JOC Article

One-Pot Synthesis of Acyclic Nucleosides from Carbohydrate Derivatives, by Combination of Tandem and Sequential Reactions

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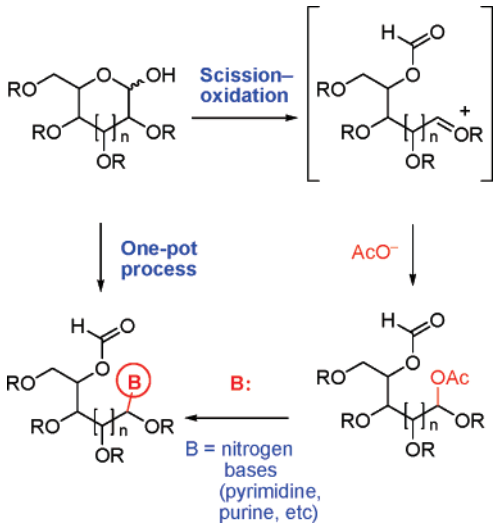

The design of processes which combine tandem and sequential reactions allows the transformation of readily available precursors into high-profit products. This strategy is illustrated by the one-pot synthesis of acyclic nucleosides, which are potential antiviral compounds, from readily available carbohydrates. The reaction conditions are mild, compatible with most functional groups. Depending on the starting sugar, both common and uncommon acyclic chains can be prepared. These polyhydroxylated chains can be combined with different bases to generate diversity.

Introduction

The development of nucleoside and nucleotide analogues has generated much interest, since many have displayed potent antiviral,[1] cytotoxic,[1b,2] or antiparasitic[3] activities. To optimize their potency, selectivity, or hydrolytic stability, different changes in the base and sugar moieties have been explored. Thus, the replacement of the sugar ring by acyclic chains has generated nucleoside analogues such as acyclovir **1** (Figure 1), ganciclovir **2**, and penciclovir **3**, active against herpes simplex, varicella zoster, and cytomegalovirus.[1a] Among the nucleotide analogues, the acyclic phosphonates adefovir **4**, tenofovir **5**, and cidofovir **6** are clinically used to treat hepatitis B, AIDS,[1a,c−f] and cancer-associated human papilloma virus infections.[2a,b]

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(1) (a) For interesting introductions to the subject, see: de Clercq, E. *Antiviral Res.* **2005**, *67*, 56−75. (b) Holý, A. Synthesis and biological activity of isopolar acyclic nucleotide analogs. In *Recent Advances in Nucleosides*: *Chemistry and Chemotherapy*; Chu, C. K., Ed.; Elsevier: New York, 2002; pp 167−238. (c) For other reviews, see: de Clercq, E. *Biochem. Pharmacol.* **2007**, *73*, 911−922. (d) de Clercq, E. *Antiviral Res.* **2007**, *75*, 1−13. (e) Lee, W. A.; Martin, J. C. *Antiviral Res.* **2006**, *71*, 254−259. (f) Holý, A. *Antiviral Res.* **2006**, *71*, 248−253. (g) Meier, C. *Eur. J. Org. Chem.* **2006**, 1081−1102. (h) Meier, C.; Balzarini, J. *Antiviral Res.* **2006**, *71*, 282−292. (i) Griffiths, P. D. *Antiviral Res.* **2006**, *71*, 192−200. (j) Biron, K. K. *Antiviral Res.* **2006**, *71*, 154−163. (k) Golankiewicz, B.; Ostrowski, T. *Antiviral Res.* **2006**, *71*, 134−140. (l) de Clercq, E. *Rev. Med. Virol.* **2004**, *14*, 289−300. (m) de Clercq, E. *Trends Pharmacol. Sci.* **2002**, *23*, 456−458. (n) Fung, H. B.; Stone, E. A.; Piacenti, F. J. *Clin. Ther.* **2002**, *24*, 1515−1548. (o) Gao, H.; Mitra, A. K. *Synthesis* **2000**, 329−351.

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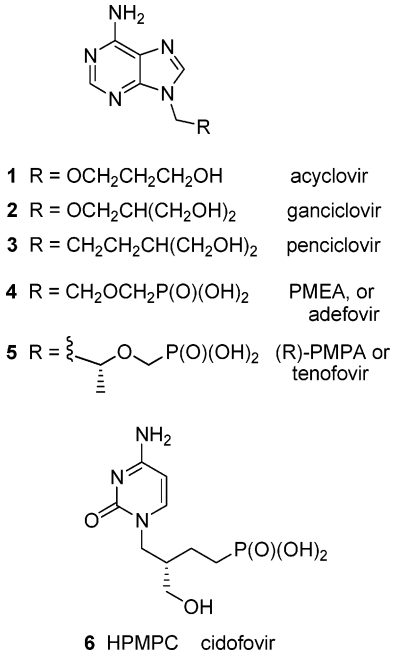
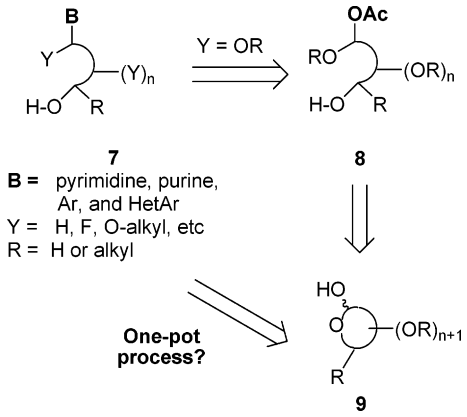


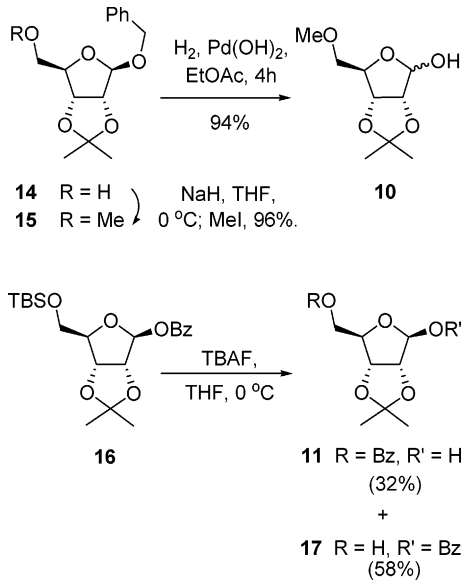
FIGURE 1. Antiviral acyclic nucleoside and nucleotide analogues.

SCHEME 1. Preparation of Acyclic Nucleoside Analogues with Different Bases, Chain Lengths, and Functional Groups

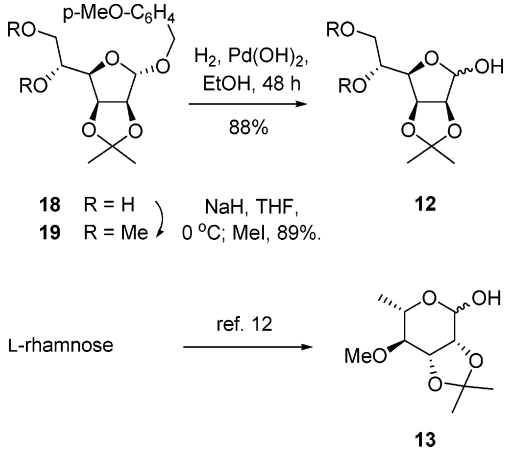


Fuelled by these successes, there is an active search for new nucleoside[1,4] or nucleotide[1,5] analogues, to treat other viral diseases or to overcome possible resistances. To obtain the maximum possible diversity, methodologies are needed which can generate many analogues in few steps from readily available substrates. Ideally, the purification of synthetic intermediates should be avoided, in order to save time and materials and to reduce the waste.

SCHEME 2. Synthesis of Substrates 10 and 11



SCHEME 3. Synthesis of Substrates 12 and 13



Our group is currently developing acyclic nucleoside analogues **7** (Scheme 1), with different bases, chain lengths, and functional groups. At least one hydroxy group is left unprotected,

(2) (a) For a review, see: Abdulkarim, B.; Bourhis, J. *Lancet Oncol.* **2001**, *2*, 622−630. (b) For some articles on the subject, see: Tristram, A.; Fiander, A. *Gynecol. Oncol.* **2005**, *99*, 652−655. (c) Votruba, I.; Pomeisl, K.; Tloust'ová, E.; Holý, A.; Otová, B. *Biochem. Pharmacol.* **2005**, *69*, 1517−1521. (d) He, L.; Liu, Y.; Zhang, W.; Li, M.; Chen, Q. *Tetrahedron* **2005**, *65*, 8505−8511. (e) Hájek, M.; Matulová, N.; Votruba, I.; Holý, A.; Tloustová, E. *Biochem. Pharmacol.* **2005**, *70*, 894−900. (f) Bobková, K.; Otová, B.; Marinov, I.; Mandys, V.; Panczak, A.; Votruba, I.; Holý, A. *Anticancer Res.* **2000**, *20*, 1041−1048 and references cited therein.

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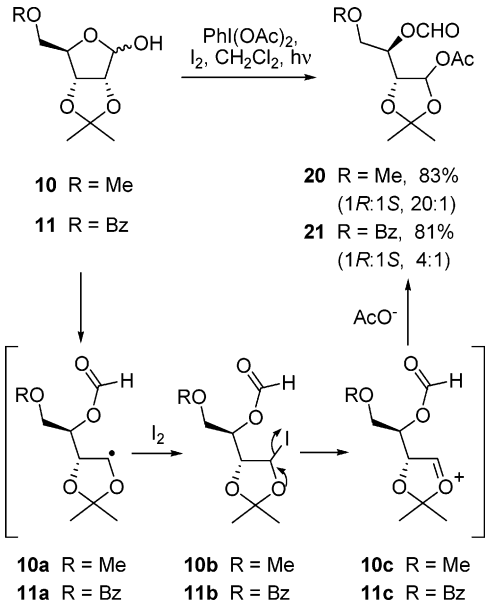
SCHEME 4. Synthesis of Acetoxy Acetals 20 and 21

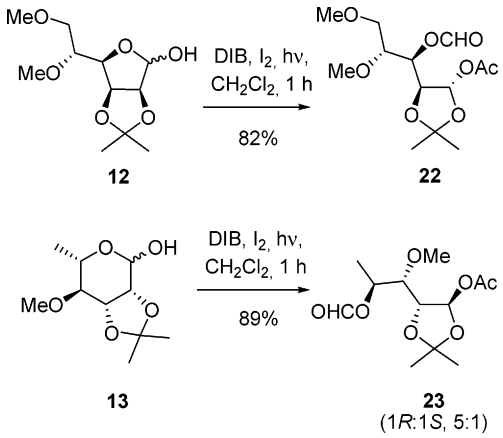


to allow the phosphorylation of the analogue and its incorporation to the viral nucleic acid chain. By the choice of appropriate Y groups, further elongation of the nucleic acid chain is hindered (Y ≠ OH) or, alternatively, nonfunctional, distorted chains are formed.

The preparation of analogues **7** with polyhydroxylated chains (Y = OR) could be carried out by reaction of the silylated base (or aromatic organometallic reagents) with aldehydes, acetals, or acetoxyacetals (such as compound **8)**. These acyclic intermediates can be obtained from carbohydrates **9**, according to different methodologies.[1−5]

We reasoned that this procedure could be shortened by the use of tandem and sequential reactions.[6] For instance, we have reported that the tandem radical scission-oxidation of sugar derivatives **9** with (diacetoxyiodo)benzene and iodine affords acetoxy acetals **8**.[7] Depending on the starting sugar, both common and uncommon acyclic chains can be prepared. If this tandem reaction could be coupled with the introduction of nitrogen nucleophiles (such as pyrimidine and purine bases), a wide range of acyclic nucleosides **7** could be prepared from sugar derivatives **9** in just one step. Such a procedure would be very useful for a high-throughput screening and to avoid troublesome separations in a scaled-up synthesis. Herein we show the feasibility of this approach.

SCHEME 5. Synthesis of Acetoxy Acetals 22 and 23



Results and Discussion

The substrates for the fragmentation reaction, compounds **10**−**13** (Schemes 2 and 3), are ribose, mannose, and rhamnose derivatives, which were synthesized in a few steps by conventional carbohydrate methodologies. Substrate **10** (Scheme 2) was prepared from known benzyl 2,3-*O*-isopropylideneribose **14**,[8] which was methylated to compound **15**. Removal of the benzyl protecting group afforded the fragmentation substrate **10**.

The 5-benzoyloxy analogue **11** (Scheme 2) was synthesized from ribose derivative **16**[9,10] by cleavage of the 5-silyloxy function followed by transposition of the anomeric benzoyl group. The major product was, however, 1-*O*-benzoyl-2,3-*O*-isopropylidene ribose **17**.[10]

The mannose derivative **12** (Scheme 3) was prepared from known *p*-methoxybenzyl 2,3-*O*-isopropylidene mannofuranose **18**,[11] by methylation to compound **19** and cleavage of the anomeric protecting group. The rhamnose substrate **13** was synthesized according to reported procedures.[12]

Prior to developing the one-pot scission−base addition process, we studied the tandem radical fragmentation−oxidation

(5) (a) For some recent articles on nucleotide analogues, see: Krečmerová, M.; Holý, A.; Pískala, A.; Masojídková, M.; Andrei, G.; Naesens, L.; Neyts, J.; Balzarini, J.; de Clercq, E.; Snoeck, R. *J. Med. Chem.* **2007**, *50*, 1069−1077. (b) Choo, H.; Beadle, J. R.; Chong, Y.; Trahan, J.; Hostetler, K. Y. *Bioorg. Med. Chem.* **2007**, *15*, 1771−1779. (c) Valiaeva, N.; Beadle, J. R.; Aldern, K. A.; Trahan, J.; Hostetler, K. Y. *Antiviral Res.* **2006**, *72*, 10−19. (d) Horejsí, K.; Andrei, G.; de Clercq, E.; Snoeck, R.; Pohl, R.; Holý, A. *Bioorg. Med. Chem.* **2006**, *14*, 8057−8065. (e) Beadle, J. R.; Wan, W. B.; Ciesla, S. L.; Keith, K. A.; Hartline, C.; Kern, E. R.; Hostetler, K. Y. *J. Med. Chem.* **2006**, *49*, 2010−2015. (f) Barral, K.; Priet, S.; Sire, J.; Neyts, J.; Balzarini, J.; Canard, B.; Alvarez, K. *J. Med. Chem.* **2006**, *49*, 7799−7806. (g) Sauerbrei, A.; Meier, C.; Meerbach, A.; Schiel, M.; Helbig, B.; Wutzler, P. *Antiviral Res.* **2005**, *67*, 147−154.

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(7) (a) Boto, A.; Hernández, D.; Hernández, R. *Org. Lett.* **2007**, *9*, 1721−1724. (b) Boto, A.; Hernández, R.; Suárez, E. *Tetrahedron Lett.* **2001**, *42*, 9176−9170. (c) Francisco, C. G.; González, C.; Suárez, E.; *J. Org. Chem.* **1998**, *63*, 8092−8093. (d) de Armas, P.; Francisco, C. G.; Suárez, E. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 772−774. (e) For a review on the modification of carbohydrates through radical chemistry, see: Hansen, S. G.; Skrydstrup, T. *Top. Curr. Chem.* **2006**, *264*, 135−162.

(8) Duvold, T.; Francis, G. W.; Papaioannou, D. *Tetrahedron Lett.* **1995**, *36*, 3153−3156.

(9) Kaskar, B.; Heise, G. L.; Michalak, R. S.; Vishnuvajjala, B. R. *Synthesis* **1990**, 1031−1032.

(10) Francisco, C. G.; González, C.; Suárez, E. *J. Org. Chem.* **1998**, *63*, 2099−2109.

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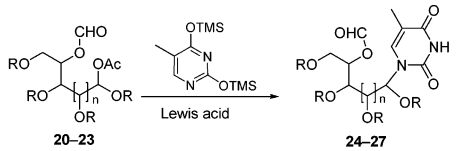
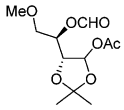
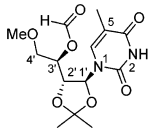
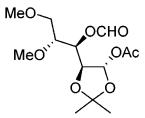
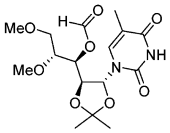
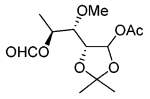
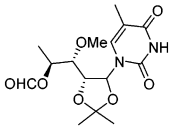
TABLE 1. Addition of Bis(TMS)thymine to Acetoxy Acetals 20−23



20–23 **24–27**

method	acetoxy acetals 20–23	products 24–33	product yield (%)	d.r.[c]
A[a]			**24** (94%)	99:1
B[b]	**20**	**24**	**24** (99%)	99:1
A[a]			**25** (83%)	99:1
B[b]	**22**	**25**	**25** (99%)	99:1
B[b]			**26** (83%) **27** (16%)	4:1
	23	**26** (1′*S*) **27** (1′*R*)		

[a] Condition A: Acetates **20**−**23**, CH_2Cl_2, 0 °C, $BF_3{\cdot}OEt_2$, base, 0.5 h. Then 0 °C→rt, 2 h. Yields are given for products purified by chromatography. [b] Condition B: Similar to condition A, using TMSOTf as the Lewis acid and MeCN as the solvent. [c] The dr was determined by ^{1}H NMR experiments.

reaction, in the absence of nitrogen nucleophiles. The scission of carbohydrate substrates **10** and **11** (Scheme 4) was carried out by treatment with (diacetoxyiodo)benzene (DIB) and iodine in dry dichloromethane at room temperature (26 °C), under irradiation with visible light (80-W tungsten-filament lamp). After 1 h, the acetoxy acetals **20** and **21** were isolated in good yields and stereoselectivities.

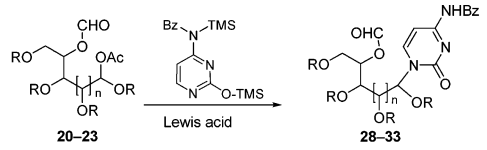
The first step of this tandem reaction was the generation of anomeric alkoxyl radicals, which underwent β-scission to the *C*-radicals **10a** or **11a** (Scheme 4). These intermediates probably reacted with iodine, forming unstable 1-iodoethers **10b** or **11b**. The extrusion of iodide generated the oxycarbenium ions **10c** or **11c**,[13] which were trapped by acetoxy ions from the reagent, affording acetals **20** and **21**.

In a similar way, the mannose and rhamnose derivatives **12** and **13** were transformed into their acetoxy acetals **22** and **23** (Scheme 5).

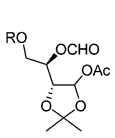
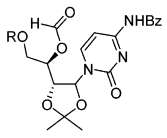
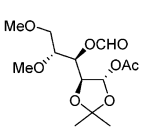
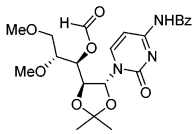
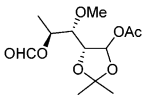
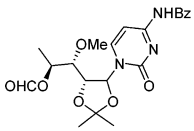
The acetates **20**−**23** were then treated with Lewis acids, to regenerate the oxycarbenium ions, and bis(trimethylsilyl)thymine (Table 1) or bis(trimethylsilyl)-4-*N*-benzoylcytosine (Table 2). Different Lewis acids and solvents were tried, in order to optimize the reaction conditions. The best ones proved to be boron trifluoride in dichloromethane (condition A) and TMSOTf in acetonitrile (condition B). The nucleophiles were prepared from thymine and cytosine by using the Vorbrüggen protocol, since the commercial reagents gave inferior results.[14]

(13) For a related mechanistic proposal, see: Boto, A.; Hernández, R.; León, Y.; Murguía, J. R.; Rodríguez-Afonso, A. *Eur. J. Org. Chem.* **2005**, 673−682.

TABLE 2. Addition of Bis(trimethylsilyl)-4-*N*-benzoylcytosine to Acetates 20−23



20–23 **28–33**

method	acetoxy acetals 20–23	products 28–33	product yield (%)	d.r.[c]
				
A[a]	**20** R = Me	**28** (1′*S*), R = Me	**28** (84%)	99:1
B[b]			**28** (84%)	99:1
A[a]	**21** R = Bz	**29** (1′*S*), R = Bz **30** (1′*R*), R = Bz	**29** (61%), **30** (28%)	2:1
B[b]			**29** (66%), **30** (33%)	2:1
				
A[a]	**22**	**31**	**31** (88%)	99:1
B[b]			**31** (93%)	99:1
				
B	**23**	**32** (1′*S*) **33** (1′*R*)	**32** (82%) **33** (15%)	5:1

[a] Condition A: Acetates **20**−**23**, CH_2Cl_2, 0 °C, $BF_3{\cdot}OEt_2$, base, 0.5 h. Then 0 °C→rt, 2 h. Yields are given for products purified by chromatography. [b] Condition B: Similar to condition A, using TMSOTf as the Lewis acid and MeCN as the solvent. [c] The dr was determined by ^{1}H NMR experiments.

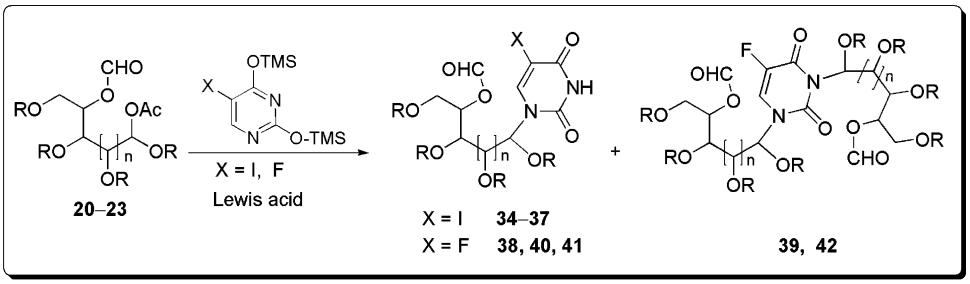
To our delight, the desired acyclic nucleosides **24**−**33** (Table 1) were obtained in good to excellent yields. The 1′,2′-trans diastereomers were the major or exclusive ones, since the nucleophilic addition took place from the less hindered side of the oxycarbenium ions. The stereochemistry of compound **29** was confirmed by X-ray analysis.[15]

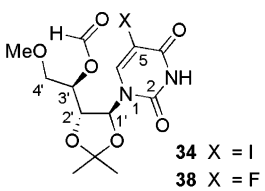
Although the diastereoselectivity is mainly controlled by the dioxolane ring, the chain substituents also play a significant role. Thus, the reaction of acetate **20** (with a 4-methoxy group) afforded exclusively the 1′,2′-trans nucleoside **28**, while acetate **21** (with a bulkier 4-benzoyloxy group) gave a separable mixture of the trans and cis nucleosides **29** and **30** (**29**:**30**, 2:1). Besides, while the furanose substrates **20** and **22** afforded the corresponding acyclic nucleosides in excellent trans stereoselectivity, the pyranose substrate **23** gave mixtures of the trans and cis isomers (trans:cis, 5:1).

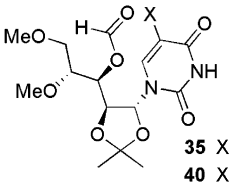
(14) (a) Vorbrüggen, H. *Acta Biochem. Pol.* **1996**, *43*, 25−36. (b) Drew, M. G. B.; Gorsuch, S.; Gould, J. H. M.; Mann, J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 969−978.

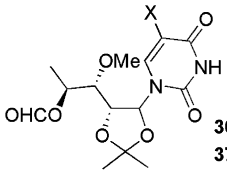
(15) Crystallographic data for the compounds studied in the solid state have also been deposited in the Cambridge Crystallographic Data Centre as nos. CCDC-645469 (**29**), CCDC-645470 (**36**), CCDC-645471 (**37**), and CCDC-645472 (**45**). These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road Cambridge CB21EZ, UK; fax (+44) 1223−336-033; e-mail deposit@ccdc.cam.ac.uk).

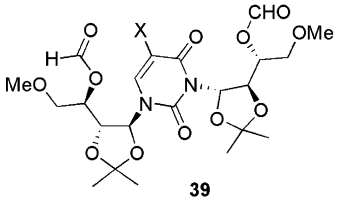
TABLE 3. Addition of Halogenated Pyrimidine Bases to Acetates 20−23

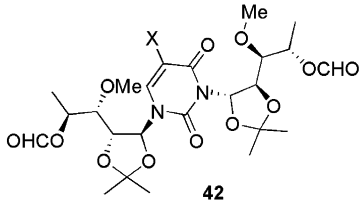












X	acetal 20–23	method	products 34–42, yield (%)	d.r.[c]
I	**20**	**A**[a]	**34** (83%)	99:1
		B[b]	**34** (99%)	99:1
	22	**A**[a]	**35** (93%)	99:1
		B[b]	**35** (97%)	99:1
	23	**B**[b]	**36** (54%), **37** (26%)	2:1
F	**20**	**A**[a]	**38** (0%), **39** (75%)	99:1
		B[b]	**38** (86%), **39** (0%)	99:1
	22	**A**[a]	**40** (99%)	99:1
		B[b]	**40** (97%)	99:1
	23	**A**[a]	**41** (0%), **42** (70%)	99:1
		B[b]	**41** (83%), **42** (9%)	99:1

[a] Conditon A: Acetates **20**−**23**, CH_2Cl_2, 0 °C, $BF_3{\cdot}OEt_2$, base, 0.5 h, then 0 °C→rt, 2 h. [b] Condition B: Similar to A, using TMSOTf as the Lewis acid and MeCN as the solvent. [c] The dr was determined by ^1H NMR.

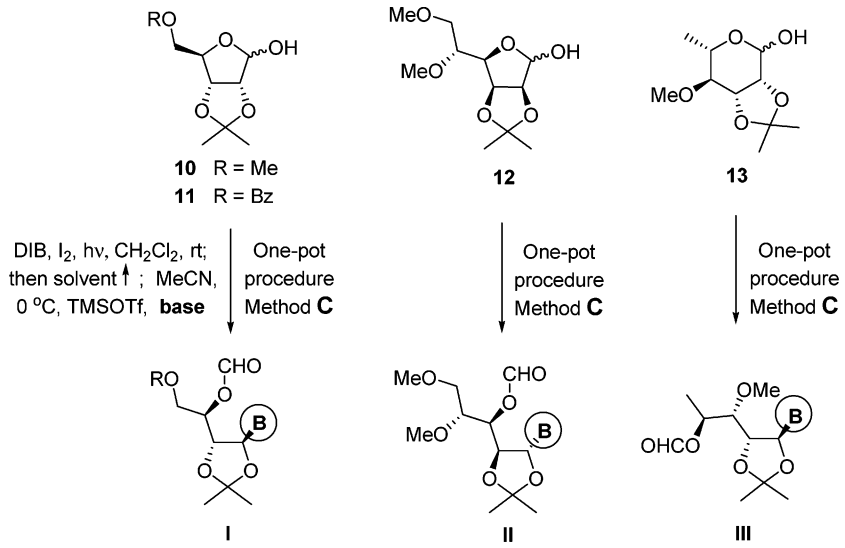
To study the effect of substituents on the pyrimidine ring, bis(TMS) derivatives of iodo- and fluorouracil were used as nucleophiles (Table 3). The reaction of the iodouracil reagent proceeded as expected, under both conditions A and B, affording the acyclic nucleosides **34**−**37** in excellent yield. While the acetates **20** and **22** gave exclusively the trans derivatives **34** and **35**, the acetate **23** afforded a diastereomer mixture (**36**:**37**, 2:1). The structures of compounds **36** and **37** were confirmed by X-ray analysis.

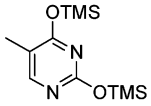
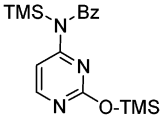
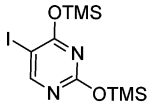
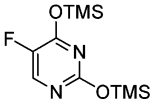
When the addition was repeated with the fluorouracil reagent under condition B, the desired nucleosides **38**, **40**, and **41** were isolated in good yield. However, when condition A was used with acetoxy acetals **20** and **23**, an unexpected result was obtained. The bis(silylated) fluorouracil reacted as a bidentate nucleophile, and the dimeric products **39** and **42** were formed. Surprisingly, no monomeric products **38** or **41** were detected. The activity of these dimeric nucleoside derivatives is currently being tested.[16]

Once the two-step fragmentation and base addition procedure was optimized, its one-pot version was explored. Thus, the *tandem* scission−oxidation reaction was the first step of a *sequential* process (Table 4). Different reaction conditions were tried: when the scission was carried out in CH_2Cl_2 and then boron trifluoride (or TMSOTf) and the nucleophile was added, the acyclic nucleosides were formed in low yields. If the scission was carried out in acetonitrile, followed by Lewis acid ($BF_3{\cdot}OEt_2$ or TMSOTf) and nucleophile addition, poor yields were obtained. Finally, an in situ solvent-replacement strategy gave excellent results: after the fragmentation step, the solvent (CH_2Cl_2) was removed under vacuum, and the crude residue was

(16) For examples of other type of dimeric acyclic nucleosides, see: Doláková, P.; Dracínský, M.; Holý, A. *Antiviral Res.* **2007**, *74*, 109 (A72).

TABLE 4. One-Pot Fragmentation−Nucleophilic Addition



base	products **I** (%)[a]	products **II** (%)[a]	products **III** (%)[a]
	R = Me; **24** (86%)	**25** (99%)	**26** (1′*S*) (74%), **27** (1′*R*) (11%)
	R = Me; **28** (81%) R = Bz; **29** (59%) + **30** (40%)	**31** (82%)	**32** (1′*S*) (78%) **33** (1′*R*) (11%)
	R = Me **34** (88%)	**35** (94%)	**36** (85%) **37** (6%)
	R = Me **38** (81%) + **39** (0%)	**40** (98%)	**41** (83%) + **42** (8%)

[a] For comparison, the global yields for the two-step procedure were as follows: **24** (82%), **25** (81%), **26** (74%) + **27** (14%), **28** (70%), **29** (53%) + **30** (28%), **31** (67%), **32** (69%) + **33** (10%), **34** (73%), **35** (80%), **36** (76%) + **37** (5%), **38** (71%) + **39** (0%), **40** (80%), **41** (74%) + **42** (7%).

redissolved in acetonitrile and treated with TMSOTf and the nucleophile at 0 °C (method C).

The overall yields for the one-step process are comparable or superior to those obtained with the two-step procedure. Moreover, since no workup or purification of the acetoxy intermediates **20**−**23** is needed, time is saved and the amount of waste is reduced.[17]

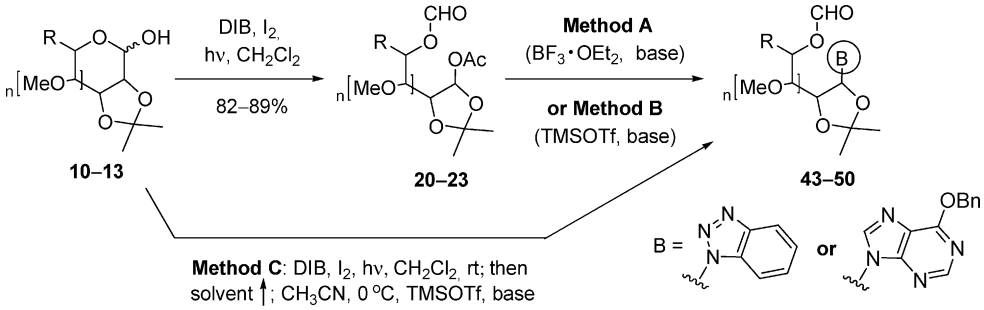
The addition of benzotriazolyl and purine nucleophiles was tried next. Since several cyclic benzotriazolyl nucleosides have shown promising antitumor activity,[18] the study of their acyclic analogues is of interest. On the other hand, many commercial antivirals present purine bases, as commented on before. The addition of (trimethylsilyl)benzotriazole and bis(trimethylsilyl)-benzyloxypurine to acetates **20**−**23** is shown in Table 5.

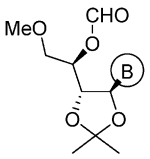
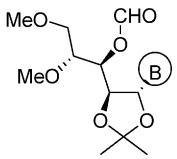
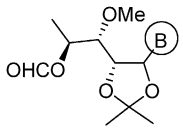
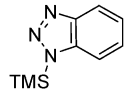
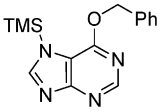
The benzotriazolyl and purine derivatives from ribose and mannose (products **43**, **44**, **47**, and **48**) were exclusively 1,2-trans diastereomers. The reaction with rhamnose afforded a separable mixture of the 1,2-trans and 1,2-cis diastereomers (**45**:**46**, 3:1; **49**:**50**, 1.5:1). The stereochemistry of the trans diastereomer **45** was confirmed by X-ray analysis. Again, the one-pot process gave similar or superior yields to the two-step procedure.

To be biologically active, the acyclic nucleosides must be phosphorylated and incorporated to the nucleic acid chain, so at least one hydroxy group must be left unprotected (Scheme 6). The formate group generated during the scission step can be easily cleaved by treatment with $NaHCO_3$ (1% in methanol,

(17) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259−281.
(18) (a) Heightman, T. D.; Locatelli, M.; Vasella, A. *Helv. Chim. Acta* **1996**, *79*, 2190−2200. (b) Flessner, T.; Wong, C.-H. *Tetrahedron Lett.* **2000**, *41*, 7805−7808.

TABLE 5. Formation of Benzotriazolyl and Purine Nucleosides



base			
	**Two-step method:**[a] **A** **43** (79%) **B** **43** (98%) Global: 65/80% **One-step method:**[a] **C** **43** (93%)	**Two-step method:**[a] **A** **44** (72%) **B** **44** (99%) Global: 59/81% **One-step method:**[a] **C** **44** (91%)	**Two-step method:**[a] **B** **45** (1′*S*) (58%) **46** (1′*R*) (20%) Global: **45** (52%), **46** (18%) **One-step method:**[a] **C** **45** (1′*S*) (59%) **46** (1′*R*) (18%)
	**Two-step method:**[a] **A** **47** (72%) **B** **47** (54%) Global: 60/45% **One-step method:**[a] **C** **47** (61%)	**Two-step method:**[a] **A** **48** (80%) **B** **48** (76%) Global: 66/63% **One-step method:**[a] **C** **48** (68%)	**Two-step method:**[a] **B** **49** (1′*S*) (35%) **50** (1′*R*) (27%) Global: **49** (31%), **50** (24%) **One-step method:**[a] **C** **49** (1′*S*) (42%) **50** (1′*R*) (24%)

[a] Yields are given for purified products.

rt, 1 h), and therefore, the alcohols **51**−**58** (Scheme 6) were formed in very good yields.

The mild conditions are compatible with most protecting groups; however, the substrate can affect the reaction results. The cytosine derivative **28** was transformed into the alcohol **55** without cleavage of the benzamide group. In contrast, the cytosine derivative **32** gave product **56**, where both the formate and the benzamide group have been hydrolyzed.

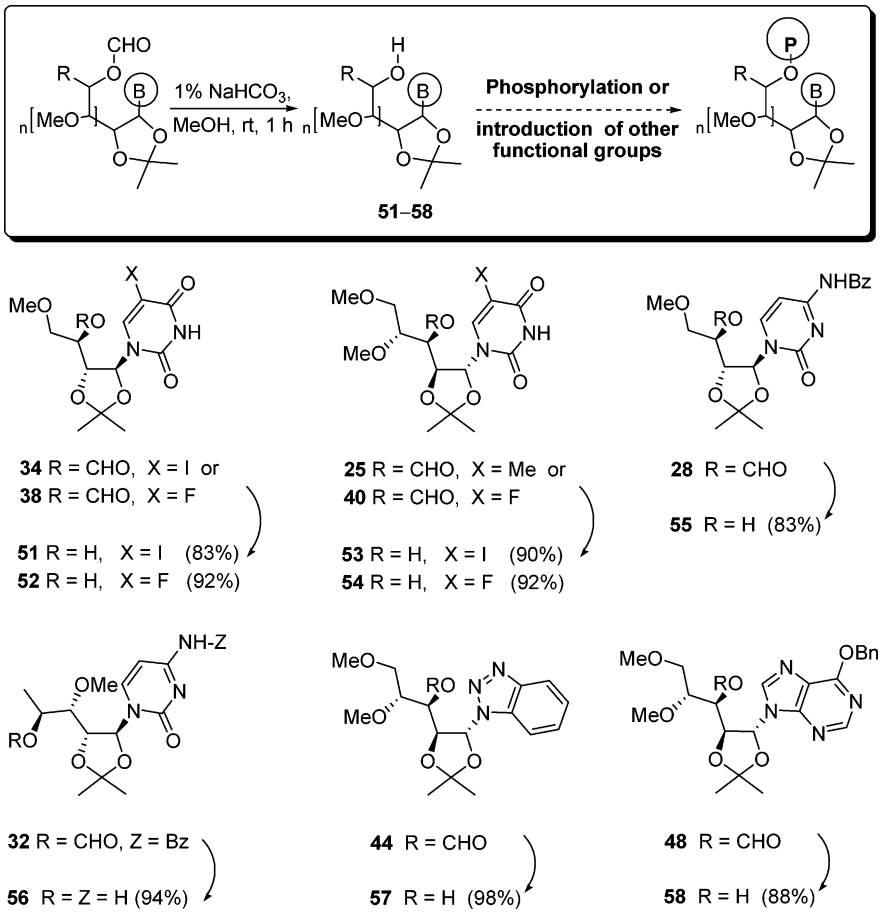
The free alcohols **51**−**58** and the formate derivatives **24**−**50** are analogues of antiviral acyclic nucleosides such as penciclovir **3**.[19] Besides, the free alcohols can be used as precursors of other drug candidates such as acyclic nucleotide analogues (*O*-methylphosphonates, phosphates, etc.).[1] In this moment, we are engaged in the preparation of new nucleoside and nucleotide derivatives, with different bases and chain substituents, and in the replacement of the 1-alkoxy group by other functionalities. Derivatives with different hydrosolubility and hydrolytic stability will be prepared, to determine their biological activities.

(19) The antiviral activity of compounds **24**−**58** is currently under study, and will be published in due time. Previously, their cytotoxic activity was tested with three tumour cell lines: MCF7 (breast), NCI-H460 (lung), and SF-268 (glioma), displaying little cytotoxicity, as needed for a selective antiviral compound.

Conclusion

This work highlights how readily available precursors can be directly transformed into high-value products by a rational combination of tandem and sequential reactions. The one-pot conversion of carbohydrates into acyclic nucleosides proceeded in good to excellent yields, and in many cases, with good to excellent stereoselectivities. This ***sequential*** process is initiated by a ***tandem*** radical fragmentation−oxidation reaction, which generates an oxycarbenium ion. This intermediate is trapped by addition of nitrogen nucleophiles, such as purine, pyrimidine, or benzotriazolyl bases. The reaction conditions are mild, compatible with most functional groups. The method is operationally simple, and environmentally friendly: no purification of intermediates is needed, and the reagents have low toxicity. Highly functionalized chains can be obtained, and the modification of these chains can afford new derivatives. An important

SCHEME 6. Cleavage of the Formate Group



diversity can be generated by a combination of different bases and polyhydroxylated chains.

Experimental Section

General Procedure for the β-Fragmentation of Carbohydrate Derivatives 10−13. To a solution of the carbohydrate (1.0 mmol) in dry CH_2Cl_2 (10 mL) under nitrogen were added (diacetoxyiodo)-benzene (DIB) (386 mg, 1.2 mmol) and iodine (254 mg, 1.0 mmol). The reaction mixture was stirred at room temperature (26 °C) under irradiation with visible light (80-W tungsten-filament lamp) for 1 h. Then it was poured into aqueous 10% sodium thiosulfate ($Na_2S_2O_3$) and extracted with dichloromethane. The organic layer was washed with brine, dried on Na_2SO_4, filtered, and evaporated under vacuum. The residue was purified by chromatography on silica gel (hexanes/EtOAc), yielding the purified acetoxy acetals **20**−**23**.

(1*R*)- and (1*S*)-Acetoxy-3-*O*-formyl-1,2-isopropylidene-4-*O*-methyl-D-erythritol ((1*R*)-20 and (1*S*)-20). Separable mixture of the (1*R*)-**20** (79%) and the (1*S*)-**20** (4%) (global yield, 83%). When the β-scission was carried out in acetonitrile, smaller yields were obtained (60%, (1*R*)-**20**:(1*S*)-**20**, 21:1). Product (1*R*)-**20**: amorphous; $[\alpha]_D$ +82 (*c* 0.11, $CHCl_3$); IR ($CHCl_3$) 1733, 1230 cm^{-1}; ^1H NMR (500 MHz) δ_H 1.44 (3H, s), 1.47 (3H, s), 2.07 (3H, s), 3.34 (3H, s), 3.58 (2H, d, J = 4.2 Hz), 4.38 (1H, dd, J = 2.3, 5.8 Hz), 5.15 (1H, ddd, J = 4.4, 4.4, 4.4 Hz), 6.25 (1H, d, J = 2.3 Hz), 8.09 (1H, s); ^{13}C NMR (125.7 MHz) δ_C 21.1 (CH_3), 26.5 (CH_3), 27.2 (CH_3), 59.2 (CH_3), 70.3 (CH_2), 70.9 (CH), 80.4 (CH), 95.9 (CH), 112.9 (C), 159.9 (CH), 169.9 (C); MS *m*/*z* (rel intensity) 247 (M^+ − Me, 100), 145 (M^+ − [Me_2C=O + $MeCO_2$], 92); HRMS calcd for $C_{10}H_{15}O_7$ 247.0818, found 247.0811; calcd for $C_6H_9O_4$ 145.0501, found 145.0496. Anal. Calcd for $C_{11}H_{18}O_7$: C, 50.38; H, 6.92. Found: C, 50.28; H, 7.02. Product (1*S*)-**20**: amorphous; $[\alpha]_D$ −68 (*c* 0.14, $CHCl_3$); IR ($CHCl_3$) 1731, 1228 cm^{-1}; ^1H NMR (500 MHz) δ_H 1.41 (3H, s), 1.51 (3H, s), 2.05 (3H, s), 3.41 (3H, s), 3.66 (1H, dd, J = 4.9, 11.3 Hz), 3.72 (1H, dd, J = 2.3, 11.2 Hz), 4.38 (1H, dd, J = 3.5, 9.2 Hz), 5.39 (1H, ddd, J = 2.1, 4.9, 9.3 Hz), 6.31 (1H, d, J = 3.5 Hz), 8.01 (1H, s); ^{13}C NMR (125.7 MHz) δ_C 21.1 (CH_3), 26.1 (CH_3), 28.1 (CH_3), 59.4 (CH_3), 69.6 (CH), 71.5 (CH_2), 76.0 (CH), 93.2 (CH), 112.7 (C), 159.5 (CH), 170.1 (C); MS *m*/*z* (rel intensity) 247 (M^+ − Me, 73), 203 (M^+ − $MeCO_2$, 19), 145 (M^+ − [(Me_2C=O + $MeCO_2$], 100); HRMS calcd for $C_{10}H_{15}O_7$ 247.0818, found 247.0812; calcd for $C_6H_9O_4$ 145.0501, found 145.0482. Anal. Calcd for $C_{11}H_{18}O_7$: C, 50.38; H, 6.92. Found: C, 50.30; H, 7.01.

(1*R*)- and (1*S*)-Acetoxy-3-*O*-formyl-1,2-isopropylidene-4-*O*-benzoyl-D-erythritol ((1*R*)-21 and (1*S*)-21). Separable mixture of the (1*R*)-**21** (65%) and the (1*S*)-**21** (16%) (global yield, 81%). When the β-scission was carried out in acetonitrile, smaller yields were obtained (61%, (1*R*)-**21**:(1*S*)-**21**, 4:1). Product (1*R*)-**21**: crystalline solid; mp 78−81 °C (from *n*-hexane); $[\alpha]_D$ +51 (*c* 0.56, $CHCl_3$); IR ($CHCl_3$) 3089, 3067, 1732, 1602 cm^{-1}; ^1H NMR (500 MHz) δ_H 1.51 (3H, s), 1.52 (3H, s), 2.04 (3H, s), 4.44 (1H, dd, J = 2.2, 6.4 Hz), 4.49 (1H, dd, J = 5.8, 12.3 Hz), 4.67 (1H, dd, J = 3.1, 12.3 Hz), 5.43 (1H, ddd, J = 3.1, 6.0, 6.0 Hz), 6.32 (1H, d, J = 2.2 Hz), 7.46 (2H, dd, J = 7.7, 7.8 Hz), 7.58 (1H, dd, J = 7.4, 7.5 Hz), 8.02 (2H, d, J = 7.3 Hz), 8.13 (1H, s); ^{13}C NMR (125.7 MHz) δ_C 21.1 (CH_3), 26.7 (CH_3), 27.4 (CH_3), 62.6 (CH_2), 70.0 (CH), 80.5 (CH), 96.1 (CH), 113.6 (C), 128.5 (2 × CH), 129.4 (C), 129.7 (2 × CH), 133.4 (CH), 159.7 (CH), 166.0 (C), 169.9 (C); MS *m*/*z* (rel intensity) 337 (M^+ − Me, 41), 235 (M^+ − [OAc + Me_2C=O)], 2), 105 ([PhCO]$^+$, 100); HRMS calcd for $C_{16}H_{17}O_8$ 337.0923, found 337.0924; calcd for C_7H_5O 105.0340, found 105.0358. Anal. Calcd for $C_{17}H_{20}O_8$: C, 57.95; H, 5.72. Found: C, 57.79; H, 5.95.

Product (1*S*)-**21**: colorless crystals; mp 71−72 °C (from *n*-hexane); $[\alpha]_D$ −69 (*c* 0.63, $CHCl_3$); IR ($CHCl_3$) 3098, 3066, 1732, 1602 cm^{-1}; ^1H NMR (500 MHz) δ_H 1.42 (3H, s), 1.54 (3H, s), 2.09 (3H, s), 4.42 (1H, dd, J = 3.5, 9.0 Hz), 4.46 (1H, dd, J = 6.3, 12.3 Hz), 4.82 (1H, dd, J = 2.4, 12.3 Hz), 5.65 (1H, ddd, J = 2.2, 6.3, 8.7 Hz), 6.38 (1H, d, J = 3.5 Hz), 7.46 (2H, dd, J = 7.7, 7.9 Hz), 7.58 (1H, dd, J = 7.4, 7.5 Hz), 8.02 (1H, s), 8.03 (2H, d, J = 7.2 Hz); ^{13}C NMR (127.5 MHz) δ_C 21.1 (CH_3), 26.0 (CH_3), 28.1 (CH_3), 63.9 (CH_2), 68.3 (CH), 76.5 (CH), 93.0 (CH), 113.0 (C), 128.5 (2 × CH), 129.6 (C), 129.7 (2 × CH), 133.3 (CH), 159.3 (CH), 166.1 (C), 170.0 (C); MS *m*/*z* (rel intensity) 337 (M^+ − Me, 100), 235 (M^+ − [OAc + Me_2C═O], 45); HRMS calcd for $C_{16}H_{17}O_8$ 337.0923, found 337.0875. Anal. Calcd for $C_{17}H_{20}O_8$: C, 57.95; H, 5.72. Found: C, 58.06; H, 6.00.

(1*S*)-1-Acetoxy-3-*O*-formyl-1,2-*O*-isopropylidene-4,5-di-*O*-methyl-D-arabinitol (22). The acetate was obtained as the 1,2-trans isomer (82%). Colorless crystals; mp 49−51 °C (from EtOAc/*n*-hexane); $[\alpha]_D$ −51 (*c* 0.35, $CHCl_3$); IR ($CHCl_3$) 1746, 1732, 1114 cm^{-1}; ^1H NMR (500 MHz) δ_H 1.48 (3H, s), 1.49 (3H, s), 2.07 (3H, s), 3.33 (3H, s), 3.36 (1H, dd, J = 4.5, 10.6 Hz), 3.45 (3H, s), 3.52 (1H, ddd, J = 4.4, 4.4, 7.8 Hz), 3.58 (1H, dd, J = 3.1, 10.6 Hz), 4.53 (1H, dd, J = 2.3, 3.8 Hz), 5.25 (1H, dd, J = 4.0, 7.9 Hz), 6.13 (1H, d, J = 2.3 Hz), 8.11 (1H, s); ^{13}C NMR (125.7 MHz) δ_C 21.1 (CH_3), 26.9 (CH_3), 27.1 (CH_3), 58.4 (CH_3), 59.3 (CH_3), 69.9 (CH), 70.4 (CH_2), 78.3 (CH), 80.8 (CH), 96.5 (CH), 113.2 (C), 159.9 (CH), 170.0 (C); MS *m*/*z* (rel intensity) 291 (M^+ − Me, 48), 89 ([$MeOCH_2CHOMe$]$^+$, 100), 59 ([Me_2C═OH]$^+$, 93); HRMS calcd for $C_{12}H_{19}O_8$ 291.1080, found 291.1062; calcd for $C_4H_9O_2$ 89.0602;, found 89.0615. Anal. Calcd for $C_{13}H_{22}O_8$: C, 50.98; H, 7.24. Found: C, 50.92; H, 6.91.

(1*R*/*S*)-1-Acetoxy-5-deoxy-4-*O*-formyl-1,2-*O*-isopropylidene-3-*O*-methyl-L-arabinitol (23). Acetate **23** was obtained as an inseparable diastereomer mixture (89%, trans/cis, 5:1). Colorless oil; $[\alpha]_D$ +25 (*c* 0.52, $CHCl_3$); IR ($CHCl_3$) 1751, 1724, 1179 cm^{-1}; ^1H NMR (500 MHz) major diastereomer δ_H 1.35 (3H, d, J = 6.5 Hz), 1.46 (3H, s), 1.48 (3H, s), 2.09 (3H, s), 3.44 (1H, dd, J = 4.6, 4.6 Hz), 3.54 (3H, s), 4.25 (1H, dd, J = 2.8, 4.4 Hz), 5.13 (1H, dddd, J = 5.7, 5.8, 6.3, 6.3 Hz), 6.19 (1H, d, J = 2.7 Hz), 8.03 (1H, s); minor diastereomer δ_H 1.28 (3H, d, J = 6.6 Hz), 1.39 (3H, s), 1.52 (3H, s), 2.12 (3H, s), 3.59 (3H, s), 3.65 (1H, dd, J = 3.9, 10.0 Hz), 4.03 (1H, dd, J = 3.8, 10.0 Hz), 4.96 (1H, dddd, J = 3.2, 6.6, 6.6, 6.6 Hz), 6.21 (1H, d, J = 3.3 Hz), 8.01 (1H, s); ^{13}C NMR (125.7 MHz) major diastereomer δ_C 15.6 (CH_3), 21.2 (CH_3), 26.4 (CH_3), 26.7 (CH_3), 60.8 (CH_3), 70.9 (CH), 81.5 (CH), 82.5 (CH), 97.0 (CH), 113.1 (C), 160.1 (CH), 170.5 (C); minor diastereomer δ_C 14.6 (CH_3), 21.2 (CH_3), 25.8 (CH_3), 28.2 (CH_3), 60.8 (CH_3), 69.7 (CH), 80.2 (CH), 81.0 (CH), 92.5 (CH), 111.8 (C), 159.9 (CH), 170.5 (C); MS *m*/*z* (rel intensity) 261 (M^+ − Me, 26), 125 (M^+ − [($MeCO_2H$ + Me + MeO + OCHO)], 100); HRMS calcd for $C_{11}H_{17}O_7$ 261.0974, found 261.0978; calcd for $C_7H_9O_2$ 125.0603, found 125.0585. Anal. Calcd for $C_{12}H_{20}O_7$: C, 52.17; H, 7.30. Found: C, 52.32; H, 7.18.

Preparation of Trimethylsilyl Derivatives of the Nitrogen Bases. Some trimethylsilyl derivatives from the nitrogen bases are commercial products, but they gave variable yields. However, the reagents can be readily prepared as follows. The bases (0.4 mmol) and *N*,*O*-bis(trimethylsilyl)acetamide (297 μL, 244 mg, 1.2 mmol) under nitrogen were heated to 130 °C and stirred for 1 h. The mixture was then cooled to rt and dry toluene (1 mL) was added; the volatiles were removed under vacuum, and the operation was repeated twice. The reagent was used in the next step without further purification.

Synthesis of Acyclic Nucleosides. Method A (Reaction of the Acetoxy Acetals with Silylated Nitrogen Bases and Lewis Acids). To a solution of the acetate (0.2 mmol) in dry CH_2Cl_2 (2 mL) at 0 °C and under nitrogen was added dropwise freshly prepared nucleophile (0.3−0.4 mmol) and boron trifluoride etherate (51 μL, 57 mg, 0.4 mmol). The mixture was stirred for 30 min, then was poured into aqueous saturated $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was dried on Na_2SO_4, filtered, and evaporated under vacuum. The residue was purified by chromatography on silica gel (hexanes/EtOAc) to give the acyclic nucleosides.

Method B (Reaction of the Acetoxy Acetals with Silylated Nitrogen Bases and Lewis Acids). To a solution of the acetoxy acetal (0.2 mmol) in dry CH_3CN (2 mL), at 0 °C and under nitrogen, was added freshly prepared nucleophile (0.3−0.4 mmol) and then trimethylsilyl triflate (TMSOTf) (46 μL, 89 mg, 0.4 mmol) was injected dropwise for 15 min. The stirring was continued at rt for 3 h, followed by the usual workup and purification.

Method C (One-Pot Procedure). The reaction flask was attached to a standard vacuum/nitrogen system. The photolysis was performed as in Method A and then the solvent was removed under vacuum. The flask was flushed with nitrogen and the crude residue was redissolved in acetonitrile (2 mL) and treated as described in Method B.

(4-*N*-Benzoyl)-1-[(1*S*)- (29) and (4-*N*-Benzoyl)-1-[(1*R*)-4-*O*-benzoyl-3-*O*-formyl-1,2-*O*-isopropylidene-D-erythritol-1-yl]cytosine (30). Compounds **29** and **30** were obtained from acetoxy acetal **21**, using bis(trimethylsilyl)-4-*N*-benzoylcytosine as the nucleophile. Method A: 61% for product **29** and 28% for product **30**. Method B: 66% for product **29** and 33% for product **30**. One-pot procedure (Method C) from 2,3-*O*-isopropylidene-4-*O*-benzoyl-D-ribofuranose **11**: 59% for product **29** and 40% for product **30**. Compound **29**: colorless crystals; mp 199−201 °C (from CH_2Cl_2/MeOH); $[\alpha]_D$ −23 (*c* 0.19, $CHCl_3$); IR ($CHCl_3$) 3406, 3112, 3090, 3068, 1728, 1706, 1672, 1627, 1602, 1553, 1480 cm^{-1}; ^1H NMR (500 MHz) δ_H 1.58 (3H, s), 1.59 (3H, s), 4.35 (1H, dd, J = 5.7, 5.8 Hz), 4.52 (1H, dd, J = 6.5, 12.2 Hz), 4.72 (1H, dd, J = 3.4, 12.2 Hz), 5.81 (1H, ddd, J = 3.3, 6.4, 6.5 Hz), 6.30 (1H, d, J = 5.1 Hz), 7.42 (2H, dd, J = 7.7, 7.7 Hz), 7.50 (2H, dd, J = 7.5, 7.6 Hz), 7.55 (1H, dd, J = 7.4, 7.4 Hz), 7.60 (1H, dd, J = 7.3, 7.4 Hz), 7.61 (1H, br b), 7.91 (1H, d, J = 7.1 Hz), 7.92 (2H, d, J = 7.5 Hz), 7.99 (2H, d, J = 7.4 Hz), 8.12 (1H, s), 9.10 (1H, br s); ^{13}C NMR (125.7 MHz, 60 °C) δ_C 27.0 (CH_3), 27.6 (CH_3), 62.8 (CH_2), 70.2 (CH), 81.1 (CH), 86.0 (CH), 97.7 (CH), 112.8 (C), 127.7 (2 × CH), 128.4 (2 × CH), 129.0 (2 × CH), 129.6 (C), 129.7 (2 × CH), 133.1 (C), 133.2 (2 × CH), 143.2 (CH), 154.2 (C), 159.7 (CH), 162.4 (C), 166.0 (C), 166.7 (C); MS *m*/*z* (rel intensity) 507 (M^+, <1), 215 (*N*-benzoylcytosine$^+$, 6), 105 ([Ph-CO]$^+$, 100); HRMS calcd for $C_{26}H_{25}N_3O_8$ 507.1642, found 507.1650; calcd for C_7H_5O 105.0340, found 105.0404. Anal. Calcd for $C_{26}H_{25}N_3O_8$: C, 61.53; H, 4.97; N, 8.28. Found: C, 61.75; H, 5.11; N, 8.00. Crystal data[20] for $C_{26}H_{25}N_3O_8$: M_r = 507.49, colorless needle (0.15 × 0.10 × 0.05 mm^3) from methanol; orthorhombic, space group $P2_12_12_1$ (no. 19), a = 7.2301(2) Å, b = 17.5814(8) Å, c = 19.1174(8) Å, V = 2430.11(16) Å,^{3} Z = 4, ρ_{calcd} = 1.387 g cm^{-3}, λ(Mo Kα_1) = 0.71073 Å, F(000) = 1064, μ = 0.104 mm^{-1}, T = 100(2) K. 24500 Reflections were collected from a Bruker-AXS X8Kappa APEX II CCD diffractometer in the range 6.02 < 2θ < 61.08° and 4188 independent reflections [R(int) = 0.0686] were used in the structural analysis. Reflections were corrected for Lorentz polarization effects and absorption applied by (SADABS).[20a] The structure was solved by direct methods (SIR-97)[20b] and refined against all F^2 data by full-matrix least-squares techniques (SHELXTL-6.12)[20c] to $R1$ = 0.0420, $wR2$ = 0.0855 [I > 2σ(I)], and to $R1$ = 0.0790, $wR2$ = 0.0983 for all data, with a Goodness-of-fit on F^2, S = 1.022 and 335 parameters. The asymmetric unit of the structure is formed by one molecule of compound **29**. Because of a large *su* on the Flack parameter of 0.0(8), the Friedel pairs were averaged in the refinement (MERG

(20) (a) Area-Detector Absorption Correction. SADABS within SAINT+ package, v. 7.06, 1996, BRUKER-AXS Inc., 5465 East Cheryl Parkway, Madison, WI. (b) Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G. L.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G.; Polidori, G.; Spagna, R. *J. Appl. Crystallogr.* **1999**, *32*, 115−119. (c) Program for Structure Solution, Refinement and Presentation, BRUKER-AXS Inc., 5465 East Cheryl Parkway, Madison, WI. (d) Flack, H. D. *Acta Crystallogr.* **1983**, *A39*, 876−881.

4 command). Thereby, the absolute configuration of new chiral center C1′ has been assigned as *S* by reference to other unchanging chiral centers in the synthetic procedure of known absolute configuration. All the non-hydrogen atoms were refined with anisotropic displacement parameters. A few reflections to low angle that present values very much below their calculated values, possibly partially covered for "beam stopper", were eliminated at the end of the refinement (OMIT command). The hydrogen atoms were included from calculated positions and refined riding on their respective carbon atoms with isotropic displacement parameters. The final difference map displayed no electron density higher than 0.240 e $Å^{-3}$.

Compound 30: Colorless crystals; mp 123−126 °C (from MeOH); $[\alpha]_D$ +81 (*c* 0.23, $CHCl_3$); IR ($CHCl_3$) 3406, 3109, 3067, 1732, 1668, 1625, 1602, 1555, 1481 cm^{-1}; ^1H NMR (500 MHz) δ_H 1.49 (3H, s), 1.70 (3H, s), 4.41 (1H, dd, J = 6.3, 12.3 Hz), 4.70 (1H, dd, J = 2.4, 12.3 Hz), 4.79 (1H, dd, J = 5.4, 9.4 Hz), 5.23 (1H, ddd, J = 2.1, 6.2, 8.9 Hz), 6.72 (1H, d, J = 5.4 Hz), 7.41 (2H, dd, J = 7.7, 7.8 Hz), 7.51 (2H, dd, J = 7.6, 7.7 Hz), 7.54 (1H, dd, J = 7.4, 7.4 Hz), 7.61 (1H, dd, J = 7.4, 7.4 Hz), 7.64 (1H, br b), 7.82 (1H, d, J = 7.4 Hz), 7.91 (2H, br d, J = 7.1 Hz), 7.94 (1H, s), 7.97 (2H, d, J = 7.5 Hz), 9.10 (1H, br b); ^{13}C NMR (125.7 MHz) δ_C 24.4 (CH_3), 26.3 (CH_3), 63.8 (CH_2), 67.0 (CH), 75.9 (CH), 83.1 (CH), 97.6 (CH), 111.2 (C), 127.6 (2 × CH), 128.5 (2 × CH), 129.1 (2 × CH), 129.3 (C), 129.7 (2 × CH), 132.9 (C), 133.2 (CH), 133.3 (CH), 144.5 (CH), 155.1 (C), 159.4 (CH), 162.4 (C), 165.9 (C), 166.5 (C); MS *m*/*z* (rel intensity) 507 (M^+, 1), 492 (M^+ − Me, 2), 105 ([PhCO]$^+$, 100); HRMS calcd for $C_{26}H_{25}N_3O_8$ 507.1642, found 507.1680; calcd for C_7H_5O 105.0340, found 105.0365. Anal. Calcd for $C_{26}H_{25}N_3O_8$: C, 61.53; H, 4.97; N, 8.28. Found: C, 61.78; H, 5.08; N, 7.91.

1-[(1*S*)-3-*O*-Formyl-1,2-*O*-isopropylidene-4-*O*-methyl-D-erythritol-1-yl]-5-fluorouracil (38). Compound **38** was obtained from acetoxy acetal **20**, using bis(trimethylsilyl)-5-fluorouracil as the nucleophile. Method B: 86%. One-pot procedure (Method C) from 2,3-*O*-isopropylidene-4-*O*-methyl-D-ribofuranose **10**: 81%. Syrup; $[\alpha]_D$ −23 (*c* 0.50, $CHCl_3$); IR ($CHCl_3$) 3381, 1727, 1714, 1671, 1165 cm^{-1}; ^1H NMR (500 MHz) δ_H 1.47 (3H, s), 1.56 (3H, s), 3.32 (3H, s), 3.62 (2H, d, J = 4.1 Hz), 4.22 (1H, dd, J = 5.8, 6.9 Hz), 5.32 (1H, ddd, J = 4.0, 4.0, 7.1 Hz), 6.18 (1H, dd, J = 1.4, 5.6 Hz), 7.38 (1H, d, J_{HF} = 5.8 Hz), 8.06 (1H, s), 9.87 (1H, br s); ^{13}C NMR (125.7 MHz) δ_C 27.2 (CH_3), 27.6 (CH_3), 59.3 (CH_3), 70.2 (CH_2), 70.7 (CH), 78.3 (CH), 84.2 (CH), 111.9 (C), 123.3 (CH, J_{CF} = 34.1 Hz), 140.9 (C, J_{CF} = 240.1 Hz), 148.9 (C), 156.6 (C, J_{CF} = 26.8 Hz), 160.1 (CH); MS *m*/*z* (rel intensity) 317 (M^+ − Me, 16), 145 ([M + H]$^+$ − [fluorouracil + Me_2C═O], 100); HRMS calcd for $C_{12}H_{14}FN_2O_7$ 317.0785, found 317.0770; calcd for $C_6H_9O_4$ 145.0501, found 145.0472. Anal. Calcd for $C_{13}H_{17}FN_2O_7$: C, 46.99; H, 5.16; N, 8.43. Found: C, 47.02; H, 5.41; N, 8.17.

1,3-Bis[(1*S*)-3-*O*-Formyl-1,2-*O*-isopropylidene-4-*O*-methyl-D-erythritol-1-yl]-5-fluorouracil (39). Product **39** was obtained from the acetoxy acetal (1*S*/*R*)-**20**, using Method A, with bis(trimethylsilyl)-5-fluorouracil as the nucleophile: 75%. Amorphous; $[\alpha]_D$ −20 (*c* 0.51, $CHCl_3$); IR ($CHCl_3$) 1731, 1694, 1679, 1168 cm^{-1}; ^1H NMR (500 MHz) δ_H 1.43 (3H, s), 1.49 (3H, s), 1.58 (3H, s), 1.59 (3H, s), 3.30 (3H, s), 3.35 (3H, s), 3.59 (1H, dd, J = 4.3, 10.5 Hz), 3.61 (1H, dd, J = 3.6, 10.7 Hz), 3.63 (2H, d, J = 4.0 Hz), 4.19 (1H, dd, J = 5.7, 7.2 Hz), 4.96 (1H, dd, J = 6.4, 6.6 Hz), 5.24 (1H, ddd, J = 3.8, 3.9, 7.4 Hz), 5.32 (1H, ddd, J = 3.9, 3.9, 7.5 Hz), 6.25 (1H, dd, J = 1.6, 5.6 Hz), 6.51 (1H, d, J = 6.0 Hz), 7.36 (1H, d, J_{HF} = 5.3 Hz), 8.06 (2H, s); ^{13}C NMR (125.7 MHz) δ_C 26.2 (CH_3), 27.2 (CH_3), 27.7 (CH_3), 28.6 (CH_3), 59.2 (CH_3), 59.4 (CH_3), 70.2 (CH_2), 70.7 (CH_2), 70.9 (CH), 72.1 (CH), 74.3 (CH), 78.1 (CH), 83.2 (CH), 84.6 (CH), 111.9 (C), 112.4 (C), 121.8 (CH, J_{CF} = 33.9 Hz), 140.0 (C, J_{CF} = 237.8 Hz), 148.5 (C), 156.2 (C, J_{CF} = 26.9 Hz), 159.9 (CH), 160.0 (CH); MS *m*/*z* (rel intensity) 519 (M^+ − Me, 3), 145 ([4-(1,2-dimethoxyethyl)-2,2-dimethyl-1,3-dioxolane − H − Me_2C═O)]$^+$, 100); HRMS calcd for $C_{21}H_{28}FN_2O_{12}$ 519.1626, found 519.1615; calcd for $C_6H_9O_4$ 145.0501, found 145.0573. Anal. Calcd for $C_{22}H_{31}FN_2O_{12}$: C, 49.44; H, 5.85; N, 5.24. Found: C, 49.24; H, 5.75; N, 5.25.

6-Benzyloxy-9-[(1*R*)-3-*O*-formyl-1,2-*O*-isopropylidene-4,5-di-*O*-methyl-D-arabinitol-1-yl]purine (48). Compound **48** was obtained from acetoxy acetal **22**, using trimethylsilyl-6-benzyloxypurine as the nucleophile. Method A: 80%. Method B: 76%. One-pot procedure (Method C) from 2,3-*O*-isopropylidene-5,6-di-*O*-methyl-D-mannofuranose **12**: 68%. Yellow oil; $[\alpha]_D$ −18 (*c* 0.42, $CHCl_3$); IR ($CHCl_3$) 1732, 1600, 1117, 1046 cm^{-1}; ^1H NMR (500 MHz) δ_H 1.55 (3H, s), 1.58 (3H, s), 3.24 (3H, s), 3.30 (3H, s), 3.34 (1H, dd, J = 3.9, 10.5 Hz), 3.53 (1H, ddd, J = 3.6, 3.8, 7.4 Hz), 3.58 (1H, dd, J = 3.4, 10.5 Hz), 5.20 (1H, dd, J = 5.1, 5.1 Hz), 5.39 (1H, dd, J = 4.6, 7.4 Hz), 5.66 (1H, d, J = 12.5 Hz), 5.69 (1H, d, J = 12.4 Hz), 6.17 (1H, d, J = 5.6 Hz), 7.31 (1H, dd, J = 7.2, 7.3 Hz), 7.35 (2H, dd, J = 6.9, 7.7 Hz), 7.52 (2H, d, J = 7.2 Hz), 8.10 (1H, s), 8.23 (1H, s), 8.55 (1H, s); ^{13}C NMR (125.7 MHz) δ_C 26.9 (CH_3), 27.5 (CH_3), 58.0 (CH_3), 59.2 (CH_3), 68.5 (CH_2), 69.8 (CH_2), 69.8 (CH), 78.6 (2 × CH), 83.5 (CH), 112.4 (C), 121.9 (C), 128.1 (CH), 128.3 (2 × CH), 128.4 (2 × CH), 136.0 (C), 140.7 (CH), 151.8 (C), 152.3 (CH), 160.2 (CH), 160.5 (C); MS *m*/*z* (rel intensity) 472 (M^+, 10), 246 (M^+ − benzyloxypurine, 38), 226 ([benzyloxypurine]$^+$, 56), 91 ([$PhCH_2$]$^+$, 100); HRMS calcd for $C_{23}H_{28}N_4O_7$ 472.1958, found 472.1886; calcd for C_7H_7 91.0548, found 91.0563. Anal. Calcd for $C_{23}H_{28}N_4O_7$: C, 58.47; H, 5.97; N, 11.86. Found: C, 58.63; H, 5.85; N, 11.59.

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Supporting Information Available: Synthesis and spectroscopic data of starting materials **10**−**13**, the acyclic nucleosides **24**−**28**, **31**−**37**, **40**−**47**, **49**, and **50**, and the alcohols **51**−**58**; ORTEP drawings for compounds **29**, **36**, **37**, and **45**; ^1H and ^{13}C NMR spectra for compounds **24**−**58**; and crystal structure data (in CIF format) for compounds **29**, **36**, **37**, and **45**. This material is available free of charge via the Internet at http://pubs.acs.org.

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