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Synthesis and Biological Evaluation of New Bicyclic Fluorinated Uracils through Ring-Closing Metathesis§

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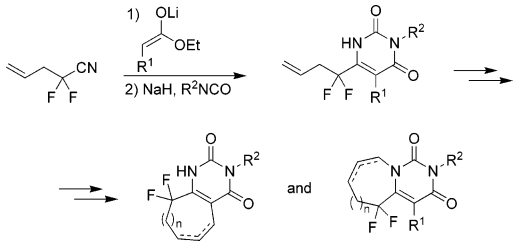
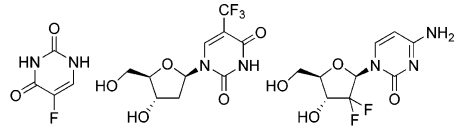


Two families of bicyclic fluorinated uracils have been prepared starting from a *gem*-difluorinated unsaturated nitrile, by means of a ring-closing metathesis reaction to form the new ring, which is fused at the C-5/C-6 or N-1/C-6 positions of the uracil moiety. The selective formation of olefin regioisomers in the metathesis process can be controlled according to the reaction conditions (catalyst, solvent, and temperature). The acaricidal activities of the resulting compounds have also been investigated.

Disrupting the biological mechanisms associated with nucleic acids in order to develop effective agents with antitumoral and/or antiviral activities has become a major field in drug discovery research. In this context, the preparation of molecules that mimic the structures of nucleic acids or their building blocks has provided many therapeutically useful compounds.[1] In addition, because the introduction of fluorine atoms into organic molecules usually promotes dramatic changes in their biological properties, this particular strategy has been used successfully to synthesize biologically active fluorinated nucleotides and nucleosides.[2] Two emblematic examples of this are 5-fluorouracil and trifluridine (Chart 1), both potent inhibitors of thymidylate synthase. Thus, 5-fluorouracil is now a widely used drug in the treatment of several types of cancer, and trifluridine has proven to be an effective antiviral agent against *Herpes simplex* infections. By carefully positioning the fluorine atoms, compounds with different effects can be formed, as is the case with the antitumoral compound gemcitabine, in which the fluorine atoms are positioned in the sugar moiety.[3]

CHART 1. Examples of Fluorinated Nucleosides and Bases



More examples of biologically active compounds formed in this fashion include C-6 fluorinated uracils, which have important applications as agrochemicals, especially as herbicides, insecticides, and acaricides.[4] In fact, we recently reported our preparation of uracils **3** with a fluoroalkyl substituent at C-6, in which fluorinated nitriles (R_FCN) **1** and esters **2** were used as precursors (Scheme 1).[5,6] As an extension of this methodology, we now describe the preparation of two new classes of bicyclic fluorinated uracils,[7] both of which have a fused ring either between C-5 and C-6 (**4**) or between N-1 and C-6 (**5**) (Scheme 2). The starting material for both **4** and **5** is 2,2-difluoropent-4-enenitrile **6**, and the key step is a ring-closing metathesis (RCM) reaction,[8,9] which is carried out after suitable olefin substituents have been introduced within the uracil framework. In addition, we have also undertaken a preliminary evaluation of the acaricidal activity of the resulting derivatives.

§ In Memoriam of Professor Marcial Moreno-Mañas.

† Universidad de Valencia.

‡ Centro de Investigación Príncipe Felipe.

(1) *Nucleosides and Nucleotides as Antitumor and Antiviral Agents*; Chu, C. K., Baker, D. C., Eds.; Plenum Press: New York, 1993.

(2) (a) Ozaki, S. *Med. Res. Rev.* **1996**, *16*, 51−86. (b) Ojima, I.; McCarthy, J. R.; Welch, J. T. In *Biomedical Frontiers of Fluorine Chemistry*; ACS Symposium Series 639; American Chemical Society: Washington, DC, 1996. (c) Filler, R.; Kobayashi, Y. *Biomedicinal Aspects of Fluorine Chemistry*; Elsevier Biomedical Press: New York and Kodansha Ltd: Tokyo, 1982. (d) Pankiewicz, K. W. *Carbohydr. Res.* **2000**, *327*, 87−105.

(3) (a) Kotra, L. P.; Xiang, Y.; Newton, M. G.; Schinazi, R. F.; Cheng, Y.-C.; Chu, C. K. *J. Med. Chem.* **1997**, *40*, 3635−3644. (b) Hertel, L. W.; Kroin, J. S.; Misner, J. W.; Tustin, J. M. *J. Org. Chem.* **1988**, *53*, 2406−2409.

(4) As examples, see: (a) Tohyama, Y.; Sanemitsu, Y. PCT Int. Appl. EP 1122244 A1, 2001; *Chem. Abst.* **2001**, *135*, 152820. (b) Theodoridis, G.; Crawford, S. D. PCT Int. Appl. US 6277847 B1, 2001; *Chem. Abst.* **2001**, *135*, 180781. (c) Drewes, M.-W.; Andree, R.; Dollinger, M. PCT Int. Appl. DE 19632005 A1, 1998; *Chem. Abst.* **1998**, *128*, 167437. (d) Koiso, T.; Ono, S.; Kondo, H.; Asada, T. PCT Int. Appl. JP 09241245 A2, 1997; *Chem. Abst.* **1997**, *127*, 274174. (e) Kameswaran, V. PCT Int. Appl. US 6191275 B1, 2001; *Chem. Abst.* **2001**, *134*, 178567. (f) Yagi, K.; Akimoto, K.; Mimori, N.; Miyake, T.; Kudo, M.; Arai, K.; Ishii, S. *Pest. Manag. Sci.* **2000**, *56*, 65−73.

(5) Fustero, S.; Piera, J.; Sanz-Cervera, J. F.; Catalán, S.; Ramírez de Arellano, C. *Org. Lett.* **2004**, *6*, 1417−1420.

(6) For a different synthetic approach leading to C-6 fluorinated uracils, see: Fustero, S.; Salavert, E.; Sanz-Cervera, J. F.; Piera, J.; Asensio, A. *Chem. Commun.* **2003**, 844−845.

(7) The synthesis of nonfluorinated, polycyclic uracils has been previously reported. For some examples, see: (a) García Martínez, A.; Herrera Fernández, A.; Moreno Jiménez, F.; Muñoz Martínez, P. J.; Alonso Martín, C.; Subramanian, L. R. *Tetrahedron* **1996**, *52*, 7973−7982. (b) Macchia, M.; Antonelli, G.; Balsamo, A.; Barontini, S.; Calvani, F.; Gentili, D.; Martinelli, A.; Rossello, A.; Turriziani, O.; Tesoro, R. *Il Farmaco* **1999**, *54*, 242−247.

(8) For reviews of the metathesis reaction, see: (a) Grubbs, R. H. In *Handbook of Metathesis*; Wiley-VCH Verlag Gmbh and Co. KGaA: Weinheim, 2003; Vols. 1−3. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450. (c) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012−3043. (d) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592−4633. (e) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117−7140.

(9) The metathesis reaction has been widely used for the preparation of nucleosides and analogues, mostly for building the sugar ring. For a recent review, see: Amblard, F.; Nolan, S. P.; Agrofolio, L. A. *Tetrahedron* **2005**, *71*, 7067−7080.

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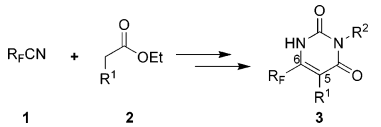
SCHEME 1



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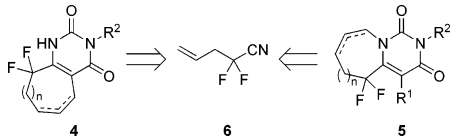

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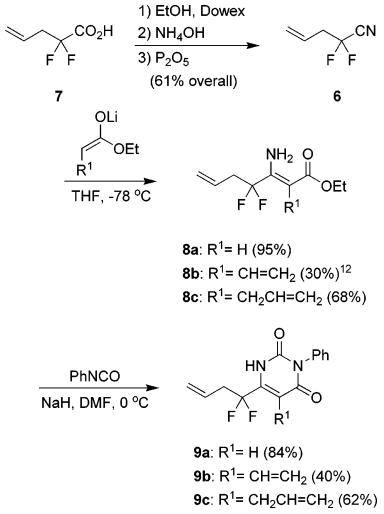
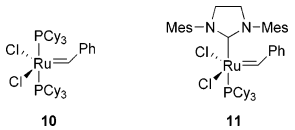


CHART 2. Structures of First (10) and Second (11) Generation Grubbs' Catalysts



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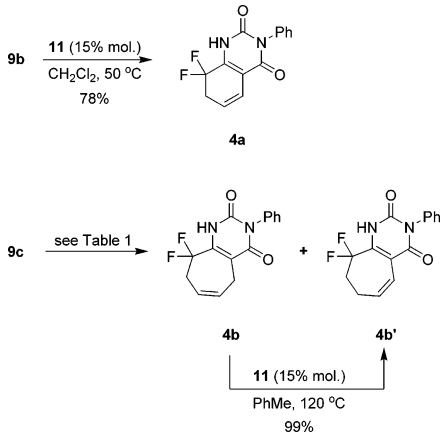


TABLE 1. Reaction Conditions for the RCM of 9c

entry	catalyst (15 mol %)	solvent	temp (°C)	**4b**:**4b′** ratio	yield (%)[a]
1	**11**	CH_2Cl_2	50	72:28	74
2	**10**	CH_2Cl_2	50	100:0	71
3	**11**	PhMe	120	0:100	70

[a] Isolated yield of pure products.

The starting nitrile **6** was obtained from the known[10] 2,2-difluoropent-4-enoic acid **7** in three standard steps, namely, ethyl ester formation, transformation to the corresponding primary amide, and dehydration to the nitrile[11] (Scheme 3). Next, **6** was treated at −78 °C with the lithium enolates derived from ethyl acetate (R^1 = H), ethyl but-3-enoate (R^1 = vinyl),[12] or ethyl pent-4-enoate (R^1 = allyl), all of which were generated by their reaction with LDA, to afford *β*-enamino esters **8a**−**c**. The latter compounds, isolated solely in their enamino tautomeric form, were then deprotonated with NaH, and further addition of phenyl isocyanate gave uracils **9a**−**c**.[13]

Uracils **9b** and **9c**, which already contained two olefinic moieties, were the direct precursors of bicyclic uracils **4**. Thus, the RCM reaction of compound **9b** was carried out in the presence of Grubbs' second generation catalyst **11** (Chart 2) and CH_2Cl_2 as solvent by heating (50 °C) in a sealed flask to obtain the six-membered cyclized product **4a** in good yield (Scheme 4). However, when the same reaction conditions were used on substrate **9c**, a mixture of the seven-membered isomeric uracils **4b** and **4b′** was obtained (72:28 ratio), with the minor product coming from the isomerization of the double bond after the metathesis reaction[14] (Table 1, entry 1). We found, however, that by fine-tuning the reaction conditions,[15] we could successfully carry out the regioselective preparation of either bicyclic uracil. Thus, the use of Grubbs' first generation catalyst **10** in CH_2Cl_2 yielded only **4b** (entry 2), whereas heating in the presence of the second generation catalyst **11** in toluene (120 °C in a sealed flask) led to the isomerization of the double bond to give **4b′** as a single product (entry 3). It should be noted that the other possible isomer (coming from the migration of the double bond toward the fluorine atoms) was not detected, apparently due to a stereoelectronic effect of the contiguous difluoromethylene moiety.[15] Furthermore, the metathesis reaction proceeded much faster than the isomerization since no ring-contraction product, namely **4a**, was formed from **9c**. Finally, we found that a two-step procedure involving metathesis followed by isomerization was also efficient for the preparation of compound **4b′**.[16]

We next focused on the preparation of the second family of bicyclic uracils **5**, which was accessible from compound **9a** after the introduction of a second olefinic substituent at N-1.

(10) (a) Greuter, H.; Lang, R. W.; Romann, A. J. *Tetrahedron Lett.* **1988**, *29*, 3291−3294. (b) Xu, F.; Simmons, B.; Armstrong, J., III; Murry, J. *J. Org. Chem.* **2005**, *70*, 6105−6107.

(11) An alternative access to nitrile **6** from ethyl difluoroiodoacetate has been reported; see: Hung, M.-H.; Logothetis, A. L. PCT Int. Appl. WO 9705122 A1, 1997; *Chem. Abst.* **1997**, *126*, 239542.

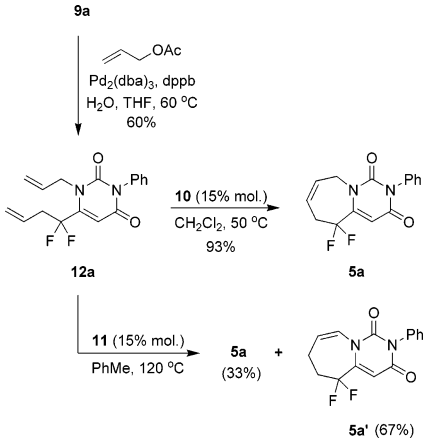
(12) The lithium enolate of ethyl but-3-enoate also afforded the *γ*-alkylation product as a side reaction (30% yield).

(13) Yields of uracils **9** are sometimes compromised as a result of their difficult separation from byproducts formed when isocyanates react with liberated EtOH.

(14) (a) These isomerizations usually take place *before* the metathesis process and are promoted by the presence of ruthenium hydride species formed by decomposition of catalyst **11**; see: Hong, S. H.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2004**, *126*, 7414−7415. (b) For a review, see: Schmidt, B. *Eur. J. Org. Chem.* **2004**, 1865−1880.

(15) We have also been able to control these RCM reaction conditions with or without the double bond isomerization in a variety of fluorinated and non-fluorinated substrates. For a mechanistic explanation, see: Fustero, S.; Sánchez-Roselló, M.; Jiménez, D.; Sanz-Cervera, J. F.; del Pozo, C.; Aceña, J. L. *J. Org. Chem.* **2006**, *71*, 2706−2714.

SCHEME 5



Unfortunately, the reaction of **9a** with allyl bromide and NaH afforded mixtures of *N*- and *O*-allylation products that were difficult to separate. After some experimentation, we finally discovered that treatment of **9a** with allyl acetate under Pd(0) catalysis[17] yielded the desired *N*-allyl uracil **12a** as the only product (Scheme 5). When we subjected this compound to the previously optimized RCM conditions using Grubbs' first generation catalyst **10**, bicyclic uracil **5a** was obtained as a single isomer. However, in sharp contrast to bicyclic uracils **4**, the double bond was only partially isomerized in the presence of the second generation catalyst **11** in toluene, resulting in a mixture of **5a** and **5a′** (33:67 ratio). These were subsequently separated by means of column chromatography. Forcing the reaction conditions[18] did not improve the yield of the isomerized product **5a′**. Moreover, treatment of **5a** with catalyst **11** only produced a mixture of both isomers **5a** and **5a′** (50:50 ratio). It would thus seem that the electron-withdrawing group attached to the N-1 nitrogen atom precludes the isomerization, despite the effect of the difluoromethylene group.[15]

After optimizing this synthetic strategy, we then proceeded to prepare a small library of different bicyclic uracils **4** and **5**, all with a seven-membered fused ring, using a variety of isocyanates in the reaction with enamino esters **8**. In this manner, different substituents R^2 can be introduced at the N-3 position, including aliphatic, aromatic, electron-withdrawing, electron-donating, and chiral groups (Chart 3).

Finally, representative examples of these bicyclic uracils and their precursors (**4b**, **4e**, **4e′**, **5a**, **5a′**, **5d**, **9b**, and **9g**) were tested as acaricides against *Tetranychus urticae* (twospotted spider mite), a parasite of crops and common houseplants, using the commercially available miticide tebufenpyrad[19] as reference standard. Preliminary results from a 24-, 96-, and 144-h assay[20] showed that only those compounds shown in Table 2 were active at a concentration of 4.0−5.0 mg/mL, in terms of both mortality and fecundity inhibition (**4b** inhibited fecundity only, entry 2). Although promising, these results did not establish a clear structure−activity relationship but nevertheless served to confirm the potential of C-6 fluorinated uracils as acaricides.[4]

In summary, we have prepared a small library of two new families of fused bicyclic fluorinated uracils, through a straightforward synthetic route starting from a simple fluorinated nitrile, using either a RCM or a tandem RCM−isomerization to construct the second ring. More experiments to determine the usefulness of these compounds are underway.

Experimental Section

General Procedure for Ring-Closing Metathesis Reaction (Method A). Grubbs' first generation catalyst **10** (15% molar equiv, 0.045 mmol) was added to a solution of compound **9** or **12** (0.3 mmol) in CH_2Cl_2 (0.02 M) at room temperature. The reaction mixture was stirred at 50 °C in a sealed flask under inert atmosphere for 2 h. The solvent was then removed under vacuum. The crude product **4** or **5** was purified through a silica gel column with solvent mixtures as indicated in each case.

General Procedure for Tandem RCM−Isomerization Reaction (Method B). Grubbs' second generation catalyst **11** (15% molar equiv, 0.045 mmol) was added to a solution of compound **9** or **12** (0.3 mmol) in toluene (0.02 M) at room temperature. The reaction mixture was stirred at 120 °C in a sealed flask under inert atmosphere for 3 h. The solvent was then removed under vacuum. The crude product **4′** or **5′** was purified through a silica gel column with solvent mixtures as indicated in each case.

8,8-Difluoro-7,8-dihydro-3-phenylquinazoline-2,4(1*H*,3*H*)-dione (4a). Starting from **9b**, and after subsequent purification of the crude product by means of flash chromatography (*n*-hexane/EtOAc, 2:1), use of Method A with catalyst **11** gave **4a** as a white solid (78% yield): R_f = 0.23 (*n*-hexane/EtOAc, 2:1); mp 204−206 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.06 (tq, J = 21.0, 2.0 Hz, 2H), 5.88−5.92 (m, 1H), 6.65 (dt, J = 10.0, 2.0 Hz, 1H), 7.23−7.25 (m, 2H), 7.39−7.54 (m, 3H), 8.69 (br, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 34.5 (t, $^2J_{CF}$ = 24.9 Hz), 110.2 (t, $^3J_{CF}$ = 6.0 Hz), 116.9 (t, $^1J_{CF}$ = 243.1 Hz), 118.3 (t, $^4J_{CF}$ = 3.0 Hz), 119.7 (t, $^3J_{CF}$ = 5.7 Hz), 128.1, 129.1, 129.4, 134.0, 136.1 (t, $^2J_{CF}$ = 25.7 Hz), 150.4, 161.0; ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −95.1 (t, J_{HF} = 21.0 Hz, 2F); IR (film) 3079, 2995, 1723, 1664, 1429, 1350, 1173, 1042 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{10}F_2N_2O_2$ (M^+) 276.0710, found 276.0679.

9,9-Difluoro-8,9-dihydro-3-phenyl-1*H*-cyclohepta[*d*]pyrimidine-2,4(3*H*,5*H*)-dione (4b). Starting from **9c**, and after subsequent purification of the crude product by means of flash chromatography (*n*-hexane/EtOAc, 2:1), Method A gave **4b** as a white solid (71% yield): R_f = 0.25 (*n*-hexane/EtOAc, 2:1); mp 213−215 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.94 (tdd, J = 15.1, 6.0, 1.5 Hz, 2H), 3.34−3.37 (m, 2H), 5.62−5.69 (m, 1H), 6.00−6.07 (m, 1H), 7.14−7.19 (m, 2H), 7.35−7.47 (m, 3H), 7.93 (br, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.2, 35.2 (t, $^2J_{CF}$ = 25.8 Hz), 112.6 (t, $^3J_{CF}$ = 5.8 Hz), 116.5 (t, $^1J_{CF}$ = 243.7 Hz), 121.9 (t, $^3J_{CF}$ = 6.3 Hz), 128.4, 129.5, 129.9, 131.7, 134.8, 141.3 (t, $^2J_{CF}$ = 27.0 Hz), 150.2, 163.6;

(16) Structural assignation of both isomers **4b** and **4b′** was carried out on the basis of their ^{1}H NMR spectra: compound **4b** presents two signals (5.65 and 6.05 ppm) corresponding to an isolated double bond, whereas their chemical shifts in **4b′** (5.96 and 6.58 ppm) indicates the conjugation of the double bond with the uracil ring.

(17) (a) Moreno-Mañas, M.; Pleixats, R.; Villarroya, M. *Tetrahedron* **1993**, *49*, 1457−1464. (b) Goux, C.; Sigismondi, S.; Sinou, D.; Pérez, M.; Moreno-Mañas, M.; Pleixats, R.; Villarroya, M. *Tetrahedron* **1996**, *52*, 9521−9534.

(18) These modifications included longer reaction times, higher amounts of catalyst (up to 25 mol %), or the use of different solvents, e.g., trifluorotoluene.

(19) Kim, Y.-J.; Lee. H.-S.; Lee, S.-W.; Kim, G.-H.; Ahn, Y.-J. *J. Econ. Entomol.* **1999**, *92*, 187−192.

(20) **Acaricide Assay.** Bean leaf disks (2 cm diameter) were sprayed by using a Potter tower with an aqueous solution of the compound, a commercial solution of tebufenpyrad [*N*-(4-*tert*-butylbenzyl)-4-chloro-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxamide, containing 1.5 mg/mL of active component] or H_2O as control (0.1% of a wetting agent was added to all solutions). Adult female mites were transferred to the disks (3 mites per disk) and placed on Petri dishes supported by wet cotton pads. The mites were kept at 20−25 °C, 50−80% relative humidity and a 16:8 h photoperiod (light:dark). The number of surviving mites and eggs were counted after 24, 96, and 144 h, and percent mortality was calculated using Abbott's equation, which corrects for mortality in the controls: [(number surviving in control − number surviving treatment)/number surviving in control] × 100.

CHART 3. Bicyclic Uracils (Yields of the RCM Reaction in Brackets)

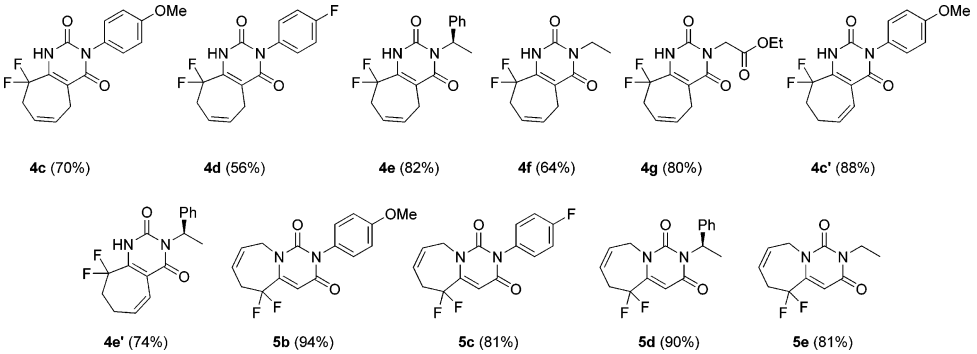


TABLE 2. Acaricide Activities of Fluorinated Uracils

entry	compd	[M] (mg/mL)	mortality (%)			fecundity inhibition (%)		
			24 h	96 h	144 h	24 h	96 h	144 h
1	tebufen-pyrad	1.5	58.8	70.4	86.7	96.8	99.6	100.0
2	**4b**	5.0	0.0	0.0	0.0	15.5	57.0	81.5
3	**4e**	4.0	38.2	66.7	86.7	78.6	46.7	68.3
4	**4e′**	4.5	11.8	56.6	100.0	57.1	53.3	74.7
5	**5d**	5.0	33.8	16.7	73.3	70.2	72.8	84.5

^{19}F NMR (282.4 MHz, $CDCl_3$) δ −92.7 (t, J_{HF} = 15.4 Hz, 2F); IR (film) 3186, 3128, 1723, 1652, 1495, 1423, 1329, 1193 cm^{-1}. HRMS (EI) calcd for $C_{15}H_{12}F_2N_2O_2$ (M^+) 290.0867, found 290.0816.

9,9-Difluoro-8,9-dihydro-3-phenyl-1*H*-cyclohepta[*d*]pyrimidine-2,4(3*H*,7*H*)-dione (4b′). Starting with **9c**, and after subsequent purification of the crude product by means of flash chromatography (*n*-hexane/EtOAc, 2:1), Method B gave **4b′** as a white solid (70% yield): R_f = 0.32 (*n*-hexane/EtOAc, 2:1); mp 247−249 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.35−2.44 (m, 2H), 2.47−2.54 (m, 2H), 5.96 (dt, J = 12.4, 5.0 Hz, 1H), 6.58 (dt, J = 12.4, 1.8 Hz, 1H), 7.16−7.19 (m, 2H), 7.36−7.48 (m, 3H), 8.09 (br, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.3 (t, $^3J_{CF}$ = 6.4 Hz), 32.5 (t, $^2J_{CF}$ = 24.6 Hz), 109.3, 118.0 (t, $^1J_{CF}$ = 243.8 Hz), 118.6, 128.0, 129.1, 129.5, 131.9, 134.3, 139.8 (t, $^2J_{CF}$ = 26.9 Hz), 149.2, 162.9; ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −93.2 (t, J_{HF} = 14.4 Hz, 2F); IR (film) 3122, 2983, 1720, 1657, 1436, 1411, 1340, 1205, 1116, 1064 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{12}F_2N_2O_2$ (M^+) 290.0867, found 290.0872.

General Procedure for Preparation of Compounds 12. A solution of allyl acetate (4.0 mmol) in THF (1.5 mL) was transferred to a flask containing bis(dibenzylideneacetone)palladium (0.08 mmol) and 1,4-bis(diphenylphosphino)butane (0.16 mmol). This solution was added to a mixture of compound **9** (1.0 mmol) in water (4 mL). After being heated at 60 °C for 27 h, the mixture was partitioned between CH_2Cl_2 and water. The organic layer was then dried and concentrated. The residue was digested with Et_2O, the ethereal filtrate was concentrated, and the residue was purified by means of column chromatography on silica gel with *n*-hexanes/ethyl acetate mixtures of increasing polarity to afford 1-allyluracils **12**.

1-Allyl-6-(1,1-difluorobut-3-enyl)-3-phenylpyrimidine-2,4-(1*H*,3*H*)-dione (12a). Flash chromatography (*n*-hexane/EtOAc, 4:1 to 2:1) of the crude reaction mixture on silica gel gave **12a** as a white solid (60% yield): R_f = 0.42 (*n*-hexane/EtOAc, 2:1); mp 86−88 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.95 (td, J = 17.6, 7.0 Hz, 2H), 4.54 (d, J = 5.4 Hz, 2H), 5.15−5.30 (m, 4H), 5.67−5.89 (m, 2H), 6.08 (s, 1H), 7.12−7.16 (m, 2H), 7.36−7.46 (m, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 40.1 (t, $^2J_{CF}$ = 25.6 Hz), 47.8 (t, $^4J_{CF}$ = 5.4 Hz), 102.1 (t, $^3J_{CF}$ = 7.7 Hz), 117.2 (t, $^1J_{CF}$ = 246.3 Hz), 117.3, 121.4, 125.6 (t, $^3J_{CF}$ = 5.2 Hz), 126.9, 128.0, 128.4, 130.8, 133.6, 145.8 (t, $^2J_{CF}$ = 27.6 Hz), 150.7, 160.5; ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −95.5 (t, J = 16.5 Hz, 2F); IR (film) 1720, 1675, 1451, 1381, 1226 cm^{-1}. HRMS (EI) calcd for $C_{17}H_{16}F_2N_2O_2$ (M^+) 318.1180, found 318.1212.

5,5-Difluoro-5,6-dihydro-2-phenylpyrimido[1,6*a*]azepine-1,3-(2*H*,9*H*)-dione (5a). Starting from **12a**, and after subsequent purification of the crude product by means of flash chromatography (*n*-hexane/EtOAc, 2:1), Method A gave **5a** as a white solid (93% yield): R_f = 0.36 (*n*-hexane/EtOAc, 2:1); mp 136−138 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.00 (tq, J = 15.6, 1.9 Hz, 2H), 4.70 (dt, J = 4.3, 1.4 Hz, 2H), 5.63−5.69 (m, 1H), 5.87−5.94 (m, 1H), 6.19 (s, 1H), 7.12−7.15 (m, 2H), 7.35−7.44 (m, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 37.6 (t, $^2J_{CF}$ = 27.6 Hz), 39.6 (t, $^4J_{CF}$ = 5.1 Hz), 99.5 (t, $^3J_{CF}$ = 8.6 Hz), 116.1 (t, $^1J_{CF}$ = 245.1 Hz), 123.6, 123.8 (t, $^3J_{CF}$ = 6.3 Hz), 126.9, 127.9, 128.4, 133.9, 147.2 (t, $^2J_{CF}$ = 28.4 Hz), 150.4, 160.6; ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −97.1 (t, J = 15.9 Hz, 2F); IR (film) 1716, 1690, 1452, 1365, 1205, 1101 cm^{-1}. HRMS (EI) calcd for $C_{15}H_{12}F_2N_2O_2$ (M^+) 290.0866, found 290.0950.

5,5-Difluoro-5,6-dihydro-2-phenylpyrimido[1,6*a*]azepine-1,3-(2*H*,5*H*)-dione (5a′). Starting from **12a**, and after subsequent purification of the crude product by means of flash chromatography (*n*-hexane/EtOAc, 2:1), Method B gave a mixture of **5a** (33% yield) and **5a′** (67% yield). Data for **5a′**: R_f = 0.30 (*n*-hexane/EtOAc, 2:1); mp 98−100 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.36 (q, J = 7.1 Hz, 2H), 2.58 (tt, J = 15.1, 7.1 Hz, 2H), 5.74 (dt, J = 7.1, 6.8 Hz, 1H), 6.22 (s, 1H), 6.67 (d, J = 8.3 Hz, 1H), 7.16−7.19 (m, 2H), 7.36−7.39 (m, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.4 (t, $^3J_{CF}$ = 5.3 Hz), 38.8 (t, $^2J_{CF}$ = 24.6 Hz), 100.9 (t, $^3J_{CF}$ = 9.1 Hz), 117.4 (t, $^1J_{CF}$ = 245.6 Hz), 120.3, 126.2, 127.9, 129.1, 129.4, 134.2, 147.4 (t, $^2J_{CF}$ = 28.6 Hz), 150.4, 161.2; ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −91.8 (t, J = 14.6 Hz, 2F); IR (film) 1719, 1675, 1468, 1383, 1349, 1148, 1128 cm^{-1}. HRMS (EI) calcd for $C_{15}H_{12}F_2N_2O_2$ (M^+) 290.0866, found 290.0856.

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Supporting Information Available: Characterization data for compounds **4c**−**g**, **4c′**, **4e′**, **5b**−**e**, **8a**−**c**, **9a**−**l**, and **12b**−**e**; copies of the NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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