[4.2.0]octane-3,5-dione, 90296-03-0; (1α,6α,7β)-6-fluoro-7,8,8-trimethyl-2,4-diazabicyclo[4.2.0]octane-3,5-dione, 90365-49-4; (1α,6α,8α)-6-fluoro-7,7,8-trimethyl-2,4-diazabicyclo[4.2.0]octane-3,5-dione, 90296-04-1; (1α,6α,8β)-6-fluoro-7,7,8-trimethyl-2,4-diazabicyclo[4.2.0]octane-3,5-dione, 90365-50-7; isopropenyl acetate, 108-22-5; cyclohexenyl acetate, 1424-22-2; cyclopentenyl acetate, 933-06-2; tetramethylene, 563-79-1; 1-methylcyclopentene, 693-89-0; 2-methyl-2-butene, 513-35-9; propene, 115-07-1; isobutylene, 115-11-7; methylenecyclopentane, 1528-30-9; methylenecyclohexane, 1192-37-6; methylenecycloheptane, 2505-03-5.

A Novel Mechanism for Conversion of 5-Fluorouracil-Olefin Photocycloaddition Products to 5-Substituted Uracils. A Synthon for the Uracil 5-Carbanion

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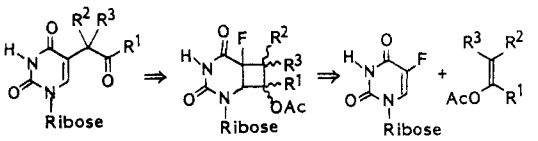
The photocycloaddition products of 5-fluorouracil and enol acetates undergo fragmentation reactions to afford 5-substituted uracils in good yields. Unexpectedly, certain 5-fluorouracil–olefin photocycloaddition products react with 3 equiv of potassium *tert*-butoxide in *tert*-butyl alcohol to give high yields of 5-substituted uracils. Kinetic, labeling, and product studies of this novel reaction support a reaction mechanism in which the dianion of the cycloadduct rearranges to a spirocyclopropane intermediate which then affords the 5-substituted uracil.

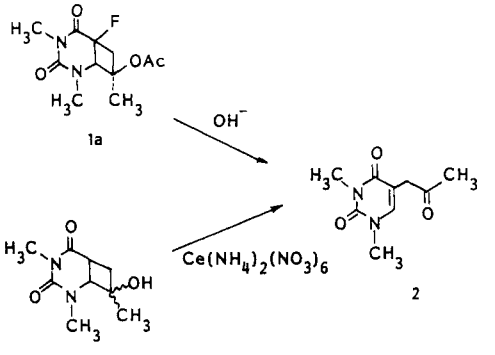
Several years ago we became interested in methods for the direct functionalization of unprotected nucleoside derivatives.[1,2] The intended strategy was to employ 5-fluorouracil as a synthon for the 5-carbanion of uracil by using a sequence of photocycloaddition and fragmentation (Scheme I).[1,3] This route was especially attractive since a variety of nucleosides of 5-fluorouracil have been prepared.[4] Furthermore, the entire reaction sequence would involve only light and base and thus be applicable to systems having a variety of labile functionalities on the carbohydrate portion of the molecule. While this work was never extensively applied to nucleoside functionalization, the model studies for implementing this strategy are of interest. The preceding paper has detailed the preparative aspects of the photocycloaddition chemistry of 5-fluorouracil with olefins.[5] Herein we report details on the fragmentation reactions of 5-fluorouracil–enol acetate and 5-fluorouracil–olefin cycloaddition products to 5-substituted uracils. The mechanism of the unprecedented fragmentations of the latter series of compounds has been extensively studied, and a reasonable interpretation of the reaction pathway is presented.

Scheme I. Strategy for Functionalization of Nucleosides



Fragmentation Reactions of 1,3-Dimethyl-5-fluorouracil–Enol Acetate and 5-Fluorouracil–Enol Acetate Adducts

Reaction of **1a**, the major product from the photocycloaddition of 1,3-dimethyl-5-fluorouracil and isopropenyl acetate, with either aqueous sodium hydroxide or sodium carbonate gave **2** in 66% isolated yield. Gas



chromatographic analysis of the progress of the reaction showed that a transient intermediate was formed, presumably the alcohol, which was converted to **2** as the reaction progressed. Compound **2** was identical with the product obtained from ceric ammonium nitrate oxidation[3] of **3**.

Interestingly, reaction of the minor product from the 1,3-dimethyl-5-fluorouracil–isopropenyl acetate photocycloaddition reaction, **1b**, with base did not afford **2** but rather a new product in 85% yield. The same type of product was obtained from **1c** in 82% yield. Spectroscopic and analytical data for these products, including a detailed ^{1}H NMR,[6] are presented in the supplementary materials section. From a mechanistic viewpoint, we favor structures

(1) (a) Wexler, A. J.; Balchunis, R. J.; Swenton, J. S. *J. Chem. Soc., Chem. Commun.* **1975**, 601. (b) Wexler, A. J.; Swenton, J. S. *J. Am. Chem. Soc.* **1976**, *98*, 1602. Swenton, J. S.; Balchunis, R. J. *J. Heterocycl. Chem.* **1974**, *11*, 917.

(2) For recent methods involving functionalization of protected nucleosides at C-5, see: Ruth, J. L.; Bergstrom, D. E. *J. Org. Chem.* **1978**, *43*, 2870. Bergstrom, D. E.; Ogawa, M. K. *J. Am. Chem. Soc.* **1978**, *100*, 8106. Bigge, C. F.; Kalaritis, P.; Deck, J. R.; Mertes, M. P. *Ibid.* **1980**, *102*, 2033. Robins, R. J.; Berr, P. J. *J. Org. Chem.* **1983**, *48*, 1854.

(3) See also: Hunter, N. R.; MacAlpine, G. A.; Lui, H. J.; Valenta, A. *Can. J. Chem.* **1970**, *48*, 1436. Ho, P.-T; Lee, S. F.; Chang, D.; Wiesner, K. *Experientia* **1971**, *27*, 1377. Bergstrom, D. E.; Agosta, W. C. *Tetrahedron* **1968**, 5643.

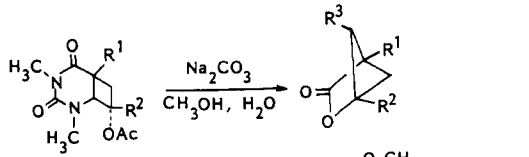
(4) Fikus, M.; Wierchowski, K. L.; Shugar, D. *Biochem. Biophys. Res. Commun.* **1964**, *16*, 478.

(5) Wexler, A. J.; Balchunis, R. J.; Swenton, J. S. *J. Org. Chem.*, preceding paper in this issue.

(6) Distinguishing between structures **4** and **5** on the basis of the dihedral angle dependence of J_{HF} is not rigorous since J_{HF} depends not only on the dihedral angle but is a dramatic function of the electronegativity of attached groups: Abraham, R. J.; Cavalli, L. *Mol. Phys.* **1965**, *9*, 67.

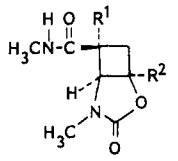
0022-3263/84/1949-2738$01.50/0

4b and **4c** for these two products, but structures **5b** and **5c** cannot be rigorously excluded.



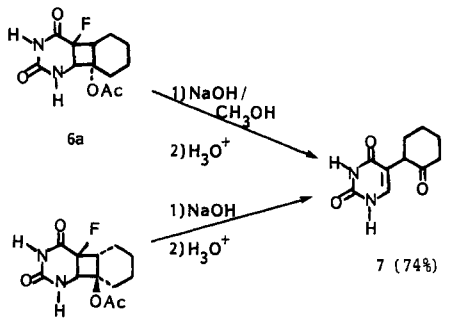
1b, $R^1 = F$, $R^2 = CH_3$
c, $R^1 = H$, $R^2 = CH_3$

4, $R^3 = CH_3-N(C=O)-CN(H)(CH_3)$



5

While the fragmentation reactions of the 1,3-dimethyl-5-fluorouracil cycloadduct having the endo acetate group did not afford the desired fragmentation product, the fragmentation reaction occurred without regard to acetate stereochemistry for the corresponding 5-fluorouracil photocycloaddition products. Thus, reaction of **6a** or **6b** with methanolic sodium hydroxide gave the functionalized uracil **7** in 74% yield. The structure assignment



6a, 6b

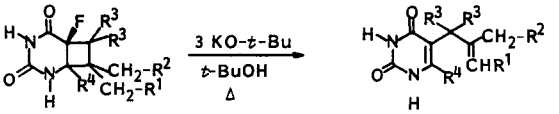
7 (74%)

was supported by combustion analysis, ^1H NMR, ^{13}C NMR, UV, and IR spectroscopy as detailed in the Experimental Section. Fragmentation of the 5-fluorouracil cycloadducts of cyclopentenyl acetate and isopropenyl acetate also afforded the respective functionalized uracils (see Experimental Section for details).

Fragmentation of 5-Fluorouracil–Olefin Cycloadducts. An Unexpected Reaction

On the basis of the idea that elimination of hydrogen fluoride from 5-fluorouracil–olefin cycloadducts would afford an interesting series of fused cyclobutene derivatives, the reaction of **8a** (the 5-fluorouracil–isobutylene photoadduct) with 3 equiv of potassium *tert*-butyl alcohol was examined. Instead of a cyclobutene product, an 83% yield of a new product was obtained. The product was analyzed for $C_8H_{10}N_2O_2$ and showed a UV (CH_3OH) absorption characteristic of a thymine derivative[7] (λ_{max} 286 nm, ϵ 7200). Likewise, the ^{13}C NMR absorptions at δ 164.2, 151.3, 138.8, 109.7 and the signal in the ^1H NMR at δ 7.13 correspond to those reported for thymine itself.[8] The remaining ^1H NMR absorptions are very similar to those of 2β-methallyl-2-cyclohexenone[9] (**10**): for **9a** (Me_2SO-d_6)

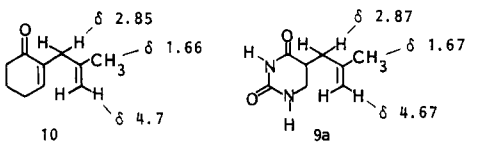
Table I. Yields of 5-Substituted Uracils from 5-Fluorouracil–Olefin Photoadducts



8 9

	R_1	R_2	R_3	R_4	9, %
a	H	H	H	H	83
b	H	H	H	D	83
c	$-(CH_2)_2-$		H	H	86
d	$-(CH_2)_3-$		H	H	100
e	$-(CH_2)_4-$		H	H	97
f	H	H	CH_3	H	99

δ 4.67 (br s, 2 H), 2.87 (br s, 2 H), 1.67 (s, 3 H); for **10** (CCl_4) δ 4.7 (m, 2 H), 2.85 (br, 2 H), 1.66 (t, J = 1 Hz, 3 H). These spectroscopic data strongly support the structure of this product as **9a**. The structures for the remaining reactions recorded in Table I were similarly supported by analytical and spectroscopic data as described in the Experimental Section.



10 9a

Mechanistic Aspects of the Fragmentation Reaction

A number of mechanisms can be envisioned for the **8** → **9** transformation. Any mechanism involving β-elimination of hydrogen fluoride to give a cyclobutene system followed by subsequent rearrangement can be ruled out since reaction of the deuterated system **8b** gave **9b** with complete retention of deuterium, and **8f** gave **9f** (Table I). Two simplified mechanisms proceeding via the dianion **12** remained (Scheme II).[10] One involves proton abstraction from the C_8-methyl group concerted with the ring opening (**12** → **13**). The second proceeds via a cyclobutyl to cyclopropyl ring contraction followed by opening of the cyclopropane ring and proton loss (**12** → **14** → **13**). Product and kinetic studies can distinguish between these two basic reaction pathways in addition to giving more explicit details for a particular mechanism.

Kinetically, potassium *tert*-butoxide would be involved in the rate-determining step of the **12** → **13** reaction. However, no base dependence would be expected for this step in the **12** → **14** → **13** sequence since the ring contraction of **12** to **14** should be rate determining. Thus, kinetic studies establishing the order of the reaction with respect to potassium *tert*-butoxide would aid in distinguishing between the two pathways. First, some knowledge of the first and second pK_as of **8a** was required. Relative first and second pK_a measurements of 5-fluorouracil and **8a** were determined by using a standard potentiometric titration method in *tert*-butyl alcohol with potassium *tert*-butoxide as base.[10] While 5-fluorouracil showed two end points upon titration, a second end point for **8a** could not be observed. This indicates that potassium *tert*-butoxide is not a sufficiently strong base to completely deprotonate **8a** at N-2. This preequilibrium between **11** and **12** would have to be accounted for in the kinetic scheme.

With use of a standard steady-state treatment (see

(7) Hall, R. H. "The Modified Nucleosides in Nucleic Acids"; Columbia Press: Hudson, NY, 1971.
(8) Tarpley, A. R.; Goldstein, J. H. *J. Am. Chem. Soc.* **1971**, *93*, 3573.
(9) Cantrell, T. S.; Haller, W. S.; Williams, J. C. *J. Org. Chem.* **1969**, *34*, 509.
(10) For details and leading references, see: Kaminski, V. V.; Comber, R. V.; Wexler, A. J.; Swenton, J. S. *J. Org. Chem.* **1983**, *48*, 2337.

Scheme II. Two Mechanistic Possibilities for 8 → 9 Conversion

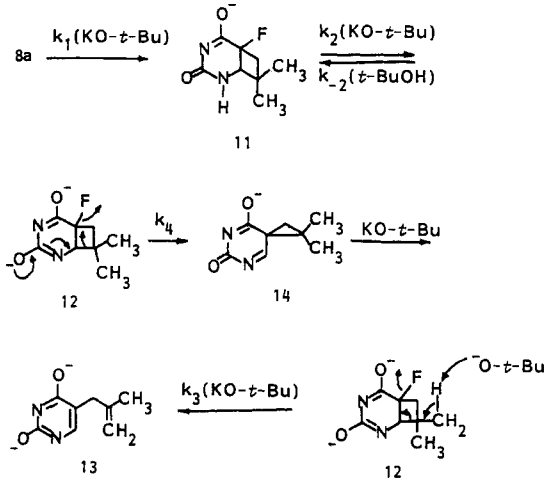


Table II. Rate Data for 11 → 12 → 14 → 13 and 11 → 12 → 13 Mechanisms

entry	temp	[KO-t-Bu], M	[8a], M	k_{obsd},[c] M^{-1} s^{-1}	k'_{obsd},[d] M^{-2} s^{-1}
1	99.1	0.046	0.015	2.00×10^{-2}	5.35×10^{-2}
2	99.1	0.058	0.018	1.80×10^{-2}	2.77×10^{-2}
3[a]	99.1	0.077	0.018	1.87×10^{-2}	2.25×10^{-2}
4[a]	115.0	0.028	0.0088	3.22×10^{-2}	1.58×10^{-2}
5[a]	115.0	0.022	0.0045	3.25×10^{-2}	1.68×10^{-2}
6[a,b]	99.2	0.046	0.015	2.29×10^{-2}	

[a] Average of duplicate runs. [b] This measurement was performed on the adduct of 5-fluorouracil and $(CD_3)_2C{=}CH_2$. [c] $k_{obsd} = k_4k_2/k_{-2}[t\text{-BuOH}]$. [d] $k'_{obsd} = k_3k_2/k_{-2}[t\text{-BuOH}]$.

supplementary materials section for details), the rate expression for the 11 → 12 → 14 → 13 mechanism becomes

$$\frac{d[13]}{dt} = \frac{k_4k_2[11][KO\text{-}t\text{-Bu}]}{k_{-2}[t\text{-BuOH}]} = k_{obsd}[KO\text{-}t\text{-Bu}][11]$$

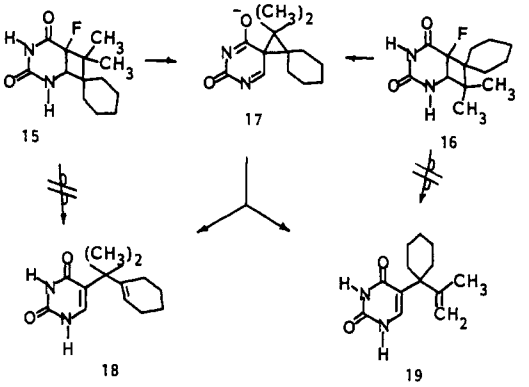
while that for the 11 → 12 → 13 mechanism is

$$\frac{d[13]}{dt} = \frac{k_3k_2[11][KO\text{-}t\text{-Bu}]^2}{k_{-2}[t\text{-BuOH}]} = k'_{obsd}[KO\text{-}t\text{-Bu}]^2[11]$$

The observed rate constants for these two expressions were calculated by using a nonlinear least-squares regression program.[11] As illustrated by the data of Table II, only a rate law unimolecular in potassium *tert*-butoxide gives consistent values of k_{obsd} with different concentrations of base and **8a**. These kinetic data rule out the mechanistic sequence 11 → 12 → 13. Additionally, if appreciable carbon–hydrogen bond breakage were occurring in the rate-determining step (e.g., 12 → 13), the reaction should show a primary isotope effect when the methyl groups at C-8 are replaced with perdeutero methyl groups. In fact (Table II, entry 6), a small inverse isotope effect was observed for the 5-fluorouracil–isobutylene-d_6 adduct.

While kinetic studies were supportive of the 11 → 12 → 14 → 13 mechanism, additional evidence was sought for the spiro intermediate (i.e., 14). Unfortunately, all attempts to trap spiro intermediates in several different systems failed (vida supra). If a spiro intermediate were involved in the reaction, then **15** and **16** would afford the same intermediate **17** and identical ratios of **18** and **19** would result from rearrangement (Scheme III). A mechanism not allowing C-7 and C-8 to become equivalent

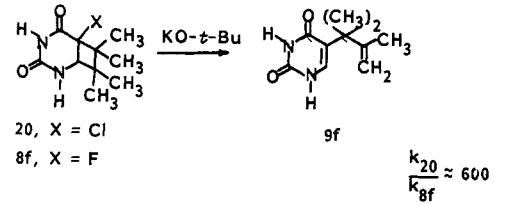
Scheme III. Fragmentation Reactions of Regioisomeric Compounds 15 and 16



would result in conversion of **15** to **18** and **16** to **19**. The required compounds **15** and **16** were prepared by photocycloaddition of 5-fluorouracil to isopropylidenecyclohexane followed by chromatographic separation. The structures could be rigorously assigned by the appearance of the methyl groups in the ^1H NMR spectra. For **15** one methyl group appeared as a doublet at δ 1.09 (J = 3.4 Hz) and the second methyl group appeared as a sharp singlet at δ 0.96; for **16** both methyl groups appeared as sharp singlets at δ 1.07 and 0.82. Since the fluorine–hydrogen long-range coupling occurs only when the vectors along the carbon–fluorine and carbon–hydrogen bonds intersect at a reasonable distance,[12,13] the regiochemical assignment is secure.

When the fragmentation reactions of **15** and **16** were performed, both compounds yielded the same mixture of **18** and **19** (1:3.5). These results require that the two cyclobutane ring carbons become equivalent at some stage in the reaction, and a reasonable interpretation is that the reaction proceeds through a spiro intermediate such as **17**.

Finally, to probe the extent of bond breakage of the leaving group at C-6 in the rate-determining step of the reaction, the kinetics of the fragmentation reaction of **20**, in which a chlorine is substituted for a fluorine, was examined. If the leaving group ability is important in the reaction, then the chloro system should undergo the fragmentation reaction much faster.[14] At 77 °C under the same reaction conditions the chloro system **20** produced the fragmentation product **9f** about 600 times faster than the analogous fluoro system **8f**.



(11) Steinberg, D. I. "Computational Matrix Algebra"; McGraw-Hill: New York, 1974. Searle, S. R. "Matrix Algebra Useful for Statistics"; Wiley: New York, 1982.

(12) Cross, A. D.; Landis, P. W. *J. Am. Chem. Soc.* **1962**, *84*, 1736; **1962**, *84*, 3784. Bhacca, N. S.; Williams, D. H. "Applications of NMR Spectroscopy in Organic Chemistry"; Holden Day: San Francisco, 1964; pp 123–131.

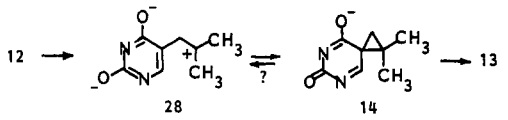
(13) The head-to-tail photocycloadduct of 5-fluorouracil and isobutylene shows in the ^1H NMR (Me_2SO-d_6) spectrum two sharp singlets at δ 1.18 and 0.90. By contrast, the photocycloadduct of 5-fluorouracil and tetramethylethylene shows in the ^1H NMR (Me_2SO-d_6) spectrum three methyl groups as sharp singlets at δ 0.82, 0.94, and 1.03, and one methyl group as a doublet (J_{HF} = 3 Hz) at δ 1.13.

(14) On the basis of bond strength arguments, breakage of the carbon–fluorine bond should be slower than that of a carbon–chlorine bond. No analogous process to compare with the leaving group effect could be found. However, 1-phenylethyl chloride solvolyzes 10^6 times faster than 1-phenylethyl fluoride[15] and undergoes E_2 elimination 68 times faster.[16]

(15) Noyce, D. S.; Virgilio, J. A. *J. Org. Chem.* **1972**, *37*, 2643.

(16) Stirling, C. J. M. *Acc. Chem. Res.* **1979**, *12*, 198.

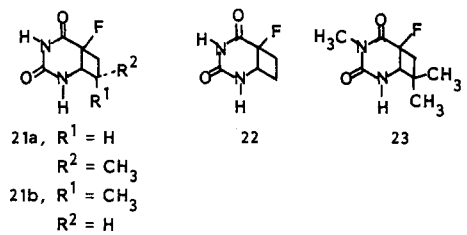
Scheme IV. Mechanistic View of the Fragmentation Reaction



28 14

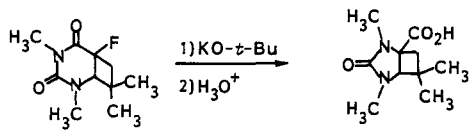
Discussion

The photocycloaddition reaction of 5-fluorouracil to vinyl acetates and the subsequent fragmentation of these photoadducts to 5-substituted uracil provide good methodology for the preparation of 5-substituted uracil derivatives under mild conditions and require little comment. The unexpected fragmentation reaction of 5-fluorouracil–alkene adducts to 5-substituted uracil derivatives proceeds in excellent yield for compounds having two alkyl groups substituted at C-8. Compounds such as **21a** and **21b** lacking this substitution are recovered largely unchanged under the fragmentation reaction conditions. Likewise, **22**, which was studied with the hope of isolating the spiro intermediate discussed earlier, was recovered largely unchanged under the fragmentation reaction conditions. The requirement of the dianion form of the uracil photoadduct for a facile fragmentation reaction is apparent from a study of the chemistry of **23** and **24**. While **23** was stable under the normal reaction conditions, **24** underwent rearrangement to **25**.[17]



21a, R^1 = H, R^2 = CH_3 21b, R^1 = CH_3, R^2 = H

22 23



24 25 (67%)

The kinetic and product studies reported herein support the intervention of a spirocyclopropyl type of intermediate (Scheme IV) in the rearrangement of the cycloadducts **8a–f**. Although this type of rearrangement is formally similar to ring contractions reported for cyclobutyl carbinols (e.g., **26** → **27**),[18] the chemistry reported herein is

26 27

not strictly analogous. This is evidenced by the failure of the anion of **23** or the dianions of **21a**, **21b**, and **22** to undergo the ring contraction. Clearly, if a simple 1,2-alkyl migration were involved in the ring contraction, then **21a** and **21b** would give the appropriate 5-substituted uracil. That C-8 disubstitution is a necessary, but not sufficient, factor for rearrangement is demonstrated by the absence of facile fragmentation of **23**.

All of the mechanistic data can be accounted for in the more refined mechanism outlined in Scheme IV.[19] Instead of a concerted 1,2-migration, ring opening occurs with loss of fluoride to give **28**. This explains the dependence of rate on the leaving group and the structural requirement of C-8 disubstitution for facile reaction. Fast intramolecular ring closure of **28** gives the spiro intermediate **14** which then is converted to **13**. This spiro intermediate is required to explain the results from fragmentation of compounds **15** and **16**. The generation of the aromatic nucleus and formation of the tertiary carbonium center at C-8 in **28** may supply the driving force for the rearrangement and may also explain why **21a**, **21b**, **22**, and **23** do not undergo the same ring contraction. The requirement of the dianion form of the dihydrouracil for facile rearrangement provides another example of the unique chemistry derived from these heterocyclic dianions.[10]

Experimental Section[20]

1,3-Dimethyl-5-(2-oxopropyl)-2,4(1*H*,3*H*)-pyrimidinedione (2) via Hydrolysis. A solution of **1a** (0.1 g, 0.39 mmol), 10% aqueous CH_3OH (5 mL), and Na_2CO_3 (0.1 g, sufficient to maintain basicity) was stirred for 21 h at room temperature. The solution was neutralized (5% HCl), extracted with $CHCl_3$, and then worked up as usual to give 83 mg of **2**. Recrystallization of this material from Et_2O/EtOH gave 0.05 g (66%) of pure **2**: mp 112–114 °C; IR (KBr) 1691 (s), 1653 (s), 1626 (s), 1471–1335 (br, m); ^1H NMR δ 7.16 (s, 1 H), 3.44 (s, 2 H), 3.40 (s, 3 H), 3.33 (s, 3 H), 2.25 (s, 3 H). Anal. Calcd for $C_9H_{12}N_2O_3$: C, 55.2; H, 6.1, N, 14.3. Found: C, 54.9; H, 6.1; N, 14.3.

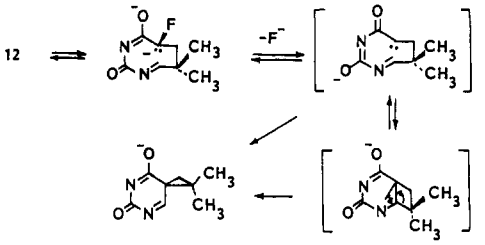
1,3-Dimethyl-5-(2-oxopropyl)-2,4(1*H*,3*H*)-pyrimidinedione (2) via Oxidation. This reaction can be performed with either epimer of **3**. The alcohol (0.1 g, 0.5 mmol) in 75% aqueous HOAc was reacted with $Ce(NH_4)_2(NO_3)_6$ (0.6 g, 1.1 mmol) at room temperature for 0.5 h. The initial yellow-orange color faded to give a colorless, clear solution. After addition of 10 mL of saturated NaCl, the solution was extracted with $CHCl_3$ and worked up as usual to give 0.09 g (quantitative) of **2**, mp 112–114 °C.

5-(2-Oxocyclohexyl)-2,4(1*H*,3*H*)-pyrimidinedione (7). To **6a** (0.211 g, 0.8 mmol) was added 1 N methanolic NaOH (2.4 mL). The solid immediately dissolved, and after 2 min a white solid precipitated. The solution was then heated to reflux for 10 min,

(17) We acknowledge Dr. Frances Grimm Dennis for conducting this experiment.

(18) Brady, W. T.; Patel, A. D. *J. Org. Chem.* **1973**, *38*, 4106.

(19) A referee has suggested an alternative mechanism shown below.



(20) Melting points below 180 °C were taken with a Thomas-Hoover capillary melting-point apparatus and melting points over 180 °C were taken on a hot-stage apparatus. Both sets of melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 283-B grating spectrophotomer and are reported in cm^{-1}. ^1H NMR spectra were taken with a Varian EM-390 (90 MHz) and Bruker WP-200 (200 MHz) or a Bruker (300 MHz) instrument. Chemical shifts are reported in ppm downfield from tetramethylsilane. The ^{13}C NMR spectra were recorded on a Bruker HX-90 at 20 MHz by Dr. Charles Cottrell and Mr. Carl Engelman. The ^{19}F NMR spectra were determined at 84.6 MHz on a Bruker HX-90 in the indicated solvent and the chemical shifts were corrected to $CClF_3$ as standard subtracting 162.9 from the shift observed relative to hexafluorobenzene. Negative chemical shifts correspond to peaks upfield from the standard. Mass spectra and exact mass measurements were obtained by Mr. C. R. Weisenberger on a Consolidated Electronics MS-9 double-focusing mass spectrometer. Analytical samples were determined by Scandinavian Microanalytical Laboratory, Herlev, Denmark. Silica gel was from E. Merck Co. and Florisil was from J. T. Baker Chemical Co. The following abbreviations are used throughout the Experimental Section: Me_2SO (dimethyl sulfoxide), *n*-BuLi (*n*-butyllithium), Et_2O (diethyl ether), EtOAc (ethyl acetate), PE (petroleum ether, 35–60 °C), and THF (tetrahydrofuran). Workup as usual consisted of extraction ($CHCl_3$ or CH_2Cl_2), drying over $CaSO_4$, and concentration in vacuo, followed by vacuum drying at 0.3 mm.

and the solvent was removed in vacuo. The ice-cooled residue was acidified with 1 N HCl (2.4 mL), and the product was filtered and dried to afford 0.123 g (76%) of **7**. The analytical sample was recrystallized from benzene/CH_3OH to afford a white solid: mp 280–283 °C; IR (KBr) 1724 (s), 1680 (s); ^{13}C NMR (Me_2SO-d_6) δ 208.2, 163.7, 151.1, 138.6, 110.8, 47.6, 41.4 (overlapping with solvent), 31.7, 26.8, and 24.7; UV (CH_3OH) λ_{max} 264 nm (ϵ 7700). Anal. Calcd for $C_{10}H_{12}O_3N_2$: C, 57.7; H, 5.8; N, 13.5. Found: C, 57.4; H, 5.9; N, 13.2.

5-(2-Oxocyclopentyl)-2,4(1*H*,3*H*)-pyrimidinedione. The endo acetate adduct of 5-fluorouracil with cyclopentenyl acetate (0.41 g, 1.6 mmol) was added to 4 N methanolic NaOH (4.8 mL), and the reaction mixture was refluxed for 10 min. Workup as for **7** gave 223 mg (73%) of the title compound. The analytical sample was crystallized from toluene/CH_3OH: mp 252–253 °C; IR (KBr) 1739 (s), 1666 (s); ^{13}C NMR (Me_2SO-d_6) δ 217.3, 163.6, 151.3, 140.0, 111.1, 47.9, 37.5 (overlapping with solvent), 29.1, 20.7; UV (CH_3OH) λ_{max} 264 nm (ϵ 7700). Anal. Calcd for $C_9H_{10}N_2O_3$: C, 55.7; H, 5.2; N, 14.45. Found: C, 55.5; H, 5.2; N, 14.4.

5-(2-Oxopropyl)-2,4(1*H*,3*H*)-pyrimidinedione. A mixture of the endo acetate adduct of 5-fluorouracil and isopropenyl acetate (0.12 g, 0.5 mmol) and 1:1 CH_3OH/H_2O (5 mL) was stirred at room temperature for 3 h and then neutralized with AG50W ion exchange resin. The mixture was filtered and evaporated in vacuo. The crystalline product was collected and dried to afford 25 mg (34%) of the title compound. The product was obtained in 60% yield when isolated by preparative TLC: mp 250–254 °C; IR (KBr) 1745 (s), 1669 (s); ^1H NMR (Me_2SO-D_6) δ 7.30 (s, 1 H), 3.33 (s, 2 H), 2.10 (s, 3 H); UV (CH_3OH) λ_{max} 264 nm (ϵ 7200). Anal. Calcd for $C_7H_8N_2O_3$: C, 50.0; H, 4.76; N, 16.7. Found; C, 49.7; H, 4.7; N, 16.7.

General Procedure for the Transformation of Alkene Cycloadducts to 5-Substituted Uracils. Potassium *tert*-butoxide was prepared by stirring dry *t*-BuOH under N_2 with the required amount of potassium. After all of the potassium had dissolved, the indicated amount of 5-fluoro-2,4-diazabicyclo-[4.2.0]octan-3,5-dione was added, and the yellow solution was heated to reflux for the indicated time. The reactions were followed by removing an aliquot and diluting it with 1 N NaOH and observing the increase in the ca. 285-nm absorption by UV spectroscopy. When the absorption ceased to increase, the reaction was cooled, and the solvent was removed in vacuo. The residue was dissolved in water and cooled in an ice bath. The cooled aqueous solution was acidified (pH 3) with concentrated HCl, and the product precipitated from the aqueous solution. A detailed procedure is given for **8a** with only physical and spectroscopic properties given for reactions which are similar.

5-(2-Methyl-2-propenyl)-2,4(1*H*,3*H*)-pyrimidinedione (9a). To potassium (235 mg) dissolved in *t*-BuOH (20 mL) was added cycloadduct **8a** (372 mg, 2 mmol). The stirred solution was brought to reflux (bath temperature 130 °C) for 0.5 h. After 10 min of reflux, the solution turned milky. The reaction was conveniently followed by diluting aliquots into 1 N NaOH and observing the appearance of a UV absorption maximum at λ_{max} 286 nm. After 0.5 h no further increase was noted. The solvent was removed in vacuo (0.3 mm), and the resultant glass was taken up in water (5 mL). The solution was cooled in an ice bath and acidified until pH 3 (red to hydrion paper) by dropwise addition of concentrated HCl. The precipitate was filtered and dried in vacuo, affording 277 mg (83%) of **8a**. Recrystallization from EtOH/H_2O gave analytically pure **8a**: mp 272–274 °C; IR (KBr) 3180 (s, br), 3040 (s, br), 1740 (s), 1660 (s); ^1H NMR (Me_2SO-d_6, 60 MHz) δ 1.67 (s, 3 H), 2.87 (br s, 2 H), 4.67 (br s, 2 H), 7.13 (s, 1 H); ^{13}C NMR δ 22.1 (q), 33.3 (t), 109.7 (s), 111.2 (t), 138.8 (d), 143.4 (s), 151.3 (s), 164.2 (s). UV (CH_3OH) λ_{max} 265 nm (ϵ 7200); UV (1 N NaOH) λ_{max} 286 nm (ϵ 6500). Anal. Calcd for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.09; N, 16.86. Found: C, 57.47; H, 6.18; N, 16.57.

5-(1-Cyclopenten-1-ylmethyl)-2,4(1*H*,3*H*)-pyrimidinedione (9c). Recrystallization of the crude product from EtOH/H_2O gave 0.165 g (86%): mp 265–267 °C; IR (KBr) 1720 (s), 1665 (s); ^1H NMR (Me_2SO-d_6, 60 MHz) 1.4–2.4 (br str m, 6 H), 2.95 (br s, 2 H), 5.29 (br s, 1 H), 7.13 (s, 1 H); exact mass calcd for $C_{10}H_{12}N_2O_2$ *m/e* 192.0899, obsd *m/e* 192.0901.

5-(1-Cyclohexen-1-ylmethyl)-2,4(1*H*,3*H*)-pyrimidinedione (9d). Analytically pure material from EtOH/H_2O had the following: mp 277–279 °C; IR (KBr) 1720 (s), 1665 (s); ^1H NMR (Me_2SO-d_6, 60 MHz) 1.50 (br m, 4 H), 1.85 (br m, 4 H), 2.7 (br s, 2 H), 5.38 (br s, 1 H), 7.05 (d, J = 5 Hz, 1 H); ^{13}C NMR (Me_2SO-d_6, Me_4Si as internal standard) 11 lines 21.9, 22.4, 24.7, 27.7, 33.37 (t), 110.0 (s), 121.8 (d), 135.3 (s), 138.3 (d), 151.3 (s), 164.3 (s); UV (CH_3OH) λ_{max} 266 (ϵ 6000) (12 N NaOH), λ_{max} 287 (ϵ 6300). Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 63.80; H, 7.02; N, 13.10.

5-(1-Cyclohepten-1-ylmethyl)-2,4(1*H*,3*H*)-pyrimidinedione (9e). Analytically pure material from EtOH/H_2O had the following: mp 282–283 °C dec; IR (KBr) 1715 (s), 1660 (s); ^1H NMR (Me_2SO-d_6) δ 1.5 (br m, 6 H), 2.01 (br m, 4 H), 2.75 (br s, 2 H), 5.54 (t, J = 6 Hz, 1 H), 7.06 (s, 1 H); UV (CH_3OH) λ_{max} 266 (ϵ 7500). Anal. Calcd for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.22; H, 7.25; N, 12.78.

5-(1,1,2-Trimethyl-2-propenyl)-2,4(1*H*,3*H*)-pyrimidinedione (9f). To potassium (236 mg, 6 mmol) dissolved in *t*-BuOH (35 mL) was added cycloadduct **8f** (428 mg, 2 mmol). This material appeared less soluble under the reaction conditions, and the heterogeneous mixture had to be refluxed for 18 h at a bath temperature of 130 °C. The standard workup precipitated 387 mg (88%) of **9f** homogeneous by TLC: mp 270 °C dec; IR (KBr) 1700 (s), 1660 (s); ^1H NMR (Me_2SO-d_6, 60 MHz) δ 1.3 (s, 6 H), 1.6 (s, 3 H), 4.73 (s, 2 H), 7.03 (s, 1 H); UV (CH_3OH) λ_{max} 260 nm (ϵ 6600); exact mass calcd for $C_{10}H_{14}N_2O_2$ *m/e* 194.10550, obsd *m/e* 194.10578.

Photocycloaddition of 5-Fluorouracil and Isobutylene-d_6.[21] A 1-L flask was equipped with an addition funnel, N_2 inlet, magnetic stirrer, and N_2 outlet. A photoaddition cell equipped with a dry ice condenser and magnetic stirring bar was charged with a solution of 5-fluorouracil (120 mg, 0.92 mmol) in acetone (75 mL, reagent), and the two systems were connected so that the N_2 outlet tube was immersed in the acetone solution. With a gentle flow of N_2 passing through the acetone, the flask was charged with magnesium (4 g) and mercury (80 mL). The flask was gently heated in an oil bath (40–50 °C) and stirred to amalgamate the magnesium (30–40 min). The flask was cooled to room temperature, and acetone-d_6 (4 mL) in dry THF (10 mL) was added. The N_2 inlet was removed, and the flask was sealed. Then a solution of CH_2I_2 (18 g, 0.067 mol), acetone-d_6 (4 mL), and THF (40 mL) was added dropwise to the stirred amalgam over a 30–40-min period. Isobutylene-d_6 was allowed to bubble through the acetone solution, and the reaction was driven to completion by heating the flask to 50 °C for 15 min. The N_2 outlet tubing was then removed from the photocell and replaced by a stopper. The acetone solution was irradiated through Corex (Hanovia 450-W) for 3.5 h. The solution was filtered, and the acetone and olefin were removed on a steam bath to give a crude product which was recrystallized from EtOAc/PE to give 150 mg (85%) of **8a**-d_6.

Photocycloaddition of 5-Fluorouracil to Isopropylidenecyclohexane. To a solution of 5-fluorouracil (152 mg, 1.11 mmol) in acetone (100 mL) was added isopropylidenecyclohexane[22] (3.0 g, 24.2 mmol). The stirred solution was irradiated through Corex with a 450-W Hanovia mercury arc lamp for 4 h, and then the solution was filtered and the filtrate was concentrated. The resulting crude white solid was washed several times with PE (bp 35–60 °C) and dried under vacuum to yield 250 mg (86%) of a mixture of **15**, **16**, and dimer in the ratio 5:6:1 by ^{19}F NMR. TLC analysis (silica gel, 50% Et_2O as eluant) resolved the adducts with R_f values of 0.30 and 0.27. Fractional recrystallization from EtOAc afforded the slower moving spot **16** pure by ^{19}F NMR: mp 276–279 °C; IR (KBr) 1710 (s), 1690 (s), ^1H NMR (Me_2SO-d_6, 200 MHz) 7.98 (d, J = 3.7 Hz, 1 H), 3.76 (d of d, J = 3.8, 24 Hz, 1 H), 1.60–1.20 (m, 10 H), 1.07 (s, 3 H), 0.82 (s, 3 H); ^{19}F NMR (pyridine/C_6H_6) −154.6 (d, J = 26 Hz).

MPLC chromatography [Lobar prepacked column (310-29, 40-63 μm) size no. 2] of crude hot mixture (95 mg) was carried out as follows: 700 mL of 25% EtOAc/PE and 100 mL of 50% EtOAc/PE, nil; 50 mL of 50% EtOAc/PE, 37 mg of **15**, 30 mL of 50% EtOAc/PE, 24 g of **15** and **16**; 120 mL of 50% EtOAc/PE,

(21) The isobutylene-d_6 was prepared via a modified procedure from that reported earlier: Hasselman, D. *Chem. Ber.* **1969**, *107*, 3486. Wexler, A. J.; Hyatt, J. A.; Raynolds, P. W.; Cottrell, C.; Swenton, J. S. *J. Am. Chem. Soc.* **1978**, *100*, 512.

(22) Adam, W.; Baeza, J.; Liu, J. *J. Am. Chem. Soc.* **1972**, *94*, 2000.

30 mg of **16**. Spectral data of **15** showed the following: mp 272–276 °C; IR (KBr) 1725 (sh, s), 1730 (s); ^{1}H NMR δ (Me_2SO-d_6, 200 MHz) δ 10.60 (s, 1 H), 8.15 (br s, 1 H), 3.79 (d of d, J = 3.3, 21 Hz, 1 H), 1.6–1.1 (br m, 10 H), 1.09 (d, J = 3.4 Hz, 3 H), 0.96 (s, 3 H); ^{19}F NMR (pyridine/C_6F_6) −156.6 (d, J = 24 Hz).

Fragmentation of 5-Fluorouracil–Isopropilidenecyclohexane Photoadducts. These fragmentations were performed as described for **8a** with the use of **15** (0.1 g) and **16** (0.35 mg). The crude solid obtained from these fragmentations was analyzed by ^{1}H NMR, which indicated a 3.4:1 mixture of **19** and **18** from **15** and 3.5:1 mixture of the same two compounds from **16** in yields of 82% and 84%, respectively. Anal. Calcd for $C_{13}H_{18}N_2O_2$: C, 66.6; H, 7.74. Found: C, 66.5; H, 7.90.

The major isomer **19** was isolated by fractional recrystallization from EtOAc: mp >300 °C; IR (KBr) 1710 (br, s), 1665 (br, s); ^{1}H NMR (Me_2SO-d_6, 200 MHz) δ 1.39 (br m, 10 H), 1.57 (s, 3 H), 4.82 (s, br, 1 H), 4.87 (s, br, 1 H), 7.01 (s, 1 H); ^{13}C NMR (Me_2SO-d_6) δ 163.1, 150.9, 147.9, 139.1, 114.6, 111.9, 44.1, 32.1, 25.9, 22.0, 19.7. Anal. Calcd for $C_{13}H_{18}N_2O_2$: C, 66.6; H, 7.74. Found: C, 66.1; H, 7.80. The minor adduct **18** was not isolated, but its structure was obtained from the crude spectrum of the mixture of **18** and **19** by subtracting the known spectrum of **19**: ^{1}H NMR (Me_2SO-d_6, 200 MHz) δ 1.23 (s, 6 H), 1.37 (br, m, 9 H), 5.42 (br, m, 1 H), 6.94 (s, 1 H).

6-Fluoro-4,8,8-trimethyl-*cis*-2,4-diazabicylo[4.2.0]octane-3,5-dione (23). A mixture of **8a** (700 mg, 3.76 mmol), K_2CO_3 (3.5 g, 25.3 mmol), $(CH_3)_2SO_4$ (4.0 mL, 42.18 mmol), and acetone (40 mL) was heated at 60–70 °C, and the reaction was monitored by TLC (CH_2Cl_2) until all of **8a** was gone (~3 h). The mixture was filtered through a sintered glass frit, and the acetone was removed in vacuo to give a yellow oil. Silica gel chromatography (2.2 × 16 cm column) proceeded as follows: 200 mL of CH_2Cl_2, trashy oil; 100 mL of CH_2Cl_2; 15 mL of 1% CH_3OH/CH_2Cl_2, 15 mg of material corresponding to the known the photoadduct of 1,3-dimethyl-5-fluorouracil and isobutylene; 25 mL of 1% CH_3OH/CH_2Cl_2, 30 mg of a mixture of the above compound and **23**; 200 mL of 1% CH_3OH/CH_2Cl_2, 550 mg of a viscous oil which crystallized after drying in vacuo: mp 101–103 °C; IR (KBr) 2960 (s, br), 1730–1680 (s, v br), 1445 (s), 1308 (s), 1288 (s), 1207 (s); ^{1}H NMR ($CDCl_3$) δ 6.96 (s, br, 1 H), 3.82 (d of d, J = 4, 21 Hz, 1 H), 3.22 (s, 3 H), 2.50–1.95 (m, 2 H), 1.27 (s, 3 H), 0.97 (s, 3 H); exact mass calcd for $C_9H_{13}O_2N_2F$ m/e 200.092, obsd m/e 200.096.

2,4,7,7-Tetramethyl-3-oxo-2,4-diazabicyclo[3.2.0]heptane-5-carboxylic Acid (25). In a manner similar to the other fragmentations, **24** (0.64 g, 3 mmol), KO-*t*-Bu (0.74 g, 6.6 mmol), and *t*-BuOH (30 mL) were heated to reflux for 20 min. The solvent was removed in vacuo, water (50 mL) was added to the residue, and the aqueous layer was acidified (pH 2) with concentrated HCl. The product was extracted with $CHCl_3$ (5 × 50 mL) and worked up to give 0.51 g of a yellow solid. Recrystallization of this material from benzene/H gave 0.435 g (68%) of **25** as white crystals: mp 168–169 °C; IR (KBr) 3500–2400 (br, m), 1730 (s), 1665 (s), 1641 (vs); ^{1}H NMR ($CDCl_3$, 80 MHz) δ 1.08 (s, 3 H), 1.27 (s, 3 H), 1.93 (d, J = 13 Hz, 1 H), 2.43 (d of d, J = 1.5, 13 Hz, 1 H), 2.82 (s, 6 H), 3.75 (br, 1 H), 10.2 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 174.1 (s), 161.3 (s), 66.3 (d), 59.3 (s), 40.3 (t), 38.06 (s), 30.9 (q), 28.6 (q), 26.7 (q), 23.4 (q). Anal. Calcd for $C_{10}H_{16}N_2O_3$; C, 56.6; H, 7.6; N, 13.2. Found: C, 56.7; H, 7.6; N, 13.2.

5-Fluorouracil-6-d_1. To sodium deuteriohydroxide (0.138 g of Na in 12 mL of D_2O) was added 5-fluorouracil (0.39 g, 3 mmol), and the resulting solution was stirred at 60 °C for 6 h. The solution was cooled in ice and acidified to pH 3 with concentrated HCl. The precipitated white solid was collected, washed with cold deionized water, and dried to afford 0.262 g (66%) of the title compound. Analysis for deuterium content by ^{1}H NMR (Me_2SO-d_6) using 1,3,6-trimethyluracil as standard indicated at least 95% deuterium incorporation.

General Procedure for Kinetics. For all kinetic runs, the solutions of **8a**, **8f**, and **20** were prepared in volumetric flasks at room temperature. Base solutions were prepared immediately prior to use by dissolving freshly cut potassium in *t*-BuOH distilled from sodium. This standard solution was titrated with 1.004 M sulfuric acid with phenolphthalein as indicator. The required amount of each solution was transferred via syringe to a stoppered flask and diluted to desired concentration with the appropriate amount of *t*-BuOH. Aliquots from this stock solution were then sealed into ampules and placed in a constant-temperature bath. The ampules were pulled from the bath at appropriate time intervals so that most points would be pulled within the first 3 half-lives of the reaction. The ampules were labeled and placed in a dry ice/isopropyl alcohol bath to quench the reaction. The ampules were then warmed to room temperature in a water bath and analyzed by removing an aliquot (40 L) and diluting in 2% NaOH [2.5 mL]. Spectrophotometric analysis at 285 nm gave the concentration of the product uracil.

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Registry No. **1a**, 57767-87-0; **2**, 57767-91-6; **3** (isomer 1), 90344-77-7; **3** (isomer 2), 90410-21-2; **6a**, 57767-85-8; **7**, 57767-89-2; **8a**, 59137-86-9; **8a**-d_6, 90344-78-8; **9a**, 59137-97-2; **9c**, 59137-98-3; **9d**, 59137-99-4; **9e**, 59138-00-0; **9f**, 90296-01-8; **15**, 90367-66-1; **16**, 90344-79-9; **18**, 90344-80-2; **19**, 90344-81-3; **23**, 90344-82-4; **25**, 90344-83-5; $(CD_3)C{=}CH_2$, 1560-62-9; (4α,4bβ,7aβ,7bα)-4a-fluoro-7a-acetoxydecahydro-1*H*-cyclopenta[3,4]cyclobuta[1,2-*d*]pyrimidine-2,4-dione, 57767-84-7; (5aα,7β,7aα)-7-acetoxy-7-methyl-2,4-diazabicyclo[4.2.0]octane-3,5-dione, 57767-86-9; 5-(2-oxopropyl)-2,4(1*H*,3*H*)-pyrimidinedione, 57767-90-5; 5-fluorouracil, 51-21-8; isopropylidenecyclohexane, 5749-72-4; 5-fluorouracil-6-*d*, 90344-84-6; 5-(2-oxocyclopentyl)-2,4(1*H*,3*H*)-pyrimidinedione, 57767-88-1.

Supplementary Material Available: Experimental procedures for **4b** and **4c** derivation of rate expressions; analyses of kinetic data; ^{1}H NMR spectra of **4b**, **4c**, **15**, and **16**; ^{19}F NMR spectrum of **4b** (9 pages). Ordering information is given in any current masthead page.