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α-Phosphono Lactone Analogues of Cytidine and Cytosine Arabinoside Diphosphates: Synthesis via Ring Closing Metathesis

Xuemei Chen and David F. Wiemer*

Department of Chemistry, University of Iowa, Iowa City, Iowa 52242-1294

david-wiemer@uiowa.edu

Received January 13, 2003

α-Phosphono lactone derivatives of the nucleosides cytidine and cytosine arabinoside have been prepared from the corresponding nucleoside aldehydes. The stereochemical outcome of allylation reactions with these aldehydes was found to be dependent upon both the choice of protecting groups for the 2′- and 3′-hydroxyl groups and, to some extent, the nature of the Lewis acid catalyst employed. Ultimately, conditions were found that favored either the 5′*R* or 5′*S* diastereomer from different cytidine aldehydes, and gave some stereoselectivity in additions to an aldehyde derivative of ara-C. The resulting homoallylic alcohols were used as substrates in attempted Knovenagel and Horner−Wadsworth−Emmons condensations, but elimination was found to predominate over lactone formation under the conditions employed. The desired α-phosphono lactones could be prepared through a reaction sequence that included ring-closing metathesis on acrylate esters of the homoallylic alcohols, followed by reduction of the resulting α,*β*-unsaturated lactones and carbon−phosphorus bond formation on enolates generated from the saturated lactones.

Cytosine arabinoside (**1**, ara-C, Figure 1) is an effective agent for treatment of many myeloid leukemias, but patients whose disease fails to respond to the initial chemotherapy do poorly and patients who relapse frequently develop a resistance to this drug that limits its therapeutic usefulness.[1] We have prepared some ara-C phosphonates (e.g. **2** and **3**) designed to mimic ara-C monophosphate (**4**) and perhaps bypass metabolic adaptations that underlie the known mechanisms for resistance to ara-C.[2] During the course of these studies we became interested in compounds which might serve as mimics of ara-CDP (**5**) because some CDP analogues are believed to inhibit processes required for DNA synthesis.[3]

Mimics of phosphate esters often are based on phosphonic acids, and the carbon−phosphorus bond is believed to enhance metabolic stability. In a parallel sense, phosphonoacetic acid has been recognized as an analogue of pyrophosphate, and has antiviral activity against herpes simplex viruses.[4] Coupling phosphonoacetic acid through an ester linkage to the 5′-position of a nucleoside already has been used to produce nucleoside diphosphate analogues that were investigated for their antiviral and protein binding activity.[5−7] While design of conformationally restricted nucleotides has drawn recent attention due to potential therapeutic applications,[8] at this time there are no reports of such constraints imposed within a phosphonate-based pyrophosphate analogue. One approach to this goal would rely on introduction of an α-phosphono lactone system to incorporate a C−P bond and to hold the pyrophosphate mimic in a conformation parallel to that reported in different studies of nucleoside diphosphate conformations.[9] From this perspective, it is reasonable to expect that a lactone phosphonate such as compound **6** could mimic some key spatial and electronic features of the diphosphate and may express biological activity. In this paper we report the first synthesis of diethyl α-phosphonolactones derived from the pyrimidine nucleosides cytidine and ara-C, compounds designed to probe these hypotheses.

The retrosynthesis shown in Figure 2 was devised to approach the desired α-phosphono lactones with control of the 5′ stereochemistry. According to this strategy, the α-phosphono lactone derivatives would be made from the corresponding α-phosphono-α,*β*-unsaturated lactones **7** via hydrogenation. To obtain the vinyl phosphonates, an intramolecular Knoevenagel reaction would be employed

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(4) (a) Shipkowitz, N. L.; Bower, R. R.; Appell, R. N.; Nordeen, C. W.; Overby, L. R.; Roderick, W. R.; Schleicher, J. B.; Von Esch, A. M. *Appl. Microbiol.* **1973**, *27*, 264. (b) Helgstrand, E.; Eriksson, B. F. H.; Johansson, N. G.; Lannero, B.; Larsson, A.; Misiorny, A.; Noren, J. O.; Sjoberg, B.; Stenberg, K.; Stening, G.; Stridh, S.; Oberg, B.; Alenius, S.; Philipson, L. *Science* **1978**, *201*, 819−821.
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(7) Vincent, S.; Grenier, S.; Valleix, A.; Salesse, C.; Lebeau, L.; Mioskowski, C. *J. Org. Chem.* **1998**, *63*, 7244−7257.
(8) (a) Kool, E. T. *Chem. Rev.* **1997**, *97*, 1473−1487. (b) Sorensen, A. M.; Nielsen, P. *Org. Lett.* **2000**, *2*, 4217−4219. (c) Liu, F.; Austin, D. *Org. Lett.* **2001**, *3*, 2273−2276. (d) Groziak, M. P.; Thomas, D. W. *J. Org. Chem.* **2002**, *67*, 2152−2159.
(9) Both a single-crystal diffraction analysis[10] and more recent ENDOR studies[11] suggest that the phosphoryl groups in ADP adopt an extended conformation with a dihedral angle in the C5′−O5′−P−O6′ region (−59° or −52°) consistent with a pseudo-chair conformation of a lactone ring.

10.1021/jo0300136 CCC: $25.00
Published on Web 07/31/2003

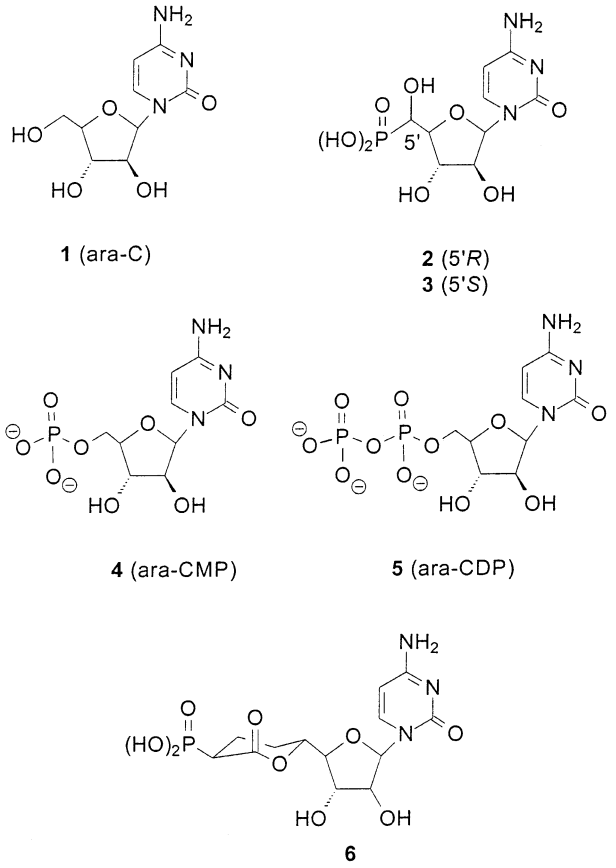

FIGURE 1. Ara-C and some phosphonate and phosphate derivatives.

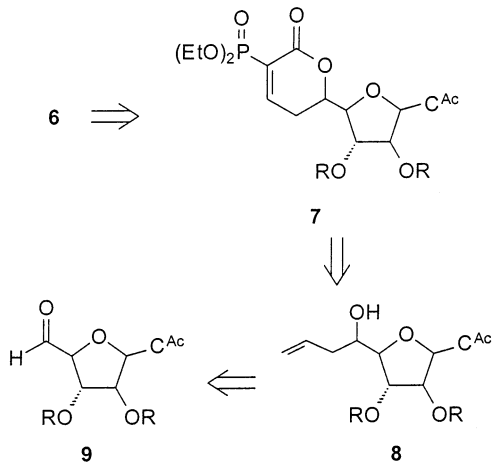

FIGURE 2. Retrosynthetic analysis.

with an α-phosphono acetate derivative of a homoallylic alcohol (**8**) as a substrate. Addition of allyl organometallic reagents to protected cytidine and ara-C aldehydes (**9**) would be a straightforward method for the synthesis of alcohol **8** from the protected nucleosides, and might allow preparation of both 5′ stereoisomers in each series.

Some precedents for stereoselective allylation of carbohydrates and nucleosides are known. For example, allylation of furanose **10** through reaction with allyltrimethylsilane under catalysis by $BF_3{\cdot}OEt_2$ or $TiCl_4$ has been reported by Danishefsky et al.[12] (Figure 3). With $BF_3{\cdot}OEt_2$ as the catalyst (Method A), high Cram−Felkin

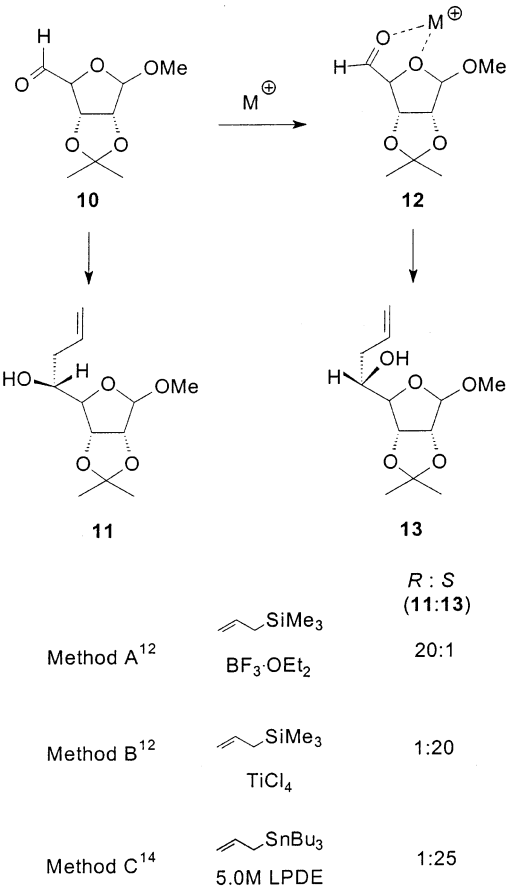

FIGURE 3. Allyl additions to a ribose aldehyde.

selectivity was realized to afford the 5′*R* homoallylic alcohol **11**, and similar stereocontrol was found in the preparation of the corresponding homoallylic alcohol derived from uridine.[13] Reversal of the stereochemical outcome was achieved under catalysis by $TiCl_4$ (Method B) and was suggested to require a change in the reactive conformation. This Lewis acid was assumed to chelate between the aldehyde and ring oxygens, thereby favoring conformer **12** in the stereochemically determinative step. Under these conditions, the 5′*S* product **13** was preferred by a factor of 20:1 over its 5′*R* epimer as predicted by a Cram cyclic model. Chelation-controlled addition of allyltributylstannane to α-alkoxy aldehydes in 5 M lithium perchlorate−diethyl ether (LPDE) also has been reported as a mild allylation reaction (Method C),[14] and high stereoselectivity in favor of the 5′*S* isomer has been observed with the dialdose derivative **10**.[14]

These different reaction conditions now have been applied to allylation of the cytidine-derived aldehyde **15**[15] (Scheme 1). With $BF_3{\cdot}OEt_2$ as the catalyst, the allyl adducts were obtained in 44% overall yield and one isomer, ultimately shown to be the 5′*R* diastereomer **16**,

(10) Viswamitra, M. A.; Hosur, M. V.; Shakked, Z.; Kennard, O. *Nature* **1976**, *262*, 234−236.
(11) Mustafi, D.; Telser, J.; Makinen, M. W. *J. Am. Chem. Soc.* **1992**, *114*, 6219−6226.
(12) Danishefsky, S. J.; DeNinno, M. P.; Phillips, G. B.; Zelle, R. E.; Lartey, P. A. *Tetrahedron* **1986**, *42*, 2809−2819.
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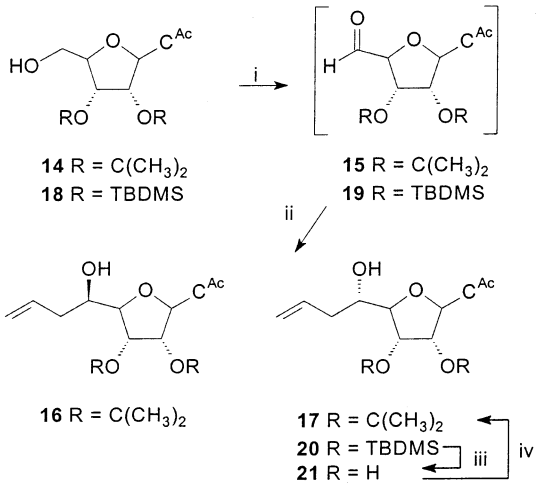
(14) Henry, K. J., Jr.; Grieco, P. A.; Jagoe, C. T. *Tetrahedron Lett.* **1992**, *33*, 1817−1820.

SCHEME 1[a]



[a] Reagents and conditions: (i) DMSO, EDC, pyr, TFA, benzene; (ii) Methods A−C; (iii) TBAF, THF; (iv) dimethoxypropane, $HClO_4$ (cat.), acetone.

TABLE 1. Stereoselective Allylation of 5′-Nucleoside Aldehydes

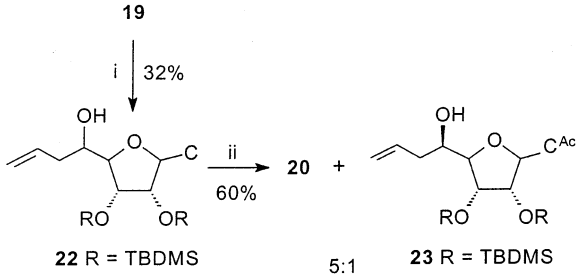
substrate	major diastereomer	method	yield,[a] %	ratio *R*:*S*
15	**16**	A	44	6:1
		B	–	–
		C	39	3:2
19	**20**	A	67	0:1
		B	54	0:1
		C	79	0:1
25	**26**	A	85	15:1
		B	84	3:1
		C	78	5:1

[a] Yields were calculated for the two steps from the 5′ alcohols.

was highly favored (Table 1). When the nucleoside aldehyde **15** was subjected to allylation in LPDE, a mixture of the homoallylic alcohol **16** and its 5′*S* epimer **17** was obtained in a ratio of 3:2 and 39% total yield. When $TiCl_4$ was employed as the catalyst for the attempted reaction with allyltrimethylsilane, none of the desired product was obtained. Instead, the NMR of the initial reaction mixture indicated that allylation might have occurred along with cleavage of the acetonide group.

In a study of diethyl phosphite addition to nucleoside aldehydes, we found that significantly different stereoselectivity was observed for reaction of a cytidine aldehyde protected with 2′- and 3′-*O*-*tert*-butyldimethylsilyl groups compared to the analogous cytidine acetonide.[2] To determine if this difference in stereoselectivity would extend to allylation reactions, the TBDMS protected nucleoside **18** was oxidized to the aldehyde **19** and then treated under the three allylation conditions. While there was some variation in terms of yield, in each reaction only one isomer of the allyl adduct **20** was observed in 54−79% yield (Table 1). After removal of TBDMS groups (**21**) and installation of an acetonide (Scheme 1), the homoallylic alcohol **17** was obtained. Because the NMR data for compound **17** clearly were distinct from those obtained for compound **16**, these compounds must be epimeric. An X-ray diffraction analysis conducted on alcohol **17**[16] revealed it has the 5′*S* configuration, which

SCHEME 2[a]



[a] Reagents and conditions: (i) (−)-Ipc$_2$B-allyl, THF, and Et_2O, − 78 °C, and then 3.0 M NaOH, 30% H_2O_2; (ii) Ac_2O, MeOH, reflux.

indicates that compound **16** must be the 5′*R* isomer. This stereochemical outcome could be rationalized by a transition state conformation parallel to that postulated for phosphonylation of the *β*-silyloxy aldehyde **19**.[2] This transition state apparently is so preferred by aldehyde **19** that there is no change in the reactive conformation even upon exposure to $TiCl_4$ or LPDE.

To complement the procedures described above, where stereoselectivity at the 5′ position was derived from the substrate, it was of interest to examine the possibility of stereochemical control through use of a nonracemic allylation reagent such as allyldiisopinocampheylborane (Ipc$_2$B-allyl).[17] Exposure of aldehyde **19** to (−)-Ipc$_2$B-allyl, which has shown high selectivity in favor of the *R*-homoallylic alcohol with achiral aldehydes,[17b] resulted in a mixture of two epimeric homoallylic alcohols (**22**) in a ratio of 1:5 after alkaline workup (Scheme 2). Under these reaction conditions the N^4-acyl group was cleaved but after reinstallation of the *N*-acyl group the stereochemistry of the resulting homoallylic alcohol could be determined by comparison with materials prepared earlier. With this borane reagent, allylation of the TBDMS-protected aldehyde again favored the 5′*S* isomer **20**, although a small amount of 5′*R* isomer **23** was obtained. Thus even though the yield is modest, reaction of the acetonide aldehyde **15** with allyltrimethylsilane and $BF_3{\cdot}OEt_2$ proved to be the best path to the 5′*R* homoallylic alcohol **16**, and reaction of the TBDMS-protected aldehyde **19** under any of the conditions examined favored formation of the 5′*S* isomer.

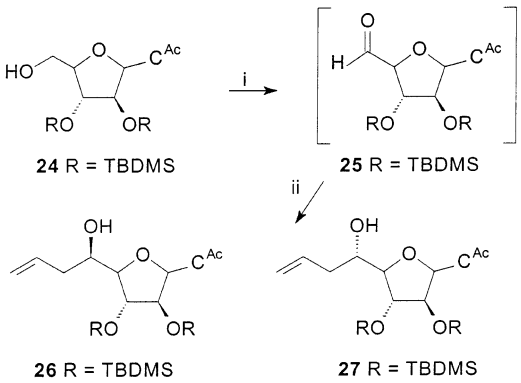
After the stereoselective synthesis of the two diastereomeric cytidine derivatives was achieved, the protected ara-C **24** was oxidized to the aldehyde **25** and then was treated with the achiral allylation reagents in the presence of catalytic $BF_3{\cdot}OEt_2$, $TiCl_4$, or LDPE. The $BF_3{\cdot}OEt_2$-catalyzed addition of allyltrimethylsilane proceeded with high diastereoselectivity and in excellent yields (Scheme 3 and Table 1). The stereochemistry of the major isomer **26** was determined by a single-crystal diffraction analysis as the *R* isomer.[16] The addition reactions catalyzed by $TiCl_4$ and LPDE gave rise to increased amounts of the

(15) (a) Jung, K. Y.; Hohl, R. J.; Wiemer, A. J.; Wiemer, D. F. *Bioorg. Med. Chem.* **2000**, *8*, 2501−2509. (b) Chen, X.; Jung, K.; Wiemer, D. F.; Wiemer, A. J.; Hohl, R. J. *Phosphorus, Sulfur, Silicon* **2002**, *177*, 1783−1786.

(16) The X-ray diffraction data for single crystals of compounds **17** and **26** are available from the Cambridge Crystallographic Data Centre with reference numbers CCDC 197773 and CCDC 197775.

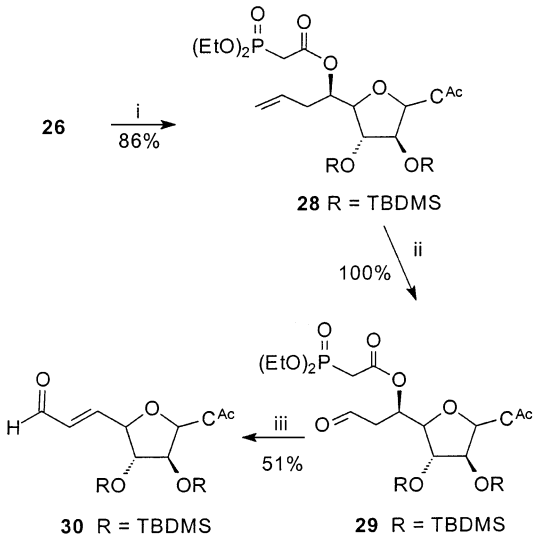
(17) (a) Jadhav, P. K.; Bhat, K. S.; Perumal, P. T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432−439. (b) Brown, H. C.; Bhat, K. S.; Randad, R. S. *J. Org. Chem.* **1989**, *54*, 1570−1576.

SCHEME 3[a]



[a] Reagents and conditions: (i) DMSO, EDC, pyr, TFA, benzene; (ii) Methods A−C.

SCHEME 4[a]

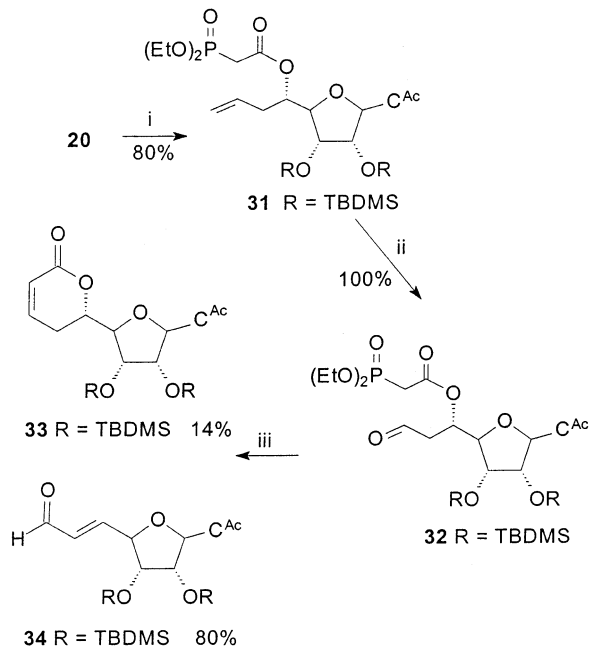


[a] Reagents and conditions: (i) $(EtO)_2$ $P(O)CH_2CO_2H$, EDC, DMAP, CH_2Cl_2, rt; (ii) K_2OsO_4, $NaIO_4$, THF:H_2O (1:1), rt; (iii) $TiCl_4$, *N*-methylmorpholine, THF, 0 °C to room temperature.

5′*S* isomer **27**, although the *R* isomer **26** was still the major product.

With homoallylic alcohol derivatives of cytidine and ara-C in hand, construction of the α-phosphono-α,*β*-unsaturated lactones became the next objective. Coupling of alcohol **26** with diethyl phosphonoacetic acid was achieved in good yield to afford phosphonate **28** (Scheme 4). Ozonolysis of compound **28** led to extensive decomposition, but oxidative cleavage with $NaIO_4$ and K_2OsO_4[18] gave aldehyde **29** in quantitative yield. Unfortunately, exposure of aldehyde **29** to *N*-methylmorpholine/$TiCl_4$[19] gave rise to the elimination product **30** in 51% yield. Other Knoevenagel condensation conditions,[20] such as heating at reflux with a catalytic amount of piperidine in benzene with acetic acid or with TsOH also were

SCHEME 5[a]



[a] Reagents and conditions: (i) $(EtO)_2P(O)CH_2CO_2H$, EDC, DMAP, CH_2Cl_2, rt; (ii) K_2OsO_4, $NaIO_4$, THF:H_2O (1:1), rt; (iii) NaH, THF, 0 °C to rt.

tested, but elimination was the main process under all conditions examined.

Because the intramolecular Knoevenagel condensation failed to afford the α-phosphono-α,*β*-unsaturated lactone, the synthetic route was reorganized to pursue construction of the lactone ring prior to formation of the P−C bond. Two procedures we have studied extensively allow facile preparation of α-phosphono lactones via an intermediate lactone enolate. One is based upon a 1,3-phosphorus rearrangement in a dialkyl vinyl phosphate,[21] while the other strategy is based upon trapping the lactone enolate on carbon by reaction with diethyl chlorophosphite followed by oxidation of the P(III) intermediate to the α-phosphono lactone.[22] Although these methods have been employed in the synthesis of α-phosphono lactone derivatives of farnesol and other systems,[23] their application to the synthesis of nucleoside derivatives has not been investigated. The second methodology appeared to be more compatible with nucleosides because it avoids use of excess strong base.

To obtain the nucleoside lactone, an intramolecular Horner−Wadsworth−Emmons (HWE) reaction[24] was explored with the cytidine derivative **32** (Scheme 5), obtained through coupling of homoallylic alcohol **20** with diethylphosphonoacetic acid to give ester **31**, and subsequent OsO_4-catalyzed olefin cleavage. Upon treatment

(18) Baggiolini, E. G.; Iacobelli, J. A.; Hennessy, B. M.; Batcho, A. D.; Sereno, J. F.; Uskokovic, M. R. *J. Org. Chem.* **1986**, *51*, 3098−3108.

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(20) McIntosh, J. M.; Sieler, R. A. *Can. J. Chem.* **1978**, *56*, 226−231.

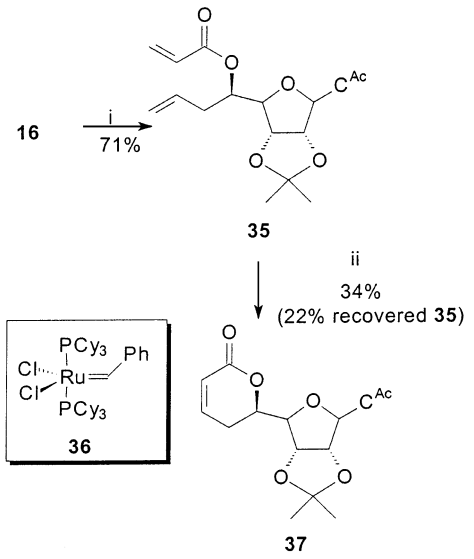
(21) Jackson, J. A.; Hammond, G. B.; Wiemer, D. F. *J. Org. Chem.* **1989**, *54*, 4750−4754.

(22) (a) Lee, K.; Wiemer, D. F. *J. Org. Chem.* **1991**, *56*, 5556−5560. (b) Boeckman, R. K., Jr.; Kamenecka, T. M.; Nelson, S. G.; Pruit, J. R.; Barta, T. E. *Tetrahedron Lett.* **1991**, *32*, 2581−2584.

(23) (a) Du, Y.; Wiemer, D. F. *J. Org. Chem.* **2002**, *67*, 5701−5708. (b) Lee, K.; Jackson, J. A.; Wiemer, D. F. *J. Org. Chem.* **1993**, *58*, 5967−5971.

(24) (a) Weihe, G. R.; McMorris, T. C. *J. Org. Chem.* **1978**, *43*, 3942−3946. (b) Davenport, R. J.; Regan, A. C. *Tetrahedron Lett.* **2000**, *41*, 7619−7622.

SCHEME 6[a]



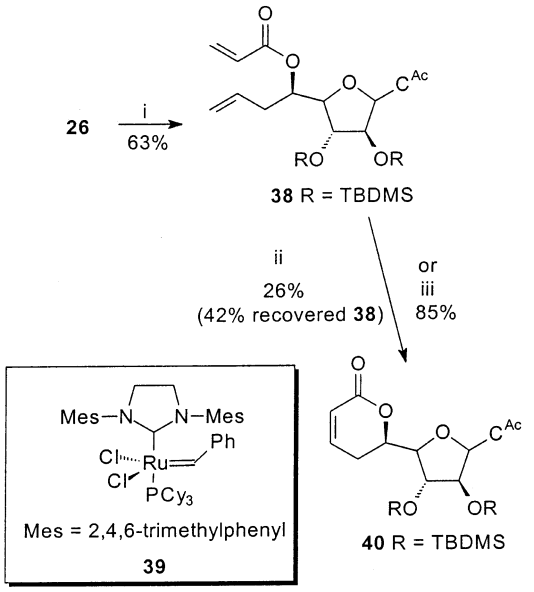
[a] Reagents and conditions: (i) acryloyl chloride, Et_3N, DMAP, CH_2Cl_2:CH_3CN (2:1), rt; (ii) **36**, CH_2Cl_2, reflux.

with NaH, aldehyde **32** gave the α,β-unsaturated lactone **33** in 14% yield with the α,β-unsaturated aldehyde **34** as the major product (80%), indicating that elimination competes with the desired condensation.[24b] Thus it became necessary to find a different strategy to obtain the desired lactones.

Olefin ring-closing metathesis (RCM) has been reported to provide convenient access to five- or six-membered lactones via acrylate esters.[25] Even though this method has not been applied to the synthesis of nucleoside lactones, several current reports have indicated that nucleoside substrates are compatible with Grubbs' catalyst.[26] To prepare the RCM substrate, the homoallylic alcohol **16** (Scheme 6) was converted to acrylate **35**. When a solution of compound **35** in CH_2Cl_2 was heated at reflux for 24 h in the presence of Grubbs' catalyst **36**, only 34% of the desired α,β-unsaturated lactone **37** was obtained along with 22% recovered starting material.

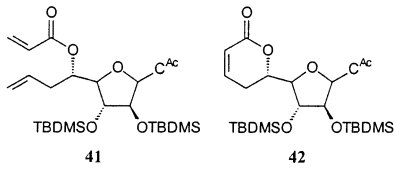
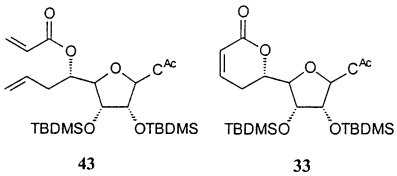
Various studies of ring-closing metathesis have suggested that the formation of unproductive seven-membered chelates may account for low conversions.[25a] The presence of $Ti(O^iPr)_4$ was reported to be able to destabilize such unproductive complexes and result in effective cyclization.[25a] However, treatment of the allylic acrylate **38** (Scheme 7) under these conditions did not improve conversion.

SCHEME 7[a]



[a] Reagents and conditions: (i) acryloyl chloride, Et_3N, DMAP, THF, rt; (ii) **39**, 0.3 equiv of $Ti(O^iPr)_4$, CH_2Cl_2, reflux; (iii) **39**, CH_2Cl_2, reflux.

TABLE 2. Synthesis of α,β-Unsaturated Lactones through RCM

Substrate	Product	Catalyst	Time	Yield
 41	42	**39**	5 h	77%
 43	33	**39**	3 h	74%

TBDMSO OTBDMS Ac

Recently the olefin metathesis catalyst **39** was found to display unique activity toward otherwise unreactive substrates.[27] When the allylic acrylate **38** was heated at reflux with catalyst **39** in CH_2Cl_2 for just 2 h, the α,β-unsaturated lactone **40** was obtained in 85% yield (Scheme 7). Encouraged by this result, the allylic acrylates **41** and **43** (Table 2) were prepared in 81% and 73% yields, respectively. RCM of these compounds in the presence of catalyst **39** gave the α,β-unsaturated lactones **42** and **33** in good yields.

Catalytic hydrogenation of the α,β-unsaturated lactones **33** and **40** gave the saturated lactones **44** and **46** in excellent yields (Scheme 8). To bring about C–P bond

(25) For ring-closure metathesis strategy applications to preparation of unsatuarated γ- and δ-lactones see: (a) Ghosh, A. K.; Cappiello, J.; Shin, D. *Tetrahedron Lett.* **1998**, *39*, 4651–4654. (b) Cossy, J.; Bauer, D.; Bellosta, V. *Tetrahedron Lett.* **1999**, *40*, 4187–4188. (c) Furstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H. J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204–2207. (d) Morgan, J. P.; Grubbs, R. H. *Org. Lett.* **2000**, *2*, 3153–3155. (e) Greer, P. B.; Donaldson, W. A. *Tetrahedron Lett.* **2000**, *41*, 3801–3803. (f) Ghosh, A. K.; Bilcer, G. *Tetrahedron Lett.* **2000**, *41*, 1003–1006. (g) Ghosh, A. K.; Wang, Y. *Tetrahedron Lett.* **2000**, *41*, 2319–2322. (h) Ghosh, A. K.; Lei, H. *J. Org. Chem.* **2000**, *65*, 4779–4781. (i) Ramachandran, P. V.; Reddy, M. V. R.; Brown, H. C. *Tetrahedron Lett.* **2000**, *41*, 583–586.

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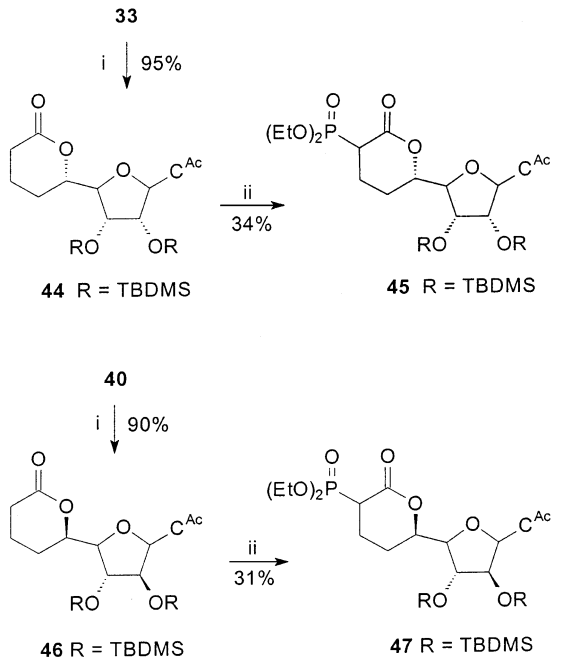
SCHEME 8[a]



[a] Reagents and conditions: (i)Pd/C, H_2, EtOAc; (ii) (a) LDA, HMPA, −78 °C, then ClP $(OEt)_2$, −78−20 °C; (b) H^+, air.

formation, each of the resulting lactones was treated with an excess of freshly prepared LDA in HMPA/THF, followed by reaction with diethylchlorophosphite. After the reactions were quenched with acetic acid, the mixtures were exposed to air to oxidize the phosphonite intermediates and the phosphonates **45** and **47** were obtained in modest yields as mixtures of diastereomers at the α position. The two diastereomers of compound **45** could be separated by HPLC with close to baseline resolution. Unfortunately after the two components were collected and concentrated, it was found that each isomer readily epimerized into a mixture of the two original diastereomers, as shown by HPLC. It is possible that isomerization would be slower in the corresponding phosphonic acids, but deprotection of phosphonates **45** and **47** has proven to be problematic due to competition from lactone hydrolysis. Rather than investigating these issues further with the phosphonates now in hand, exploration of other reagents for the key C−P bond formation would be attractive because that approach may address both issues at the same time.

These investigations of addition of allyl organometallic reagents to cytidine and ara-C aldehydes have indicated that substrate control is the predominant factor in determination of the resulting stereochemistry. The stereoselective allylations can provide both diastereomers at the C-5′ position, and the stereochemistry at this position may be critical for bioactivity.[2] These studies also have shown that ring-closing metathesis is an efficient approach to making lactone derivatives of cytidine and ara-C, and that it is possible to prepare the corresponding α-phosphono lactones through reaction of the lactone enolates with diethyl chlorophosphite followed by air oxidation. Further studies on the biological activity of phosphonic acid derivatives of these new nucleoside lactones will be reported in due course.

Experimental Section

5′(*R*)-Allyl-2′,3′-*O*-isopropylidene-*N*⁴-acetylcytidine (16). Method A: $BF_3{\cdot}OEt_2$ (0.78 mL, 6.2 mmol) was added to a flask with unpurified aldehyde **15**[15a] (prepared from alcohol **14** (404 mg, 1.2 mmol)) in CH_2Cl_2 (5 mL) at −78 °C. After 15 min, allyltrimethylsilane (1.0 mL, 6.2 mmol) was added. The reaction mixture was stirred for 3 h at −78 °C and allowed to warm to room temperature. After the reaction was quenched with sat. $NaHCO_3$, the aqueous layer was extracted with $CHCl_3$, and the combined organic layers were dried (Na_2SO_4) and filtered. After concentration of the filtrate, the residue was purified by flash chromatography by using a gradient system of methanol and EtOAc to give allyl alcohols **16** and **17** (6:1) as a white solid (160 mg, 44%**,** based on recovered alcohol **14** (91 mg)): ^{1}H NMR (CD_3OD) δ 8.27 (d, J = 7.4 Hz, 1H), 7.42 (d, J = 7.4 Hz, 1H), 5.90 (d, J = 2.2 Hz, 1H), 5.89 (m, 1H), 5.13 (br d, J = 16.2 Hz, 1H), 5.09 (br d, J = 10.1 Hz, 1H), 4.96 (dd, J = 6.4, 3.7 Hz, 1H), 4.87 (m, 1H), 4.15 (dd, J = 4.0, 3.7 Hz, 1H), 3.93 (m, 1H), 2.29 (m, 2H), 2.19 (s, 3H), 1.55 (s, 3H), 1.35 (s, 3H); ^{13}C NMR δ 173.2, 164.8, 158.0, 148.0, 135.6, 118.3, 115.1, 98.0, 95.8, 91.0, 86.8, 81.0, 71.8, 39.5, 27.7, 25.7, 24.7. Anal. Calcd for $C_{17}H_{23}N_3O_6$: C, 55.88; H, 6.34; N, 11.50. Found: C, 55.45; H, 6.48; N, 11.38.

Method C: The crude aldehyde **15** prepared from alcohol **14** (658 mg, 2.0 mmol) was suspended in 15 mL of 5.0 M $LiClO_4$ in diethyl ether, and acetonitrile (5 mL) was added. After all reagents were dissolved, allyltributyltin (0.7 mL, 2.25 mmol) was added. The reaction mixture was stirred at room temperature for 3 h and then was quenched by addition of sat. $NaHCO_3$. The resulting mixture was extracted with ethyl acetate, the organic phase was washed with brine, and the combined organic solvent was dried over $MgSO_4$. Flash chromatography of the concentrated residue with a gradient system of methanol and CH_2Cl_2 provided a mixture of **16** and its epimer **17** as a white solid (5′*R*:5′*S* = 3:2, 290 mg, 39% from alcohol **14**).

5′(*S*)-Allyl-2′,3′-di-*O*-*tert*-butyldimethylsilyl-*N*⁴-acetylcytidine (20). Method B: To a solution of crude aldehyde **19** prepared from alcohol **18**[2] (664 mg, 1.3 mmol) in CH_2Cl_2 (10 mL) was added 1 M $TiCl_4$ in CH_2Cl_2 (6.5 mL) at −78 °C. After 15 min, allyltrimethylsilane (1.03 mL, 6.5 mmol) was added to the reaction mixture. The reaction mixture was stirred at −78 °C for 3 h, and then was allowed to warm to room temperature. The reaction was quenched by addition of sat. $NaHCO_3$ and extracted with ethyl acetate, and the organic phase was washed with brine and dried ($MgSO_4$). Flash chromatography of the concentrated residue (hexane:EtOAc, 1:1) afforded allyl alcohol **20** (390 mg, 54% from nucleoside **18**) as a white solid: ^{1}H NMR δ 10.20 (s, 1H), 8.14 (d, J = 7.6 Hz, 1H), 7.46 (d, J = 7.6 Hz, 1H), 5.84 (m, 1H), 5.46 (d, J = 4.1 Hz, 1H), 5.19 (d, J = 6.3 Hz, 1H), 5.15 (s, 1H), 4.65 (dd, J = 4.3, 4.3 Hz, 1H), 4.17 (dd, J = 4.1, 4.0 Hz, 1H), 4.04 (d, J = 4.0 Hz, 1H), 3.72 (br td, J = 6.7, 6.7 Hz, 1H), 3.52 (d, J = 6.7 Hz, 1H), 2.37 (m, 2H), 2.30 (s, 3H), 0.90 (s, 9H), 0.88 (s, 9H), 0.064 (s, 6H), 0.058 (s, 3H), 0.04 (s, 3H); ^{13}C NMR δ 171.5, 163.5, 155.3, 148.0, 134.8, 118.6, 96.9, 95.8, 87.0, 73.4, 72.4, 69.6, 39.1, 26.1 (6C), 25.2, 18.3, 18.2, −4.2, −4.4, −4.59, −4.62. Anal. Calcd for $C_{26}H_{47}N_3O_6Si_2$: C, 56.38; H, 8.55; N, 7.59. Found: C, 56.24; H, 8.61; N, 7.46.

5′(*R*)-Allyl-2′,3′-*O*-isopropylidene-*N*⁴-acetylcytidine (17). To a solution of alcohol **20** (996 mg, 1.8 mmol) in THF (15 mL) was added 1 M TBAF in THF (9 mL). The reaction mixture was stirred at room temperature for 4 h, and then the solvent was removed under vacuum. The residue was purified by flash chromatograph (8% MeOH in CH_2Cl_2) to give alcohol **21** with a small amount of TBAF (445 mg, 76%).

Without further purification, alcohol **21** was dissolved in acetone (10 mL). Dimethoxypropane (2.53 mL, 20.5 mmol) was added, followed by very slow addition of $HClO_4$ (0.1 mL). After the solution was stirred at room temperature for 2 h, the reaction was quenched by addition of sat. $NaHCO_3$. After concentration under vacuum, the residue was dissolved in

EtOAc. The EtOAc layer was washed with brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated and purified by flash chromatography (5% MeOH in CH_2Cl_2) to provide alcohol **17** (250 mg, 50%) as a white solid. ^{1}H NMR (CD_3OD) δ 8.39 (d, J = 7.5 Hz, 1H), 7.41 (d, J = 7.5 Hz, 1H), 5.98 (d, J = 1.3 Hz, 1H), 5.90 (m, 1H), 5.14 (dm, J = 18.0 Hz, 1H), 5.10 (dm, J = 9.0 Hz, 1H), 4.86 (m, 2H), 4.16 (m, 1H), 3.80 (m, 1H), 2.36 (m, 2H), 2.18 (s, 3H), 1.56 (s, 3H), 1.35 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 171.3, 163.8, 155.4, 148.0, 134.4, 118.3, 114.4, 98.5, 97.4, 88.7, 83.4, 81.7, 71.4, 38.7, 27.5, 25.5, 25.2; HRMS (ESI) m/z calcd for $C_{17}H_{24}N_3O_6$ $(M + H)^+$ 366.1665, found 366.1665. Anal. Calcd for $C_{17}H_{23}N_3O_6 \cdot 0.5H_2O$: C, 54.54; H, 6.46; N, 11.22. Found: C, 54.64; H, 6.35; N, 11.07.

5′(*R*)-Allyl-5′-*O*-diethylphosphonoacetyl-2′,3′-di-*O*-*tert*-butyldimethylsilyl-*N*^{4}-acetylcytosinearabinoside (28). To a solution of homoallylic alcohol **26** (447 mg, 0.8 mmol), EDC (169 mg, 0.9 mmol), and DMAP (10 mg, 0.1 mmol) in CH_2Cl_2 (10 mL) was added diethylphosphonoacetic acid (0.14 mL, 0.9 mmol) dropwise at room temperature. After the mixture was stirred for 18 h, it was diluted by addition of CH_2Cl_2 and washed with cold, dilute acid (pH 3). The CH_2Cl_2 layer was dried ($MgSO_4$) and filtered, and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (20% hexane in EtOAc) to obtain phosphonoacetate **28** as a white solid (482 mg, 82%): ^{1}H NMR δ 9.06 (br s, 1H), 7.85 (d, J = 7.5 Hz, 1H), 7.40 (d, J = 7.3 Hz, 1H), 6.24 (d, J = 2.6 Hz, 1H), 5.87 (m, 1H), 5.16 (m, 2H), 4.24−4.13 (m, 6H), 4.09 (s, 1H), 3.96 (d, J = 9.4 Hz, 1H), 2.99 (dd, J = 22.0, 14.2 Hz, 1H), 2.92 (dd, J = 21.5, 14.4 Hz, 1H), 2.66 (m, 1H), 2.46 (m, 1H), 2.25 (s, 3H), 1.35 (t, J = 7.0 Hz, 6H), 0.91 (s, 9H), 0.78 (s, 9H), 0.12 (s, 3H), 0.12 (s, 3H), 0.01 (s, 3H), −0.19 (s, 3H); ^{13}C NMR δ 170.7, 164.5 (d, J_{CP} = 6.6 Hz), 162.6, 154.7, 146.4, 132.2, 118.9, 95.5, 88.5, 86.3, 78.7, 75.9, 73.5, 62.8 (d, J_{CP} = 7.9 Hz), 62.7 (d, J_{CP} = 6.4 Hz), 35.4, 34.3 (d, J_{CP} = 135.4 Hz), 25.7 (3C), 25.7 (3C), 25.0, 17.9, 17.8, 16.4 (d, J_{CP} = 1.4 Hz), 16.3 (d, J_{CP} = 1.4 Hz), −4.6, −4.7, −5.0, −5.4; ^{31}P NMR δ 19.6. Anal. Calcd for $C_{32}H_{58}N_3O_{10}PSi_2$: C, 52.51; H, 7.99; N, 5.74. Found: C, 52.24; H, 8.15; N, 5.67.

Phosphonoacetyl Aldehyde of Cytosine Arabinoside 29. A suspension of $NaIO_4$ (166 mg, 0.8 mmol) and K_2OsO_4 (1 mg, 0.003 mmol) in water (3 mL) was transferred by pipet into a solution of allylic acetate **28** (229 mg, 0.3 mmol) in THF (3 mL). After the reaction mixture was stirred vigorously for 7 h, the THF was removed in vacuo and the aqueous residue was extracted with EtOAc. The combined organic phase was washed with NH_4Cl, $NaHCO_3$, and brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated and dried in vacuo to give aldehyde **29** as an off-white solid (226 mg, 99%): ^{1}H NMR δ 9.81 (dd, J = 1.8, 1.3 Hz, 1H), 9.15 (br s, 1H), 7.83 (d, J = 7.5 Hz, 1H), 7.43 (d, J = 7.5 Hz, 1H), 6.26 (d, J = 2.4 Hz, 1H), 5.49 (m, 1H), 4.23−4.12 (m, 6H), 4.01 (d, J = 8.9 Hz, 1H), 2.99 (dd, J = 22.0, 14.2 Hz, 1H), 2.93 (dd, J = 22.0, 14.2 Hz, 1H), 2.95 (m, 1H), 2.56 (ddd, J = 17.2, 6.0, 2.1 Hz, 1H), 2.25 (s, 3H), 1.35 (t, J = 7.0 Hz, 6H), 0.92 (s, 9H), 0.80 (s, 9H), 0.14 (s, 3H), 0.14 (s, 3H), 0.02 (s, 3H), −0.19 (s, 3H); ^{13}C NMR δ 198.3, 170.4, 164.9 (d, J_{CP} = 6.0 Hz), 162.5, 154.8, 146.9, 95.7, 88.5, 87.0, 78.7, 76.0, 69.9, 63.1 (d, J_{CP} = 3.4 Hz), 63.1 (d, J_{CP} = 4.0 Hz), 45.8, 34.6 (d, J_{CP} = 133.8 Hz), 25.9 (3C), 25.9 (3C), 25.2, 18.1, 18.0, 16.6 (d, J_{CP} = 1.5 Hz), 16.5 (d, J_{CP} = 1.7 Hz), −4.4, −4.5, −4.8, −5.2; ^{31}P NMR δ 18.6; HRMS (ESI) m/z calcd for $C_{31}H_{57}N_3O_{11}PSi_2$ $(M + H)^+$ 734.3269, found 734.3283.

1-(2′,3′-Di-*O*-*tert*-butyldimethylsilyl-β-D-arabino-hept-(5*E*)-enodialdo-1,4-furanosyl)-*N*^{4}-acetylcytosine (30). To a mixture of $TiCl_4$ (1 M in CH_2Cl_2) in THF (2 mL) at 0 °C was added a solution of aldehyde **29** (96 mg, 0.1 mmol) in THF, and then *N*-methylmorpholine (0.014 mL) was added. After 30 min, a second portion of *N*-methylmorpholine (0.014 mL) was added and the reaction mixture was allowed to warm to room temperature and stirred for 8 h. After water (5 mL) was added, the reaction mixture was extracted with EtOAc. The combined EtOAc layers were washed with NH_4Cl, $NaHCO_3$,and brine. After the extracts were dried ($NaSO_4$) and filtered, the filtrate was purified by flash chromatography (40% hexane in EtOAc) to provide aldehyde **30** (35.7 mg, 51%): ^{1}H NMR δ 9.88 (br s, 1H), 9.59 (d, J = 7.8 Hz, 1H), 7.97 (d, J = 7.4 Hz, 1H), 7.46 (d, J = 7.4 Hz, 1H), 6.92 (dd, J = 15.8, 7.1 Hz, 1H), 6.31 (d, J = 2.7 Hz, 1H), 6.28 (d, J = 16.1, 7.8, 1.2, 1H), 4.67 (d, J = 7.1 Hz, 1H), 4.35 (d, J = 2.7 Hz, 1H), 4.07(s, 1H), 2.28 (s, 3H), 0.93 (s, 9H), 0.77 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H), 0.02 (s, 3H), −0.21 (s, 3H); ^{13}C NMR δ 192.8, 171.0, 163.0, 154.9, 152.7, 146.2, 132.3, 95.9, 89.6, 86.8, 82.8, 75.9, 25.9 (3C), 25.8 (3C), 25.1, 18.1, 17.9, −4.4, −4.5, −5.0, −5.2; HRMS (ESI) calcd for $C_{25}H_{44}N_3O_6Si_2$ $(M + H)^+$ 538.2769, found 538.2792.

5′(*S*)-[1′-(2′,3′-*O*-Di-*tert*-butyldimethylsilyl-β-D-ribo-5′-penta-1′,4′-furanosyl)-*N*^{4}-acetylcytosyl] α,β-Unsaturated δ-Lactone (33). To a solution of aldehyde **32** (502 mg, 0.7 mmol) in THF (5 mL) was added NaH (17 mg, 0.7 mmol) suspended in THF (3 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 4 h. Acetic acid (0.1 mL) was added, the solvent was removed under vacuum, and the residue was partitioned between EtOAc and water. After the aqueous layer was extracted with EtOAc, the combined EtOAc layers were dried (Na_2SO_4) and filtered. The filtrate was concentrated and purified by flash chromatography with a gradient eluent of hexane and EtOAc to give unsaturated lactone **33** (56 mg, 14%) and aldehyde **34** (301 mg, 80%) as white solids. For lactone **33**: ^{1}H NMR δ 10.03 (s, 1H), 8.27 (d, J = 7.4 Hz, 1H), 7.45 (d, J = 7.4 Hz, 1H), 7.04 (m, 1H), 6.10 (dd, J = 9.7, 2.4 Hz, 1H), 5.78 (s, 1H), 4.56 (dd, J = 13.0, 3.1 Hz,1H), 4.19 (m, 3H), 2.92 (m, 1H), 2.41 (m, 1H), 2.28 (s, 3H), 0.94 (s, 9H), 0.88 (s, 9H), 0.27 (s, 3H), 0.14 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR δ 171.1, 163.3, 162.8, 155.2, 146.1, 144.4, 121.3, 96.9, 91.8, 81.9, 76.2, 74.2, 69.0, 27.0, 26.1 (3C), 26.1 (3C), 25.0, 18.3, 18.2, −4.0, −4.1, −4.8, −5.0; HRMS (ESI) m/z calcd for $C_{27}H_{46}N_3O_7Si_2$ $(M + H)^+$ 580.2874, found 580.2884. Anal. Calcd for $C_{27}H_{45}N_3O_7Si_2$: C, 55.93; H, 7.82; N, 7.25. Found: C, 55.45; H, 7.67; N, 7.07.

5′(*R*)-Allyl-5′-*O*-acryloyl-2′,3′-*O*-isopropylidene-*N*^{4}-acetylcytidine (35). Acryloyl chloride (0.15 mL, 1.8 mmol) was added to allyl alcohol **16** (114.4 mg, 0.3 mmol) and DMAP (11.6 mg, 0.3 mmol) dissolved in a mixture of acetonitrile and CH_2Cl_2 (10 mL, 1:1) at 0 °C, followed by triethylamine (0.39 mL, 28.2 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 26 h. The reaction mixture was filtered through a pad of Celite into water (5 mL), and the product was extracted with CH_2Cl_2. The organic extracts were combined and dried over $MgSO_4$. The concentrated residue was purified on a short column of silica gel (3% methanol in CH_2Cl_2) to afford compound **35** as a yellow solid (92.6 mg, 71%): ^{1}H NMR δ 10.00 (s, 1H), 7.65 (d, J = 7.6 Hz, 1H), 7.36 (d, J = 7.6 Hz, 1H), 6.41 (dd, J = 17.1, 1.4 Hz, 1H), 6.08 (dd, J = 17.4, 10.4 Hz, 1H), 5.88 (dd, J = 10.4, 1.3 Hz, 1H), 5.80 (d, J = 1.5 Hz, 1H), 5.78 (m, 1H), 5.36 (m, 1H), 5.16 (br d, J = 11.3 Hz, 1H), 5.11 (br d, J = 4.2 Hz, 1H), 4.90 (m, 2H), 4.31 (dd, J = 4.1 Hz, 1H), 2.46 (m, 2H), 2.29 (s, 3H), 1.58 (s, 3H), 1.36 (s, 3H); ^{13}C NMR δ 170.9, 165.4, 163.2, 154.4, 145.5, 132.3, 132.1, 128.0, 119.4, 114.8, 96.6, 94.6, 87.2, 85.4, 79.8, 72.4, 35.5, 27.4, 25.6, 25.1; HRMS (ESI) m/z calcd for $C_{20}H_{26}N_3O_7$ $(M + H)^+$ 420.1771, found 420.1782.

5′(*R*)-Lactone 37. A solution of compound **35** in CH_2Cl_2 (16 mL) was heated at reflux under argon. To this solution was added dropwise Grubbs' catalyst **36** (13.2 mg, 0.016 mmol) dissolved in CH_2Cl_2 (2 mL). The reaction was monitored by TLC, and stopped after 24 h. Solvent was removed by rotary evaporation, and the residue was purified by flash chromatography with a gradient solvent system of hexane and ethyl acetate to give lactone **37** (22 mg, 34%) and recovered **35** (14 mg, 21%). For lactone **37**: ^{1}H NMR δ 9.84 (s, 1H), 7.83 (d, J = 7.4 Hz, 1H), 7.47 (d, J = 7.4 Hz, 1H), 6.89 (dt, J = 9.7, 4.2 Hz, 1H), 6.05 (d, J = 9.7 Hz, 1H), 5.75 (d, J = 1.5 Hz, 1H), 5.11 (dd, J = 6.5, 3.4 Hz, 1H), 5.07 (dd, J = 6.5, 1.8 Hz, 1H), 4.86 (dt, J = 7.8, 6.0 Hz, 1H), 4.29 (dd, J = 6.0, 3.3 Hz, 1H), 2.46 (m, 2H), 2.27 (s, 3H), 1.58 (s, 3H), 1.35 (s, 3H); ^{13}C NMR δ 171.0, 163.7, 163.0, 155.0, 147.1, 144.8, 121.5, 114.6, 97.2, 96.8,

88.4, 84.7, 80.9, 76.6, 27.2, 25.9, 25.3. 25.1. HRMS (ESI) *m*/*z* calcd for $C_{18}H_{22}N_3O_7$ $(M + H)^+$ 392.1458, found 392.1465.

5′(*R*)-Lactone 40. Acrylate ester **38** (141 mg, 0.23 mmol) was coevaporated with anhydrous CH_2Cl_2, and then was dissolved in anhydrous CH_2Cl_2 (20 mL). To this solution was added dropwise Grubbs' catalyst 39 (20 mg, 0.02 mmol) in CH_2Cl_2 (3 mL), and the reaction was monitored by TLC. After it was stirred for 2 h, the reaction mixture was allowed to cool to room temperature, and the solvent was removed under low pressure. The residue was purified by flash chromatography (hexane and ethyl acetate gradient) to give unsaturated lactone **40** (113 mg, 85%) as a light-brown solid: ^{1}H NMR δ 9.98 (s, 1H), 7.72 (d, J = 7.5 Hz, 1H), 7.43 (d, J = 7.5 Hz, 1H), 6.95 (ddd, J = 9.8, 5.2, 3.3 Hz, 1H), 6.28 (d, J = 2.2 Hz, 1H), 6.09 (dd, J = 9.8, 0.9 Hz, 1H), 4.61 (ddd, J = 9.8, 9.8, 4.5 Hz, 1H), 4.44 (s, 1H), 4.27 (d, J = 2.2 Hz, 1H), 4.01 (d, J = 9.8 Hz, 1H), 2.72 (dddd, J = 18.4, 5.0, 5.0, 0.9 Hz, 1H), 2.52 (dddd, J = 18.4, 9.8, 2.8, 2.6 Hz, 1H), 2.30 (s, 3H), 0.92 (d, 9H), 0.76 (s, 9H), 0.17 (s, 3H), 0.16 (s, 3H), 0.04 (s, 3H), −0.22 (s, 3H); ^{13}C NMR δ 171.0, 162.8, 162.3, 154.6, 145.8, 144.2, 121.6, 95.6, 88.7, 87.2, 77.8, 76.0, 75.8, 27.0, 25.7 (3C), 25.6 (3C), 24.9, 17.8, 17.7, −4.7 (2C), −5.2, −5.4; HRMS (ESI) *m*/*z* calcd for $C_{27}H_{46}N_3O_7Si_2$ $(M + H)^+$ 580.2874, found 580.2892.

***(S)*-Lactone 44.** Argon was passed through a solution of unsaturated lactone **33** (788 mg, 1.4 mmol) and palladium (10 wt % on activated carbon, 145 mg) in EtOAc, and the reaction flask was connected to a balloon filled with H_2. After the flask was flushed with H_2, the reaction mixture was stirred at room temperature for 5 h. After dilution with CH_2Cl_2, the mixture was filtered through a pad of Celite and all solvents were removed under low pressure. The residue was purified by flash chromatography (50% hexane in EtOAc) to give lactone **44** (752 mg, 95%) as a light-brown solid: ^{1}H NMR δ 10.04 (s, 1H), 8.17 (d, J = 7.6 Hz, 1H), 7.44 (d, J = 7.6 Hz, 1H), 5.79 (s, 1H), 4.45 (m, 1H), 4.12 (m, 3H), 2.60 (m, 2H), 2.28 (s, 3H), 2.08−1.88 (m, 4H), 0.93 (s, 9H), 0.89 (s, 9H), 0.26 (s, 3H), 0.13 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR δ 171.1, 170.3, 163.3, 155.2, 144.4, 97.0, 91.6, 82.8, 76.4, 76.0, 69.5, 29.8, 26.1 (6C), 25.4, 25.0, 18.8, 18.3 (2C), −3.99, −4.05, −4.8, −5.0; HRMS (ESI) *m*/*z* calcd for $C_{27}H_{48}N_3O_7Si_2$ $(M + H)^+$ 582.3031, found 582.3025.

5′(*S*)-[1′-(2′,3′-*O*-Di-*tert*-butyldimethylsilyl-*β*-D-ribo-5′-penta-1′,4′-furanosyl)-N^4-acetylcytosyl]-α-diethylphosphonyl-*δ*-lactone (45). A solution of lactone **44** (234 mg, 0.4 mmol) in THF (5 mL) was added dropwise via cannula to a solution of LDA (1.0 mmol) prepared in situ from diisopropylamine (0.15 mL, 1.07 mmol) and *n*-BuLi (2.26 M in hexane, 0.44 mL) in ethyl ether at −78 °C. After 1 h, HMPA (0.076 mL, 0.44 mmol) and diethyl chlorophosphite (0.064 mL, 0.4 mmol) were added sequentially, and the resulting mixture was allowed to warm to room temperature over 2 h. The reaction was quenched by slow addition of acetic acid (1 M in ether, 1.6 mL), and the resulting mixture was filtered through a pad of Celite and the pad was washed with EtOAc. The filtrate was concentrated and purified with flash chromatography (EtOAc gradient in hexane) to give α-phosphono lactone **45** (97 mg, 34%) as a mixture of two diastereomers in a 3:2 ratio: ^{1}H NMR (400 MHz) δ 9.90 (s, 0.6H), 9.84(s, 0.4H), 8.26 (d, J = 7.6 Hz, 0.4H), 8.16 (d, J = 7.6 Hz, 0.6H), 7.40 (d, J = 7.5 Hz, 0.6H), 7.39 (d, J = 7.5 Hz, 0.4H), 5.77 (s, 0.6H), 5.68 (s, 0.4H), 4.64 (dd, J = 7.4, 7.0 Hz, 0.6H), 4.43 (dd, J = 11.6, 2.9 Hz, 0.4H), 4.28−4.18 (m, 5H), 4.13−4.06 (m, 2H), 3.35 (ddd, J = 27.8, 8.7, 8.6 Hz, 0.6H), 3.21 (ddd, J = 27.0, 7.2, 2.9 Hz, 0.4H), 2.58−2.48 (m, 1H), 2.36 −2.20 (m, 1H), 2.26 (s, 1.8H), 2.25 (s, 1.2H), 2.06 (m, 1.2H), 1.91 (m, 0.8H), 1.40 −1.31 (m, 6H), 0.92 (s, 3.6H), 0.91(s, 5.4H), 0.88 (s, 5.4H), 0.87 (s, 3.6H), 0.26 (s, 1.2H), 0.24 (s, 1.8H), 0.13 (s, 1.2H), 0.11 (s, 1.8H), 0.08 (s, 1.8H), 0.06 (s, 1.2H), 0.04 (s, 1.8H), 0.04 (s, 1.2H); ^{13}C NMR δ 170.8 (0.6C), 170.7 (0.4C), 165.5 (d, J_{CP} = 4.5 Hz, 0.6C), 165.5 (d, J_{CP} = 4.7 Hz, 0.4C), 163.0 (0.4C), 162.9 (0.6C), 155.0 (0.4C), 155.0 (0.6C), 144.8 (0.4C), 144.1 (0.6C), 96.7 (0.6C), 96.3 (0.4C), 91.7 (0.4C), 91.2 (0.6C), 82.6 (0.6C), 82.4 (0.4C), 77.7 (0.4C), 76.7 (0.6C), 75.8 (0.6C), 75.6 (0.4C), 69.2 (0.6C), 69.0 (0.4C), 63.8 (d, J_{CP} = 6.8 Hz, 0.4C), 63.6 (d, J_{CP} = 6.8 Hz, 0.6C), 62.9 (d, J_{CP} = 6.7 Hz, 0.4C), 62.9 (d, J_{CP} = 6.6 Hz, 0.6C), 40.2 (d, J_{CP} = 135.9 Hz, 0.6C), 39.8 (d, J_{CP} = 134,4, 0.4C), 25.9 (2.4C), 25.9 (3.6C), 25.1 (d, J_{CP} = 9.0 Hz, 0.6C), 24.8 (0.4C), 24.8 (0.6C), 22.7 (d, J_{CP} = 2.5 Hz, 0.4C), 21.3 (d, J_{CP} = 4.6 Hz, 0.4C), 21.1 (d, J_{CP} = 4.1 Hz, 0.6C), 18.0, 18.0, 16.4 (d, J_{CP} = 5.6 Hz, 0.4C), 16.4 (d, J_{CP} = 6.1 Hz, 0.6C), 16.3 (d, J_{CP} = 6.6 Hz), −4.2 (0.4C), −4.2 (0.6C), −4.3 (0.4C), −4.4 (0.6C), −5.0, −5.2 (0.6C), −5.3 (0.4C); ^{31}P NMR δ 21.8 (0.4P), 21.7(0.6P); HRMS (ESI) *m*/*z* calcd for $C_{31}H_{57}N_3O_{10}Si_2P$ $(M + H)^+$ 718.3320, found 718.3346. Anal. Calcd for $C_{31}H_{56}N_3O_{10}PSi_2 \cdot H_2O$: C, 50.59; H, 7.94; N, 5.71. Found: C, 50.93; H, 7.64; N, 5.60.

Acknowledgment. We would like to thank Dr. Dale Swenson for his assistance with the diffraction analyses, the Center for Biocatalysis and Bioprocessing for a predoctoral fellowship, and the Leukemia and Lymphoma Society (LLS99-6059) and The Roy J. Carver Charitable Trust for financial support.

Supporting Information Available: General experimental protocols, additional examples of reactions described in the Experimental Section, ^{1}H and ^{13}C NMR spectra for compounds **29**, **30**, **32**, **33**, **35**, **37**, **40**, and **42**−**47**, and ORTEP drawings for compounds **17** and **26**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0300136