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Synthetic Intermediates Potentially Useful for the Synthesis of Tetrodotoxin and Derivatives. 8.[1] A Series of Highly Functionalized Pyrimidinones

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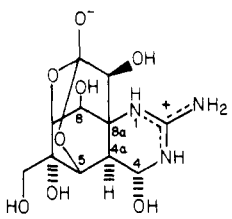
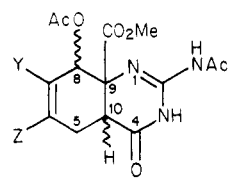
The synthesis of a versatile series of highly functionalized pyrimidinones is described, some of which served to test the feasibility of an intramolecular Diels–Alder approach to tetrodotoxin while others have been shown subsequently to serve as dienophiles in an intermolecular approach to the toxin. The series of 6-(acetic acid)-substituted pyrimidinones **4–12** and **15–21** were prepared from pyrimidinone ester amine **3**. The series of 6-acylpyrimidinones was derived from pyrimidinone ketal **23**. The key step which allowed regioselective functionalization of the acetyl group was conversion of **23** into enol ethers **27–29**. From these latter heterocycles 6-acylpyrimidinones **33**, **34**, **36–39**, and **42–49** as well as ketals **50–54** were synthesized.

The development of convenient synthetic routes[2] to physiologically important derivatives of the potent neuropoison tetrodotoxin (TTX, **1**) continues to be of interest,



1 (TTX)



2

hydroquinazoline numbering shown

especially owing to the wide application[3] of TTX and some of its derivatives as neurophysiological tools. Our approach[1] has utilized an intermolecular Diels–Alder reaction between an oxygen-substituted 1,3-diene[4] and a 6-carbomethoxypyrimidinone for assembly[5] of the hydroquinazoline ring system **2**, similar to that of the toxin. One improvement would be to utilize pyrimidinones (e.g., **3**) which already incorporated an oxygenated two-carbon fragment at position 6 (pyrimidinone numbering; becomes position 9, hydroquinazoline numbering; position 8a, TTX numbering) which is potentially convertible into the hydroxyacetic acid substituent characteristic of TTX. Also envisaged was construction of the hydroquinazoline ring system by means of an intramolecular Diels–Alder reaction[6] between the pyrimidinone and a 1,3-diene unit attached to the two-carbon side chain at position 6. Herein, we describe the synthesis of a series of highly functionalized pyrimidinones, some of which served to test the feasibility of the intramolecular approach while others have been shown subsequently to serve as dienophiles in an intermolecular approach.[7]

Results and Discussion

A Diels–Alder reaction between keto ester **5** and 1,3-dienes was shown earlier[1] to occur across the ketone carbonyl group rather than the pyrimidinone double bond. As the former mode of addition should be disfavored (four-membered ring formation) in an intramolecular reaction involving the general structure **22**, precursors to **22**, esters **15** and **19–21**, became the first objective. A switch

(1) For the preceding paper in this series see: Keana, J. F. W.; Eckler, P. E. *J. Org. Chem.* **1976**, *41*, 2850.

(2) An elegant total synthesis of TTX has been reported: Kishi, Y.; Fukuyama, T.; Aratani, M.; Nakatsubo, F.; Goto, T.; Inoue, S.; Tanino, H.; Sugiura, S.; Kakoi, H. *J. Am. Chem. Soc.* **1972**, *94*, 9219.

(3) See, inter alia: Gage, P. W. In "Neuropoisons: Their Pathophysiological Actions"; Simpson, L. L., Ed.; Plenum Press: New York, 1971; Chapter 9. Ritchie, J. M.; Rogart, R. B. *Rev. Physiol. Biochem. Pharmacol.* **1977**, *79*, 1. Chicheportiche, R.; Balerna, M.; Lombet, A.; Romey, G.; Lazdunski, M. *J. Biol. Chem.* **1979**, *254*, 1552. Guillory, R. J.; Rayner, M. D.; D'Arrigo, J. S. *Science (Washington, D.C.)* **1977**, *196*, 883.

(4) For leading references see: Keana, J. F. W.; Taneja, H. R.; Erion, M. *Synth. Commun.* **1982**, *12*, 167.

(5) Keana, J. F. W.; Bland, J. S.; Eckler, P. E.; Nelson, V.; Gougoutas, J. Z. *J. Org. Chem.* **1976**, *41*, 2124.

(6) Brieger, G.; Bennett, J. N. *Chem. Rev.* **1980**, *80*, 63.

(7) Keana, J. F. W.; Bland, J. S.; Boyle, P. J.; Erion, M.; Hartling, R.; Husman, J. R.; Roman, R. B.; Ferguson, G.; Parvez, M., following paper in this issue.

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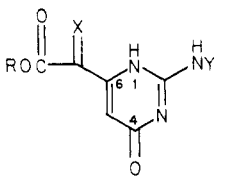
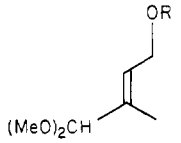




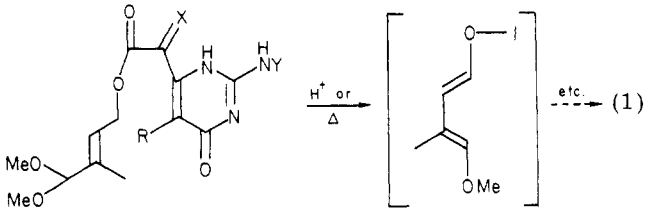
13, R = Ac
14, R = H

3, R = Me; X = H, H; Y = H
4, R = Me; X = H, H; Y = Ac
5, R = Me; X = O; Y = Ac
6, R = Me; X = H, H; Y = $COC(CH_3)_3$
7, R = H; X = H, H; Y = $COC(CH_3)_3$
8, R = Me; X = O; Y = $COC(CH_3)_3$
9, R = Me; X = H, Br; Y = $COC(CH_3)_3$
10, R = Me; X = Br, Br; Y = $COC(CH_3)_3$
11, R = Me; X = H, H; Y = $CO(CH_2)_{16}CH_3$
12, R = Me; X = O; Y = $CO(CH_2)_{16}CH_3$

from *N*-acetyl to *N*-pivaloyl or *N*-stearoyl substrates was made to improve the solubility characteristics of the intermediates.

Pivalamide **6** and stearamide **11** were prepared by acylation[8] of amine **3**[9] with either pivalic anhydride or stearoyl chloride. Treatment of **6** with 5 equiv of sodium ethanethiolate in *N,N*-dimethylformamide (DMF)[10] at 25 °C followed by acidification gave the carboxylic acid **7**. Crude **7** reacted readily in tetrahydrofuran (THF) with *N,N*-carbonyldiimidazole (CDI) with evolution of CO_2 to give a clear solution which was immediately treated with 1 equiv of alcohol **14**.[11] Ester **15** was thus obtained in 91% yield. Stearoyl derivative **20** was prepared in a similar manner from ester **11**. Alcohol **14**[11] was prepared from (*E*)-4-acetoxy-2-methyl-2-butenal[12] by reaction with trimethylorthoformate to give **13** and subsequent treatment of **13** with NaOMe in methanol.

Heating a solution of ester **15** in xylene containing toluenesulfonic acid smoothly led (by NMR) to dienol ether **22** (air sensitive) (eq 1). Diene **22**, however, failed

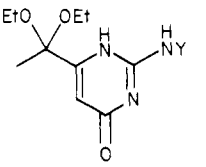


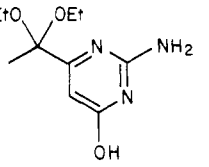
(1)

15, X = H, H; R = H; Y = $COC(CH_3)_3$ 22
16, X = H, Cl; R = H; Y = $COC(CH_3)_3$
17, X = H, Br; R = Br; Y = $COC(CH_3)_3$
18, X = H, H; R = Br; Y = $COC(CH_3)_3$
19, X = O; R = H; Y = $COC(CH_3)_3$
20, X = H, H; R = H; Y = $CO(CH_2)_{16}CH_3$
21, X = O; R = H; Y = $CO(CH_2)_{16}CH_3$

to undergo an intramolecular Diels–Alder reaction under a variety of conditions, undoubtedly reflecting, in part, the lack of additional activation of the pyrimidone double bond provided by a carbonyl group in the α-position.[13] Direct oxidation of the α-position of **15** or **20** with SeO_2 failed to give any **19** or **21**, probably owing to the presence of the sensitive acetal function since esters **6** and **11** readily afforded keto esters **8** and **12**, respectively, with this reagent.[14] Selective chlorination of **15** with *N*-chlorosuccinimide (NCS)[8] in DMF gave **16** in only modest yield while NBS led to a mixture of undesired **18** and dibromide **17**, a pattern of halogenation consistent with that observed earlier with **4** as the substrate.[8] Bromination at the α-position of the model ester **6** to give **9** and **10** was achieved with cupric bromide in $CHCl_3$ containing BaO. However, ester **15** failed to undergo α-bromination cleanly. Heating monobromide **9** in Me_2SO-d_6 at 45 °C gave keto ester **8**[1] (by NMR) thus establishing an alternative route to the SeO_2 methodology for preparing α-keto esters from suitable 6-(acetic acid)-substituted pyrimidinones.

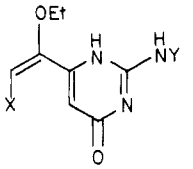
With the aim of preserving the dienophilic activation of the pyrimidinone double bond provided by an adjacent carbonyl group[1] while simultaneously incorporating an oxidized two-carbon appendage at the 6-position, we prepared a series of 6-acylpyrimidinones. Treatment of pyrimidinone **31**, obtained by acetylation of **30**,[15] with NBS

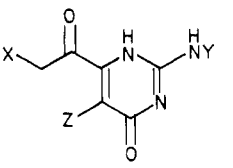




23, Y = H
24, Y = Ac
25, Y = $COC(CH_3)_3$

26 (or tautomer)





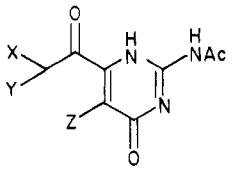
27, X = H; Y = Ac
28, X = H; Y = $CO(CH_3)_3$
29, X = Br; Y = Ac

30, X = Y = Z = H
31, X = Z = H; Y = Ac
32, X = Z = H; Y = $COC(CH_3)_3$
33, X = Br; Y = Ac; Z = H
34, X = Br; Y = $COC(CH_3)_3$; Z = H
35, X = H; Y = Ac; Z = Br

cleanly gave ring-brominated **35**. Ross et al.[15] also observed ring bromination with **30**. The desired regioselective bromination was achieved as follows. Ketal **23**, an uncharacterized intermediate toward **30**,[15] and a less soluble tautomer, **26**,[16] were isolated from the condensation of guanidine carbonate with ethyl 3-oxo-4,4-diethoxypentanoate.[15] Acetylation of **23** gave **24** from which ethanol was eliminated in an acid-catalyzed thermal reaction, forming the key intermediate enol ether **27** in 95% yield. NBS reacted with **27** in aqueous acetone regioselectively to give bromo ketone **33**. By an analogous route (**23** → **25** → **28** → **34**) the corresponding bromo *N*-pivaloyl derivative **34** was prepared.

A Pummerer rearrangement was the key step in providing several disubstituted acetylpyrimidinones. Bromo ketone **33** was treated with thiophenoxide ion, and the intermediate thioether **36** was oxidized to the corresponding sulfoxide. Heating the sulfoxide in acetic anhydride gave the Pummerer rearrangement product **37**. Treatment of **37** with cupric acetate in methanol[17] gave

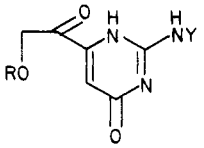
(8) Keana, J. F. W.; Mason, F. P. *J. Org. Chem.* **1970**, *35*, 838.
(9) Worrall, D. E. *J. Am. Chem. Soc.* **1943**, *65*, 2053.
(10) Feutrill, G. I.; Mirrington, R. N. *Aust. J. Chem.* **1972**, *25*, 1731.
(11) Steiner, K. Ger. Offen. 2412517 (cl. c07c), Oct 3, 1974; *Chem. Abstr.* **1975**, *82*, p42414m.
(12) Keana, J. F. W.; Eckler, P. E. *J. Org. Chem.* **1976**, *41*, 2625.
(13) Attempts to effect an intermolecular Diels–Alder reaction between a variety of dienes[5] and a pyrimidone bearing a "nonactivating" XCH_2 group at the 6-position were also unsuccessful.
(14) The methodology developed for the synthesis of esters **15** and **20**, when applied to keto esters **8** and **12**, did not lead to esters **19** or **21**.
(15) Ross, L. O.; Acton, E. M.; Skinner, W. A.; Goodman, L.; Baker, B. R. *J. Org. Chem.* **1961**, *26*, 3395.
(16) Tautomers **26** and **23** differed in their Nujol IR spectra. Attempted recrystallization of **26** gave **23** instead. Whereas **23** gave the expected NMR spectrum in $CDCl_3$, **26** was insoluble in $CDCl_3$. The NMR spectra of **26** and **23** were identical when measured in D_2O–Na_2CO_3 solution.
(17) Connor, D. T.; Young, P. A.; von Strandtmann, M., *Synthesis* **1978**, 209.



36, X = Z = H; Y = SC_6H_5
37, X = OAc; Y = SC_6H_5; Z = H
38, X = OAc; Y = OMe; Z = H
39, X = OAc; Y = $OCH_2CH{=}CH_2$; Z = H
40, X = Y = Br; Z = H
41, X = Z = Br; Y = H
42, X = Y = Z = Br

mixed acetal **38**, a highly functionalized potential dienophile. Allyl alcohol could be used in place of methanol, affording allyloxy derivative **39**.[18]

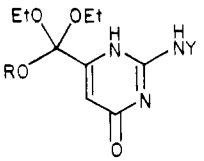
Enol ethers **27** and **28** also served as substrates for the introduction of an oxygen function on the β-carbon atom of the side chain. Oxidation of **27** with peracetic acid in aqueous THF gave the rather insoluble hydroxy ketone **43**. Through use of an excess of trichloroethyl chloro-



43, R = H; Y = Ac
44, R = $CO_2CH_2CCl_3$; Y = Ac
45, R = CO_2CH_3; Y = Ac
46, R = CO_2CH_3; Y = $COC(CH_3)_3$
47, R = Y = Ac
48, R = Ac; Y = $COC(CH_3)_3$
49, R = $COCH_2Cl$; Y = $COC(CH_3)_3$

formate in pyridine at 55 °C, **43** could be converted into trichlorocarbonate **44**, a derivative chosen owing to its anticipated ease of selective removal with zinc dust in acetic acid.[19]

The low solubility of **43** required that the derivatives described below be prepared indirectly. Thus, oxidation of enol ether **27** with *m*-chloroperoxybenzoic acid (MCPBA) in absolute ethanol led to the nicely soluble hydroxy ketal **50**. Mild hydrolysis of **50** with 90% acetic



50, R = H; Y = Ac
51, R = CO_2Me; Y = Ac
52, R = H; Y = $COC(CH_3)_3$
53, R = CO_2Me; Y = $COC(CH_3)_3$
54, R = $CH_2OCH_2CH_2OCH_3$; Y = $COC(CH_3)_3$

acid gave ketone **43**, providing a confirmation of both structures. Ketal **50** gave carbomethoxy derivative **51** upon treatment with methyl chloroformate in pyridine. Selective hydrolysis of **51** with hot aqueous formic acid gave potential dienophile **45**. A parallel series of transformations was also done in the *N*-pivaloyl series, affording hydroxy ketal **52**, carbomethoxy derivative **53**, and, upon selective hydrolysis, potential dienophile **46**. Hydroxy ketal **52** was also converted into its MEM derivative **54**; however, selective acid-catalyzed hydrolysis of the ketal group without cleavage of the MEM group did not prove feasible in our hands.

This series of highly functionalized pyrimidinone dienophiles concludes with the introduction of an acetoxy function on the acetyl group of pyrimidinones **31** and **32**. This was accomplished by displacement of the bromine atom in bromo ketones **33** and **34** with potassium acetate in hot acetic acid, giving, respectively, acetoxy ketones **47** and **48**. An analogous reaction with bromo ketone **34** and sodium chloroacetate gave **49**. With an eye toward possible displacement of two α-bromine atoms, dibromo ketone **40** was sought. Thus, the intermediate bromo ketal formed by treatment of enol ether **27** with NBS in absolute ethanol was treated with toluenesulfonic acid in refluxing xylene, affording bromo enol ether **29**. Reaction of **29** with 1 equiv of NBS in aqueous acetone, however, gave a mixture of tribromide **42** and starting **29** rather than dibromides **40** or **41**. Pure **42** could be obtained by addition of second equivalent of NBS.

Many of the above functionalized pyrimidinones constitute attractive intermediates for the synthesis of novel heterocycles. In particular, several have been used to prepare a series of highly functionalized hydroquinazolines potentially useful for the synthesis of TTX and derivatives. These applications are described in the accompanying paper.

Experimental Section[20]

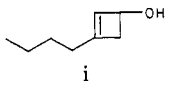
Methyl [2-Pivalamido-4(1*H*)-oxopyrimidin-6-yl]acetate (6). Amine **3**[9] (6.76 g) and 22 mL of pivalic anhydride were heated at 120 °C for 10 min and then cooled to 25 °C. The precipitate was collected, washed with cyclohexane, and then recrystallized from cyclohexane–acetone (10:1), yielding **6**: 8.17 g (93%); NMR δ 1.31 (s, 9), 3.46 (s, 2), 3.74 (s, 3), 6.10 (s, 1). Anal. Calcd for $C_{12}H_{17}N_3O_4$: C, 53.92; H, 6.41; N, 15.72. Found: C, 53.81; H, 6.35; N, 15.60.

Methyl [2-Stearamido-4(1*H*)-oxopyrimidin-6-yl]acetate (11). Amine **3**[9] (4.00 g) was suspended in pyridine/THF (1:1, 75 mL), cooled to 0 °C, and treated with stearoyl chloride (7.00 g). After 1 h at 25 °C, the solvent was removed in vacuo, and the residue was dissolved in $CHCl_3$, washed with dilute HCl, dried (Na_2SO_4), concentrated, and crystallized from EtOAc to give **11** as white plates: 8.98 g (85%); mp 128–129 °C; NMR δ 0.86 (br t, 3), 1.26 (br m, 28 H), 1.66 (br m, 2), 2.44 (br t, 2), 3.45 (s, 2), 3.73 (s, 3), 6.10 (s, 1). Anal. Calcd for $C_{25}H_{43}N_3O_4{\cdot}0.1H_2O$: C, 66.50; H, 9.64; N, 9.31. Found: C, 66.22; H, 9.24; N, 9.55.

(2-Pivalamido-4(1*H*)-oxopyrimidin-6-yl)acetic Acid (7). To ester **6** (5.00 g, 18.8 mmol) was added sodium ethanethiolate (7.90 g, 94.0 mmol) dissolved in DMF (80 mL). The resulting thick mixture was stirred for 20 h at 25 °C. The solvent was removed in vacuo, 30 mL of water was added to the residue, and then 1 M HCl was added until the mixture was slightly acidic. The precipitate was collected and washed with water followed by MeOH. The resulting crude white solid (4.26 g) was used, after being dried at 55 °C (0.005 mm) for 24 h, directly in further experiments: mp 188–192 °C; NMR (CD_3CO_2D) δ 1.38 (s, 9), 3.64 (s, 2), 6.41 (s, 1).

(*E*)-4,4-Dimethoxy-3-methyl-2-buten-1-ol (14).[11] (*E*)-4-Acetoxy-2-methyl-2-butenal[12] (18.2 g, 0.154 mol), trimethyl orthoformate (16.7 g, 0.158 mol), ammonium nitrate (0.50 g, 6.25 mmol),[21] and MeOH (9 mL) were stirred at 25 °C for 24 h. Then

(18) More complex allylic alcohols such as **14** or the diene precursor i[4] proved unsatisfactory for this reaction, however.



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(19) Windholz, T. B.; Johnson, D. B. R. *Tetrahedron Lett.* **1967**, 2557.

(20) Melting points were obtained in a Thomas-Hoover apparatus and are uncorrected. NMR spectra were recorded on a Varian XL-100 spectrometer in $CDCl_3$ unless otherwise stated. Chemical shifts are expressed in δ units with Me_4Si as an internal standard. *J* values are in hertz. Elemental analyses were determined at the University of Oregon by Dr. R. Wielesek. All reactions were run routinely under a N_2 atmosphere. Solvents were routinely distilled prior to use.

Na_2CO_3 (0.70 g) was added, and the mixture was distilled until the distillate reached 110 °C, at which time distillation was continued at reduced pressure. The main fraction was collected [bp 65–70 °C (0.015 mm)] and added to MeOH (100 mL) containing NaOMe (0.3 mol). After a 1-h stir at 25 °C most of the MeOH was removed in vacuo, and water (200 mL) was added. The mixture was extracted with ether. The usual workup gave a clear oil which was distilled [bp 68 °C (0.05 mm)], affording 16.2 g (90%) of alcohol **14**[11] of suitable quality for the next experiment: NMR δ 1.64 (s, 3), 2.00 (br s, 1), 3.30 (s, 6), 4.22 (br d, 2), 4.40 (s, 1), 5.76 (t, 1).

(*E*)-4,4-Dimethoxy-3-methyl-2-butenyl [2-Pivalamido-4-(1*H*)-oxopyrimidin-6-yl]acetate (15). Acid **7** (2.95 g, 11.7 mmol) was suspended in dry THF (50 mL) and 1,1'-carbonyldiimidazole (1.89 g, 11.7 mmol) dissolved in THF (15 mL) was added. After a 1-h stir at 25 °C (gas evolution), alcohol **14** (1.70 g, 11.7 mmol) was added. After a 20-h stir at 45 °C, the solution was concentrated, taken up in $CHCl_3$ (30 mL), washed with brine, dried (Na_2SO_4), and concentrated somewhat. Filtration of the crude product over silica gel (20 g) with $CH_3CN/CHCl_3$ (1:4) as the eluent followed by crystallization from EtOAc/hexanes gave ester **15** as powdery crystals: 4.23 g (91%); mp 103–105 °C; NMR δ 1.30 (s, 9), 1.68 (s, 3), 3.31 (s, 6), 3.45 (s, 2), 4.53 (s, 1), 4.73 (d, J = 7, 2), 5.75 (t, J = 7, 1), 6.10 (s, 1). Anal. Calcd for $C_{18}H_{27}N_3O_6$: C, 59.68; H, 7.14; N, 11.02. Found: C, 56.50; H, 7.19; N, 10.94.

(*E*)-4,4-Dimethoxy-3-methyl-2-butenyl [2-Stearamido-4-(1*H*)-oxopyrimidin-6-yl]acetate (20). The procedures for obtaining **15** from **6** were applied to ester **11**, affording ester **20**: 90% yield; mp 93–96 °C; NMR δ 0.88 (br t, 3), 1.27 (br m, 28), 1.67 (s, 3), 1.66 (br m, 2), 2.52 (t, 2), 3.30 (s, 6), 3.47 (s, 2), 4.52 (s, 1), 4.70 (d, 2), 5.74 (t, 1), 6.11 (s, 1). Anal. Calcd for $C_{31}H_{53}N_3O_6$: C, 66.05; H, 9.47; N, 7.45. Found: C, 65.92; H, 9.81; N, 7.22.

(*E*)-4,4-Dimethoxy-3-methyl-2-butenyl [2-Pivalamido-4-(1*H*)-oxopyrimidin-6-yl]chloroacetate (16). Pyrimidinone **15** (500 mg, 1.21 mmol) and NCS (209 mg, 1.57 mmol) were stirred in boiling CCl_4 (15 mL) for 10 min. The mixture was filtered and the filtrate was concentrated and purified by preparative TLC (elution with ether) to give 179 mg (33%) of **16**. Recrystallization from ether/hexanes gave the analytical specimen: mp 86–91 °C; NMR δ 1.67 (s, 3), 3.30 (s, 6), 4.52 (s, 1), 4.75 (d, 2), 5.16 (s, 1), 5.74 (t, 1), 6.40 (s, 1); MS, m/e 384.131 (calcd for $C_{18}H_{26}N_3O_6Cl$ – CH_3O, 384.132).

(*E*)-4,4-Dimethoxy-3-methyl-2-butenyl [5-Bromo-2-pivalamido-4(1*H*)-oxopyrimidin-6-yl]bromoacetate (17) and (*E*)-4,4-Dimethoxy-3-methyl-2-butenyl [5-Bromo-2-pivalamido-4(1*H*)-oxopyrimidin-6-yl]acetate (18). Pyrimidinone **15** (200 mg, 0.52 mmol) and NBS (176 mg, 0.55 mmol) were refluxed in $CHCl_3$ (10 mL) for 3 h. Preparative TLC (silica gel, EtOAc/hexanes, 2:3) gave, after crystallization from the same solvent, dibromide **17**: 115 mg (41%); mp 135.5–141 °C; NMR δ 1.27 (s, 9), 1.52 (s, 3), 3.26 (s, 6), 4.50 (s, 1), 4.76 (d, 2), 5.70 (t, 1), 5.79 (s, 1); MS, m/e 506.986 (calcd for $C_{18}H_{25}N_3O_6Br_2$–CH_3OH, 506.983). Also recovered from the TLC was crude monobromide **18** as an oil: 40 mg (17%); NMR δ 1.29 (s, 9), 1.66 (s, 3), 3.29 (s, 6), 3.77 (s, 2), 4.52 (s, 1), 4.75 (d, 2), 5.75 (t, 1).

Methyl [2-Pivalamido-4(1*H*)-oxopyrimidin-6-yl]bromoacetate (9) and Methyl [2-Pivalamido-4(1*H*)-oxopyrimidin-6-yl]dibromoacetate (10). Pyrimidinone **6** (1.00 g, 3.75 mmol), $CUBr_2$ (1.67 g, 7.50 mmol), and BaO (4.02 g, 26.2 mmol) were refluxed in $CHCl_3$ (20 mL) for 1.5 h. After filtration, the filtrate was treated with silica gel (3 g) and concentrated to dryness. The silica gel was deposited over a 6 × 10 cm column of silica gel and eluted with EtOAc–hexanes (1:1). Recrystallization of the desired fractions from EtOAc/cyclohexane gave **9**: 298 mg (23%); mp 129–138 °C dec; NMR δ 1.29 (s, 9), 3.82 (s, 3), 5.08 (s, 1), 6.38 (s, 1); MS, m/e 345.034 (calcd for $C_{12}H_{16}N_3O_4Br$, 345.032). Also isolated as an oil was **10**: 16 mg (1%); NMR δ 1.32 (s, 9), 3.90 (s, 3), 6.8m (s, 1); MS, m/e 424.940 (calcd for $C_{12}H_{15}N_3O_4Br_2$, 424.941).

Methyl [2-Pivalamido-4(1*H*)-oxopyrimidin-6-yl]glyoxylate (8). The procedure of Keana and Eckler[1] was followed exactly. From 4.16 g of ester **6** there was obtained **8** as tan needles after recrystallization from CH_3CN: 660 mg (15%); mp 209–210 °C; NMR δ 1.16 (s, 9), 3.84 (s, 3), 6.84 (s, 1). Anal. Calcd for $C_{12}H_{15}N_3O_5$: C, 51.24; H, 5.38; N, 14.94. Found: C, 51.26; H, 5.21; N, 15.25.

Methyl [2-Stearamido-4(1*H*)-oxopyrimidin-6-yl]glyoxylate (12). Ester **11** (10.0 g, 22.3 mmol), H_2SeO_3 (2.87 g, 22.3 mmol), HOAc (35 mL), and Ac_2O (5 mL) were combined and heated at 90 °C for 5 h. The mixture was filtered through Celite and concentrated, and the resulting oil was dissolved in $CHCl_3$ and chromatographed over silica gel. Elution with $CHCl_3$ followed by $CHCl_3$/MeOH (98:2) gave 5.0 g of a white solid which was recrystallized from EtOAc, affording ester **12**: 3.5 g (35%); mp 150–151 °C; NMR δ 0.86 (br t, 3), 1.26 (br m, 28), 1.66 (br m, 2), 2.44 (br t, 2), 3.95 (s, 3), 6.88 (s, 1). Anal. Calcd for $C_{25}H_{41}N_3O_5$: C, 64.77; H, 8.91; N, 9.06. Found: C, 64.62; H, 8.75; N, 8.90.

2-Acetamido-6-acetyl-4(1*H*)-pyrimidinone (31). A mixture of 5.70 g (37.3 mmol) of amine **30**[15,22] and 20 mL of Ac_2O was heated at 120 °C for 15 min. A yellow-brown solid which separated upon cooling was collected, rinsed with EtOAc, and dried, yielding **31** as a light tan solid: 5.41 g (75%); mp 204–207 °C. Two recrystallizations from CH_3CN gave the analytical specimen as colorless needles: mp 205.5–207 °C; NMR (Me_2SO-d_6) δ 2.20 (s, 3), 2.50 (s, 3), 3.3 (br, 1), 6.50 (s, 1); UV max (EtOH) 211 nm (ε 11 800), 223 (sh, 9650), 330 (4640). Anal. Calcd for $C_8H_9N_3O_3$: C, 49.22; H, 4.64. Found: C, 49.55; H, 4.59.

2-Acetamido-5-bromo-6-acetyl-4(1*H*)-pyrimidinone (35). A mixture of 214 mg of pyrimidinone **31**, 213 mg of NBS, and 2 mL of DMF was stirred at 25 °C for 1 h (became homogeneous) and then at 60 °C for 3.5 h. The mixture was concentrated, and the succinimide was removed by sublimation [100 °C (0.1 mm)]. The NMR spectrum of the residue showed no ring vinyl proton. The solid was recrystallized from EtOH, affording the analytical sample: mp 227–230 °C dec; NMR ($CDCl_3$ + MeSO-d_6) δ 2.52 (s, 3), 2.25 (s, 3). Anal. Calcd for $C_8H_8N_3O_3Br$: C, 35.06; H, 2.94; N, 15.33. Found: C, 34.65; H, 2.78; N, 15.24.

2-Amino-6-(1,1-diethoxyethyl)-4(1*H*)-pyrimidinone (23) and Tautomer 26. The procedure of Ross et al.[15] was modified to allow for isolation of **23**. Thus, 101.4 g (0.437 mol) of ethyl 3-oxo-4,4-diethoxypentanoate, 95.1 g (0.528 mol) of guanidine carbonate, and 1.2 L of absolute EtOH were combined and stirred under reflux for 17 h. After filtration, the fitrate was concentrated to dryness, affording a yellow foam, to which was added 600 mL of water. The mixture was adjusted to pH 8 by the addition of ~360 mL of 1 M HCl. The resulting yellow precipitate was collected, washed with water and dried. The solid was slurried with 500 mL of EtOAc/EtOH (1:1), heated to boiling, and filtered while hot, using three 50-mL rinses of hot solvent. The insoluble solid was dried [60 °C (20 mm)] to yield 32.45 g (33%) of **26** as a white powder, mp 204–207 °C dec. A sample of **26** from another run showed the following: mp 215 °C dec; IR (Nujol) 3.01, 3.29 (sh), 6.03, 6.7 (br), 7.84, 8.07, 8.44, 8.93, 9.20, 9.4 (br), 10.39, 11.53 μm. The NMR spectrum of **26** in D_2O/Na_2CO_3 was identical with that of **23** in this solvent. Anal. Calcd for $C_{10}H_{17}N_3O_3$: C, 52.85; H, 7.54; N, 18.49. Found: C, 52.65; H, 7.68; N, 18.35.

The hot filtrate from **26** was concentrated and allowed to crystallize slowly at 4 °C, affording **23**: 41.47 g (42%); mp 203–203.5 dec. A sample of **23** from another run showed the following: mp 215 °C dec; IR (Nujol) 2.84, 2.97, 3.16, 5.99, 6.12 (st), 6.78, 7.29, 8.08, 8.56, 8.86, 9.42, 9.49, 10.13, 10.42, 11.61, 12.04 μm; NMR ($CDCl_3$) 1.19 (t, 6), 1.53 (s, 3), 3.50 (ABX_3, 4), 6.10 (s, 1), 7.1 (br s, 2). Anal. Calcd for $C_{10}H_{17}N_3O_3$: C, 52.85; H, 7.54; N, 18.49. Found: C, 52.83; H, 7.65; N, 18.29. Attempts to induce **23** to crystallize as the tautomer **26** through the use of seed crystals etc. failed.

2-Acetamido-6-(1,1-diethoxyethyl)-4(1*H*)-pyrimidinone (24). A slurry of 1.70 g of **23** in 10 mL of Ac_2O was stirred at 100 °C for 10 min. The solution was concentrated to dryness and the residue was recrystallized from cyclohexane, affording **24**: 1.44 g (67%); mp 147–151 °C. Recrystallization afforded the analytical specimen: mp 155.5–156.5 °C; NMR δ 1.23 (t, 6), 1.57 (s, 3), 2.40 (s, 3), 3.49 (ABX_3, 4), 6.45 (s, 1); UV max (EtOH) 233 nm (ε 6830), 443 (sh). Anal. Calcd for $C_{12}H_{19}N_3O_4$: C, 53.52; H, 7.11; N, 15.60. Found: C, 53.44; H, 7.18; N, 15.81.

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2-Acetamido-6-(1-ethoxyvinyl)-4(1*H*)-pyrimidinone (27). Xylenes (20 mL) containing 14 mg of toluenesulfonic acid and 982 mg of **24** was heated at reflux with slow distillation for 15 min. The cooled reaction mixture afforded 773 mg (95%) of **27** as a tan solid which was recrystallized from EtOH, giving the analytical sample as cream-colored plates: mp 212–216 °C dec; NMR ($CDCl_3$ + 1 drop of Me_2SO-d_6) δ 1.38 (t, 3), 2.24 (s, 3), 3.89 (q, 2), 4.42 (d, 1), 5.32 (d, 1), 6.50 (s, 1). Anal. Calcd for $C_{10}H_{13}N_3O_3$: C, 53.81; H, 5.87; N, 18.82. Found: C, 53.50; H, 6.10; N, 18.67.

2-Acetamido-6-(bromoacetyl)-4(1*H*)-pyrimidinone (33). The crude tan solid **27** (5.54 g, 24.8 mmol) was slurried in 100 mL of H_2O/acetone (1:9), and 4.42 g (24.8 mmol) of NBS was added. The resulting clear yellow warm solution was cooled to 0 °C, affording 4.88 g of **33**. The analytical specimen was obtained by recrystallization from CH_3CN: mp 197–198 °C dec; NMR ($CDCl_3$ + Me_2SO-d_6) δ 2.28 (s, 3), 4.57 (s, 2), 6.72 (s, 1), 11.50 (br s, 1), 12.25 (br s, 1). Anal. Calcd for $C_8H_8N_3O_3Br$: C, 35.06; H, 2.94; N, 15.33. Found: C, 35.16; H, 2.85; N, 15.46.

2-Pivalamido-6-(1,1-diethoxyethyl)-4(1*H*)-pyrimidinone (25). A crude mixture of tautomers **23** and **26** (3.02 g) and pivalic anhydride (7.17 g) was heated at 100 °C for 30 min, and then the solvent was removed in vacuo. The residue was crystallized from cyclohexane, affording 2.87 g (70%) of **25**. Recrystallization from cyclohexane afforded the analytical specimen, mp 169–170 °C. Anal. Calcd for $C_{15}H_{25}N_3O_4$: C, 57.86; H, 8.09; N, 13.49. Found: C, 57.88; H, 7.95; N, 13.24.

2-Pivalamido-6-(1-ethoxyvinyl)-4(1*H*)-pyrimidinone (28). The procedure was the same as that for **27**. From 2.82 g of **25** there was obtained 2.05 g (87%) of **28**. Recrystallization from xylenes afforded the analytical specimen, mp 213–214 °C. Anal. Calcd for $C_{13}H_{19}N_3O_3$: C, 58.85; H, 7.22; N, 15.84. Found: C, 58.82; H, 7.19; N, 15.84.

2-Pivalamido-6-(bromoacetyl)-4(1*H*)-pyrimidinone (34). Ether **28** (10.0 g, 37.7 mmol) and NBS (6.72 g, 37.7 mmol) were refluxed in water/acetone (1:9, 200 mL) until all the solids dissolved. Cooling the solution afforded crystals which were recrystallized from acetone, affording **34**: 10.7 g (90%) mp 182–184 °C. Anal. Calcd for $C_{11}H_{14}N_3O_3Br$: C, 41.79; H, 4.46; N, 13.29. Found: C, 41.70; H, 4.08; N, 13.35.

2-Acetamido-6-[(phenylthio)acetyl]-4(1*H*)-pyrimidinone (36). The salt prepared by mixing 405 mg (3.67 mmol) of thiophenol and 95 mg (3.96 mmol) of NaH in 10 mL of dry THF was treated with a solution of 1.00 g (3.65 mmol) of **33** dissolved in 30 mL of THF. After 20 min at 25 °C, the mixture was centrifuged, the supernatent was evaporated, and the residue was dissolved in EtOAc and passed over 1 g of silica gel. Crude sulfide **36** (996 mg, 90%) was obtained as a yellow foam which was used in subsequent experiments without further purification: NMR δ 2.24 (s, 3), 5.02 (s, 2), 6.21 (s, 1), 7.2 (m, 5).

2-Acetamido-6-[acetoxy(phenylthio)acetyl]-4(1*H*)-pyrimidinone (37). Crude **36** was oxidized to the corresponding sulfoxide by addition of 1 equiv of MCPBA to a CH_2Cl_2 solution of **36** at −78 °C followed by a warming period to 25 °C. The product was chromatographed over silica gel and eluted with $CHCl_3$/MeOH (95:5) to give the crude sulfoxide (100%) as a yellow foam: NMR δ 2.26 (s, 3), 4.52 (d of d, 2), 6.61 (s, 1), 7.5 (m, 5). The semipurified sulfoxide (2.719 g) was dissolved in 35 mL of Ac_2O and heated at 110 °C for 4 h, during which period a tan solid crystallized from the hot solution. The mixture was cooled to 0 °C overnight. The solid was collected, washed with cold CH_3CN, and dried to yield 1.643 g (53%) of **37**. Recrystallization from CH_3CN afforded the analytical specimen as creamy plates: mp 206–207 °C; NMR δ 2.21 (s, 3), 2.28 (s, 3), 6.69 (s, 1), 7.22 (s, 1), 7.4 (m, 5). Anal. Calcd for $C_{16}H_{15}N_3O_5S$: C, 53.18; H, 4..18; N, 11.63. Found: C, 53.33; H, 4.16; N, 11.24.

2-Acetamido-6-(acetoxymethoxyacetyl)-4(1*H*)-pyrimidinone (38). To a stirred refluxing solution of 1.50 g (4.15 mmol) of acetoxy sulfide **37** in 430 mL of dry MeOH was added 830 mg (4.15 mmol) of $Cu(OAc)_2 \cdot H_2O$ dissolved in 120 mL of hot MeOH. The solution immediately became green, and a solid precipitated out. After a 1-h reflux period, the mixture was cooled and filtered, and the filtrate was concentrated to dryness. The residue was dissolved in $CHCl_3$ and chromatographed over silica gel. Elution with $CHCl_3$/MeOH (95:5) brought down a bluish fraction which was evaporated, redissolved in EtOAc, and treated with 3 drops of thiophenol. The flocculent precipitate was removed by centrifugation, and the solution was concentrated and diluted with hexane until cloudy. The mixture was cooled at 0 °C for 2 days, affording **38** as white rosettes: 602 mg (51%); mp 172.5–173 °C; NMR δ 2.23 (s, 3), 2.28 (s, 3), 3.78 (s, 3), 5.78 (s, 1), 6.37 (s, 1); UV max (EtOH) 280 nm (ε 8310) 223 (13 100). Anal. Calcd for $C_{11}H_{13}N_3O_6$: C, 46.65; H, 4.63; N, 14.84. Found: C, 46.74; H, 4.73; N, 14.99.

2-Acetamido-6-[acetoxy(allyloxy)acetyl]-4(1*H*)-pyrimidinone (39). Thioether **37** (23 mg, 0.060 mmol) was suspended in allyl alcohol (4.5 mL) at 70 °C and treated with $Cu(OAc)_2 \cdot H_2O$ (12 mg, 0.060 mmol). After 1 h, the mixture was cooled and treated with several drops of ethanethiol. The mixture was filtered, and the filtrate was concentrated to dryness. Preparative TLC over silica gel ($CHCl_3$/MeOH, 10:1) gave 11 mg (56%) of crude **39** which was crystallized from EtOAc/hexanes to give the analytical specimen: mp 157.5–159 °C; MS, *m/e* 309.094 (calcd for $C_{13}H_{15}N_3O_6$, 309.096).

2-Acetamido-6-(hydroxyacetyl)-4(1*H*)-pyrimidinone (43). To a stirred suspension of 10.42 g of **27** in 410 mL of THF at 45 °C was added 28.84 g of peracetic acid solution (2.5 equiv of oxidant) in 22 mL of water. The suspension dissolved immediately, and after 5 min the product began to crystallize. After 4.5 h at 45 °C, the mixture was cooled and filtered, affording 7.942 g (78%) of **43**. Recrystallization from DMF afforded the analytical specimen: mp 245 °C (phb) dec; NMR (Me_2SO-d_6) δ 2.15 (s, 3), 4.70 (s, 2), 6.54 (s, 1). Anal. Calcd for $C_8H_9N_3O_4$: C, 45.50; H, 4.30; N, 19.90. Found: C, 45.54; H, 4.14; N, 20.03.

2-Acetamido-6-[[[(β,β,β-trichloroethoxy)carbonyl]oxy]acetyl]-4(1*H*)-pyrimidinone (44). A stirred suspension of 100 mg of alcohol **43** in 2.6 mL of dry pyridine was heated at 55 °C for 5 min and then treated with dropwise addition of 135 mg (1.35 equiv) of 2,2,2-trichloroethyl chloroformate. After 5 min the deep red solution was concentrated to dryness in vacuo, and the residue was triturated with THF. The soluble portion was passed over 1.5 g of silica gel and eluted with EtOAc, affording 173 mg (95%) of **44** as an orange solid. The analytical specimen was obtained by recrystallization from EtOAc, mp 218–220 °C dec. Anal. Calcd for $C_{11}H_{10}N_3O_6Cl_3 \cdot {}^1/_3EtOAc$: C, 34.63; H, 2.74; N, 10.65. Found: C, 34.86; H, 2.69; N, 10.62.

2-Acetamido-6-(1,1-diethoxy-2-hydroxyethyl)-4(1*H*)-pyrimidinone (50). To a solution of 200 mg of **27** in 14 mL of dry EtOH was added 237 mg (1.3 equiv) of MCPBA and 2 mg of the radical inhibitor BHT. After a 2-h reflux period, the solvent was removed in vacuo, and the residue was chromatographed over silica gel by using a reflux–recycle column. Elution with $CHCl_3$ for 1 h removed impurities. A switch to $CHCl_3$/MeOH (98.5:1:5) gave 220 mg (86%) of **50** as a pure white foam. Crystallization from toluene gave the analytical specimen: mp 161–162 °C; NMR δ 1.21 (t, 6), 2.28 (s, 3), 3.52 (ABX_3, 4), 3.66 (s, 2), 6.38 (s, 1). Anal. Calcd for $C_{12}H_{19}N_3O_5 \cdot {}^1/_3H_2O$: C, 49.48; H, 6.80; N, 14.42. Found: C, 49.69; H, 6.84; N, 14.12.

2-Acetamido-6-[1,1-diethoxy-2-[(methoxycarbonyl)oxy]ethyl]-4(1*H*)-pyrimidinone (51). To a stirred solution of 950 mg of **50** in 8.5 mL of pyridine at 0 °C was added 0.52 mL of methyl chloroformate. After 1.5 h at 0 °C, the usual workup gave 1.04 g (91%) of essentially pure **51** as a yellow foam. Crystallization from EtOAc/hexanes gave 901 mg of white needles: mp 148–149 °C; NMR δ 1.10 (t, 6), 2.36 (s, 3), 3.5 (ABX_3, 4), 3.70 (s, 3), 4.39 (s, 2), 6.50 (s, 1). Anal. Calcd for $C_{14}H_{21}N_3O_7 \cdot {}^1/_3H_2O$: C, 48.14; H, 6.21; N, 12.03. Found: C, 48.38; H, 6.10; N, 11.86.

2-Acetamido-6-[[(methoxycarbonyl)oxy]acetyl]-4(1*H*)-pyrimidinone (45). Ketal **51** (394 mg) was dissolved in 10 mL of 88% formic acid and heated at 100 °C for 30 min. After removal of the solvent in vacuo, the residue was dissolved in 4 mL of Ac_2O (to replace the *N*-acetyls) and heated at 100 °C for 5 min. The usual workup followed by chromatography over silica gel and elution with EtOAc gave 284 mg (92%) of **45** as a pure white solid. Crystallization from EtOAc afforded the analytical specimen as white needls: mp 180–181 °C dec; NMR (acetone-d_6) δ 2.33 (s, 3), 4.60 (s, 3), 5.32 (s, 2), 6.53 (s, 1). Anal. Calcd for $C_{10}H_{11}N_3O_6$: C, 44.61; H, 4.12. Found: C, 44.34; H, 3.92.

2-Pivalamido-6-(1,1-diethoxy-2-hydroxyethyl)-4(1*H*)-pyrimidinone (52). Ketal **52** was prepared in 81% yield from ether **28** by following the procedure for **50**. Ketal **52**: mp 187–188 °C (toluene/hexane). Anal. Calcd for $C_{15}H_{25}N_3O_5$: C, 55.04; H, 7.64;

N, 12.84. Found: 55.45; H, 7.52; N, 12.50.

2-Pivalamido-6-[1,1-diethoxy-2-[(methoxycarbonyl)oxy]-ethyl]-4(1*H*)-pyrimidinone (53). Ester **53** was prepared in 89% yield from alcohol **52** by following the procedure for **51**. Ester **53**: white needles; mp 179.5–180.5 °C (EtOAc/hexane). Anal. Calcd for $C_{17}H_{25}N_3O_7$: C, 52.98; H, 7.06; N, 10.90. Found: C, 52.75; H, 6.82; N, 10.84.

2-Pivalamido-6-[[(methoxycarbonyl)oxy]acetyl]-4(1*H*)-pyrimidinone (46). Ketal **53** (2.43 g) was heated at 100 °C in 10 mL of 88% formic acid for 30 min. The usual workup followed by crystallization from THF gave **46**: 1.55 g (80%); white flakes; mp 207–209 °C. Anal. Calcd for $C_{13}H_{17}N_3O_6$: C, 50.16; H, 5.50; N, 13.50. Found: C, 49.95; H, 5.20; N, 13.22.

2-Pivalamido-6-[1,1-diethoxy-2-[(methoxyethoxy)methoxy]ethyl]-4(1*H*)-pyrimidinone (54). To a solution of 97 mg of **52** in dry CH_2Cl_2 (3 mL) was added diisopropylethylamine (58 mg) followed by (methoxyethoxy)methyl chloride (56 mg). After a 24-h stir at 25 °C, the usual workup afforded 70 mg (56%) of essentially pure **54** as an oil. Crystallization from EtOAc/hexanes afforded the analytical specimen, mp 105–107 °C. Anal. Calcd for $C_{19}H_{33}N_3O_7$: C, 54.99; H, 8.01; N, 10.11. Found: C, 54.74; H, 8.22; N, 10.47.

2-Acetamido-6-(acetoxyacetyl)-4(1*H*)-pyrimidinone (47). A slurry of 1.23 g of **33** and 8.99 g of a 12% (w/w) KOAc/HOAc solution was stirred at 100 °C for 20 min. During this period, the suspension dissolved, the solution turned red, and KBr precipitated. The cooled mixture was filtered, and the filtrate was treated with 7 mL of acetone/toluene (3:4), affording after concentration a pink solid (2.3 g). This was suspended in 20 mL of EtOAc and treated with 0.7 mL of 0.8 N HCl, 0.4 mL of brine, and 0.4 mL of water. After these were mixed, the organic phase was concentrated to dryness, and the process was repeated. Eventually, addition of acetone and toluene to the EtOAc solution gave 1.06 g (93%) of **47** as a light yellow solid. Two recrystallizations from EtOAc gave the analytical specimen as small white needles, mp 187–188 °C. Anal. Calcd for $C_{10}H_{11}N_3O_5$: C, 47.43; H, 4.38; N, 16.59. Found: C, 47.25; H, 4.22; N, 16.56.

2-Pivalamido-6-(acetoxyacetyl)-4(1*H*)-pyrimidinone (48). Ester **48** [mp 170–172 °C (EtOAc/cyclohexane)] was prepared from **34** in 52% yield by using the method for **33** → **47** described above. Anal. Calcd for $C_{13}H_{17}N_3O_5$: C, 52.87; H, 5.80; N, 14.23. Found: C, 52.88; H, 5.73; N, 14.48.

2-Pivalamido-6-[(chloroacetoxy)acetyl]-4(1*H*)-pyrimidinone (49). NaH (285 mg, 5.94 mmol) was suspended in DMF (3.4 mL) at 0 °C and treated with chloroacetic acid (2.70 g, 28.1 mmol). Then at 25 °C bromide **34** (1.70 g, 5.40 mmol) dissolved in DMF (4 mL) was added. The mixture was heated at 100 °C for 2 h, and then the solvent was removed in vacuo. $CHCl_3$ (50 mL) was added, and the solution was extracted with aqueous $NaHCO_3$ and dried (Na_2SO_4). Evaporation and crystallization of the residue from EtOAc/hexanes gave **49**: 516 mg (29%); mp 128–129 °C; NMR δ 1.36 (s, 9), 4.22 (s, 2), 5.40 (s, 2), 6.75 (s, 1). Anal. Calcd for $C_{13}H_{16}N_3O_5Cl \cdot {}^1/_3H_2O$: C, 46.49; H, 4.97; N, 12.52. Found: C, 46.18; H, 4.45; N, 12.57.

2-Acetoxy-6-(1-ethoxy-2-bromoethenyl)-4(1*H*)-pyrimidinone (29). A solution of enol ether **27** (239 mg) and NBS (99 mg) in dry EtOH (5 mL) was heated at 35 °C until a clear colorless solution resulted. The solvent was evaporated, and the residue was suspended in xylene (20 mL) containing toluenesulfonic acid (8.5 mg) and heated such that slow distillation of the xylene took place. The mixture was concentrated to dryness, and the residue was leached with MeOH. Evaporation of the MeOH gave 286 mg of crude **29**. Two recrystallizations from CH_3CN afforded **29** as fine white platelets: 100 mg (48%); mp 224–225 °C; NMR δ 1.40 (t, 3), 2.29 (s, 3), 4.02 (q, 2), 6.40 (s, 1), 6.95 (s, 1). Anal. Calcd for $C_{10}H_{12}N_3O_3Br$: C, 39.75; H, 4.00; H, 13.91. Found: C, 39.90; H, 3.95; N, 13.94.

2-Acetamido-5-bromo-6-(dibromoacetyl)-4(1*H*)-pyrimidinone (42). To a solution of **29** (50 mg, 0.17 mmol) in acetone/water (85:15, 3 mL) was added NBS (58 mg, 0.33 mmol). After a brief warming period, the solvent was evaporated, and the residue was dissolved in CH_3CN. When the mixture cooled, **42** crystallized out as white stars: 42 mg (59%); mp 249–250 °C; NMR (Me_2SO-d_6) δ 2.18 (s, 3), 7.23 (s, 1). Anal. Calcd for $C_8H_6H_3O_3Br_3$: C, 22.25; H, 1.40; N, 9.73. Found: C, 22.07; H, 1.22; N, 9.97.

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