).

entry	silylated base	glycosyl donor	conditions	nucleoside, isolated yield
1	*N*-Bz(TMS)$_2$-adenine	**42**	c	**43A**, 90%
2	*N*-Ac(TMS)$_3$-guanine	**42**	c	**43G**, 77% (10:1)
3	*N, N*-Me$_2$(TMS)adenine	**42**	c	**43A'**, 71%
4	(TMS)$_2$-uracil	**44**	e	**43U**, 80%
5	(TMS)$_2$-thymine	**44**	e	**43T**, 86%
6	*N*-Ac(TMS)$_2$-cytosine	**44**	e	**43C**, 71%
7	*N*-Bz(TMS)$_2$-adenine	**44**	e	**43A**, 16%

Scheme 11. Mechanism for Alkynol Cycloisomerization (X = Nonbasic Group, H, NHC(O)R)



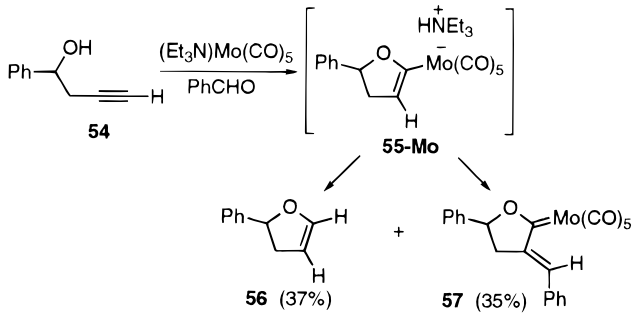
Scheme 12. Mechanism for Furan Formation (X = N_3, or Basic Groups, i.e., NH_2, OR)



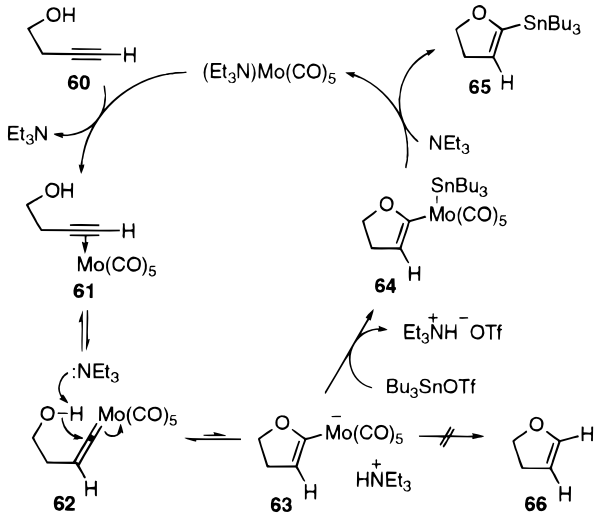
Finally, we propose that each of the mechanistic steps between alkynol substrate and the cyclic molybdenum carbene anion are reversible, including the carbon−oxygen bond-forming step in the intramolecular hydroxyl addition to molybdenum vinylidene carbene (**47** to **48**, Scheme 11; **62** to **63**, Scheme 14). This hypothesis is based on the following observations: primary alkynols are unreactive to triethylamine−molybdenum pentacarbonyl (for example, >80% of 3-butyn-1-ol (**60**) is recovered, and no trace of 2,3-dihydrofuran **66** is observed),[9b,d] yet when **60** is reacted with triethylamine−molybdenum pentacarbonyl in the presence of tributyltin triflate, the cyclized α-stannyldihydrofuran **65** is obtained in good yield. This suggests that the electrophilic tin reagent drives the overall equilibrium through the carbene anion **63** more effectively than does protonation by the trialkylammonium cation.

Stereoselective Syntheses of 3′-Amido-2′,3′-dideoxynucleosides from Furanoid Glycals. Although acid-catalyzed addition of nucleophiles to the unfunctionalized glycals proceeded without significant stereoinduction, we observed that nucleophilic addition to the 2-deoxy-3-amidoglycosyl acceptors **29**, **36**, and **37** generally proceeded from the β-face (*anti* to the 3-substituent), provided that the reaction was conducted at lower temperatures (kinetic control) and in acetonitrile as solvent. Our working hypothesis (Scheme 15) is that acetonitrile adds nonstereoselectively to give anomeric acetonitrilium ions **67*β*** and **67α**. Acetonitrilium ion **67*β*** is prone to intramolecular S_N2 displacement by the acetamido group to give the cyclic imidate intermediate **68**,[22] which subsequently undergoes intermolecular S_N2 displacement by the glycosyl acceptor (Nu:) to give β-nucleoside **35**. We propose that the acetonitrilium anomer **67α** may undergo intermolecular S_N2 displacement without the

Scheme 13. Interception of Carbene Anion Intermediates with Electrophiles



Scheme 14. Molybdenum-Catalyzed Cyclization of 3-Butyn-1-ol (**60**)

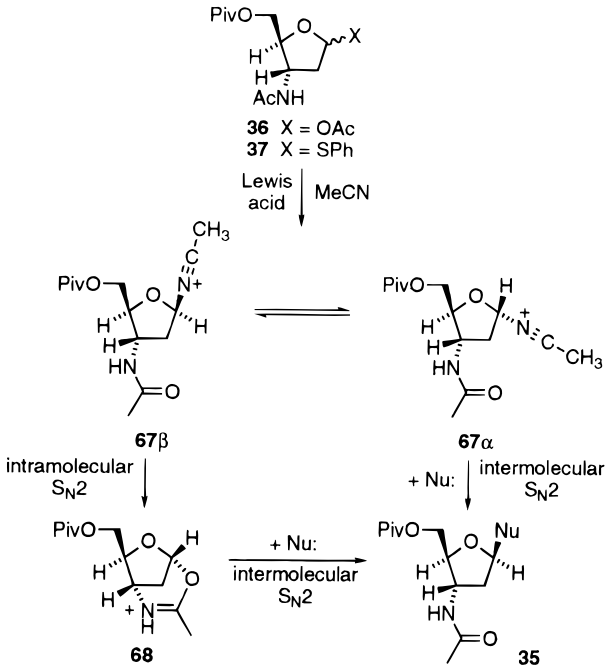


intermediacy of cyclic imidate **68**, as the acetonitrilium ion of **67α** is improperly configured for intramolecular displacement.

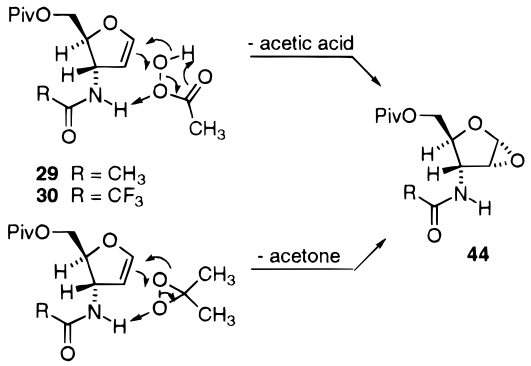
Supporting evidence for the intermediacy of **68** includes the observation that neither the electron-withdrawing 3-trifluoroacetamido glycal **30** nor the derived anomeric acetate (the trifluoroacetamide analog of **36**) can be glycosylated with reasonable stereoselectivity. When the glycosylation of **36** is conducted above room temperature, selectivity for β-pyrimidine nucleosides **35** is lost. Furthermore, 2′-deoxypurine nucleosides (which are known to suffer equilibration under acidic conditions) cannot be formed with high β-selectivities with these approaches even at 0 °C, although satisfactory β-stereoselectivity is obtained with glycosylations conducted at lower temperatures from the more reactive thioglycoside donor **37**.

Stereochemical assignments were made by careful comparisons of nuclear Overhauser effects (nOe) for the β- and α-anomers of the thymine nucleoside **35T**. The 3′-amido-2′,3′-dideoxynucleosides β-**35U,C,A,G** showed similar chemical shifts and coupling constants for the anomeric hydrogen, and were assigned by analogy to β-**35T** (see the supporting information). We note that the kinetically favored β-nucleoside

Scheme 15. Stereoselectivity of Kinetic Glycosylations of **36** and **37**



Scheme 16. Proposed Mechanisms for Amide-Directed Epoxidations of **29** and **30**



anomer was consistently less mobile by silica gel chromatography (TLC, flash column chromatography). Regiochemical assignments for guanosine nucleosides were determined by examining chemical shift differences at H-8;[25] the isomer with the upfield chemical shift is assigned as the N-9 regioisomer (**35G**, δ(H-8) = 8.01; N-7 regioisomer **35G***, δ(H-8) = 8.21).

Stereoselective Syntheses of 3′-Amido-3′-deoxynucleosides from Furanoid Glycals. Amide-directed peracid epoxidations have been known for nearly 40 years,[26] although this effect is not as widely known as the analogous directing effect with allylic alcohol substrates.[31] We were initially concerned that the higher nucleophilicity of enol ethers relative to other alkenes might override preassociation of the amide and peracid prior to oxygen atom transfer. However, we observed that epoxidations of both **29** and **30** occur from the α-face (Scheme 16), as determined by acetylation and Lewis acid-induced *trans*-glycosylation to give the desired β-nucleosides **40** and **43**, respectively (Schemes 9 and 10). In addition, dimethyldioxirane epoxidation is similarly directed from the secondary amide;[28d] the crude epoxide **44** can be glycosylated by *anti* addition of silylated pyrimidine bases to give the same β-nucleosides **43T,U,C** (Scheme 10). The stereochemical assignments of the epoxide-derived nucleoside products were confirmed by nOe

(31) Henbest, H. B.; Wilson, R. A. L. *J. Chem. Soc.* **1956**, 3289.

experiments on the thymidine derivative β-**43T**, and comparison with a sample of the α-anomer of **43T** prepared by an independent route (see the supporting information).

Conclusion

This work demonstrates the efficacy of our novel alkynol cyclization strategy coupled with glycal functionalization for the stereoselective synthesis of unusual deoxynucleoside substitution patterns, with applications to the antibiotic compounds d4T (**2**), cordycepin (**34**), and aminonucleosides including **3** and puromycin aminonucleoside (**4**). We have determined that the triethylamine−molybdenum pentacarbonyl-catalyzed alkynol cycloisomerization proceeds through a carbene anion catalytic intermediate. The mechanistic consequences of this reaction are consistent with the production of furans from 1-alkyn-4-ol substrates containing good leaving groups or basic groups at the propargylic position (C3). However, this methodology is compatible with alkynol substrates containing nonbasic propargylic *N*-carboxamide functional groups, and the resultant 3-amidofuranose glycal is the common synthetic intermediate for efficient preparation of a variety of 3′-aminodeoxynucleosides. Future directions include extension of the alkynol cyclization approach to the asymmetric synthesis of pyranosyl glycals and glycoconjugates.

Experimental Section

General Methods. All reactions were magnetically stirred in oven-dried glassware under a nitrogen atmosphere. Commercial grade reagents were used without further purification unless stated otherwise. The solvents tetrahydrofuran and diethyl ether were distilled from sodium−benzophenone ketyl prior to use; dichloromethane, toluene, acetonitrile, and triethylamine were distilled from calcium hydride prior to use. Photochemical irradiation was accomplished with a Rayonet photoreactor.

(*S*)-Oxiranemethanol Trimethylacetate (12). To a flame-dried 250 mL three-neck flask equipped with a stir bar and nitrogen inlet were added 3 Å powdered molecular sieves (1.75 g), D-(−)-diisopropyl tartrate (0.695 g, 2.98 mmol), allyl alcohol (**11**) (2.91 g, 50.0 mmol), and CH_2Cl_2 (95 mL). The stirred suspension was chilled to −5 to −10 °C. Ti(O-*i*-Pr)$_4$ (0.77 mL, 730 mg, 2.5 mmol) was added dropwise and stirred at −5 to −10 °C for 30 min. Cumene hydroperoxide (15 g, 100 mmol, dried over 3 Å molecular sieves) was added dropwise over 30 min, keeping the temperature at −5 to −10 °C. The mixture was stoppered and transferred to a freezer (−5 °C) for 23 h. The temperature was then adjusted to −40 °C, and trimethyl phosphite (8.85 mL, 9.31 g, 75.0 mmol) was added slowly over 60 min, keeping the temperature below −20 °C. In situ protection was accomplished at −20 °C by addition of triethylamine (8.4 mL, 6.1 g, 60.0 mmol) followed by trimethylacetyl chloride (6.2 mL, 6.0 g, 50.0 mmol) to the crude epoxidation mixture. The temperature was adjusted to 0 °C, and the mixture was stirred for 1 h and then filtered through a pad of Celite, eluting with CH_2Cl_2. The organic phase was washed with 10% tartaric acid (2 × 50 mL), saturated $NaHCO_3$, and brine, dried over Na_2SO_4, filtered through a 3 cm plug of silica gel, and concentrated. The residue was purified by silica gel chromatography (pentane:Et_2O = 10:1 to 4:1) to yield **12** as a colorless oil (2.98 g, 37% yield): $[\alpha]^{23}_D$ +21.1° ($CHCl_3$, c = 1.3); IR (neat) 2974, 2875, 1736, 1481, 1397, 1367, 1285, 1154, 1036, 991, 911, 858, 771 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.40 (1 H, dd, J = 12.3, 2.9 Hz), 3.91 (1 H, dd, J = 12.2, 6.1 Hz), 3.22−3.17 (1 H, m), 2.84 (1 H, dd, J = 4.5, 4.5 Hz), 2.64 (1 H, dd, J = 4.9, 2.6 Hz), 1.21 (9 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.1, 64.6, 49.4, 44.4, 38.7, 27.0.

(*S*)-1-Pentyne-4,5-diol 5-Trimethylacetate (13). A flame-dried 100 mL three-neck flask equipped with a dropping funnel, stir bar, and nitrogen inlet was charged with anhydrous THF (25.0 mL) and chilled to −78 °C. Acetylene was bubbled into the THF at −78 °C to form a saturated solution, to which *n*-butyllithium (2.5 M in hexane, 6.4 mL, 16.0 mmol) was added dropwise over 15 min. Boron trifluoride etherate (1.97 mL, 16.0 mmol) was added, followed by dropwise addition of **12** (2.11 g, 13.3 mmol, in 10 mL THF) over 20 min. The solution was allowed to warm to ca. −10 °C over a period of 1 h and was quenched by addition of water (10 mL) and saturated aqueous $NaHCO_3$ (15 mL). The mixture was stirred until all bubbling had ceased and two clear layers had formed. The aqueous layer was extracted with Et_2O (4 × 40 mL). The combined organic layers were washed once with brine, dried over Na_2SO_4, and concentrated. The residue was purified by chromatography on silica gel (pentane:EtOAc = 4:1) to yield **13** as a colorless oil (1.71 g, 70% yield): $[\alpha]^{23}_D$ +11.6° ($CHCl_3$, c = 0.69); IR (neat) 3462, 3293, 2966, 2875, 2122, 1727, 1481, 1399, 1286, 1161, 1103, 1037, 939 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.23−4.11 (2 H, m), 4.04−3.99 (1 H, m), 2.46 (2 H, dd, J = 6.3, 2.7 Hz), 2.35 (1 H, br d, J = 4.5 Hz), 2.06 (1 H, dd, J = 2.6, 2.6 Hz), 1.21 (9 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.6, 79.5, 71.0, 68.0, 66.7, 38.7, 27.0, 23.6; HRMS calcd for $C_{10}H_{17}O_3$ [(M + H)$^+$] 185.1177, found 185.1165.

(2*R*,3*R*)-3-Ethynyl-2-(hydroxymethyl)oxirane (15). (*E*)-2-Penten-4-yn-1-ol (**14**; 2.32 g, 28.3 mmol; dried over 3 Å molecular sieves), D-(−)-diisopropyl tartrate (815 mg, 3.40 mmol), and CH_2Cl_2 (56 mL) were added to powdered 3 Å molecular sieves (1.2 g, flame dried). The mixture was chilled to −5 to −10 °C. Ti(O-*i*-Pr)$_4$ (0.87 mL, 2.83 mmol) was added, and the mixture was stirred for 20 min at −5 to −10 °C. Cumene hydroperoxide (8.96 g, 47.1 mmol; dried over 3 Å molecular sieves) was added dropwise over 15 min. The mixture was stoppered and transferred to a freezer (−5 °C) for 24 h. The mixture was chilled to −25 °C, and P(OMe)$_3$ (4.7 mL, 4.25 mmol) was added dropwise over 10 min. Citric acid (544 mg, 2.83 mmol; dissolved in 50 mL of acetone/Et_2O (1:1)) was added, and the mixture was stirred for 45 min and allowed to warm to 20 °C. The mixture was filtered through Celite, and the solvents were evaporated. The residue was purified by silica gel chromatography using pentane/Et_2O (3:1) to yield the epoxide **15** (1.31 g, 47%) as a mixture of epoxide and diisopropyl tartrate (58 wt % epoxide by ^{1}H NMR): colorless oil; $[\alpha]^{23}_D$ −6.4° ($CHCl_3$, c = 0.502); IR (neat) 3439, 3269, 3005, 2931, 2872, 2125, 1636, 1433, 1314, 1234, 1074, 1028, 977, 880, 855, 748 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.97 (1 H, ddd, J = 13.1, 4.9, 2.3 Hz), 3.75 (1 H, ddd, J = 13.1, 8.4, 3.2 Hz), 3.47 (1 H, dd, J = 1.9, 1.8 Hz) 3.36 (1 H, m), 2.37 (1 H, d, J = 1.7 Hz), 1.68 (1 H, br d, J = 5.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 79.5, 72.3, 59.9, 59.7, 42.1.

(3*S*,4*S*)-3-Azido-1-pentyne-4,5-diol (16). Ti(O-*i*-Pr)$_4$ (2.0 mL, 6.7 mmol) and $TMSN_3$ (1.9 mL, 12 mmol) were added to toluene (50 mL) and heated to 90−110 °C for 4 h. The resulting orange solution was allowed to cool to 70−80 °C. The epoxide (545 mg, 5.56 mmol) was dissolved in toluene (7 mL) and added via cannula. The mixture was allowed to cool to 20 °C. After 16 h, the toluene was evaporated, the residue was dissolved in Et_2O (30 mL), and 5% H_2SO_4 (20 mL) was added. The biphasic mixture was stirred until two clear layers formed (1 h). The aqueous layer was extracted with EtOAc (10 × 20 mL). The organic layers were washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. The product was purified by silica gel chromatography using pentane/EtOAc (1:1) to yield **16** (602.1 mg, 77%): colorless oil; $[\alpha]^{23}_D$ +107° ($CHCl_3$, c = 0.300); IR (neat) 3382, 3289, 2938, 2894, 2110, 1308, 1233, 1112, 1038 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.32 (1 H, dd, J = 5.0, 2.3 Hz), 3.84−3.78 (3 H, m), 2.70 (1 H, d, J = 2.3 Hz), 2.61 (1 H, br d, J = 5.2 Hz), 1.98 (1 H, br s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 77.4, 76.0, 73.2, 62.7, 54.5.

(3*S*,4*S*)-3-Azido-1-pentyne-4,5-diol 5-Trimethylacetate (17). Diol **16** (1.23 g, 8.71 mmol) was dissolved in CH_2Cl_2 (80 mL) and chilled to 0 °C. Pyridine (2.2 mL, 27 mmol) was added followed by dropwise addition of trimethylacetyl chloride (1.4 mL, 11 mmol) over 5 min. The mixture was allowed to warm to 20 °C. After 13 h, the solvent was evaporated. The residue was dissolved in EtOAc (30 mL) and washed with saturated $NaHCO_3$ (20 mL). The aqueous layer was extracted with EtOAc (5 × 15 mL). The organic layers were washed with brine, dried over Na_2SO_4, and evaporated. The product was purified by silica gel chromatography using pentane/EtOAc (4:1) to yield **17** (1.56 g, 79%): colorless oil; $[\alpha]^{23}_D$ +63.9° ($CHCl_3$, c = 0.460); IR (neat) 3469, 3302, 2977, 2106, 1718, 1481, 1285, 1238, 1159, 1038, 914 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.25 (2 H, dd, J = 4.7, 1.6 Hz), 4.24 (1 H, m), 3.99 (1 H, m), 2.70 (1 H, d, J = 2.4 Hz), 2.59 (1 H, br d, J = 5.4 Hz), 1.23 (9 H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ

178.7, 77.6, 75.4, 71.7, 64.6, 54.8, 38.8, 27.1. Anal. Calcd for $C_{10}H_{15}N_3O_3$: C, 53.32; H, 6.71; N, 18.65. Found: C, 52.96; H, 6.70; N, 18.66.

(3*S*,4*S*)-3-Acetamido-1-pentyne-4,5-diol 5-Trimethylacetate (19). Azide **17** (1.19 g, 5.26 mmol) was dissolved in MeOH (52 mL). $SnCl_2$ (1.56 g, 8.08 mmol) was added, and the mixture was stirred at 20 °C for 19 h. The MeOH was evaporated, and the residue was dissolved in EtOAc (30 mL). Aqueous KF (5 M, 20 mL) was added, and the biphasic mixture was stirred until two clear layers formed (1.5 h; additional KF and water were added as needed to dissolve tin salts). The aqueous layer was extracted with EtOAc (5 × 20 mL). The organic layers were washed with brine, dried over Na_2SO_4, and evaporated to yield amine **18** (1.00 g). Crude amine **18** (1.00 g) was dissolved in MeOH/H_2O (2:1, 50 mL), Ac_2O (4.7 mL, 50 mmol) was added dropwise, and the mixture was stirred at 20 °C for 1 h. The mixture was concentrated, and the residue was purified by silica gel chromatography using pentane/EtOAc (4:1) to give **19** (1.11 g, 87% over two steps): colorless oil; $[\alpha]^{23}_D$ +8.4° ($CHCl_3$, $c = 0.308$); IR (neat) 3289, 2971, 2874, 2117, 1729, 1652, 1533, 1373, 1285, 1163, 1037, 993, 939 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.19 (1 H, br d, $J = 7.8$ Hz), 4.94 (1 H, ddd, $J = 8.4$, 2.7, 2.4 Hz), 4.30 (1 H, dd, $J = 11.4$, 6.9 Hz), 4.14 (1 H, dd, $J = 11.7$, 5.1 Hz), 3.97 (1 H, m), 2.86 (1 H, br d, $J = 6.3$ Hz), 2.38 (1 H, d, $J = 2.4$ Hz), 2.04 (3 H, s), 1.23 (9 H, s); (75 Mz, $CDCl_3$) δ 178.8, 169.8, 78.6, 73.7, 71.0, 65.2, 44.3, 38.8, 27.1, 23.0; HRMS (EI) calcd for $C_{12}H_{20}NO_4$ [(M + H)$^+$] 242.1392, found 242.1399.

(3*S*,4*S*)-3-(Trifluoroacetamido)-1-pentyne-4,5-diol 5-Trimethylacetate (20). Pyridine (0.57 mL, 7.0 mmol) and $(CF_3CO)_2O$ (0.91 mL, 6.4 mmol) were added to CH_2Cl_2 (30 mL) at −40 °C. Crude amine **18** (607 mg, 3.04 mmol), prepared as described for the preparation of **19**, was added via cannula in CH_2Cl_2 (10 mL). The mixture was allowed to warm to 20 °C. After 1 h, the solvent was evaporated, the residue was dissolved in MeOH (25 mL), and the mixture was stirred at room temperature for 2 h. The MeOH was then evaporated, and the residue was dissolved in EtOAc and washed with saturated $NaHCO_3$. The aqueous layer was extracted with EtOAc (4 × 15 mL). The organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel chromatography using pentane/EtOAc (3:1) to yield **20** (785 mg, 78% over two steps): colorless oil; $[\alpha]^{23}_D$ +22° ($CHCl_3$, $c = 0.554$); IR (neat) 3437, 3301, 3074, 2979, 2876, 2124, 1718, 1547, 1482, 1463, 1400, 1366, 1285, 1166 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.05 (1 H, br d, $J = 8.1$ Hz), 4.94 (1 H, ddd, $J = 8.7$, 2.7, 2.7 Hz), 4.37 (1 H, dd, $J = 11.7$, 6.6 Hz), 4.15 (1 H, dd, $J = 11.7$, 5.1 Hz), 4.03 (1H, m), 2.72 (1 H, br d, $J = 6.9$ Hz), 2.48 (1 H, d, $J = 2.3$ Hz), 1.24 (9H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 179.0, 156.6 (q, $J = 38.4$ Hz), 115.5 (q, $J = 263$ Hz), 76.5, 75.1, 70.1, 64.8, 44.6, 38.8, 27.0; HRMS (EI) calcd for $C_{12}N_{15}NO_3F_3$ [(M − OH)$^+$] 278.1004, found 278.0996.

1,4-Anhydro-2,3-dideoxy-D-pent-1-enitol 5-Trimethylacetate (21). An oven-dried 50 mL flask equipped with a stir bar and nitrogen inlet was charged with $Mo(CO)_6$ (311.4 mg, 1.180 mmol), trimethylamine *N*-oxide (118.3 mg, 1.064 mmol), anhydrous ether (25.0 mL), and triethylamine (4.0 mL, solvents distilled immediately prior to use). The suspension was stirred at 20 °C for 1 h. Alkynyl alcohol **13** (0.470 g, 2.55 mmol; dissolved in 10 mL of ether) was added via syringe and stirred at 20 °C for 65 h. The solvent was removed in vacuo, and the residue was purified by silica gel chromatography (pentane:ether: diethylamine = 100:0:1 to 100:5:1) to yield **21** as a colorless oil (0.376 g, 80% yield): $[\alpha]^{23}_D$ +85.4° ($CHCl_3$, $c = 1.46$); IR (neat) 2975, 2873, 1732, 1622, 1481, 1460, 1285, 1142, 1038, 951, 901, 706 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.28 (1 H, dd, $J = 2.3$, 5.0 Hz), 4.89 (1 H, dd, $J = 2.6$, 5.1 Hz), 4.80−4.70 (1 H, dddd, $J = 14.9$, 7.3, 6.2, 4.3 Hz), 4.19−4.09 (2 H, m), 2.73 (1 H, ddt, $J = 15.3$, 10.6, 2.4 Hz), 2.38 (1 H, ddt, $J = 15.3$, 7.3, 2.4 Hz), 1.21 (9 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.4, 145.1, 98.9, 78.3, 65.8, 38.9, 31.4, 27.2; HRMS calcd for $C_{10}H_{16}O_3$ (M$^+$) 184.1099, found 184.1096.

3-Acetamido-1,4-anhydro-2,3-dideoxy-D-*erythro*-pent-1-enitol 5-Trimethylacetate (29). $Mo(CO)_6$ (379 mg, 1.44 mmol) was dissolved in Et_2O (50.0 mL) and Et_3N (15.0 mL) under N_2. The colorless solution was irradiated at 350 nm under N_2 for 20 min. To the resulting yellow solution was added alkynyl alcohol **19** (1.21 g, 5.01 mmol) via syringe in CH_2Cl_2 (15 mL). The mixture was stirred at 20 °C under N_2 for 60 h. The solvents were evaporated, and the product was purified by silica gel chromatography using EtOAc/pentane (2:1, 1% Et_2NH) to yield **29** (1.087 g, 89%): colorless oil; $[\alpha]^{23}_D$ +116° ($CHCl_3$, $c = 0.418$); IR (neat) 3281, 2977, 1733, 1652, 1539, 1367, 1283, 1162, 1037, 729 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.52 (1 H, s), 5.54 (1 H, br s), 4.98−4.92 (2 H, m), 4.47 (1 H, m), 4.30, (1 H, dd, $J = 11.8$, 4.0 Hz), 4.22 (1 H, dd, $J = 11.8$, 6.0 Hz), 1.98 (3 H, s), 1.21 (9 H, s); ^{13}C NMR (75 Mz, $CDCl_3$) δ 178.1, 169.7, 149.3, 99.8, 85.5, 64.3, 54.4, 38.7, 27.0, 22.9; HRMS (EI) calcd for $C_{12}H_{19}NO_4$ (M$^+$) 241.1314, found 241.1324.

1,4-Anhydro-2,3-dideoxy-3-(trifluoroacetamido)-D-*erythro*-pent-1-enitol 5-trimethylacetate (30) was prepared by the procedure given for **29**. Alkynyl alcohol **20** (263 mg, 0.891 mmol) after silica gel chromatography (1% Et_2NH, 1% MeOH in CH_2Cl_2) gave **30** (244 mg, 92%): colorless oil; $[\alpha]^{23}_D$ +84.5° ($CHCl_3$, $c = 1.46$); IR (neat) 3314, 3088, 2978, 1722, 1616, 1550, 1481, 1456, 1399, 1368, 1283, 1154, 1077, 1036, 870 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.62 (1 H, d, $J = 1.2$ Hz), 6.31 (1 H, br s), 5.05−5.01 (2 H, m), 4.55 (1 H, ddd, $J = 8.6$, 5.1, 3.5 Hz), 4.26 (2 H, d, $J = 5.2$ Hz), 1.22 (9 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.2, 156.7 (q, $J = 37.7$ Hz), 150.8, 115.5 (q, $J = 288$ Hz), 98.4, 84.6, 63.7, 55.4, 38.8, 27.0; HRMS (EI) calcd for $C_{12}H_{16}NO_4F_3$ (M$^+$) 295.1031, found 295.1025.

1-(2′,3′-Dideoxy-2′-iodo-5′-*O*-(trimethylacetyl)-β-D-ribofuranosyl)-thymine (31). An oven-dried 25 mL flask equipped with a stir bar and nitrogen inlet was charged with **21** (76.8 mg, 0.417 mmol) and anhydrous CH_2Cl_2 (4.0 mL), which was then chilled to −30 °C. N^1,N^3-bis(trimethylsilyl)thymine[32] (160.9 mg, 0.595 mmol) was added followed by I_2 (171.6 mg, 0.676 mmol), and the mixture was stirred at −30 °C for 2 h. The mixture was diluted with CH_2Cl_2 (20 mL), warmed to 20 °C, and quenched by addition of 10% $Na_2S_2O_5$ (10 mL). The layers were separated, and the CH_2Cl_2 layer was washed again with 10% $Na_2S_2O_5$ (10 mL) and brine, dried over Na_2SO_4, and concentrated to yield **31** as a light yellow oil which solidified upon standing (177.0 mg, 94% yield, 7:1 mixture of isomers): ^1H NMR (300 MHz, $CDCl_3$) δ 8.59 (1 H, br s), 7.28 (1 H, s), 6.20 (1 H, d, $J = 5.6$ Hz), 4.68−4.60 (1 H, m), 4.47 (1 H, dd, $J = 13.5$, 5.5 Hz), 4.35−4.30 (1 H, m), 4.27 (1 H, dd, $J = 13.0$, 3.4 Hz), 2.43−2.23 (2H, m), 1.93 (3 H, s), 1.22 (9 H, s). **24** was unstable to purification on silica gel, and the best overall yields were obtained by reacting the crude iodonucleoside in the next step.

Stavudine (2). Iodonucleoside **31** (46.4 mg, 0.1064 mmol) was placed in an oven-dried 25 mL flask equipped with a stir bar and nitrogen inlet. Sodium methoxide (25 wt % in methanol, 1.5 mL, 6.6 mmol) was added and stirred at 20 °C for 18 h. The reaction was quenched by dropwise addition of 1 N HCl until solution pH tested neutral. The volatiles were evaporated, and the residue was purified by chromatography (methanol:CH_2Cl_2 = 1:25) to yield **2** as an off-white solid (19.0 mg, 80% yield): mp 163−166 °C (lit.[33] mp 164−166 °C); $[\alpha]^{23}_D$ −42° (H_2O, $c = 0.52$) (lit.[33] $[\alpha]^{20}_D$ −46.1° (H_2O, $c = 0.7$)); IR (KBr) 3472, 3176, 3035, 1672, 1465, 1256, 1095 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 7.56 (1 H, s), 6.87 (1 H, d, $J = 1.3$ Hz), 6.40 (1 H, d, $J = 6.1$ Hz), 5.90 (1 H, d, $J = 6.1$ Hz), 4.92 (1 H, br s), 3.72 (2 H, d, $J = 3.0$ Hz), 1.78 (3 H, s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 164.1, 150.9, 136.9, 135.1, 126.0, 109.1, 89.0, 87.4, 62.4, 12.3; HRMS calcd for $C_{10}H_{12}N_2O_4$ (M$^+$) 224.0797, found 224.0805.

3-Deoxy-D-ribofuranose 1,2-Diacetate 5-Trimethylacetate (32). A 50 mL flask equipped with a stir bar and nitrogen inlet was charged with **21** (201.4 mg, 1.093 mmol), THF (11.0 mL), *t*-BuOH (0.28 mL), and H_2O (0.17 mL), and was cooled to 0 °C. *N*-Methylmorpholine *N*-oxide (203.5 mg, 1.685 mmol) was added followed by OsO_4 (ca. 2 mg), and the reaction mixture was allowed to slowly warm to 20 °C. The reaction was monitored by TLC (pentane:Et_2O = 4:1, product R_f = 0.05) until complete conversion of **21** was indicated (ca. 4 h). Solid $Na_2S_2O_5$ (392.2 mg, 2.063 mmol) was added to the reaction, which was allowed to stir for 1 h. The mixture was concentrated, and the residue was purified by filtration through a 3 cm plug of silica gel, eluting with acetone. The filtrate was concentrated to yield 158.9 mg of crude diol (ca. 0.73 mmol, 67% yield), which was dissolved in CH_2-

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Cl_2 (5.0 mL). Triethylamine (0.72 mL, 0.52 g, 5.2 mmol) and acetic anhydride (0.34 mL, 0.37 g, 3.6 mmol) were added, and the mixture was stirred at 20 °C for 22 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with saturated $NaHCO_3$ (2 × 7 mL) and brine. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography (pentane:EtOAc = 4:1 to 1:1) to yield the diacetates as an inseparable mixture of four stereoisomers favoring **32** (197.2 mg, 90% yield, 60% yield over two steps). Spectral data for major isomer **32**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.16 (1 H, s), 5.20 (1 H, t, J = 3.0 Hz), 4.63−4.53 (1 H, m), 4.16 (2 H, dd, J = 6.8, 2.2 Hz), 2.25−1.98 (2 H, m), 2.11 (3 H, s), 2.07 (3 H, s), 1.21 (9 H, s).

9-(2′-*O*-Acetyl-3′-deoxy-5′-(trimethylacetyl)-*β*-D-ribofuranosyl)-*N*-benzoyladenine (33). An oven-dried 25 mL flask equipped with a reflux condenser, stir bar, and nitrogen inlet was charged with N^4,N^7-bis(trimethylsilyl)-N^7-benzoyladenine[34a,b] (217.1 mg, 0.566 mmol). Diacetate **32** (81.6 mg, 0.270 mmol; dissolved in 5.0 mL of 1,2-dichloroethane) was added followed by trimethylsilyl triflate (0.10 mL, 0.517 mmol). The reaction mixture was stirred and heated at reflux for 3 h. The reaction mixture was cooled to 20 °C, diluted with 30 mL of CH_2Cl_2, washed with saturated $NaHCO_3$ (2 × 15 mL) and brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel chromatography (toluene:acetone = 4:1 to 2:1) to yield **33** as a colorless oil (91.0 mg, 65% yield, 73% based on recovered starting material): $[\alpha]^{23}_D$ +5° ($CHCl_3$, c = 1.02); IR (neat) 3292, 2971, 1728, 1610, 1441, 1235, 1146, 1081 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.28 (1 H, br s), 8.74 (1 H, s), 8.12 (1 H, s), 8.03−7.96 (2 H, m), 7.58−7.41 (3 H, m), 6.09 (1 H, d, J = 1.5 Hz), 5.74 (1 H, d, J = 6.0 Hz), 4.66−4.57 (1 H, m), 4.36 (1 H, dd, J = 12.3, 3.3 Hz), 4.28 (1 H, dd, J = 12.3, 5.7 Hz), 2.70−2.60 (1 H, m), 2.22 (1 H, dd, J = 14.0, 4.4 Hz), 2.12 (3 H, s), 1.16 (9 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.2, 170.1, 164.6, 152.7, 151.1, 149.6, 141.6, 133.5, 132.7, 128.7, 127.8, 123.5, 90.0, 78.68, 77.7, 64.5, 38.8, 32.9, 27.1, 20.8; HRMS calcd for $C_{24}H_{28}N_5O_6$ [(M + H)$^+$] 482.2040, found 482.2072.

Cordycepin (34). An oven-dried 25 mL flask fitted with a stir bar and nitrogen inlet was charged with **33** (81.4 mg, 0.169 mmol). Sodium methoxide (25 wt % in methanol, 0.80 mL, 3.5 mmol) was added, and the mixture was stirred at 20 °C for 20 h. The reaction mixture was diluted with methanol (10 mL) and chilled to 0 °C, and saturated aqueous ammonium chloride was added dropwise until solution pH tested neutral. Water and methanol were removed in vacuo, and the residue was purified by silica gel chromatography (MeOH:CH_2Cl_2 = 12:1) to yield cordycepin **(34)** as a white solid (17.9 mg, 42% yield), and 16% of the N^7-benzamide derivative resulting from incomplete methanolysis. Data for **34**: mp 205−206 °C (lit.[35] mp 224−225 °C); $[\alpha]^{23}_D$ −40° (H_2O, c = 0.40) (lit.[35] $[\alpha]^{20}_D$ −44° (H_2O, c = 0.5)); IR (KBr) 3329, 3129, 1677, 1609, 1481, 1422, 1384, 1341, 1298, 1206, 1092, 717 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.36 (1 H, s), 8.14 (1 H, s), 7.30 (2 H, br s), 5.87 (1 H, d, J = 2.5 Hz), 5.68 (1 H, d, J = 4.3 Hz), 5.18 (1 H, t, J = 5.5 Hz), 4.56 (1 H, m), 4.35 (1 H, ddd, J = 8.3, 6.3 Hz), 3.72−3.66 (1 H, m), 3.55−3.47 (1 H, m), 2.25 (1 H, ddd, J = 13.7, 8.7, 5.7 Hz), 1.91 (1 H, ddd, J = 13.2, 6.6, 3.3 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 156.0, 152.4, 148.8, 139.0, 119.1, 90.8, 80.7, 74.6, 62.6, 34.1; HRMS calcd for $C_{10}H_{13}N_5O_3$ (M$^+$) 251.1018, found 251.1031.

Acetyl 3-Acetamido-2,3-dideoxy-5-*O*-(trimethylacetyl)-D-ribofuranoside (36). Dry 3 Å molecular sieves (116 mg) were added to glycal **29** (84.7 mg, 0.351 mmol) followed by Ac_2O (2.0 mL) and AcOH (2.0 mL). TsOH·H_2O (56.0 mg, 0.294 mmol) was added, and the mixture was stirred under N_2 at 20 °C for 90 h. The reaction was quenched by dilution with EtOAc (30 mL) and washing with brine and saturated $NaHCO_3$. The aqueous layers were extracted with EtOAc (4 × 15 mL). The organic layers were washed with brine, dried over Na_2SO_4, and concentrated. Purification by silica gel chromatography using 1% MeOH in CH_2Cl_2 gave **36** as a separable mixture of anomers (1.1:1 mixture, 97.5 mg, 92% combined). Careful chromatography allowed for separation of the individual anomers. Data for major anomer: colorless oil; $[\alpha]^{23}_D$ +62.7° ($CHCl_3$, c = 0.692); IR (neat) 3290, 3075, 2974, 1733, 1652, 1549, 1473, 1368, 1285, 1231, 1160, 1110, 998, 935, 849 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.41 (1 H, d, J = 5.1 Hz), 6.03 (1 H, br d, J = 7.7 Hz), 4.54 (1 H, dddd, J = 10.1, 8.3, 2.8, 1.8 Hz), 4.28 (1 H, m), 4.21 (1 H, dd, J = 11.9, 3.8 Hz), 4.13 (1 H, dd, J = 11.7, 4.2 Hz), 2.52 (1 H, ddd, J = 14.4, 8.4, 5.2 Hz), 2.10 (3 H, s), 2.06−1.92 (1 H, m), 2.01 (3 H, s), 1.20 (9 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.0, 169.6, 169.4, 98.7, 85.1, 64.3, 49.9, 38.7, 38.2, 27.1, 23.2, 21.4; HRMS (EI) calcd for $C_{14}H_{24}NO_6$ [(M + H)$^+$] 302.1604, found 302.1607. Data for minor anomer: colorless oil; $[\alpha]^{23}_D$ −47° ($CHCl_3$, c = 0.312); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.32 (1 H, d, J = 4.5 Hz), 5.88 (1 H, br d, J = 8.0 Hz), 4.61−4.57 (1 H, m), 4.27−4.15 (2 H, m), 4.06 (1 H, dd J = 10.8, 6.0 Hz), 2.47 (1 H, dd J = 13.6, 7.3 Hz), 2.09 (1 H, ddd, J = 13.9, 8.7, 5.2 Hz), 2.06 (3 H, s), 1.99 (3 H, s), 1.22 (9 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.3, 170.1, 170.0, 97.6, 82.8, 64.7, 49.7, 38.8, 38.6, 27.1, 23.2, 21.3.

1-(3′-Acetamido-2′,3′-dideoxy-5′-*O*-(trimethylacetyl)-*β*-D-ribofuranosyl)thymine (35T). Acetate **36** (38.8 mg, 0.129 mmol; dried by azeotropic evaporation from toluene, 3×) was dissolved in 3.0 mL of dry MeCN and added via cannula to 3 Å molecular sieves (72 mg) and $(TMS)_2$-thymine[32] (116.4 mg, 0.4303 mmol). The mixture was chilled to 0 °C, and TfOH (0.014 mL, 0.15 mmol) was added dropwise. After 3 h, the mixture was allowed to warm to 20 °C. After 12 h, the mixture was diluted with CH_2Cl_2 (25 mL) and washed with saturated $NaHCO_3$ (1 × 25 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The organic layers were washed with brine, dried over Na_2SO_4, and evaporated. Silica gel chromatography (3% MeOH in CH_2Cl_2) gave **35T** as an inseparable 8.4:1 (β/α) mixture of anomers (41.2 mg, 87% combined), which was characterized as follows: colorless glass; $[\alpha]^{23}_D$ +12.1° ($CHCl_3$, c = 0.446); IR (thin film) 3301, 3181, 3073, 2979, 2516, 1688, 1554, 1472, 1369, 1276, 1155, 1097, 1037, 976, 896, 734 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, β anomer) δ 10.57 (1 H, br s), 7.82 (1 H, br d, J = 5.4 Hz), 7.41 (1 H, s), 6.30 (1 H, dd, J = 8.9, 5.0 Hz), 4.47 (1 H, dd, J = 12.3, 4.5 Hz), 4.38−4.26 (3 H, m) 2.44 (1 H, dd, J = 12.7, 5.0 Hz), 2.06 (3 H, s), 2.02−1.94 (1 H, m), 1.92 (3 H, s), 1.21 (9 H, s); ^{13}C NMR (75 MHz, $CDCl_3$, β anomer) δ 178.0, 170.9, 164.1, 150.7, 134.8, 111.4, 85.4, 84.5, 64.7, 51.0, 38.8, 37.2, 27.2, 22.7, 12.4; HRMS (LSIMS) calcd for $C_{17}H_{26}N_3O_6$ [(M + H)$^+$] 368.1822, found 368.1851.

Phenyl 3-Acetamido-2,3-dideoxy-5-*O*-(trimethylacetyl)-D-1-thioribofuranoside (37). Glycal **29** (128.5 mg, 0.5326 mmol) was added to flame-dried 3 Å molecular sieves (77 mg) via cannula in MeCN (5.0 mL). Thiophenol (0.117 mL, 1.06 mmol) was added followed by TfOH (0.057 mL, 0.64 mmol). The mixture was stirred at 20 °C for 66 h. The reaction was quenched by dilution with CH_2Cl_2 and washing with saturated $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (4 × 10 mL). The organic layers were washed with brine, dried over Na_2SO_4, and concentrated. Purification by silica gel chromatography using 2.5% MeOH in CH_2Cl_2 gave **37** as a 2.1:1 mixture of isomers (inseparable, 141 mg, 75% combined). This mixture was characterized as follows: colorless oil; $[\alpha]^{23}_D$ +77.6° ($CHCl_3$, c = 0.606); IR (thin film) 3277, 3064, 2967, 2879, 1732, 1648, 1549, 1480, 1440, 1368, 1285, 1161, 1087, 1026, 959, 743, 692 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, major isomer) δ 7.52−7.49 (2 H, m), 7.34−7.26 (3 H, m), 6.09 (1 H, br d, J = 8.5 Hz), 5.71 (1 H, dd, J = 7.4, 3.1 Hz), 4.52−4.44 (1 H, m), 4.30−4.14 (3 H, m), 2.87−2.77 (1 H, m), 2.00 (3 H, s), 1.89 (1 H, ddd, J = 14.2, 3.6, 3.4 Hz), 1.20 (9 H, s); ^{13}C NMR (75 MHz, $CDCl_3$, major isomer) δ 178.1, 169.6, 133.9, 131.8, 128.9, 127.6, 86.7, 81.6, 63.9, 50.4, 39.8, 38.7, 27.1, 23.3; HRMS (EI) calcd for $C_{18}H_{26}NO_4S$ [(M + H)$^+$] 352.1582, found 352.1598.

9-(3′-Acetamido-2′,3′-dideoxy-5′-*O*-(trimethylacetyl)-*β*-D-ribofuranosyl)-*N*-6-benzoyladenine (35A). Thioglycoside **37** (92.0 mg, 0.262 mmol) was dissolved in dry MeCN (5.0 mL) and added via cannula to flame-dried 3 Å molecular sieves (102.2 mg) and *N*-Bz-$(TMS)_2$-adenine[34a,b] (209 mg, 0.545 mmol). The mixture was chilled to −40 °C. NIS (191 mg, 0.807 mmol) was added followed by TfOH (0.028 mL, 0.32 mmol), dropwise, over 1 min. The mixture was stirred at −40 °C for 1.25 h, after which the mixture was allowed to warm to 0 °C and stirred for 1.5 h. The reaction was quenched by dilution with CH_2Cl_2 and washing with 10% $Na_2S_2O_5$ and saturated $NaHCO_3$.

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The aqueous layers were extracted with CH_2Cl_2, and the organic layers were washed with brine, dried over Na_2SO_4, and concentrated. Silica gel chromatography of the residue using 2.5−5% MeOH in CH_2Cl_2 gave **35A** (53.0 mg, 42%): colorless glass; $[\alpha]^{23}_D$ −2° ($CHCl_3$, c = 0.456); IR (thin film) 3289, 3067, 2976, 1688, 1609, 1447, 1272, 1159, 1093, 1036, 954, 893, 710 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.40 (1 H, br s), 8.66 (1 H, s), 8.23 (1 H, s), 7.99 (2 H, d J = 7.2 Hz), 7.57 (1 H, t, J = 7.4 Hz), 7.47 (2 H, t, J = 7.4 Hz), 7.13 (1 H, br d, J = 7.3 Hz), 6.43 (1 H, t, J = 5.9 Hz), 4.73 (1 H, m), 4.39−4.25 (3 H, m), 2.85 (1 H, ddd, J = 13.4, 5.4, 2.5 Hz), 2.68 (1 H, ddd, J = 13.4, 6.8, 6.4 Hz), 2.00 (3 H, s), 1.16 (9 H,s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.2, 170.5, 165.0, 152.3, 151.1, 149.4, 141.2, 133.4, 132.8, 128.8, 127.8, 123.5, 84.4, 82.7, 64.0, 50.2, 38.7, 37.8, 27.1, 23.1; HRMS (LSIMS) calcd for $C_{24}H_{28}N_6O_5$ [(M + H)$^+$] 480.2121, found 480.2131.

7-(3′-Acetamido-2′,3′-dideoxy-5′-*O*-(trimethylacetyl)-*β*-D-ribofuranosyl)-*N*-2-acetylguanine (35G*). Thioglycoside **37** (37.9 mg, 0.108 mmol) was dissolved in dry EtCN (3.0 mL) and added via cannula to 3 Å molecular sieves (44 mg, flame dried) and *N*-Ac-$(TMS)_3$-guanine[36] (115 mg, 0.281 mmol). The mixture was chilled to −78 °C. NIS (81.8 mg, 0.345 mmol) was added followed by dropwise addition of TfOH (0.012 mL, 0.13 mmol). After 3 h at −78 °C, the mixture was warmed to 0 °C. The reaction was quenched by dilution with EtOAc (20 mL), and washing with 10% $Na_2S_2O_5$ (1 × 10 mL) and saturated $NaHCO_3$ (1 × 10 mL). The aqueous layers were extracted with EtOAc (4 × 15 mL), and the organic layers were washed with brine (15 mL), dried over Na_2SO_4, and concentrated. Silica gel chromatography (4−5% MeOH in CH_2Cl_2) gave **35G*** as a 7.3:1 mixture of isomers (16.3 mg, 35% combined). This mixture was characterized as follows: colorless glass; $[\alpha]^{23}_D$ +54° ($CHCl_3$, c = 0.358); IR (thin film) 3267, 3185, 3068, 2965, 1684, 1610, 1549, 1456, 1370, 1256, 1161, 1098, 969, 780 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, major isomer) δ 11.18 (1 H, br s), 8.21 (1 H, s), 7.15 (1 H, br d, J = 7.4 Hz), 6.61 (1 H, t, J = 5.4 Hz), 4.68−4.58 (1 H, m), 4.47−4.37 (2 H, m), 4.28 (1 H, ddd, J = 6.3, 4.4, 3.9 Hz), 2.86 (1 H, ddd, J = 14.1, 7.2, 6.5 Hz), 2.67 (1 H, ddd, J = 13.8, 7.5, 5.0 Hz), 2.41 (3 H, s), 2.02 (3 H, s), 1.20 (9 H, s); ^{13}C NMR (75 MHz, $CDCl_3$, major isomer) δ 178.3, 173.7, 170.6, 157.7, 152.9, 148.0, 140.6, 110.9, 86.9, 83.2, 63.9,49.2, 40.1, 38.8, 27.2, 24.5, 23.1; HRMS (LSIMS) calcd for $C_{19}H_{27}N_6O_6$ [(M + H)$^+$] 435.1992, found 435.1982.

Data for 9-(3′-acetamido-2′,3′-dideoxy-5′-*O*-(trimethylacetyl)-*β*-D-ribofuranosyl)-*N*-2-acetylguanine (35G): ^{1}H NMR (300 MHz, acetone-d_6) δ 12.04 (1 H, br s), 10.78 (1 H, br s), 8.00 (1 H, s), 7.65 (1 H, br d, J = 5.8 Hz), 6.26 (1 H, dd, J = 7.2, 5.1 Hz), 4.76−4.67 (1 H, m), 4.34 (1 H, dd, J = 12.0, 3.4 Hz), 4.23 (1 H, dd, J = 11.8, 5.8 Hz), 4.17−4.11 (1 H, m), 2.92−2.83 (1 H, m), 2.62−2.53 (1 H, m), 2.29 (3 H, s), 1.92 (3 H, s), 1.14 (9 H, s).

Acetyl 2-*O*-Acetyl-3-deoxy-3-(trifluoroacetamido)-5-*O*-(trimethylacetyl)-D-ribofuranoside (42). Glycal **30** (192.6 mg, 0.7982 mmol) was dissolved in 16 mL of CH_2Cl_2 and chilled to 0 °C. Peracetic acid (32 wt % in dilute AcOH, 0.25 mL, 1.2 mmol) was added dropwise. The mixture was allowed to warm to 20 °C. After 1.5 h, the mixture was diluted with EtOAc and washed with 10% Na_2SO_3 and saturated $NaHCO_3$. The aqueous layers were extracted with EtOAc, and the organic layers were washed with brine, dried over Na_2SO_4, and concentrated to give **41**. The crude hydroxy acetate **41** was dissolved in 7.0 mL of dry CH_2Cl_2. Pyridine (0.39 mL, 4.8 mmol), Ac_2O (0.23 mL, 2.4 mmol), and DMAP (1 mg) were added, and the mixture was stirred at 20 °C for 24 h. The volatiles were evaporated, and the residue was purified by silica gel chromatography using 2% MeOH in CH_2Cl_2 to yield **42** as an inseparable mixture of anomers (278.3 mg, 97% combined over two steps). This mixture was characterized as follows: colorless oil; $[\alpha]^{23}_D$ +25.3° ($CHCl_3$, c = 0.900); IR (neat) 3328, 2972, 1737, 1553, 1482, 1374, 1284, 1232, 1154, 1074, 1026, 973, 900, 736 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, major isomer) δ 6.50 (1 H, br d, J = 9.0 Hz), 6.18 (1 H, s), 5.20 (1 H, d, J = 5.0 Hz), 4.89 (1 H, ddd, J = 8.6, 8.5, 5.1 Hz), 4.33−4.22 (3 H, m), 2.19 (3 H, s), 2.13 (3 H, s), 1.23 (9 H, s); ^{13}C NMR (75 MHz, $CDCl_3$, major isomer) δ 178.0, 169.2, 168.9, 157.1 (q, J = 37.9 Hz), 115.4 (q, J = 285.6 Hz), 97.6, 79.9, 75.2, 63.5, 50.1, 38.8, 26.9, 20.9, 20.4.

9-(2′-*O*-Acetyl-3′-deoxy-3′-(trifluoroacetamido)-5′-*O*-(trimethylacetyl)-*β*-D-ribofuranosyl)-*N*-6-benzoyladenine (43A). *N*-Bz-$(TMS)_2$-adenine[34a,b] (154.1 mg, 0.4017 mmol) was added to flame-dried 3 Å molecular sieves (52 mg). Diacetate **42** (49.8 mg, 0.120 mmol; dried by azeotropic evaporation from toluene, 3×) was added via cannula in $ClCH_2CH_2Cl$ (3.0 mL). TMSOTf (0.028 mL, 0.14 mmol) was added at 20 °C. The mixture was heated to reflux for 4 h. The reaction was quenched by dilution with CH_2Cl_2, and washing with saturated $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2. The organic layers were washed with brine, dried over Na_2SO_4, and concentrated. Purification by silica gel chromatography using 1−1.5% MeOH in CH_2Cl_2 gave **43A** (65.0 mg, 90%): colorless glass; $[\alpha]^{23}_D$ +33.1° ($CHCl_3$, c = 0.652); IR (thin film) 3294, 3074, 2978, 1726, 1612, 1514, 1456, 1223, 1161, 897, 797, 705 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.17 (1 H, br s), 8.77 (1 H, s), 8.12 (1 H, s), 8.01 (2 H, d, J = 7.2 Hz), 7.60 (1 H, t, J = 7.4 Hz), 7.51 (2 H, t, J = 7.4 Hz), 7.18 (1 H, br d, J = 8.4 Hz), 6.12 (1 H, d, J = 2.7 Hz), 5.83 (1 H, dd, J = 6.6, 2.4 Hz), 5.52−5.47 (1 H, m), 4.48−4.42 (2 H, m), 4.32 (1 H, dd, J = 12.9, 5.4 Hz), 2.17 (3 H, s), 1.17 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.2, 169.4, 164.7, 157.2 (q, J = 37.6 Hz), 152.9, 151.2, 149.7, 142.0, 133.3, 132.9, 128.9, 127.8, 123.6, 115.5 (q, J = 287 Hz), 88.5, 80.0, 75.1, 62.9, 50.3, 38.8, 27.0, 20.4; HRMS (LSIMS) calcd for $C_{26}H_{27}N_6O_7F_3Na$ [(M + Na)$^+$] 615.1791, found 615.1812.

9-(2′-*O*-Acetyl-3′-deoxy-3′-(trifluoroacetamido)-5′-*O*-(trimethylacetyl)-*β*-D-ribofuranosyl)-*N*-6,*N*-6-dimethyladenine (43A′). TMS-6-(dimethylamino)purine[37] (0.40 mmol) was added to flame-dried 3 Å molecular sieves (50 mg). Diacetate **42** (59.7 mg, 0.144 mmol; dried by azeotropic evaporation from toluene, 3×) was added via cannula in $ClCH_2CH_2Cl$ (3.0 mL). TMSOTf (0.056 mL, 0.29 mmol) was added at 20 °C. The mixture was heated to reflux for 4 h. The reaction was quenched by dilution with CH_2Cl_2, and washing with saturated $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2. The organic layers were washed with brine, dried over Na_2SO_4, and concentrated. Purification by silica gel chromatography using 2−4% MeOH in CH_2Cl_2) gave **43A′** (53.2 mg, 71%): colorless glass; $[\alpha]^{23}_D$ +32° ($CHCl_3$, c = 0.472); IR (thin film) 3314, 3063, 2973, 2880, 1739, 1622, 1552, 1415, 1269, 1232, 1160, 1064, 918, 738 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (1 H, s), 7.97 (1 H, s), 6.69 (1 H, br d, J = 7.6 Hz), 5.97 (1 H, d, J = 1.7 Hz), 5.80 (1 H, dd, J = 6.6, 1.9 Hz), 5.82−5.74 (1 H, m), 4.55−4.49 (1 H, m) 4.41−4.33 (2 H, m), 3.96 (3 H, br s), 3.39 (3 H, br s), 2.21 (3 H, s), 1.22 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.3, 169.5, 157.1 (q, J = 38 Hz), 153.2, 152.4, 148.3, 139.7, 121.3, 115.5 (q, J = 286 Hz), 93.6, 80.8, 75.4, 63.2, 50.2, 39.9, 38.8, 38.1, 27.1, 20.5; HRMS (LSIMS) calcd for $C_{21}H_{28}N_6O_6F_3$ [(M + H)$^+$] 517.2022, found 517.2047.

1-(3′-Deoxy-3′-(trifluoroacetamido)-5′-*O*-(trimethylacetyl)-*β*-D-ribofuranosyl)thymine (43T). Glycal **30** (70.4 mg, 0.238 mmol) was dissolved in 35 mL of dry CH_2Cl_2 and chilled to 0 °C. Dimethyldioxirane (5.7 mL, 0.059 M solution in acetone) was added dropwise over 10 min. The mixture was stirred at 0 °C for 1 h. The CH_2Cl_2 was reduced in volume to 2 mL by evaporation with a stream of N_2. Dry MeCN (10 mL) was added and the volume reduced to 4 mL by evaporation with a stream of N_2. $(TMS)_2$-thymine[32] (269 mg, 0.994 mmol) was added, and the mixture was stirred at room temperature for 19 h. The mixture was diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2. The organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was dissolved in THF (1.5 mL), H_2O (1.5 mL), and Ac_2O (4.5 mL) and stirred at 20 °C for 1.5 h. The volatiles were evaporated, and the residue was purified by silica gel chromatography using 3% MeOH in CH_2Cl_2 to give **43T** (90 mg, 86%): colorless glass; $[\alpha]^{23}_D$ +18.3° (acetone, c = 1.19); IR (thin film) 3427, 3196, 3054, 2978, 1710, 1536, 1470, 1368, 1262, 1213, 1164, 912, 792 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6) δ 10.27 (1 H, br s), 8.45 (1 H, br s), 7.56 (1 H, d, J = 1.2 Hz), 5.92 (1 H, d, J = 2.8 Hz), 4.69−4.63 (2 H, m), 4.44−4.35 (3 H, m), 3.09 (1 H, br s), 1.90 (3 H, s), 1.26 (9H, s); ^{13}C NMR (75 MHz, acetone-d_6) δ 177.6, 164.0, 157.2

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(q, J = 37.0 Hz), 150.9, 136.6, 116.4 (q, J = 285 Hz), 110.7, 91.8, 79.2, 73.2, 63.4, 51.7, 38.9, 26.9, 12.0; HRMS (LSIMS) calcd for $C_{17}H_{23}N_3O_7F_3$ [(M + H)$^+$] 438.1488, found 438.1483.

1-(3′-Amino-2′,3′-dideoxy-β-D-ribofuranosyl)thymine (3T). 35T (92.3 mg, 0.219 mmol; as a 4:1 mixture of anomers) was dissolved in NaOMe in MeOH (25 wt % NaOMe in MeOH; 4.0 mL, 18 mmol) and heated to 65 °C for 43 h. The mixture was cooled to 20 °C, and aqueous saturated NH_4Cl was added until the solution was mildly basic (pH 8). The solvents were evaporated, and the residue was placed on 8 cm of silica gel and eluted with 10% MeOH in CH_2Cl_2. Silica gel chromatography was repeated (8% MeOH in CH_2Cl_2) to give **3T** (36 mg, 68%) as a 4.7:1 mixture of anomers. This mixture was characterized as follows: mp 158−160 °C (lit.[38a] mp 187−187.5 °C, lit.[38b] mp 160−161 °C); $[\alpha]^{23}_D$ +7° (H_2O, c = 0.088) (lit.[38a] $[\alpha]^{23}_D$ +20° (H_2O, c = 0.64)); IR (KBr) 3500−2800, 1675, 1486, 1405, 1275, 1117, 1014 cm^{-1}; ^{1}H NMR (300 MHz, D_2O, β anomer) δ 7.48 (1 H, s), 6.14 (1 H, t, J = 6.8 Hz), 4.10 (1 H, dd, J = 8.4, 4.8 Hz), 3.92 (1 H, m), 3.75 (1 H, dd, J = 12.6, 3.3 Hz), 3.66 (1 H, dd, J = 12.8, 4.7 Hz), 2.54−2.42 (2 H, m), 1.72 (3 H, s); ^{13}C NMR (75 MHz, DMSO-d_6, β anomer) δ 163.9, 150.5, 136.3, 109.6, 83.6, 83.1, 60.9, 50.1, 35.8, 12.4; HRMS (LSIMS) calcd for $C_{10}H_{16}N_3O_4$ [(M + H)$^+$] 242.1141, found 242.1113.

Puromycin Aminonucleoside (4). Nucleoside **43A′** (37.5 mg, 0.026 mmol) was dissolved in NaOMe in MeOH (25 wt %, 2.0 mL, 8.7 mmol) and stirred at 20 °C for 20 h. The mixture was diluted with H_2O (1.0 mL). Saturated aqueous NH_4Cl was added dropwise until pH tested slightly basic (pH 8−9). The volatiles were evaporated, and the residue was purified by silica gel chromatography (10% MeOH in CH_2Cl_2) to give **4** (18.1 mg, 84%): mp 202−205 °C (lit.[39] mp 214−216 °C); $[\alpha]^{23}_D$ −13° (CH_3OH, c = 0.462) (lit.[39] $[\alpha]^{25}_D$ −24.6° (3% in H_2O)); IR (KBr) 3600−3040 (br), 2912, 1610, 1424, 1376, 1339, 1308, 1226, 1163, 1105, 1049, 817 cm^{-1}; ^{1}H NMR (300 MHz, D_2O) δ 7.88 (1 H, s), 7.61 (1 H, s), 5.67 (1 H, d, J = 2.7 Hz), 4.29 (1 H, dd, J = 5.4, 2.7 Hz), 3.90−3.88 (1 H, m), 3.80 (1 H, dd, J = 13, 2.0 Hz), 3.62 (1 H, dd, J = 13, 3.6 Hz), 3.39 (1 H, dd, J = 7.4, 5.4 Hz), 2.92 (6 H, br s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 154.3, 151.8, 149.6, 138.1, 119.6, 89.0, 85.3, 74.7, 60.8, 52.4, 38.0; HRMS (LSIMS) calcd for $C_{12}H_{19}N_6O_3$ [(M + H)$^+$] 295.1519, found 295.1509.

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Supporting Information Available: Preparation of compounds **22**, **24**, and **26**, stereochemical assignments for nucleoside products **35** and **43**, and additional experimental and characterization data for compounds **35T**, **35U**, **35C**, **39**, **40**, **43G**, **43C**, and **43U** (7 pages). See any current masthead page for ordering and Internet access instructions.

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