A New Furan and Dihydro-4-pyrone Synthesis via Diels–Alder Reactions between Methyl 2-[2′-Acetamido-4′(1′*H*)-pyrimidon-6′-yl]glyoxylate and Diethyl Oxomalonate and Oxygenated 1,3-Dienes

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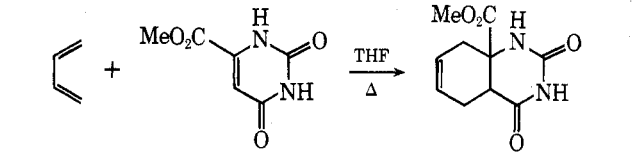
Pyrimidone **3**, required as a potential dienophile for a synthesis of tetrodotoxin, has been prepared by oxidation of **4** with H_2SeO_3. While the desired hydroquinazolines were not produced from the reaction of **3** with dienes **17** and **21**, a new route to substituted furans and dihydro-4-pyrones resulted. Thus, a Diels–Alder reaction between **3** and diene **17** afforded furan **19**. With THF as solvent dihydropyran **20** was formed. Reaction of **3** with diene **21** led to either hydropyrans **22, 23, 24,** or **25,** depending on the nature of the hydrolysis or purification step. The generality of these furan and hydropyran producing reactions was shown by employing diethyl oxomalonate (**26**) as the dienophile instead of pyrimidone **3**. Reaction of **26** with diene **17** led to either dihydropyrans **27, 29** or furan **28,** depending on workup conditions. Furan **28** was independently prepared from furan **30**. Reaction of **26** with diene **21** afforded either hydropyrans **37, 38,** or **39,** depending on the workup. A mechanistic rationalization is offered for the formation of furan **28** from adduct **27**.

Recently,[2] we described a new route to hydroquinazolines involving the Diels–Alder reaction between pyrimidones **1** and **2** and several 1,3-dienes. The hydroquinazoline ring system is present in tetrodotoxin (**6**),[3] the potent neuropoison of a variety of amphibian and marine animals.[4] Pyrimidone **3** is an attractive dienophile for synthetic studies in this series owing to the presence of the oxygenated two-carbon side chain analogous to that present in tetrodotoxin. In this present paper we describe a convenient synthesis of **3** together with some Diels–Alder reactions of **3** and diethyl oxomalonate with two oxygenated 1,3-dienes. While no hydroquinazolines were produced with **3**, a new route to substituted furans and dihydro-4-pyrones resulted and constitutes the subject of this paper.



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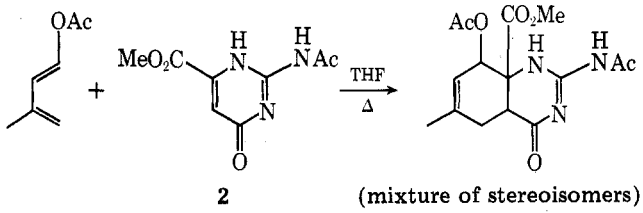
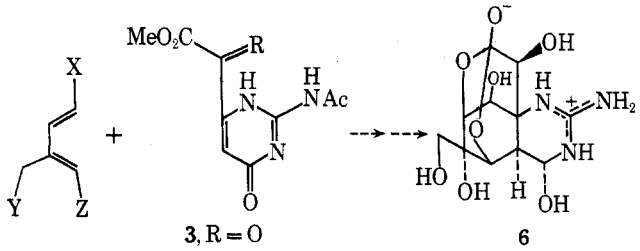
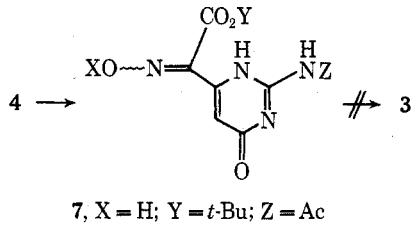


2 (mixture of stereoisomers)



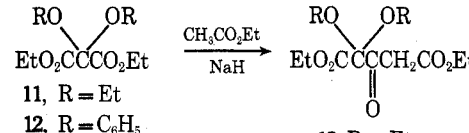
3, R = O
4, R = H, H
5, R = OH, OEt
6



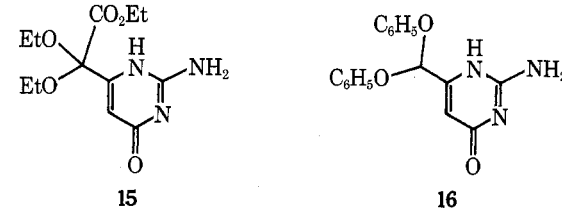
7, X = H; Y = *t*-Bu; Z = Ac
8, X = H; Y = Me; Z = Ac
9, X = Z = H; Y = Me
10, X = Z = Ac; Y = Me

Our first attempt to prepare pyrimidone **3** involved oximination of the readily available pyrimidone **4**[5] using *t*-BuOK and isoamyl nitrite in *t*-BuOH. *tert*-Butyl ester oxime **7** was obtained in 49% yield as a mixture of syn–anti isomers. The methyl ester oxime **8** was obtained in 56% yield from **4** in DMF solvent using NaH and isoamyl nitrite. Unfortunately, every attempt to convert the oxime moiety into a carbonyl group failed. Whereas hydrolysis with 1 N HCl in MeOH led to amine **9** in 84% yield; more vigorous conditions appeared to lead to decarboxylation.[6] Reacetylation of amine **9** led in 84% yield to *O,N*-diacetate **10**, identical with that made in 83% yield by acetylation of oxime **8**, confirming that oxime hydrolysis had not been achieved. Several newer methods[7] of converting oximes to ketones were also not successful with **8** or **10** in our hands.

We then turned to a synthesis of ketal **15** by a method paralleling that of Ross et al.[8] Thus, diethyl diethoxymalonate[9] (**11**) was condensed with ethyl acetate, affording ketoketal **13**. Ester **15** could be obtained directly from the condensation of **13** with guanidine carbonate. Like oxime **8**, ester **15** also proved resistant to acidic hydrolysis and afforded no pyrimidone **3** under a variety of conditions. When the same series of reactions was conducted starting with diethyl di-



11, R = Et
12, R = C_6H_5
13, R = Et
14, R = C_6H_5

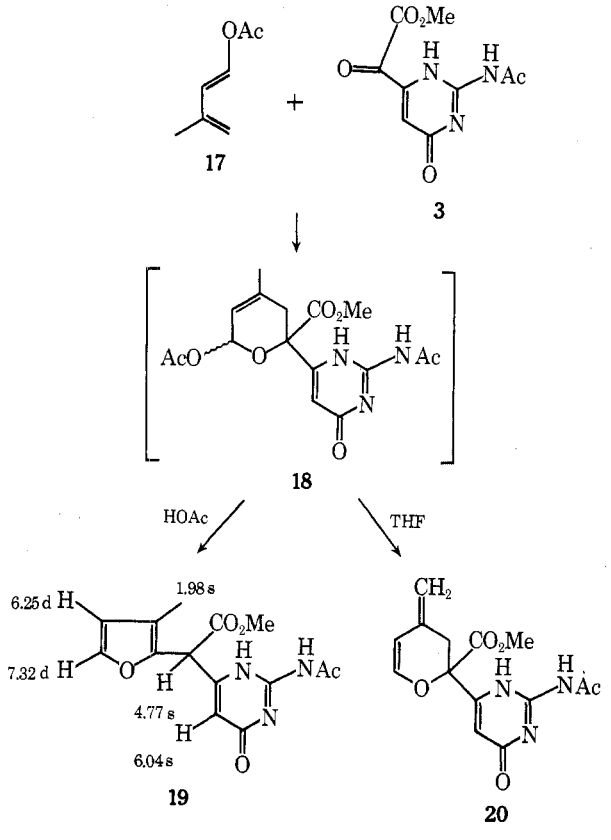


15 **16**

phenoxymalonate (12),[10] decarboxylated ketal **16** was formed.

Success was achieved through oxidation of pyrimidone **4** with H_2SeO_3 in HOAc, producing crystalline **3** in 27% yield after chromatography. In the uv spectrum of **3** in dry THF a maximum was observed at 335 nm whereas in EtOH the maximum appeared at 287 nm. This latter absorption corresponds to that of a nonconjugated 6-substituted 2-acetamido-4-pyrimidone[5,11,12] and is attributed to formation of hemiketal **5** in EtOH solution. The NMR spectrum of **3** in anhydrous deuterioacetic acid produced a methyl ester absorption at 3.98 ppm and a vinyl proton at 7.08 ppm. Interestingly, upon addition of D_2O to the sample, the methyl ester absorption shifted to 3.80 ppm and the vinyl proton appeared at 6.66 ppm. The observed change is consistent with a rapid hydration of the α-carbonyl group.[13]

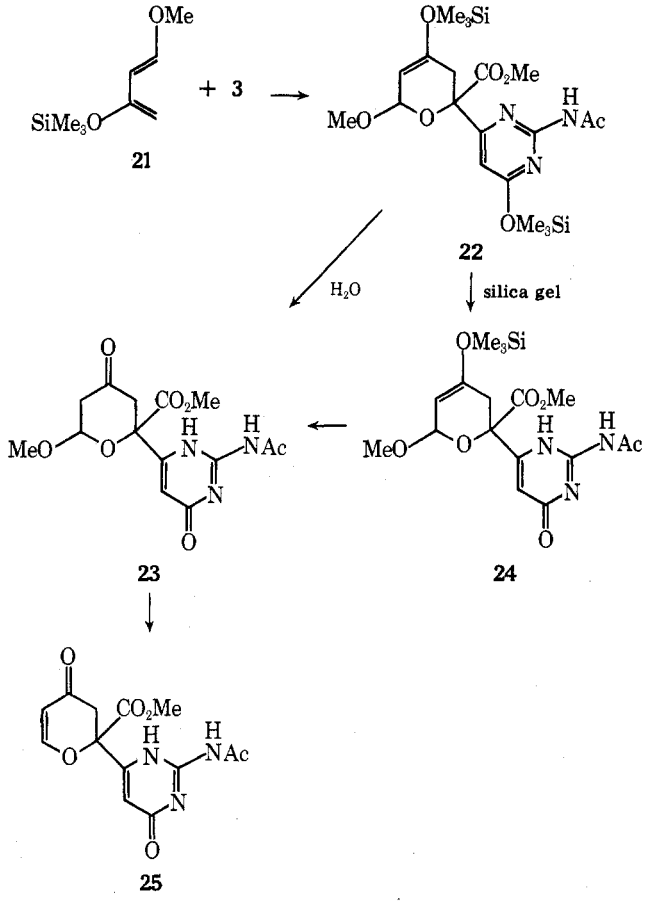
Pyrimidone **3** indeed proved to be a reactive dienophile. However, it was clear from the NMR and uv spectra of the 1:1 dienophile–diene adducts that cycloaddition occurred across the α-carbonyl group of **3** rather than at the double bond.[14] Reaction with 1-acetoxy-3-methyl-1,3-butadiene (**17**) in HOAc at 100 °C afforded crystalline furan **19** in 20% yield.



Consistent with this structure, the NMR spectrum showed a singlet at 6.04 ppm for the vinyl proton of the pyrimidone ring and a singlet at 4.77 ppm for the side chain methine proton. This proton underwent ready exchange with deuterium in either deuterioacetic acid or MeOH-d_4. The 214-nm maximum observed in the uv spectrum (EtOH) is typical of the furan ring[15] while the maxima at 236 and 285 nm are due to the pyrimidone ring. Absorption at 335 nm is likely due to a small amount of enol or enolate present since addition of a drop of NaOH to the solution gave rise to intense absorption at 335 nm.

The Diels–Alder reaction between **17** and **3** in THF at 120 °C was also accompanied by the elimination of a molecule of HOAc, leading to dihydropyran **20.** Together with the usual analytical data, the structure of **20** followed from a comparison of the uv and NMR spectral data (see Experimental Section) with those obtained from the corresponding series of adducts derived from diethyl oxomalonate (see below).

The interesting highly reactive dioxygenated diene **21** recently reported by Danishefsky[16] was also allowed to react

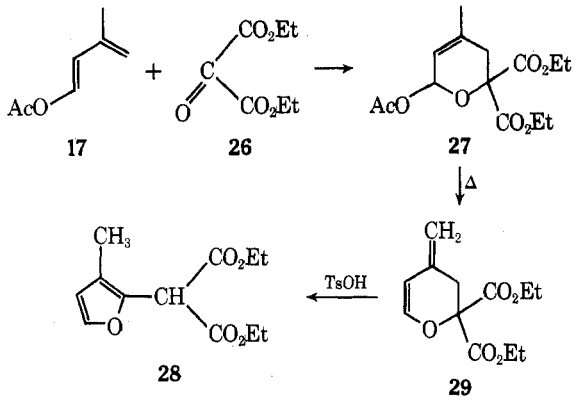


with pyrimidone **3** in THF. Evaporation of the solvent after reaction afforded adduct **22.** While adduct **22** suffered hydrolysis upon chromatography, nevertheless, a molecular ion could be obtained in the mass spectrum of the crude oil. The NMR spectrum displayed 18 trimethylsilyl protons and both the pyrimidine ring proton (6.77 ppm) and the acetyl group (2.54 ppm) appeared at lower field than those of mono-Me_3Si derivative **24** (6.54 and 2.28 ppm, respectively), consistent with the presence of a pyrimidine ring in **22.**

Passage of a solution of **22** through a silica gel column produced a mixture of mono-Me_3Si derivative **24** and methoxy ketone **23.** Attempts to purify **24** were accompanied by further hydrolysis. Ketone **23** was best prepared by direct hydrolysis of **22** with 1 equiv of water in the absence of acid. While the reaction proceeded slowly, the use of neutral conditions avoided problems with the elimination of MeOH from the product. Crystalline **23** could thus be obtained from **22** in near quantitative yield as a single stereoisomer. While mild treatment of a mixture of **23** and **24** with acid produced **25,** this latter substance was best obtained by acid hydrolysis of **22** followed by chromatography.

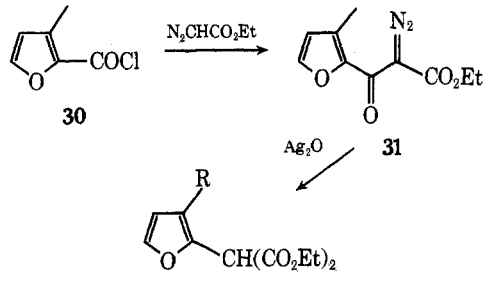
Both to confirm the structure assignments discussed above and to test the generality of these remarkable furan and dihydro-4-pyrone producing reactions, the reaction series was investigated using diethyl oxomalonate (**26**) as the dienophile rather than pyrimidone **3.** Diethyl oxomalonate,[17,18] mesoxalonitrile,[17] and formaldehyde[19] have all served as the dienophile in earlier Diels–Alder reactions with substituted 1,3-dienes.

The reaction between diene **17** and **26** in boiling THF afforded the thermally unstable adduct **27** (by NMR). Distillation afforded methylene dihydropyran **29** as the predomi-



nant product accompanied by some furan **28** [uv max (MeOH) 214 nm (ϵ 6700)[15,20]]. Treatment of **29** with TsOH in benzene also led to furan **28**.

The structure of furan **28** was confirmed by independent synthesis. Thus, reaction of ethyl diazoacetate and 3-methylfuroyl chloride (**30**)[22] afforded diazo ester **31**. An Arndt–

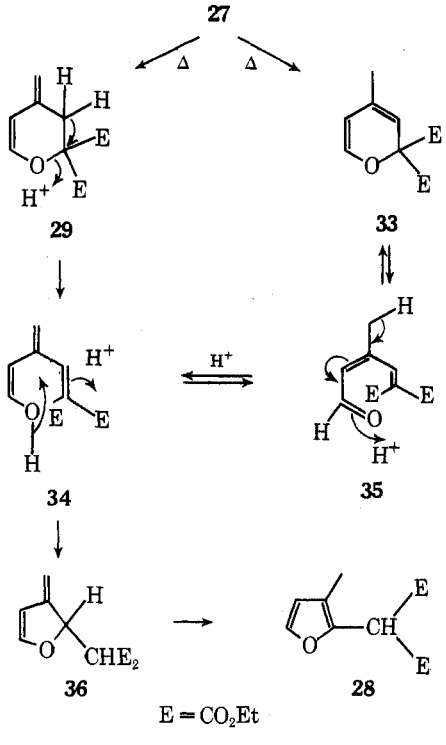


28, R = Me
32, R = H

Eistert reaction of **31** using Ag_2O gave furan **28**, identical with that obtained from the above Diels–Alder reaction. This same synthetic route was employed by Reichstein[23] for the preparation of diethyl fur-2-ylmalonate (**32**).

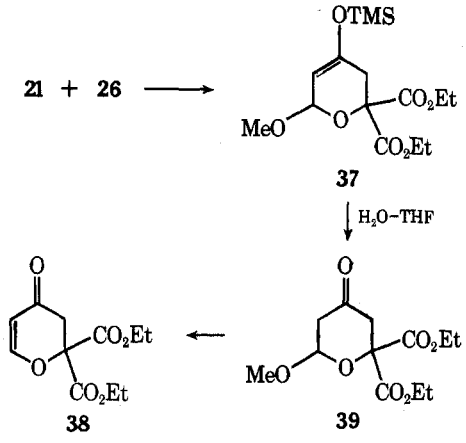
Scheme I outlines two reasonable pathways leading from **27** to furan **28**. Thus, thermal elimination of HOAc from **27** could produce either dihydropyran **29** or pyran **33**. It is not

Scheme I



surprising that we found no pyran **33** among the products in view of the known propensity of this ring system toward ring opening isomerization.[21] Aldehyde **35** is included in the scheme since its presence in the crude distillate of **29** was suggested by NMR. Recyclization of enol **34** would be expected to produce **36**, which would suffer ready isomerization to furan **28**.

The reaction of diethyl oxomalonate (**26**) with Me_3Si diene **21** proceeded analogously to that described above for pyrimidone **3**. Thus, from **26**, hydrolytically unstable Me_3Si ether



37 was formed which could be easily hydrolyzed to tetrahydropyrone **39** using THF–H_2O. This latter substance, when exposed to dilute aqueous HCl in THF, afforded dihydro-4-pyrone **38**. Ketone **38** showed spectral properties in good agreement with those of other 3,4-dihydro-4-pyrones.[24] In general, the uv and NMR spectral properties (see Experimental Section) observed for corresponding compounds derived from pyrimidone **3** and diethyl oxomalonate **26** are also in good agreement, constituting an important confirmation of the structure assignments in the pyrimidone series.

Experimental Section[25]

***tert*-Butyl [2′-Acetamido-4′(1′*H*)-pyrimidon-6′-yl]glyoxylate 2-Oxime (7).**[26] A mixture of 2.00 g (9.30 mmol) of ester **4**, mp 183–184 °C, and 48 ml (60 mmol) of 1.25 N *t*-BuOK in *t*-BuOH was stirred for 3 h at 25 °C. Then 1.36 ml (10.0 mmol) of isoamyl nitrite was added and the resulting solution was stirred for 5.5 h. The mixture was diluted with CH_2Cl_2 and neutralized with 35 ml (60 mmol) of 1.7 N HCl. The usual workup afforded 2.24 g of a yellow solid, recrystallization of which from EtOAc afforded 1.35 g (49%) of **7** as white needles, mp 200 °C dec. A second recrystallization from EtOAc afforded the analytical specimen, mp 205 °C dec, as a 5:2 mixture of syn and anti isomers: major isomer NMR (Me_2SO-d_6) δ 1.51 (s, 9), 2.22 (s, 3), 3.1–3.8 (v br s, 1), 6.28 (s, 1), 11.5–13.0 (m, 2); minor isomer NMR (Me_2SO-d_6) δ 1.57 (s, 9), 2.25 (s, 3), 3.1–3.8 (v br s, 1), 6.34 (s, 1), 11.5–13.0 (m, 2); uv max (EtOH) (mixture) 242 nm (ϵ 23 800) and 307 (4640). Anal. Calcd for $C_{12}H_{16}N_4O_5$: C, 48.64; H, 5.44; N, 18.91. Found: C, 48.83; N, 5.60; N, 18.76.

Methyl [2′-Acetamido-4′(1′*H*)-pyrimidon-6′-yl]glyoxylate 2-Oxime (8).[26] A mixture of 2.44 g (61.0 mmol) of NaH (60% dispersion in mineral oil), 12.3 g (54.5 mmol) of ester **4**, and 275 ml of DMF was heated with stirring at 80 °C for 15 min, cooled to 0 °C, and treated with 6.75 g (58.0 mmol) of isoamyl nitrite dropwise over 10 min. The mixture was then heated at 90 °C for 30 min, cooled to 0 °C, and treated with 3.32 g (61.0 mmol) of HCl in 50 ml of MeOH. The solvent was removed (15 mmol) and the residue was triturated with CCl_4 leaving a solid which was recrystallized from MeOH, affording 7.75 g (56%) of **8**, mp 205–210 °C. Two recrystallizations from MeOH afforded the analytical specimen as a single isomer: mp 227–228 °C dec; NMR (Me_2SO-d_6) δ 2.18 (s, 3), 3.80 (s, 3), 3.0–4.1 (m, 1), 6.28 (s, 1), 11.5–13.2 (m, 2); uv max (EtOH) 241 nm (ϵ 26 000) and 315 (4650). Anal. Calcd for $C_9H_{10}N_4O_5$: C, 42.52; H, 3.97; N, 22.04. Found: C, 42.60; H, 4.03; N, 21.97.

Methyl [2′-Amino-4′(1′*H*)-pyrimidon-6′-yl]glyoxylate 2-Oxime (9). A mixture of 3.40 g (13.4 mmol) of **8**, mp 220–222 °C dec, 20 ml of MeOH, and 20 ml (20 mmol) of 1.0 N HCl was refluxed for 25 min, cooled to 0 °C, and treated with 20 ml (20 mmol) of 1.0 N NaOH. The precipitated amine **9**, 2.42 g, mp 221–223 °C, was twice

recrystallized from MeOH, affording the analytical specimen as a powder: mp 227–230 °C; NMR (Me_2SO-d_6) δ 3.2–3.7 (m, 2), 3.82 (s, 3), 5.93 (s, 1), 12.2–12.6 (m, 1); uv max (EtOH) 227 nm (ε 18 500) and 325 (4930). Anal. Calcd for $C_7H_8N_4O_4$: C, 39.62; H, 3.80; N, 26.41. Found: C, 40.05; H, 4.17; N, 25.85.

Methyl [2′-Acetamido-4′(1′*H*)-pyrimidon-6′-yl]glyoxylate 2-Acetoxime (10). A. From Amine 9. A mixture of 5.0 g of **9**, mp 221–223 °C, and 25 ml of Ac_2O was heated at 130 °C for 7 min and cooled, and the solvent was removed under vacuum. The residue was triturated with CCl_4, affording 5.85 g (84%) of a white solid, mp 184–185 °C. Four recrystallizations from EtOAc afforded the analytical specimen as white needles: mp 202.5–203.5 °C; NMR (Me_2SO-d_6) δ 2.23 (s, 3), 2.28 (s, 3), 3.98 (s, 3), 6.55 (s, 1), 11.7–12.4 (m, 1); uv max (EtOH) 242 nm (ε 26 000) and 316 (4680). Anal. Calcd for $C_{11}H_{12}N_4O_6$: C, 44.60; H, 4.08; N, 18.91. Found: C, 44.87; H, 4.25; N, 18.80.

B. From Oxime 8. A 180-mg sample of oxime **8**, mp 216–219 °C, was treated with 3 ml of Ac_2O at 130 °C for 3 min. The usual workup afforded **10** identical by NMR with that obtained above, in near-quantitative yield.

Ethyl [2′-Amino-4′(1′*H*)-pyrimidon-6′-yl]glyoxylate Diethyl Ketal (15) and *N*-Acetyl Derivative. To 458 mg (19.1 mmol) of NaH was added with stirring at 0 °C a solution of 2.42 g (9.75 mmol) of diethyl diethoxymalonate[9] in 5 ml of THF followed by dropwise addition of 1.1 ml (12 mmol) of EtOAc. After a 30-min stir at 25 °C another 1.1 ml of EtOAc was added and the resulting mixture was stirred at 25 °C for 12 h. The mixture was poured over ice, neutralized to pH 5, and extracted with ether. The combined extracts were washed with water and brine, dried (Na_2SO_4), and evaporated, affording 2.284 g of viscous oil. Vacuum distillation afforded a 385-mg fraction, bp 92 °C (0.01 mm), of ketoketal **13**, pure by NMR. This entire fraction (1.31 mmol) was dissolved in 10 ml of absolute EtOH and treated with 288 mg (1.60 mmol) of guanidine carbonate and the resulting mixture was refluxed for 19 h. The solvent was evaporated, leaving a residue which was triturated with EtOAc. The residue was dissolved in ice water, neutralized to pH 5, and extracted with EtOAc. The sandy precipitate which formed between the layers was collected and dried (150 mg). Two recrystallizations from MeOH afforded 80 mg of pure **15**: mp 238–239 °C; uv max (EtOH) 224 nm (ε 10 000) and 292 (8920). Anal. Calcd for $C_{12}H_{19}N_3O_5$: C, 50.52; H, 6.71; N, 14.73. Found: C, 50.33; H, 6.74; N, 14.57.

A 27-mg portion was treated with 0.6 ml of Ac_2O at 100 °C for 1 h. Preparative TLC of the crude product afforded 23 mg of the *N*-acetyl derivative. Recrystallization from EtOAc–hexane afforded 18 mg of ethyl [2′-acetamido-4′(1′*H*)-pyrimidon-6′yl]glyoxylate diethyl ketal, mp 198–199 °C, as stocky needles: NMR ($CDCl_3$) δ 1.23 (t, 3), 1.25 (t, 6), 2.29 (s, 3), 3.50 (bq, 4), 4.24 (q, 2), 6.67 (s, 1); mass spectrum *m/e* 327.142 (calcd for $C_{14}H_{21}N_3O_6$, 327.143), 282, 254, 226.

6-(Diphenoxymethyl)-2-amino-4(1*H*)-pyrimidone (16). Crude ketoketal **14** was prepared from diethyl diphenoxymalonate[10] following the procedure for ketoketal **13** described above. Reaction (see procedure for **15** above) of 42.3 g (0.110 mol) of **14** with 22.4 g (0.130 mol) of guanidine carbonate afforded 24.0 g of crude **16**, mp 210–216 °C. Recrystallization from EtOH–water afforded the analytical specimen of **16** as white plates: mp 239–241 °C; NMR (Me_2SO-d_6) δ 5.88 (s, 1), 6.41 (s, 1), 6.75 (bs, 2), 6.9–7.5 (m, 10), 10.95 (bs, 1). Treatment of the sample with D_2O caused the signals at δ 6.75 and 10.95 to vanish. Uv max (EtOH) 292 nm (ε 6800); mass spectrum *m/e* 309 (molecular ion). Anal. Calcd for $C_{17}H_{15}N_3O_3$: C, 66.01; H, 4.89; N, 13.58. Found: C, 65.67; H, 4.96; N, 13.47.

Methyl 2-[2′-Acetamido-4′(1′*H*)-pyrimidon-6′-yl]glyoxylate (3). A mixture of 25.0 g (0.111 mol) of ester **4**, mp 181–183 °C, 14.9 g (0.115 mol) of H_2SeO_3 (Fisher), and 222 ml of HOAc was heated at 105–120 °C for 5 h; then 25 ml of Ac_2O was added and heating continued for 1 h. Filtration afforded 9.01 g (99%) of black Se. The filtrate was applied to 25 g of silica gel by evaporation of the solvent and azeotropic evaporation with toluene. The silica gel was applied to the top of a column of 100 g of silica gel packed in 3:2 EtOAc–hexanes. Elution with this solvent mixture afforded 7.08 g (27%) of ester **3** (first yellow band on the column) which crystallized directly from the eluant as fine yellow needles, mp 198–200 °C. Recrystallization from EtOAc produced the analytical specimen as white needles: mp 208.5–209 °C; NMR (Me_2SO-d_6) δ 2.15 (s, 3), 3.87 (s, 3), 6.65 (s, 1); (CD_3CO_2D) δ 2.32, 3.98, 7.08; (acetic acid-d_4–D_2O) δ 2.30, 3.80, 6.66; mass spectrum *m/e* 239 (molecular ion), 224, 211, 180, 169; uv max (THF) 335 nm (ε 4500) and 244 (11 000); (EtOH) 287 (6700), 233 (12 300), and 217 (12 700). Anal. Calcd for $C_9H_9N_3O_5$: C, 45.19; H, 3.79; N, 17.57. Found: C, 45.17; H, 3.71; N, 17.54.

Methyl 2-[2′-Acetamido-4′(1′*H*)-pyrimidon-6′-yl]-2-(3″-methylfur-2″-yl)acetate (19). A solution of 1.7 g (7.0 mmol) of keto ester **3**, mp 199–201 °C, 3.5 g (28 mmol) of diene **17**,[2] and 25 mg of 2,6-di-*tert*-butyl-4-methylphenol (Aldrich) in 10 ml of HOAc was heated at 100 °C for 7 h. The reaction mixture was deposited on 5 g of silica gel by evaporation. This was applied to the top of a 14 g silica gel column packed in 1:4 EtOAc–hexanes. Elution with this solvent system produced a total of 423 mg (20%) of good quality furan **19**, mp 200–206 °C. Recrystallization from EtOAc–hexane afforded the analytical specimen: mp 204–205 °C; NMR ($CDCl_3$–CD_3CO_2D) δ 1.98 (s, 3), 2.26 (s, 3), 3.78 (s, 3), 4.79 (s, 1, H-2), 6.04 (s, 1, H-5′), 6.25 (d, *J* = 2 Hz, 1, H-4″) and 7.32 (d, *J* = 2 Hz, 1, H-5″); uv max (EtOH) 335 nm (ε 3360), 285 (6700), 236 (16 000), and 214 (16 800); (pH ~12) 335 nm (intense). Anal. Calcd for $C_{14}H_{15}N_3O_5$: C, 55.08; H, 4.95; N, 13.76. Found: C, 54.84; H, 5.01; N, 13.50.

Methyl 4-Methylene-2,3-dihydro-2-[2′-acetamido-4′(1′*H*)-pyrimidon-6′-yl]-4*H*-pyran-2-carboxylate (20). In a 127-ml pressure reactor were combined 1.00 g (4.18 mmol) of keto ester **3**, mp 199–201 °C, 1.10 g (8.75 mmol) of diene **17**,[2] 50 mg of hydroquinone, and 25 ml of THF. The reactor was sealed and heated at 115–125 °C for 48 h. The mixture was filtered and the filtrate was applied to 5 g of silica gel by evaporation. This was placed on top of a column of 35 g of silica gel packed in 1:9 EtOAc–hexanes. Elution with this solvent system afforded 165 mg (13%) of pyran **20** as fine, white needles. Soxhlet recrystallization from EtOAc–hexanes (1:1) afforded the analytical specimen: mp 235 °C (in at 230 °C); NMR (acetone-d_6–CD_3CO_2D) δ 2.34 (s, 3), 2.83 (bd, *J* = 15 Hz, 1, H-3), 3.21 (bd, *J* = 15 Hz, 1, H-3), 3.70 (s, 3), 4.71 (bs, 1), 4.88 (bs, 1), 5.60 (d, *J* = 6 Hz, 1, H-5), 6.30 (s, 1, H-5′), 6.63 (bd, *J* = 6 Hz, 1, H-6); uv max (MeOH) 286 nm (ε 7630) and 237 (21 800); mass spectrum *m/e* 305 (molecular ion), 273, 263, 246, 245. Anal. Calcd for $C_{14}H_{15}N_3O_5$: C, 55.08; H, 4.95; N, 13.76. Found: C, 54.87; H, 5.02; N, 13.79.

Reaction of Keto Ester 3 with Diene 21. Products of Selective Hydrolysis. A solution of 1.00 g (4.18 mmol) of keto ester **3**, mp 199–201 °C, and 3.60 g (21 mmol) of diene **21**[16,27] in 10 ml of THF was heated at 55 °C for 48 h. A 1.00-ml aliquot was removed and evaporated, affording 192 mg of crude methyl 2-(2′-acetamido-4′-trimethylsilyloxypyrimidin-6′-yl)-6-methoxy-3,6-dihydro-4-trimethylsilyloxy-2*H*-pyran-2-carboxylate (**22**): NMR ($CDCl_3$) δ 0.23 (s, 9), 0.36 (s, 9), 2.54 (s, 3), 2.6 (m, 1), 3.0 (m, 1), 3.49 (s, 3), 3.74 (s, 3), 4.79 (m, 1), 5.42 (m, 1), 6.77 (s, 1); mass spectrum *m/e* 483 (molecular ion), 451, 424.

A second aliquot of the above reaction mixture was passed through a short silica gel column, affording a mixture of ketone **23** (see below) and methyl 2-[2′-acetamido-4′(1′*H*)-pyrimidon-6′-yl]-4-trimethylsilyloxy-6-methoxy-3,6-dihydro-2*H*-pyran-2-carboxylate (**24**): NMR ($CDCl_3$) δ 0.19 (s, 9), 2.28 (s, 3), 2.4 (m, 1), 2.91 (bd, *J* = 17 Hz, 1), 3.44 (s, 3), 3.71 (s, 3), 4.76 (bs, 1), 5.33 (bs, 1), 6.54 (s, 1).

A third 0.50-ml aliquot of the original reaction mixture was treated with 21 mg of water and let stand for 16 h at 25 °C. Chromatography over silica gel and elution with EtOAc afforded 53 mg of crude ketone **23**. Preparative TLC followed by crystallization from EtOAc–hexanes produced the analytical specimen of methyl 2-(2′-acetamido-4′-pyrimidon-6′-yl)-6-methoxy-2,3,5,6-tetrahydro-4-pyrone-2-carboxylate (**23**): mp 191–192 °C dec; NMR ($CDCl_3$) δ 2.29 (s, 3), 2.4–2.9 (m, 2), 2.67 (d, *J* = 18 Hz, 1, H-3), 3.19 (d, *J* = 18 Hz, 1, H-3), 3.54 (s, 3), 3.73 (s, 3), 5.00 (dd, 1, H-6), 6.61 (s, 1); uv max (MeOH) 287 nm (ε 8250) and 235 (14 400); mass spectrum *m/e* 339 (molecular ion), 307, 280, 265. Anal. Calcd for $C_{14}H_{17}N_3O_7$: C, 49.56; H, 5.05; N, 12.38. Found: C, 49.20; H, 5.00; N, 12.35.

Methyl 2-[2′-Acetamido-4′(1′*H*)-pyrimidon-6′-yl]-2,3-dihydro-4-pyrone-2-carboxylate (25). A mixture of 102 mg (0.42 mmol) of keto ester **3**, mp 199–201 °C, 360 mg (2.10 mmol) of diene **21**,[16,27] and 1 ml of THF was heated at 60 °C for 24 h. The solution was cooled, treated with 0.2 ml of 12 N HCl in 10 ml of THF for 40 min at 25 °C, and evaporated. Chromatography over silica gel, elution with 1:4 EtOAc–hexanes, and recrystallization of the crystalline fractions from EtOAc–hexanes afforded 24 mg (18%) of pure ketone **25**: mp 195–198 °C dec; NMR ($CDCl_3$) δ 2.28 (s, 3), 3.01 (d, *J* = 15 Hz, 1, H-3), 3.32 (d, *J* = 15 Hz, 1, H-3), 3.78 (s, 3), 5.53 (d, *J* = 5 Hz, 1, H-5), 6.49 (s, 1, H-5′), 7.41 (d, *J* = 6 Hz, 1, H-6); uv max (MeOH) 288 nm (ε 3070), 258 (4020), and 236 (6100); mass spectrum *m/e* 307.076 (calcd for $C_{13}H_{13}N_3O_6$, 307.080), 265, 248.

Reaction of Diethyl Oxomalonate (26) with Diene 17. A solution of 527 mg (3.03 mmol) of ketone **26** (Aldrich) and 1.00 g (8.00 mmol) of diene **17**[2] in 3 ml of THF was refluxed for 20 h. A 0.3-ml aliquot was removed and pumped down at high vacuum. NMR spectroscopy revealed the presence of diethyl 6-acetoxy-4-methyl-3,6-dihydro-2*H*-pyran-2,2-dicarboxylate (**27**) as the major product: NMR ($CDCl_3$) δ 1.29 (t, 6), 1.87 (bs, 3), 2.02 (s, 3), 2.38 (bd, *J* = 17 Hz, 1), 2.82 (bd, *J* = 17 Hz, 1), 4.0–4.6 (m, 4), 5.49 (bs, 1), 6.51 (bs, 1).

The remainder of the reaction mixture was distilled, affording 222

mg (31%) of bright yellow distillate, bp 100–120 °C (0.15 mm) (bath, 150 °C). Analysis by NMR indicated the oil to be about 50% diene **29** with lesser amounts of furan **28** and possibly aldehyde **25** and tars. Preparative VPC (column B) at 180 °C (t_R 3.0 min) produced a pure sample of diethyl 4-methylene-2,3-dihydro-4*H*-pyran-2,2-dicarboxylate (**29**) as a colorless oil: ir 1745 (s), 1640 cm^{-1} (m); NMR ($CDCl_3$) δ 1.28 (t, 6), 3.01 (bs, 2, H-3), 4.27 (q, 4), 4.74 (bs, 1), 4.88 (bs, 1), 5.51 (d, J = 5 Hz, 1, H-5), 6.53 (bd, J = 6 Hz, 1, H-6); uv max (MeOH) 245 nm (ϵ 12 700); mass spectrum *m/e* 240.097 (calcd for $C_{12}H_{16}O_5$, 240.100), 211, 194, 167.

A 268-mg sample of crude diene **29** was taken up in 5 ml of benzene containing 1 mg of $TsOH \cdot H_2O$ and refluxed for 1 h. Chromatography over silica gel and elution with $CHCl_3$ afforded 180 mg (67%) of crude furan **28**. Preparative TLC (1% EtOAc in benzene) afforded pure diethyl 3-methylfur-2-ylmalonate (**28**) as a colorless oil: NMR ($CDCl_3$) δ 1.27 (t, 6), 2.02 (s, 3), 4.25 (q, 4), 4.76 (s, 1), 6.24 (d, J = 2 Hz, 1, H-4'), 7.32 (d, J = 2 Hz, H-5'); uv max (MeOH) 280 nm (ϵ 540) and 214 (6700); mass spectrum *m/e* 240.097 (calcd for $C_{12}H_{16}O_5$, 240.100), 168, 95. Furan **28** was best obtained from diene **17** in one step. A 127-ml pressure reactor was charged with 505 mg of diene **17**, 238 mg of ketone **26**, 27 mg of hydroquinone, and 12 ml of THF, sealed, and heated at 120 °C for 36 h. Evaporation at 0.01 mm produced 552 mg (115%) of crude furan **28** as a dark oil. Distillation afforded 60 mg (much hold-up loss) of pure (by NMR) **28**.

Furan 28 by an Arndt–Eistert Synthesis.[23] A solution of 733 mg (5.10 mmol) of 3-methylfuroyl chloride[22] (**30**) and 1.14 g (10.0 mmol) of ethyl diazoacetate was allowed to stand at 25 °C for 5 days. Then 2.00 g (17.5 mmol) more ethyl diazoacetate was added. After 7 days the volatiles were removed at 0.01 mm, producing 614 mg of a yellow oil which by NMR was a 1:1 mixture of **30** and ethyl (3'-methylfuroyl)diazoacetate (**31**). A portion was purified by chromatography over Florisil: NMR (CCl_4) δ 1.33 (t, 3), 2.38 (s, 3), 4.32 (q, 2), 6.44 (d, J = 2 Hz, 1), 7.44 (d, J = 2 Hz, 1). A 518-mg portion of the above yellow oil was heated in 10 ml of EtOH at 160 °C for 1 h with 100 mg of Ag_2O and 1 ml of Newman and Beal's reagent.[28] The reaction mixture was cooled, filtered, and evaporated, and the residue was dissolved in $CHCl_3$ and passed through a short silica gel column. Preparative TLC (2% EtOAc in benzene) produced 67 mg of a pale yellow oil which by NMR and VPC analysis was 25% furan **28** and 75% ethyl 3-methylfuroate. A pure sample of furan **28** was obtained by preparative VPC and was identical with the Diels–Alder product by NMR, uv, and mass spectral analysis.

Reaction of Diene 21 with Diethyl Oxomalonate (26). A solution of 1.10 g (6.40 mmol) of diene **21**[16,27] and 507 mg (2.92 mmol) of keto ester **26** in 3 ml of THF was heated at 55 °C for 23 h. A 0.5-ml aliquot was removed and evaporated (0.01 mm), producing 116 mg (107%) of yellow oily diethyl 6-methoxy-4-trimethylsilyloxy-3,6-dihydro-2*H*-pyran-2,2-dicarboxylate (**37**) (~90% pure by NMR, too unstable for further purification): NMR ($CDCl_3$) δ 0.18 (s, 9), 1.23 (t, 6), 2.32 (bd, J = 17 Hz, 1), 2.79 (d, J = 17 Hz, 1), 3.39 (s, 3), 4.22 (bq, 4), 4.79 (bs, 1), 5.21 (bs, 1); mass spectrum *m/e* 346.144 (calcd for $C_{15}H_{26}O_7Si$, 346.145), 331, 315, 300, 273.

A 67-mg sample of crude ester **37** was treated with 2 ml of 10% aqueous THF for 2 days at 25 °C followed by a 2-h reflux. Evaporation of the solvent followed by preparative VPC (column A, 132 °C, t_R 3.2 min) afforded pure diethyl 6-methoxy-2,3,5,6-tetrahydro-4-pyrone-2,2-dicarboxylate (**39**): NMR ($CDCl_3$) δ 1.29 (t, 3), 2.66 (m, 2, H-5), 2.81 (d, J = 16 Hz, 1, H-3), 3.23 (d, J = 16 Hz, 1, H-3), 3.49 (s, 3), 4.38 (q, 4), 5.24 (dd, J = 3, 4 Hz, 1, H-6); mass spectrum *m/e* 274.106 (calcd for $C_{12}H_{18}O_7$, 274.105), 243, 229, 201.

A 1.0-ml aliquot of the initial reaction mixture was treated with 1.0 ml of 0.1 N HCl and 2 ml of THF for 30 min at 25 °C. The solution was diluted with ether, dried (Na_2SO_4), evaporated, taken up in $CHCl_3$, and passed through a short silica gel column. Evaporation followed by preparative VPC (column A, 185 °C, t_R 1.0 min) afforded pure diethyl 2,3-dihydro-4-pyrone-2,2-dicarboxylate (**38**): NMR ($CDCl_3$) δ 1.30 (t, 6), 3.14 (s, 2), 4.33 (q, 4), 5.51 (d, J = 6 Hz, 1, H-5), 7.40 (d, J = 6 Hz, 1, H-6); uv max (MeOH) 257 nm (ϵ 5960); mass spectrum *m/e* 242.081 (calcd for $C_{11}H_{14}O_6$, 242.079), 197, 169, 97.

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Registry No.—**3**, 59414-11-8; **4**, 22794-57-6; *syn*-**7**, 59414-12-9; *anti*-**7**, 59414-13-0; **8**, 33965-28-5; **9**, 59414-14-1; **10**, 59414-15-2; **11**, 29340-87-2; **12**, 4525-71-7; **13**, 59414-16-3; **14**, 59414-17-4; **15**, 59414-18-5; **15** *N*-acetyl derivative, 59414-19-6; **16**, 59414-20-9; **17**, 17616-47-6; **19**, 59414-21-0; **20**, 59414-22-1; **21**, 59414-23-2; **22**, 59414-24-3; **23**, 59414-25-4; **24**, 59414-26-5; **25**, 59414-27-6; **26**, 609-09-6; **27**, 59414-28-7; **28**, 59414-29-8; **29**, 59414-30-1; **30**, 22601-06-5; **31**, 59414-31-2; **37**, 59414-32-3; **38**, 59414-33-4; **39**, 59414-34-5.

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