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A new strategy for the synthesis of fluorinated 3,4-dihydropyrimidinones

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ABSTRACT

A new family of 3,4-dihydropyrimidinones (DHPMs) bearing fluorinated substituents at C6 have been prepared from *gem*-difluorinated nitriles, alkyl 3-butenoates and iso(thio)cyanates. This novel Biginelli-type process relies on the γ-addition of the ester-derived enolate to fluorinated nitriles. A tandem nucleophilic addition aza-Michael reaction sequence completes the synthetic process.

4-Aryl-3,4-dihydropyrimidin-2(1*H*)-ones **1** (DHPMs) were reported for the first time more than a century ago. In 1893 the Italian chemist Pietro Biginelli discovered an acid-catalyzed multicomponent reaction between aromatic aldehydes, urea and ethyl acetoacetate that produced multifunctionalized DHPMs **1** [1], in a simple one-pot process (Scheme 1).

However, the real interest in DHPMs **1** arose several decades later, having experienced a remarkable rebirth in the early 1980s [2]. This was mainly due to their structural relationship with the clinically important dihydropyridine calcium channel blockers (*e.g. nifedipine* **2**, Fig. 1), used in the treatment of high blood pressure [3]. Additionally, the multicomponent approach is considered a powerful tool for preparing biologically relevant compounds in an efficient manner, the Biginelli reaction being an emblematic example [4]. Many DHPMs have been synthesized using this methodology and many of them have shown important pharmaceutical properties, including calcium channel modulation (**3**, **4**) [5,6], antiviral (*e.g. nitractin* **5**) [7], antitumoral (*e.g. monastrol* **6**) [8], anti-inflammatory [2,9] and α_{1a}-adrenergic receptor antagonism activities (Fig. 1) [5b–c,10].

Moreover, the introduction of fluorine atoms into organic molecules usually promotes dramatic changes in their biological properties [11]. Although fluorinated entities are important in medicinal chemistry, their appearance in DHPMs is limited either as substituents in the aromatic ring on C4 or as a trifluoromethyl group in C6. In this context, we have developed a new variant of the Biginelli reaction that allows the preparation of a new family of C6-fluoroalkyl substituted DHPMs **10**. The synthetic strategy is depicted below (Scheme 2).

In an ongoing project from our laboratory aiming at the synthesis of fluorinated heterocycles [12], we found that the reaction of ester enolates with fluorinated nitriles and subsequent treatment with iso(thio)cyanates led to the formation of uracils. The reaction took place efficiently, and it was adapted both to solid phase [13] and fluorous synthesis [14]. As an extension of this methodology, we planned to prepare bicyclic uracils. To this end, the ester of choice was ethyl 3-butenoate **8**, since it would allow us to create the second ring unit by means of a ring closing metathesis reaction over uracils **13** ($R_F = CF_2$allyl) (Scheme 2) [15]. The ambident nature of the enolate of **8** explains the formation of two products in its reaction with fluorinated nitriles **7**, one coming from the attack at the γ-position (thermodynamic product, **11**) and the second one from the attack at the α-position (kinetic product, **12**). While the reaction of **12** with iso(thio)cyanates **9** led to the formation of uracils **13** [15], the same protocol applied to enamino esters **11** would lead to the formation of DHPMs **10**. Herein we describe our efforts to direct the reaction of the lithium enolate of ester **8** with fluorinated nitriles **7** towards the formation of products **11**, which in turn would react with heterocumulenes **9** to render DHMPs **10** (Scheme 3).

The first step of our study involved the search for suitable conditions to obtain the thermodynamic regioisomers **11**. When nitrile **7a** [16] was treated at −78 °C with the lithium enolate derived from **8**, a 50:50 mixture of regioisomeric enamino esters

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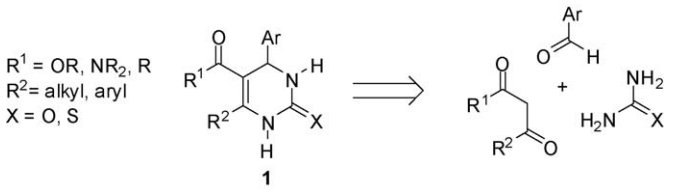
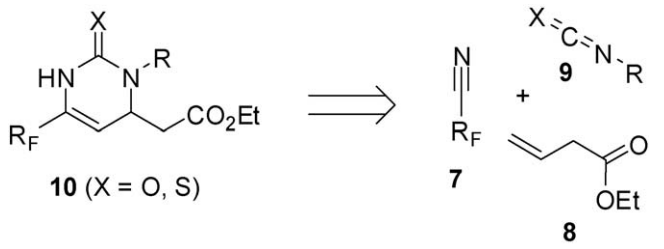


Scheme 1. Biginelli synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones **1** (DHPMs).



Scheme 2. Synthetic strategy.

11a and **12a** was obtained (Table 1, entry 1) [15]. However, a very slow addition of a THF solution of nitrile **7a** over the enolate with a syringe pump (2 mL/h) led to the selective formation of **11a** (Table 1, entry 3). When those conditions were applied to nitrile **7b**, it was possible to obtain both regioisomers selectively: the fast addition of nitrile **7b** led to the exclusive formation of **12b**, whereas the slow addition led to the preferred formation of **11b** (Table 1, entries 2, 4). Although other parameters of the reaction were also tested (temperature, solvent and reaction time), no significant improvements were observed, indicating that the addition rate of nitrile **7** was crucial in the process. It is worth mentioning that the regioisomeric mixtures were separated by flash chromatography. However, the final products were partially unstable under the purification conditions, which explains the moderated isolated yields obtained.

Enamino esters **11**, isolated exclusively in their enamino tautomeric form, were condensed with either isocyanates or isothiocyanates **9** to furnish the corresponding DHPMs **10**, through a tandem nucleophilic addition-intramolecular aza-Michael reaction sequence (Scheme 4). Hence, the treatment of compounds **11** with NaH in DMF at 0 °C, and further addition of different iso(thio)cyanates gave DHPMs **10** in moderate isolated yields (Table 2). Different substituents could be introduced at the $N-3$ position (from different iso- or isothiocyanates), including aliphatic (Table 2, entries 2, 4–8), aromatic (Table 2, entries 1, 3, 9), and chiral groups (Table 2, entries 6, 7). Although the reaction with chiral isocyanates was not very selective, it was possible to separate both diastereoisomers by flash chromatography, which allowed us to access compounds **10f** and **10g** in enantiomerically pure form [17]. It is also noteworthy that the reaction with isothiocyanates was more efficient, giving rise to the final products in good yields (Table 2, entries 2, 5).

In summary, we have prepared a small library of a new family of fluorinated 3,4-dihydropyrimidinones starting from fluorinated nitriles, using a tandem nucleophilic addition-intramolecular aza-Michael sequence. The overall process constitutes a variant of the Biginelli multicomponent reaction and allows for the preparation of DHPMs bearing fluorinated substituents at C6 other than CF_3.

1. Experimental

1.1. General experimental procedures

Reactions were carried out under nitrogen atmosphere unless otherwise indicated. The solvents were purified prior to use: CH_2Cl_2 was distilled from calcium hydride; hexanes, toluene and THF from sodium. All reagents were used as received. The reactions were monitored with the aid of thin-layer chromatography (TLC) on 0.25 mm E. Merck precoated silica gel plates. Visualization was carried out with UV light and aqueous ceric ammonium molybdate solution or potassium permanganate stain. Flash column chromatography was performed with the indicated solvents on silica gel 60 (particle size 0.040–0.063 mm). Optical rotations were measured on a Jasco P-1020 polarimeter. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a 300 MHz Bruker AC300 spectrometer and 400 MHz Bruker Avance. Chemical shifts are given in ppm (δ), and are referenced to the residual proton resonances of the solvents or to fluorotrichloromethane in the ^{19}F NMR experiments. Coupling constants (J) are given in Hertz (Hz). High-resolution mass spectra were carried out by the Universidad de Valencia Mass Spectrometry Service using a VGmAutospec (VG Analytical, Micromass Instruments).

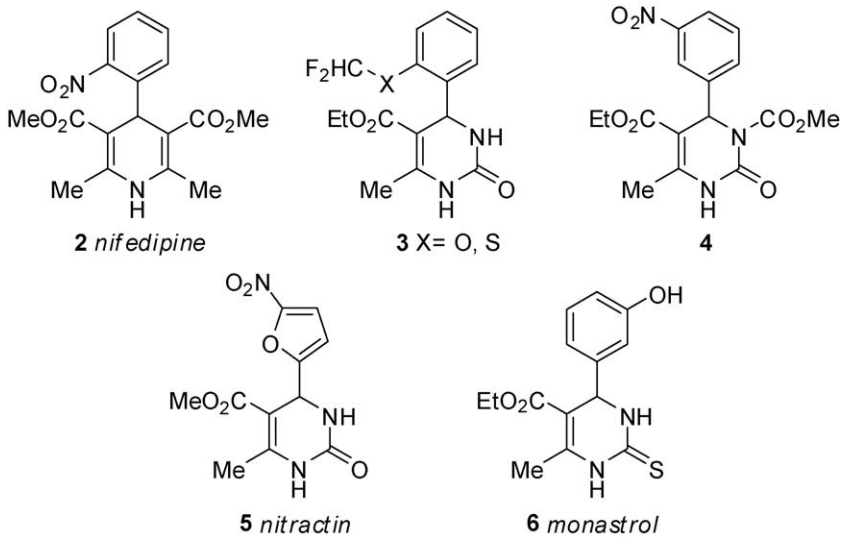
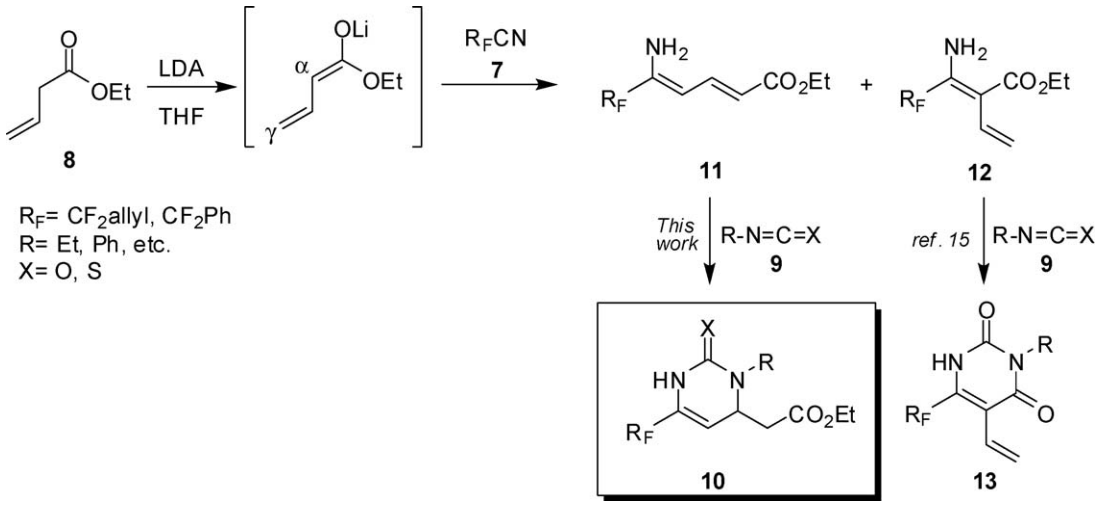
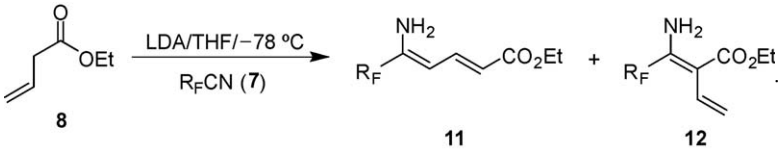


Fig. 1. Medicinally relevant DHPMs.



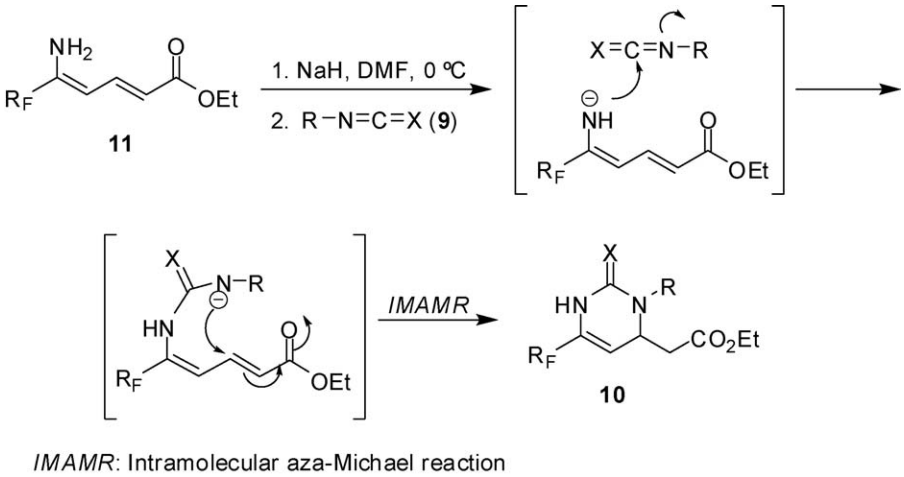
Scheme 3. Reaction pathways in the treatment of **8**-derived enolate with fluorinated nitriles 7.

Table 1
Reaction conditions for the preparation of enamino esters **11** and **12**.



Entry	7	R_F	Reaction conditions[a]	**11**:**12** ratio	Yield (%)[b]
1	**7a**	$CF_2CH_2CH{=}CH_2$	A	50:50	30 (**12a**)[c]
2	**7b**	CF_2Ph	A	0:100	42 (**12b**)
3	**7a**	$CF_2CH_2CH{=}CH_2$	B	94:6	40 (**11a**)
4	**7b**	CF_2Ph	B	95:5	50 (**11b**)

[a] *Reaction conditions*: (A) LDA/THF, −78 °C, fast addition of a solution of nitrile **7** in THF; (B) LDA/THF, −78 °C, addition of a solution of nitrile **7** in THF with a syringe pump at 2 mL/h rate.
[b] Isolated yields of **11** and **12**.
[c] 30% yield of γ-alkylation product **11a** was also obtained.



Scheme 4. Mechanism of formation of DHPMs **10**.

1.1.1. 2,2-Difluoro-4-pentenenitrile (7a)

It was prepared from 2,2-difluoro-4-pentenoic acid [18]. To a solution of this acid (3.0 g, 22 mmol) and EtOH (2.5 mL) in $CHCl_3$ (100 mL) was added DOWEX-H^+ 50XB (2.0 g) and the mixture stirred 24 h under reflux. The suspension was then cooled to room temperature, filtered and washed with CH_2Cl_2 (3 × 30 mL). The solvents were removed under reduced pressure and the crude was used in the next step without further purification. The ester was redissolved in THF (40 mL) and was treated with and aqueous NH_4OH solution (40 mL, 25% solution in water) at 0 °C. The mixture was stirred for 24 h at this temperature, and then, extracted with EtOAc (3 × 30 mL). The combined organic layers were dried over

Table 2
Reaction of enamino esters **11** with iso(thio)cyanates **9**.

Entry	R_F (**11**)	R	X	**10**	Yield (%)[a]
1	$CF_2CH_2CH{=}CH_2$ (**11a**)	Ph	O	**10a**	40
2	$CF_2CH_2CH{=}CH_2$ (**11a**)	Et	S	**10b**	61
3	CF_2Ph (**11b**)	Ph	O	**10c**	46
4	CF_2Ph (**11b**)	Et	O	**10d**	48
5	CF_2Ph (**11b**)	Et	S	**10e**	68
6	CF_2Ph (**11b**)	(*R*)-Ph(Me)CH	O	**10f**	52[b]
7	CF_2Ph (**11b**)	(*R*)-($C_{10}H_7$)(Me)CH	O	**10g**	50[c]
8	CF_2Ph (**11b**)	CH_2CO_2Et	O	**10h**	35
9	CF_2Ph (**11b**)	$Cl_3C_6H_2$	O	**10i**	40

[a] Isolated yields.
[b] Mixture of diastereoisomers (34:66), determined by ^{19}F NMR.
[c] Mixture of diastereoisomers (25:75), determined by means of ^{19}F NMR.

Na_2SO_4, filtered and evaporated in vacuo. The white solid formed (2,2-difluoro-4-pentenamide) was introduced in a distillation flask and treated with P_2O_5 (4.68 g, 33 mmol). The mixture was heated at atmospheric pressure until **7a** (1.0 g) distilled as a colorless liquid (b.p. 43–45 °C, 39% overall yield). ^1H NMR (300 MHz, $CDCl_3$) δ 2.63–2.76 (m, 2H), 5.17–5.25 (m, 2H), 5.48–5.62 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 42.4 (t, $^2J_{CF}$ = 23.8 Hz), 110.8 (t, $^1J_{CF}$ = 244.8 Hz), 112.4 (t, $^2J_{CF}$ = 45.9 Hz), 124.5, 125.2 (t, $^3J_{CF}$ = 4.9 Hz). ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −90.8 (t, J_{FH} = 14.9, 2F). HRMS (EI+): *m*/*z* calc. for $C_5H_5F_2N$ (M^+): 117.0967, found: 117.0962.

1.1.2. 2,2-Difluoro-2-phenylacetonitrile (7b)

This nitrile was commercially available in SynQuest Labs. Fluorochemical. See, also Ref. [16b].

1.2. General procedure for the preparation of fluorinated enamino esters (11 and 12)

To a solution of freshly prepared LDA (2.1 mmol) in THF (4 mL) at −50 °C, another solution of ester **8** (1.5 mmol) in THF (2 mL) was added dropwise and the reaction mixture was stirred for 30 min at this temperature. Once the enolate had been formed, the reaction was cooled until −78 °C, and a solution of nitrile **7** (1.3 mmol) in THF (2 mL) was added with the aid of a syringe pump (2 mL/h). After completing the addition, the reaction mixture was stirred for 1.5 h, and then quenched with saturated aqueous NH_4Cl (10 mL). The crude mixture was extracted with ethyl acetate (3 × 10 mL), and the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated to dryness under vacuum. After flash chromatography over silica gel, previously deactivated with a solution of hexanes/Et_3N 2% using mixtures of hexanes:ethyl acetate as eluent, the corresponding enamino esters **11** were obtained.

1.2.1. (2E,4Z)-Ethyl 5-amino-6,6-difluoro-2,4,8-nonatrienoate (11a)

By means of the general procedure previously described, **11a** was obtained from **7a** as a yellow oil (120 mg) in 40% yield after flash chromatography with hexanes:ethyl acetate (4:1) as eluent. ^1H NMR (300 MHz, $CDCl_3$) δ 1.22 (t, *J* = 7.1 Hz, 3H), 2.72 (dt, *J* = 7.2 Hz, J_{HF} = 16.2 Hz, 2H), 4.13 (q, *J* = 7.2 Hz, 2H), 4.09 (br s, 2H), 5.16 (d, *J* = 11.7 Hz, 1H), 5.21 (d, *J* = 14.1 Hz, 1H), 5.26 (d, *J* = 12.2 Hz, 1H), 5.72 (d, *J* = 14.9 Hz, 1H), 5.62–5.75 (m, 1H), 7.37 (dd, ^1J = 14.9 Hz, ^2J = 12.1 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.3, 40.5 (t, $^2J_{CF}$ = 34.5 Hz), 59.1, 96.6 (t, $^3J_{CF}$ = 6.5 Hz), 116.2, 118.7 (t, $^1J_{CF}$ = 243.3 Hz), 119.9, 127.1 (t, $^4J_{CF}$ = 5.1 Hz), 136.2, 143.3 (t, $^2J_{CF}$ = 26.0 Hz), 166.6. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −103.5 (t, J_{FH} = 15.5 Hz, 2F). HRMS (EI+): *m*/*z* calc. for $C_{11}H_{15}F_2NO_2$ (M^+): 231.1071, found: 231.1036.

1.2.2. (2E,4Z)-Ethyl 5-amino-6,6-difluoro-6-phenyl-2,4-hexadienoate (11b)

By means of the general procedure previously described, **11b** was obtained from **7b** as a yellow oil (150 mg) in 50% yield after flash chromatography with hexanes:ethyl acetate (4:1) as eluent. ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, *J* = 7.1 Hz, 3H), 4.19 (q, *J* = 7.1 Hz, 2H), 5.36 (d, *J* = 12.1 Hz, 1H), 5.77 (d, *J* = 15.0 Hz, 1H), 7.40–7.48 (m, 1H), 7.44–7.49 (m, 3H), 7.54–7.57 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.3, 60.1, 99.2 (t, $^3J_{CF}$ = 6.4 Hz), 117.8, 118.6 (t, $^1J_{CF}$ = 243.5 Hz), 125.6 (t, $^3J_{CF}$ = 5.6 Hz), 128.5, 130.6 (t, $^5J_{CF}$ = 1.6 Hz), 134.8 (t, $^2J_{CF}$ = 27.3 Hz), 137.0, 144.5 (t, $^2J_{CF}$ = 27.7 Hz), 167.5. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −98.6 (s, 2F). HRMS (EI+): *m*/*z* calc. for $C_{14}H_{15}F_2NO_2$ (M^+): 267.1071, found: 231.1087.

1.2.3. (Z)-Ethyl 3-amino-4,4-difluoro-2-vinyl-2,6-heptadienoate (12a)

By means of the general procedure previously described, **12a** was obtained with a fast addition of **7a** (Table 1, entry 1) as a yellow oil (90 mg) in 30% yield after flash chromatography with hexanes:ethyl acetate (4:1) as eluent. This compound was previously described [15].

1.2.4. (Z)-Ethyl 3-amino-4,4-difluoro-4-phenyl-2-vinyl-2-butenoate (12b)

By means of the general procedure previously described, **12b** was obtained with a fast addition of **7b** (Table 1, entry 2) as a yellow oil (126 mg) in 42% yield after flash chromatography with hexanes:ethyl acetate (4:1) as eluent. ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (t, *J* = 7.1 Hz, 3H), 4.23 (q, *J* = 7.1 Hz, 2H), 4.83 (dd, ^1J = 2.2 Hz, ^2J = 11.7 Hz, 1H), 5.22 (dd, ^1J = 2.1 Hz, ^2J = 17.4 Hz, 1H), 6.00 (tdd, ^1J = 2.6 Hz, ^2J = 11.7 Hz ^3J = 17.4 Hz, 1H), 7.26 (br s, 2H), 7.41–7.47 (m, 3H), 7.55–7.58 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.2, 60.1, 97.3 (t, $^3J_{CF}$ = 3.0 Hz), 115.2, 118.2 (t, $^1J_{CF}$ = 245.0 Hz), 125.6 (t, $^3J_{CF}$ = 5.0 Hz), 128.6, 128.9, 130.7 (t, $^5J_{CF}$ = 1.8 Hz), 134.8 (t, $^2J_{CF}$ = 26.0 Hz), 152.3 (t, $^2J_{CF}$ = 24.8 Hz), 170.3. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −90.4 (s, 2F). HRMS (EI+): *m*/*z* calc. for $C_{14}H_{15}F_2NO_2$ (M^+): 267.1071, found: 231.1045.

1.3. General procedure for the preparation of DHPMs (10)

Sodium hydride (0.9 mmol) was added to a solution of the corresponding δ-enaminoester **11** (0.5 mmol) in DMF (2 mL) at −10 °C, and the suspension was stirred for 30 min. Then, a solution of the iso- or isothiocyanate (0.6 mmol) in DMF (1 mL) was added dropwise, and the reaction mixture was allowed to reach room temperature. After 2 h (TLC revealed total consumption of the starting material), DMF was eliminated under reduced pressure and the crude mixture was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL); the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated to dryness under vacuum. The residue was then subjected to flash chromatography over silica gel using mixtures of hexanes:ethyl acetate as eluent, affording the desired DHMPs **10**.

1.3.1. 6-(1,1-Difluoro-3-butenyl)-4-(ethoxycarbonylmethyl)-3-phenyl-3,4-dihydropyrimidin-2(1H)-one (10a)

By means of the general procedure previously described, **10a** was obtained from **11a** and phenyl isocyanate as a yellow oil (70 mg) in 40% yield after flash chromatography with hexanes:ethyl acetate (2:1) as eluent. ^1H NMR (300 MHz, $CDCl_3$) δ 1.13 (t, *J* = 7.2 Hz, 3H), 2.53 (d, *J* = 7.5 Hz, 1H), 2.53 (d, *J* = 5.3 Hz, 1H), 2.71 (dt, *J* = 7.1 Hz, J_{HF} = 16.3 Hz, 2H), 3.97 (q, *J* = 7.2 Hz, 2H), 4.71–4.78 (m, 1H), 5.11 (d, *J* = 16.5 Hz, 1H), 5.16 (d, *J* = 9.5 Hz, 1H), 5.22–5.24 (m, 1H), 5.67 (ddt, ^1J = 7.0 Hz, ^2J = 10.3 Hz, ^3J = 17.2 Hz, 1H), 7.15–

7.26 (m, 3H), 7.24 (br s, 1H), 7.31–7.36 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.9, 39.4, 40.0 (t, $^2J_{CF}$ = 26.4 Hz), 56.7, 60.7, 99.6 (t, $^3J_{CF}$ = 6.9 Hz), 117.6 (t, $^1J_{CF}$ = 243.7 Hz), 121.2, 127.3, 127.9, 127.8 (t, $^3J_{CF}$ = 5.2 Hz), 129.2, 133.2 (t, $^2J_{CF}$ = 29.5 Hz), 139.8, 152.6, 169.8. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −102.4 (td, J_{FH} = 16.6 Hz, J_{FF} = 255 Hz, 1F), − 103.5 (td, J_{FH} = 16.6 Hz, J_{FF} = 255 Hz, 1F). HRMS (EI+): *m*/*z* calc. for $C_{18}H_{20}F_2N_2O_3$ (M^+): 350.1442, found: 350.1422.

1.3.2. 6-(1,1-Difluoro-3-butenyl)-4-(ethoxycarbonylmethyl)-3-ethyl-3,4-dihydropyrimidin-2(1H)-thione (10b)

By means of the general procedure previously described, **10b** was obtained from **11a** and ethyl isothiocyanate as a yellow oil (97 mg) in 61% yield after flash chromatography with hexane-s:ethyl acetate (5:1) as eluent. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, J = 7.1 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H), 2.59 (dd, ^1J = 6.7 Hz, ^2J = 14.4 Hz, 1H), 2.66 (dt, ^1J = 3.7 Hz, ^2J = 14.4 Hz, 1H), 2.76 (dt, J = 7.1 Hz, J_{HF} = 15.8 Hz, 2H), 3.33 (dq, ^1J = 7.0 Hz, ^2J = 14.0 Hz, 1H), 4.15 (q, J = 7.1 Hz, 2H), 4.48 (dq, ^1J = 7.0 Hz, ^2J = 14.0 Hz, 1H), 4.45–4.51 (m, 1H), 5.22 (d, J = 12.2 Hz, 1H), 5.26 (d, J = 3.7 Hz, 1H), 5.30–5.33 (m, 1H), 5.70 (ddt, ^1J = 7.1 Hz, ^2J = 10.4 Hz, ^3J = 17.5 Hz, 1H), 7.51 (br s, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.4, 14.1, 38.9, 40.6 (t, $^2J_{CF}$ = 26.4 Hz) 46.8, 52.6, 61.1, 101.2 (t, $^3J_{CF}$ = 6.0 Hz), 117.4 (t, $^1J_{CF}$ = 243.9 Hz), 121.7, 127.4 (t, $^3J_{CF}$ = 5.3 Hz), 132.0 (t, $^2J_{CF}$ = 29.8 Hz), 169.7, 176.1. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −102.3 (t, J_{FH} = 15.8 Hz, 2F). HRMS (EI+): *m*/*z* calc. for $C_{14}H_{20}F_2N_2O_2S$ (M^+): 318.1214, found: 318.1194.

1.3.3. 6-Difluoro(phenyl)methyl-4-(ethoxycarbonylmethyl)-3-phenyl-3,4-dihydropyrimidin-2(1H)-one (10c)

By means of the general procedure previously described, **10c** was obtained from **11b** and phenyl isocyanate as a white solid (88 mg) in 46% yield after flash chromatography with hexane-s:ethyl acetate (3:1) as eluent. m.p. 116–118 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (t, J = 7.1 Hz, 3H), 2.50 (d, J = 7.0 Hz, 1H), 2.50 (d, J = 5.6 Hz, 1H), 3.96 (dq, ^1J = 1.4 Hz, ^2J = 7.1 Hz, 2H), 4.71–4.77 (m, 1H), 5.13–5.15 (m, 1H), 7.01 (br s, 1H), 7.22–7.25 (m, 3H), 7.31–7.40 (m, 5H), 7.46 (d, J = 7.2 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.9, 39.3, 56.8, 60.8, 101.1 (t, $^3J_{CF}$ = 6.2 Hz), 116.7 (t, $^1J_{CF}$ = 242.2 Hz), 125.8 (t, $^3J_{CF}$ = 5.7 Hz), 127.5, 127.9, 128.5, 129.3, 130.7, 133.3 (t, $^2J_{CF}$ = 26.7 Hz), 134.2 (t, $^2J_{CF}$ = 31.2 Hz), 139.7, 152.1, 169.7. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −98.7 (d, J_{FF} = 264.0 Hz, 1F), −99.8 (d, J_{FF} = 264.0 Hz, 1F). HRMS (EI+): *m*/*z* calc. for $C_{21}H_{20}F_2N_2O_3$ (M^+): 386.1442, found: 386.1428.

1.3.4. 6-Difluoro(phenyl)methyl-4-(ethoxycarbonylmethyl)-3-ethyl-3,4-dihydropyrimidin-2(1H)-one (10d)

By means of the general procedure previously described, **10d** was obtained from **11b** and ethyl isocyanate as a colorless oil (81 mg) in 48% yield after flash chromatography with hexane-s:ethyl acetate (2:1) as eluent. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17 (t, J = 7.0 Hz, 3H), 1.22 (t, J = 7.2 Hz, 3H), 2.52–2.68 (m, 2H), 3.01 (dq, ^1J = 7.2 Hz, ^2J = 14.0 Hz, 1H), 3.76 (dq, ^1J = 7.2 Hz, ^2J = 14.0 Hz, 1H), 4.11 (q, J = 7.1 Hz, 2H), 4.35–4.40 (m, H), 5.02–5.04 (m, H), 6.48 (br s, 1H), 7.40–7.50 (m, 3H), 7.52 (d, J = 6.4 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.1, 14.0, 39.6, 40.2, 52.5, 60.9, 101.3 (t, $^3J_{CF}$ = 5.7 Hz), 116.8 (t, $^1J_{CF}$ = 240.5 Hz), 125.8 (t, $^3J_{CF}$ = 5.7 Hz), 128.5, 130.8, 133.4 (t, $^2J_{CF}$ = 26.3 Hz), 134.2 (t, $^2J_{CF}$ = 30.8 Hz), 152,7, 170.1. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −98.3 (d, J_{FF} = 264.0 Hz, 1F), −99.5 (d, J_{FF} = 264.0 Hz, 1F). HRMS (EI+): *m*/*z* calc. for $C_{17}H_{20}F_2N_2O_3$ (M^+): 338.1442, found: 338.1420.

1.3.5. 6-Difluoro(phenyl)methyl-4-(ethoxycarbonylmethyl)-3-ethyl-3,4-dihydropyrimidin-2(1H)-thione (10e)

By means of the general procedure previously described, **10e** was obtained from **11b** and ethyl isothiocyanate as a white solid (120 mg) in 68% yield after flash chromatography with hexane-s:ethyl acetate (4:1) as eluent. m.p. 84–86 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (t, J = 7.1 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H), 2.64 (d, J = 7.2 Hz, 1H), 2.64 (d, J = 6.0 Hz, 1H), 3.35 (dq, ^1J = 7.0 Hz, ^2J = 14.0 Hz, 1H), 4.12 (q, J = 7.1 Hz, 2H), 4.43–4.45 (m, H), 4.46 (dq, ^1J = 7.2 Hz, ^2J = 14.4 Hz, 1H), 5.14 (ddd, ^1J = 1.8 Hz, ^2J = 3.9 Hz, ^3J = 5.7 Hz, 1H), 7.45–7.50 (m, 5H), 7.52 (br s, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.4, 14.0, 39.0, 46.8, 52.8, 61.1, 102.9 (t, $^3J_{CF}$ = 5.9 Hz), 116.5 (t, $^1J_{CF}$ = 242.1 Hz), 125.7 (t, $^3J_{CF}$ = 5.7 Hz), 128.7, 131.0, 132.8 (t, $^2J_{CF}$ = 26.2 Hz), 133.0 (t, $^2J_{CF}$ = 31.4 Hz), 169.5, 176.1. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −97.6 (d, J_{FF} = 266.7 Hz, 1F), −98.6 (d, J_{FF} = 266.9 Hz, 1F). HRMS (EI+): *m*/*z* calc. for $C_{17}H_{20}F_2N_2O_2S$ (M^+): 354.1214, found: 354.1298.

1.3.6. 6-Difluoro(phenyl)methyl-4-(ethoxycarbonylmethyl)-3-[(R)-1-phenylethyl]-3,4-dihydropyrimidin-2(1H)-one (10f)

By means of the general procedure previously described, **10f** was obtained from **11b** and (*R*)-phenyl ethyl isocyanate as a 2:1 mixture of diastereoisomers, as colorless oils (72 + 36 mg) in 52% combined yield after flash chromatography with hexanes:ethyl acetate (2:1) as eluent. *Major diastereoisomer*: $[\alpha]_D^{25}$: −67.4 (*c* 1.0; CH_3Cl). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (t, J = 7.1 Hz, 3H), 1.59 (d, J = 6.7 Hz, 3H), 2.49 (dd, ^1J = 3.8 Hz, ^2J = 15.3 Hz, 1H), 2.65 (dd, ^1J = 10.2 Hz, ^2J = 15.4 Hz, 1H), 3.96–4.03 (m, 1H), 4.00 (q, J = 7.1 Hz, 2H), 4.96–4.99 (m, 1H), 5.59 (q, J = 7.1 Hz, 1H), 6.68 (br s, 1H), 7.19–7.27 (m, 5H), 7.34–7.42 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 18.4, 40.9, 48.3, 53.2, 60.7, 103.4 (t, $^3J_{CF}$ = 5.5 Hz), 116.9 (t, $^1J_{CF}$ = 240.7 Hz), 125.8 (t, $^3J_{CF}$ = 5.5 Hz), 127.1, 127.6, 128.5, 128.6, 130.8, 133.6 (t, $^2J_{CF}$ = 26.2 Hz), 134.5 (t, $^2J_{CF}$ = 31.0 Hz), 140.2, 154.0, 169.9. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −97.1 (d, J_{FF} = 264.3 Hz, 1F), −99.7 (d, J_{FF} = 264.3 Hz, 1F). HRMS (EI+): *m*/*z* calc. for $C_{23}H_{25}F_2N_2O_3$ (M+1): 415.1833, found: 415.1831. *Minor diastereoisomer*: $[\alpha]_D^{25}$: +126.7 (*c* 1.0; CH_3Cl). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (t, J = 7.1 Hz, 3H), 1.55 (dd, ^1J = 3.6 Hz, ^2J = 12.0 Hz, 1H), 1.59 (d, J = 7.2 Hz, 3H), 2.21 (dd, ^1J = 10.1 Hz, ^2J = 15.5 Hz, 1H), 3.96 (dq, ^1J = 1.1 Hz, ^2J = 7.1 Hz, 2H), 4.34–4.41 (m, 1H), 5.11–5.14 (m, 1H), 5.76 (q, J = 7.1 Hz, 1H), 6.46 (br s, 1H), 7.27–7.36 (m, 3H), 7.40–7.50 (m, 7H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 16.4, 39.4, 47.9, 52.0, 60.5, 103.1 (t, $^3J_{CF}$ = 6.0 Hz), 116.9 (t, $^1J_{CF}$ = 242.1 Hz), 125.8 (t, $^3J_{CF}$ = 5.6 Hz), 127.7, 127.9, 128.5, 128.6, 130.8, 134.7 (t, $^2J_{CF}$ = 31.0 Hz), 133.5 (t, $^2J_{CF}$ = 36.2 Hz), 140.6, 153.7, 170.0. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −97.7 (d, J_{FF} = 265.1 Hz, 1F), −98.9 (d, J_{FF} = 265.1 Hz, 1F). HRMS (EI+): *m*/*z* calc. for $C_{23}H_{25}F_2N_2O_3$ (M+1): 415.1833, found: 415.1830.

1.3.7. 6-Difluoro(phenyl)methyl-4-(ethoxycarbonylmethyl)-3-[(R)-1-naphtylethyl]-3,4-dihydropyrimidin-2(1H)-one (10g)

By means of the general procedure previously described, **10g** was obtained from **11b** and (*R*)-napthyl ethyl isocyanate as a 3:1 mixture of diastereoisomers, as light yellow oils (81 + 27 mg) in 50% combined yield after flash chromatography with hexane-s:ethyl acetate (4:1) as eluent. *Major diastereoisomer*: $[\alpha]_D^{25}$: −48.1 (*c* 1.0; CH_3Cl). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (t, J = 7.1 Hz, 3H), 1.82 (d, J = 7.0 Hz, 3H), 2.56 (dd, ^1J = 3.8 Hz, ^2J = 15.3 Hz, 1H), 2.71 (dd, ^1J = 9.3 Hz, ^2J = 15.3 Hz, 1H), 3.76–3.83 (m, 1H), 4.06 (q, J = 7.1 Hz, 2H), 4.74–4.77 (m, 1H), 6.29 (q, J = 7.0 Hz, 1H), 6.72 (br s, 1H), 7.31–7.37 (m, 3H), 7.40–7.54 (m, 5H), 7.62 (d, J = 7.1 Hz, 1H), 7.85 (dd, ^1J = 8.0 Hz, ^2J = 15.7 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 18.7, 40.9, 47.7, 49.9, 60.7, 103.2 (t, $^3J_{CF}$ = 5.5 Hz), 116.7 (t, $^1J_{CF}$ = 247.0 Hz), 123.3, 124.8, 125.1, 125.7 (t, $^3J_{CF}$ = 5.5 Hz), 125.9, 126.8, 128.4, 128.7, 129.2, 130.6, 131.6, 133.9, 134.3, 153.8, 169.8. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −95.7 (d, J_{FF} = 265.7 Hz, 1F), −100.4 (d, J_{FF} = 265.7 Hz, 1F). HRMS (EI+): *m*/*z* calc. for $C_{27}H_{26}F_2N_2O_3$ (M^+): 464.1911, found: 464.1914. *Minor diastereoisomer*: (it was not possible to obtain a pure sample of the minor diastereomer, and the data were extracted for the spectra impurified with the major product). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (t, J = 7.1 Hz, 3H), 1.50

(d, J = 6.8 Hz, 3H), 1.55–1.62 (m, 1H), 1.83 (dd, ^1J = 10.4 Hz, ^2J = 15.5 Hz, 1H), 4.09 (q, J = 7.1 Hz, 2H), 4.26–4.31 (m, 1H), 5.09–5.11 (m, 1H), 6.47 (q, J = 6.8 Hz, 1H), 6.92 (br s, 1H), 7.28–8.00 (m, 12H). ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −97.7 (d, J_{FF} = 265.0 Hz, 1F), −98.8 (d, J_{FF} = 265.0 Hz, 1F). HRMS (EI+): m/z calc. for $C_{27}H_{26}F_2N_2O_3$ (M^+): 464.1911, found: 464.1910.

*1.3.8. 3,4-(Diethoxycarbonylmethyl)-6-difluoro(phenyl)methyl-3,4-dihydropyrimidin-2(1H)-one (**10h**)*

By means of the general procedure previously described, 10 h was obtained from **11b** and ethoxycarbonyl methyl isocyanate as a yellow oil (69 mg) in 35% yield after flash chromatography with hexanes:ethyl acetate (2:1) as eluent. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (t, J = 7.1 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H), 2.56 (dd, ^1J = 7.1 Hz, ^2J = 16.1 Hz, 1H), 2.78 (dd, ^1J = 5.5 Hz, ^2J = 16.1 Hz, 1H), 3.98 (d, J = 17.6 Hz, 1H), 4.19 (d, J = 16.7 Hz, 1H), 4.10 (q, J = 7.1 Hz, 2H), 4.18 (q, J = 7.1 Hz, 2H), 4.41–4.49 (m, 1H), 5.03–5.08 (m, 1H), 6.73 (br s, 1H), 7.41–7.48 (m, 3H), 7.51–7.54 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 14.0, 39.9, 47.9, 54.5, 60.9, 61.3, 101.7 (t, $^3J_{CF}$ = 6.1 Hz), 116.8 (t, $^1J_{CF}$ = 242.1 Hz), 125.8 (t, $^3J_{CF}$ = 5.3 Hz), 128.6, 130.8, 133.7 (t, $^2J_{CF}$ = 36.3 Hz), 133.8 (t, $^2J_{CF}$ = 32.7 Hz), 152.8, 169.3, 170.3. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −98.1 (d, J_{FF} = 265 Hz, 1F), −99.7 (d, J_{FF} = 265 Hz, 1F). HRMS (EI+): m/z calc. for $C_{19}H_{22}F_2N_2O_5$ (M^+): 396.1496, found: 396.1498.

*1.3.9. 6-Difluoro(phenyl)methyl-4-(ethoxycarbonylmethyl)-3-(2,4,6-trichlorophenyl)-3,4-dihydropyrimidin-2(1H)-one (**10i**)*

By means of the general procedure previously described, **10i** was obtained from **11b** and 2,4,6-trichlorophenyl isocyanate as a white solid (98 mg) in 40% yield after flash chromatography with hexanes:ethyl acetate (3:1) as eluent. m.p. 146–148 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (t, J = 7.1 Hz, 3H), 2.73 (d, J = 7.0 Hz, 2H), 4.03 (q, J = 7.1 Hz, 2H), 4.81 (dtd, ^1J = 2.5 Hz, ^2J = 4.7 Hz, ^3J = 7.0 Hz, 1H), 5.21 (dd, ^1J = 1.9 Hz, ^2J = 3.9 Hz, 1H), 6.36 (br s, 1H), 7.42–7.59 (m, 7H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 40.1, 55.9, 60.9, 102.1 (t, $^3J_{CF}$ = 5.9 Hz), 116.8 (t, $^1J_{CF}$ = 242.1 Hz), 125.9 (t, $^3J_{CF}$ = 5.5 Hz), 128.8, 129.0, 129.3, 131.1, 133.1 (t, $^2J_{CF}$ = 26.4 Hz), 133.4 (t, $^2J_{CF}$ = 31.0 Hz), 133.9, 135.0, 135.1, 137.8, 150.3, 169.7. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −97.8 (d, J_{FF} = 265.9 Hz, 1F), −99.7 (d, J_{FF} = 265.9 Hz, 1F). HRMS (EI+): m/z calc. for $C_{21}H_{17}Cl_3F_2N_2O_3$ (M^+): 488.0273, found: 488.0280.

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References

[1] P. Biginelli, Gazz. Chim. Ital. 23 (1893) 360–416.
[2] C.O. Kappe, Tetrahedron 49 (1993) 6937–6963.
[3] (a) R. Fossheim, K. Svarteng, A. Mostad, C. Romming, E. Shefter, D.J. Triggle, J. Med. Chem. 25 (1982) 126–131;
(b) B. Loev, M.M. Goodman, K.M. Snader, R. Tedeschi, E. Macko, J. Med. Chem. 17 (1974) 956–965.
[4] For recent reviews of Biginelli and other multicomponent reactions, see: (a) S.V. Vdovina, V.A. Mamedov, Russ. Chem. Rev. 77 (2008), 1017–1053; (b) L.-Z. Gong, X.-H. Chen, X.-Y. Xu, Chem. Eur. J. 13 (2007) 8920–8926; (c) A. Dondoni, A. Massi, Acc. Chem. Res. 39 (2006) 451–463; (d) F. Liéby-Muller, C. Simon, T. Constantieux, J. Rodriguez, QSAR Comb. Sci. 25 (2006) 432–438; (e) C. Simon, T. Constantieux, J. Rodriguez, Eur. J. Org. Chem. (2004) 4957–4980; (f) C.O. Kappe, QSAR Comb. Sci. 22 (2003) 630–645.
[5] (a) Y. Hang, F. Yang, C. Zhu, J. Am. Chem. Soc. 127 (2005) 16386–16387;
(b) C.O. Kappe, Acc. Chem. Res. 33 (2000) 879–888;
(c) C.O. Kappe, Eur. J. Med. Chem. 35 (2000) 1043–1052.
[6] (a) G. Uray, P. Verdino, F. Belaj, C.O. Kappe, W.M.F. Fabian, J. Org. Chem. 66 (2001) 6685–6694, and references cited therein;
(b) B. Lagu, D. Tian, G. Chiu, D. Nagarathnam, J. Fang, Q. Shen, C. Forray, R.W. Ransom, R.S.L. Chang, K.P. Vyas, K. Zhang, C. Gluchowski, Bioorg. Med. Chem. Lett. 10 (2000) 175–178.
[7] (a) E.W. Hurst, R. Hull, J. Med. Pharm. Chem. 3 (1961) 215–229;
(b) E.W. Hurst, Ann. NY Acad. Sci. 98 (1962) 275–286;
(c) M. Windholz (Ed.), The Merck Index, Merck and Co. Inc., Rahway, 1976, p. 853.
[8] T.U. Mayer, T.M. Kapoor, S.J. Haggarty, R.W. King, S.L. Schreiber, T.J. Mitchison, Science 286 (1999) 971–974.
[9] (a) Y.S. Sadanandam, M.M. Shetty, P.V. Diwan, Eur. J. Med. Chem. 27 (1992) 87–92;
(b) D. Bozing, P. Benko, L. Petocz, M. Szecsey, P. Toempe, G. Gigler, I. Gacsalyi, Eur. Pat. Appl. EP (1991) 409, 233 [Chem. Abstr. 114 (1991) 247302z].
[10] J.C. Barrow, P.G. Nantermet, H.G. Selnick, K.L. Glass, K.E. Rittle, K.F. Gilbert, T.G. Steele, C.F. Homnick, R.M. Freidinger, R.W. Ransom, P. Kling, D. Reiss, T.P. Broten, T.W. Schorn, R.S.L. Chang, S.S. O'Malley, T.V. Olah, J.D. Ellis, A. Barrish, K. Kassahun, P. Leppert, D. Nagarathnam, C. Forray, J. Med. Chem. 43 (2000) 2703–2718, and references cited therein.
[11] (a) W.K. Hagmann, J. Med. Chem. 51 (2008) 4359–4369;
(b) S. Purser, P.R. Moore, S. Swallow, V. Gouverneur, Chem. Soc. Rev. 37 (2008) 320–330;
(c) K.L. Kirk, Org. Proc. Res. Dev. 12 (2008) 305–321;
(d) K. Müller, C. Faeh, F. Diederich, Science 457 (2007) 1881–1886.
[12] For a recent account see: S. Fustero, J.F. Sanz-Cervera, J.L. Aceña, M. Sánchez-Roselló, Synlett (2009) 525–549.
[13] S. Fustero, J. Piera, J.F. Sanz-Cervera, S. Catalán, C. Ramirez de Arellano, Org. Lett. 6 (2004) 1417–1420.
[14] S. Fustero, S. Catalán, S. Flores, D. Jiménez, C. del Pozo, J.L. Aceña, J.F. Sanz-Cervera, S. Mérida, QSAR Comb. Sci. 25 (2006) 753–760.
[15] S. Fustero, S. Catalán, J. Piera, J.F. Sanz-Cervera, B. Fernández, J.L. Aceña, J. Org. Chem. 71 (2006) 4010–4013.
[16] For the preparation of *gem*-difluorinated nitriles **7**, see: (a) Ref. [14]; (b) W.J. Middleton, E.M. Bingham, J. Org. Chem. 45 (1980) 2883–2887.
[17] The absolute configuration of the newly created stereocenter was not determined.
[18] R.W. Lang, H. Greuter, A.J. Romann, Tetrahedron Lett. 29 (1988) 3291–3294.