A Mild, Efficient Synthesis of *gem*-Difluorodihydrouracils

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Abstract: Carbodiimides react effectively with β-aryl/alkyl-β-hydroxy-α,α-difluorocarboxylic acids to afford a vast array of fully substituted *gem*-difluorodihydrouracils through a two step reaction sequence. In the first step, condensation between the two reactants leads in most cases to the formation of a mixture of the desired dihydrouracils and *N*-acylurea co-products. However, the latter could be easily recovered and efficiently converted into the target compounds. The sequence works well in very mild conditions (CH_2Cl_2, 20 °C) and the reaction resulted to be completely regioselective when asymmetric carbodiimides were used. When the *N*-acylurea derivatives are not sufficiently stable for isolation, the process could be done in a one-pot fashion leading to the direct formation of the desired dihydrouracils, although in lower yields.

Key words: N-heterocycles, fluorine, dihydrouracils, carbodiimide, domino reaction, *N*-acylureas

Many small synthetic organic molecules with high medicinal potential contain heterocyclic rings. The range of easily accessible and suitably functionalized heterocyclic building blocks is, however, surprisingly limited and the construction of even a small array of relevant heterocyclic compounds is far from trivial. Heterocyclic chemistry therefore continues to attract the attention of medicinal and synthetic chemists, and the development of novel methodologies allowing for efficient access to heterocycles is still highly beneficial.[1] One of the challenges of medicinal chemistry is the promotion of the structural diversity of a ligand, which can be achieved by the attachment of pharmacophoric groups to the rigidified molecule. Small, substituted heterocyclic compounds offer a unique possibility of different kinds and degrees of substitution. In particular, 5,6-dihydrouracils (DHUs) have been widely used in biological screenings resulting in numerous pharmaceutical applications.[2] C-Glucosylated DHUs have also proven to be C-linked analogues of N-linked natural products.[3] The observed activities usually do not arise from the heterocycle itself, but from the different ligands that have been attached to it. For this reason there is a lot of interest in developing new strategies for a straightforward synthesis of substituted DHUs both in solution and in solid phase. Furthermore, reductive or hydrolytic DHU ring opening has been used for the synthesis of biologically important compounds such as β-ureidoalcohols and acids[4] or α-substituted β-amino acids.[5] To date, the most utilized strategy to prepare substituted DHUs is the strongly acidic or basic cyclization of β-ureidopropionic acids, obtained either from reactions of α,β-unsaturated acids and urea derivatives[6] or from β-amino acids and isocyanates,[7] which requires extended reaction time, high temperature, and generally produces low yields, or by hydrogenation of uracil derivatives.[8] An alternative synthesis of DHUs consists in the reductive desulfurization of 2-thiobarbiturates[9] though sodium amalgam, Zn/HCO_2H, Raney nickel or, more recently, nickel boride.[10] However, the latter methodologies suffer from 1) low to moderate yield and 2) the starting 2-thiobarbiturates have to be prepared by condensation between malonic acid derivatives and thiourea, which often features modest yields due to the presence of side reactions like hydrolysis of the malonate, decarbethoxylation, transesterification, and urea degradation.[11] For all these reasons a better synthesis of DHUs is required.

Fluorine containing heterocyclic compounds have attracted much interest because of their unique chemical, physical, and biological activities.[12] Much attention has been paid to pharmaceuticals and agricultural chemicals containing a *gem*-difluoromethylene unit[13] because many selectively fluorinated analogues of biologically important compounds exhibit a dramatic enhancement in terms of biological activity and because the CF_2 group is considered to be isopolar and isosteric with an ether oxygen.[14] In particular, significant efforts have been made toward the synthesis of compounds containing a difluoromethylene group adjacent to a carbonyl group[1,3] because α,α-difluoro ketones have been successfully used as inhibitors of hydrolytic enzymes, and greatly enhanced biological activity has been reported compared with their nonfluorinated analogues.[12] There are in general two complementary approaches to such an important unit. One is the substitution of a carbonyl or an active methylene group by various fluorinating agents derived from fluorine gas, and the other is the use of *gem*-difluoromethylene-containing building blocks. The former approach can be hardly applied to complex molecules because of the low selectivity of fluorinating reagents such as SF_4 and diethylminosulfur trifluoride (DAST). Instead, the latter approach is predominantly employed despite the limited availability of *gem*-difluoromethylene-containing building blocks. Ex-

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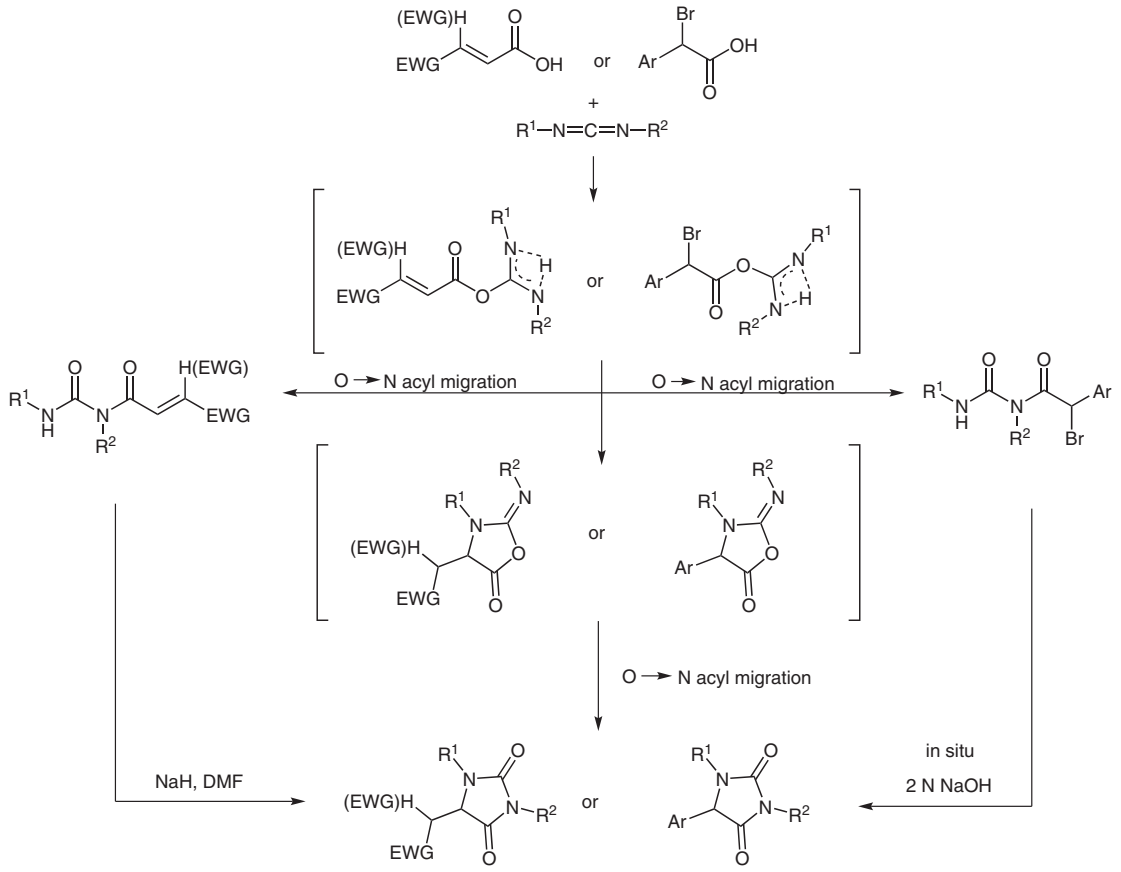


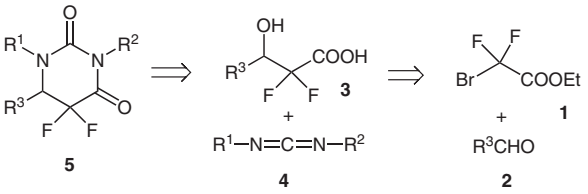
Scheme 1 One-pot, domino processes leading to 1,3,5-trisubstituted hydantoins

ploiting the building block methodology, a range of *gem*-difluoro heterocycles has been recently synthesized including unsaturated lactams,[15] dihydropyranones,[16] γ- and β-lactams,[17] and furanones[18] among others.

As a part of a research program focused on the development of novel, mild, and efficient procedures for the synthesis of small heterocycles through the use of carbodiimides,[19] we wish to report the straightforward synthesis of *gem*-difluoro-DHUs by means a new domino process between easily accessible β-hydroxy-α,α-difluorocarboxylic acids and carbodiimides. In this paper, we provide a full account on scope and limits of this new methodology, which has been studied in detail.

Recently, we demonstrated that carbodiimides, when treated with suitable carboxylic acids in the absence of a nucleophile, are useful reagents for the synthesis of small heterocycles, such as hydantoins[19a–c] and barbiturates.[19d,e] The former could be synthesized by means of a regiospecific domino process consisting in a condensation step between the two reactants, namely activated α,β-unsaturated acids or α-haloarylacetic acids with carbodiimides, leading to the formation of *O*-acylisourea intermediates, which undergo nucleophilic aza-Michael reaction or halogen displacement, respectively, followed by final O → N acyl migration step (Scheme 1). In some cases, the O → N acyl migration process resulted to be competitive with the nucleophilic step leading to the corresponding *N*-acylureas (NAUs) that could be cyclized to the target compounds.

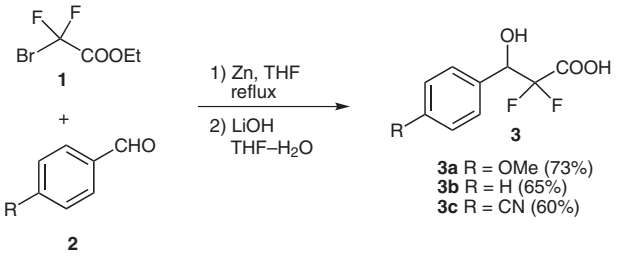
The strategies above led to the formation of the target heterocycles in very mild conditions (room temperature, avoiding the use of strong acids/bases) and in high yields making this methodology suitable for the preparation of libraries of such compounds. We therefore decided to investigate the use of this methodology for the preparation of N,N′-disubstituted difluoro-DHUs **5** starting from differently substituted carbodiimides **4** and easily accessible β-hydroxy-α,α-difluorocarboxylic acids **3** (Scheme 2).



Scheme 2 Retrosynthetic analysis for the preparation of N,N′-disubstituted difluoro-DHUs

The key step of this sequence is the nucleophilic displacement of the hydroxy group, or related leaving groups, by the *O*-acylisourea intermediate or, more likely, by the *N*-acylurea derivatives, which should be formed after the condensation between **3** and **4** and subsequent O → N acyl migration. In any case, this step is favored by the presence

of the vicinal difluoromethylene moiety that, due to the strong electronegativity of the fluorine atoms, renders this carbon highly electrophilic. To render such carbon even more electrophilic we prepared different β-hydroxy-α,α-difluorocarboxylic acids **3** having an aryl substituent in the β position. To this end, we used a known Reformatsky reaction between bromodifluoroacetic acid ester **1** and three different aryl aldheydes **2a–c** having an electron-rich, -neutral, and -poor aromatic ring, respectively, followed by basic hydrolysis of the resulting ethyl esters (Scheme 3).

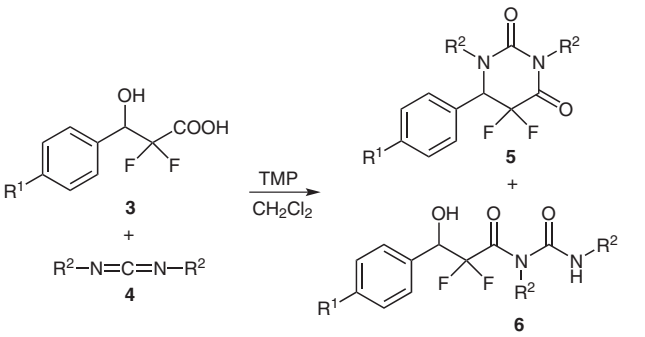


Scheme 3 Synthesis of β-aryl-β-hydroxydifluoro acids

Thus, compounds **3a–c** were reacted with commercially available symmetric *N*,*N*′-dialkylcarbodiimides such as DCC (**4a**), and DIC (**4b**) (Table 1). After fine tuning of the key parameters, such as solvent, presence of a base, and temperature, the optimized conditions were to run the reaction in apolar solvents (CH_2Cl_2) at room temperature and in the presence of a base, 2,4,6-trimethylpyridine (TMP).

To our surprise, the reaction between β-(4-methoxyphenyl)-β-hydroxy-α,α-difluorocarboxylic acid **3a** and DCC (**4a**) gave an almost 3:1 mixture of the expected NAU derivative **6a** and the DHU **5a** in excellent overall yields (Table 1, entry 1). The formation of the latter compound was unexpected at this stage because the hydroxyl group is known to be a scarce leaving group if not protonated. The reaction between the same acid **3a** and DIC (**4b**) provided the nearly exclusive formation of the NAU **6b** in good yield, with the corresponding DHU detected in trace amounts by NMR spectrum of the crude. The acid **3b** bearing an electron-neutral aromatic ring in β position reacted with **4a** producing the expected NAU derivative **6c** in very good yield essentially as the only product, while with DIC (**4b**) a nearly 2:1 mixture of NAU **6d** and the target DHU **5d** was still obtained (Table 1, entries 3, 4). Finally, by reacting in the same conditions β-(4-cyanophenyl)-β-hydroxy-α,α-difluorocarboxylic acid (**3c**) and carbodiimides **4a**,**b** we achieved the formation of a ca. 1.5:1 mixture of NAU **6e** and DHU **5e** and the exclusive formation of NAU **6f**, respectively, in excellent yields (Table 1, entries 5, 6). The direct formation of the unexpected DHU compounds **5** during the reaction between acids **3a–c** and carbodiimides **4a**,**b** is probably due to the formation of a transient benzylic carbocation due to a partial protonation of the hydroxy group. Presumably,

Table 1 Reaction between β-Aryl-β-hydroxy-α,α-difluorocarboxylic Acids and Asymmetric *N*,*N*′-Dialkylcarbodiimides



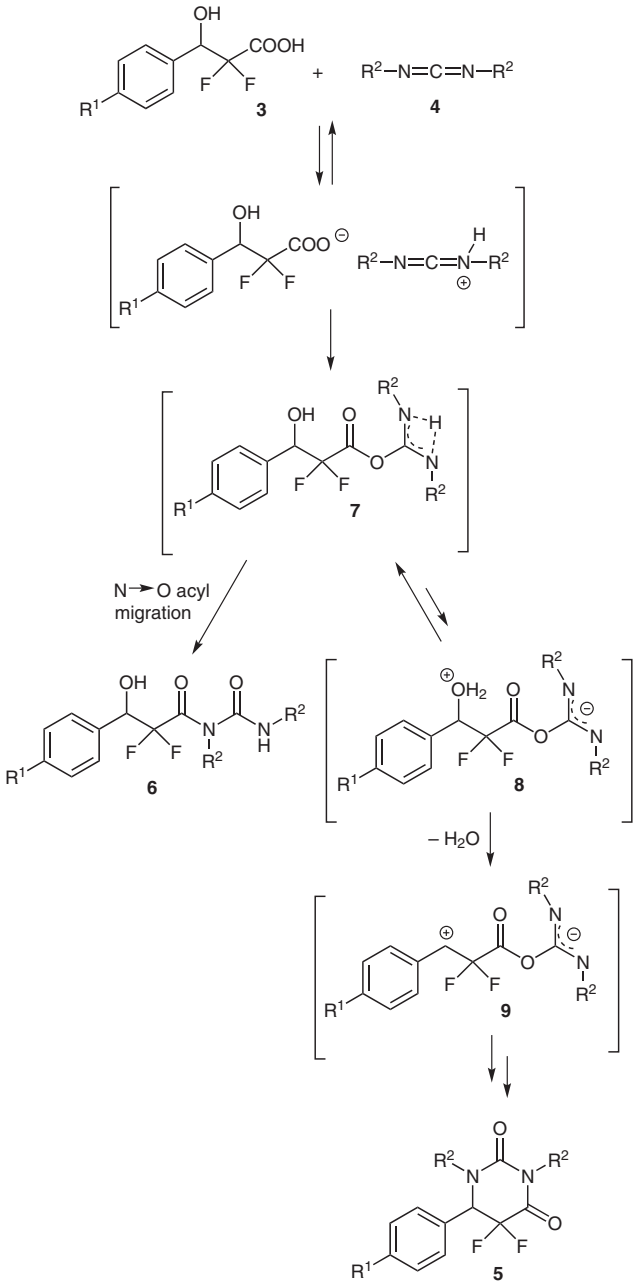
Entry	R^1 (acid)	R^2 (carbodiimide)	DHU, Yield (%)[a]	NAU, Yield (%)[a]
1	OMe (**3a**)	*c*-C_6H_{11} (**4a**)	**5a**, 24	**6a**, 61
2	OMe (**3a**)	*i*-Pr (**4b**)	trace[b]	**6b**, 78
3	H (**3b**)	*c*-C_6H_{11} (**4a**)	trace[b]	**6c**, 83
4	H (**3b**)	*i*-Pr (**4b**)	**5d**, 24	**6d**, 55
5	CN (**3c**)	*c*-C_6H_{11} (**4a**)	**5e**, 35	**6e**, 49
6	CN (**3c**)	*i*-Pr (**4b**)	–	**6f**, 98

[a] Isolated yields.
[b] Detected by the ^{1}H NMR spectrum of the crude.

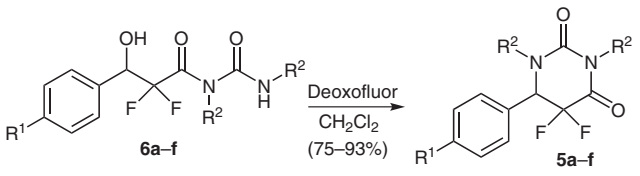
the reaction sequence involves a proton transfer from the carboxylic acid **3** to the basic nitrogen of the carbodiimide **4**, followed by addition of the carboxylate to form the *O*-acylisourea **7** which, in the absence of a nucleophile or a base, can be stable for many hours (Scheme 4).[20]

Intermediate **7** undergoes a rearrangement, the so-called O → N acyl migration, to give the NAU **6**, which is a frequently found by-product in the condensation reaction between carboxylic acids and alcohols or amines promoted by carbodiimides, and the major product in our synthesis. However, *O*-acylisourea **7** could exist in equilibrium with the zwitterion **8**, which irreversibly undergoes loss of H_2O affording the benzylic carbocation **9** and triggering the formation of DHU **5** by intramolecular nucleophilic attack of a nitrogen and subsequent O → N acyl migration.[21] Such equilibrium is probably shifted towards the *O*-acylisourea **7** because: 1) the nitrogen atom is more basic than the oxygen and 2) the carbocation is destabilized by the presence of the vicinal *gem*-difluoro moiety.[22] In fact, the DHU compounds **5**, when formed, are always found as minor products.

In order to validate our synthetic methodology, we had to find the way to convert the NAU derivatives **6** into the target DHUs **5** in mild condition and high yields. This could be achieved by treating compounds **6** with Deoxofluor in dichloromethane overnight at room temperature (Scheme 5).

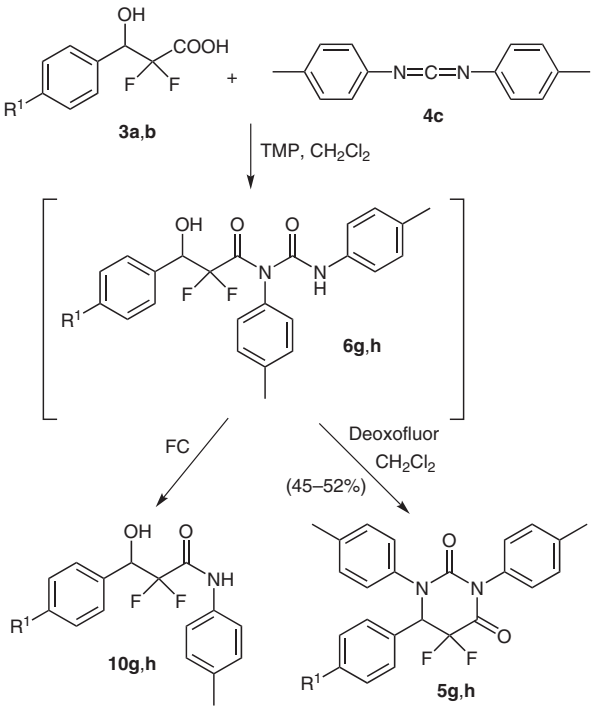


Scheme 4 The proposed mechanism for the formation of **5**



Scheme 5 Synthesis of the target DHUs

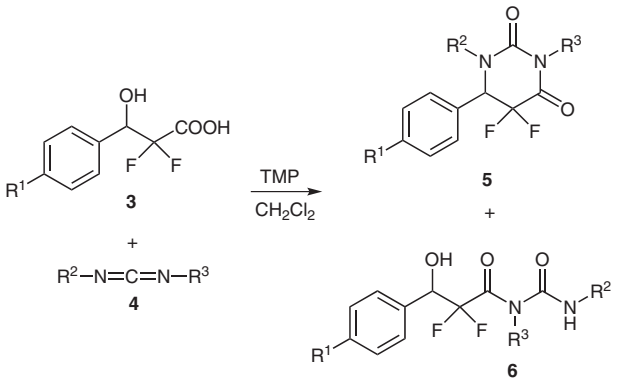
Next, we turned our attention on the reactivity of less basic/nucleophilic *N*,*N*′-diarylcarbodiimides, and in particular commercially available bis(*p*-tolyl)carbodiimide (**4c**) with acids **3a**,**b** (Scheme 6). In these cases, the resulting NAU derivatives resulted to be very instable probably due to the electron-withdrawing nature of the aryl substituent that renders the system highly electron-deficient and thus reactive. In fact, by treating carbodiimide **4c** with acids **3a**,**b** in the same conditions described above, we were able to detect the presence of the expected NAU compounds only by ^{1}H NMR of the crude reaction mixture, whereas after flash chromatography we recovered only the amide **10**. However, by treating the reaction mixture in situ with an excess of Deoxofluor after the NAU derivatives were formed, we were able to recover the target *N*,*N*′-diaryl-DHUs **5g**,**h**, which proved to be more stable than the corresponding NAUs, although in lower yields.



Scheme 6 Synthesis of *N*,*N*′-diaryl-DHUs

To our surprise, the behavior of asymmetric carbodiimides, namely carbodiimides having different substituents at the nitrogen atoms in terms of steric hindrance ('weakly asymmetric') or nucleophilic character ('strongly asymmetric')[19c] resulted to be different as compared with the symmetric ones. 'Weakly asymmetric' carbodiimides, such as *N*-allyl or -*c*-C_6H_{11}, *N*′-*tert*-butylcarbodiimides **4d**,**e**, respectively, reacted smoothly with β-aryl-β-hydroxy-α,α-difluorocarboxylic acids **3a–c** to afford NAU and DHU derivatives in ratios depending on the 'degree' of the asymmetry and on the electronic feature of the β-aryl substituent on the acids, although in all cases with total regiocontrol (Table 2). *N*-Allyl-*N*′-*tert*-butylcarbodiimide **4d**, bearing a primary and a tertiary alkyl group at the nitrogen atoms, reacted with acids **3a**,**b** giving rise to the formation of modest yields of NAU derivatives **6i**,**j**, respectively, having the bulky *tert*-butyl group attached to the imide nitrogen, while an almost 3:1 mixture NAU/DHU derivatives **5k** and **6k**, respectively, were obtained with acid **3c** bearing an electron-withdrawing group at the *para* position of the aromatic ring (Table 2, entries 1–3).

Table 2 MReaction between β-Aryl-β-hydroxy-α,α-difluorocarboxylic Acids and Asymmetric Carbodiimides



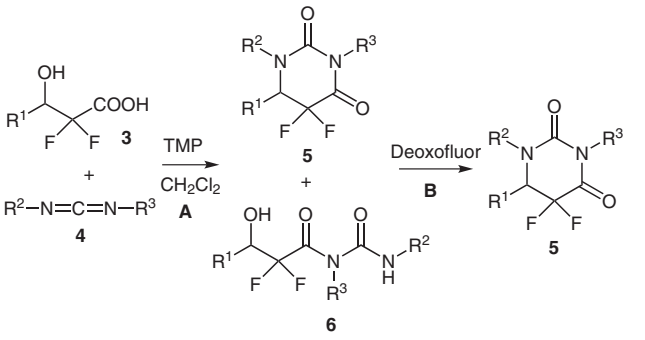
Entry	R^1 (acid)	R^2	R^3 (carbodiimide)	DHU, Yield (%)[a]	NAU, Yield (%)[a]
1	OMe (**3a**)	allyl	*t*-Bu (**4d**)	–	**6i**, 33
2	H (**3b**)	allyl	*t*-Bu (**4d**)	–	**6j**, 45
3	CN (**3c**)	allyl	*t*-Bu (**4d**)	**5k**, 15	**6k**, 42
4	CN (**3c**)	*c*-C_6H_{11}	*t*-Bu (**4e**)	**5l**, 51	–
5	OMe (**3a**)	Bn	Ph (**4f**)	–[b]	–[b]
6	CN (**3c**)	Bn	Ph (**4f**)	–[b]	–[b]

[a] Isolated yields.
[b] A complex mixture of unidentified products were formed.

These results confirm that *O*-acylurea derivatives like **7** (Scheme 4), bearing different substituents at the two nitrogen atoms, have more propensity to undergo O → N acyl transfer than the corresponding derivatives having two identical N-substituents, as already observed in previous works.[19c,f] Conversely, *N*-cyclohexyl-*N*′-*tert*-butylcarbodiimide **4e**, bearing two substituents more similar both in terms of sterical hindrance and electronic features, reacted with acid **3c** leading to the formation of DHU **5l** in a complete chemo- and regioselective fashion (Table 2, entry 4). Unexpectedly, when 'highly asymmetric' *N*-benzyl-*N*′-phenylcarbodiimide (**4f**) was reacted with acids **3a**,**c** we could isolate neither the corresponding NAU nor the DHU derivatives, regardless the use of a multi-step or a one-pot procedure (Table 2, entries 5 and 6).

Finally, we explored the reactivity of β-alkyl-β-hydroxy-α,α-difluorocarboxylic acids **3d**,**e**, which were synthesized in analogy with the β-aryl analogues (see experimental section). In these cases the carbocations like **9** (see the proposed mechanism in Scheme 4) should be less stable, thus, in theory, more difficult to form than the corresponding benzylic ones. However, the reactions of acids **3d**,**e** with symmetric *N*,*N*′-dialkylcarbodiimides **4a**,**b** led to the formation of mixtures of NAU/DHU derivatives **5m–o** and **6m–o** (Table 3, entries 1–3).[23] Interestingly, when β-alkyl,β-hydroxy-α,α-difluorocarboxylic acids **3d**,**e** were reacted with 'strongly asymmetric' carbodiimide **4f**, again we were not able to isolate the NAU intermediates after the condensation step (Table 3, step A), but this time we could isolate the desired DHUs **5p**,**q** in reasonable yields and as the only regioisomers, by performing the cyclization step (step B) in a one-pot fashion (Table 3, entries 4 and 5).

Table 3 Reaction between β-Alkyl-β-hydroxy-α,α-difluorocarboxylic Acids and Carbodiimides



Entry	R^1 (acid)	R^2	R^3 (carbodiimide)	DHU, Yield (%)[a]	NAU, Yield (%)[a]
1[b]	Bn (**3d**)	*c*-C_6H_{11}	*c*-C_6H_{11} (**4a**)	**5m**, 26	**6m**, 41
2[b]	Bn (**3d**)	*i*-Pr	*i*-Pr (**4b**)	**5n**, 20	**6n**, 45
3[b]	*n*-Bu (**3e**)	*i*-Pr	*i*-Pr (**4b**)	**5o**, 35	**6o**, 58
4[c]	Bn (**3d**)	Bn	Ph (**4f**)	**5p**, 51	–
5[c]	*n*-Bu (**3e**)	Bn	Ph (**4f**)	**5q**, 53	–

[a] Isolated yields.
[b] One-step A.
[c] One-pot, two steps A + B.

In conclusion, we have developed a new, straightforward two-step procedure for the synthesis of novel compounds such as *gem*-difluoro-DHUs. The process, which takes place in very mild conditions, is based on the condensation between easily accessible β-substituted β-hydroxy-α,α-difluorocarboxylic acids and carbodiimides. This leads to the formation of the corresponding NAU derivatives or, in most cases, to a mixture of the desired DHU and NAU derivatives, which could be cyclized to the target compounds very efficiently. When the NAU derivatives are not stable because of the electron-poor character of the N-substituents which renders these substrates very reactive, the process could be done in a one-pot fashion leading to the direct formation of the desired DHU, although in lower yields. A large array of fully substituted *gem*-difluoro-DHUs can be synthesized through this method, which looks particularly suitable for solid-phase/combinatorial chemistry. Resolution of this issue, as well as the development of a stereoselective version of the process,[24] is currently in progress in our laboratories.

^{1}H NMR spectra were run on spectrometers 250, 400, or 500 MHz. Chemical shifts are expressed in ppm (δ), using TMS as internal standard for ^{1}H and ^{13}C nuclei (δ_H and $\delta_C = 0.00$), while C_6F_6 was used as external standard ($\delta_F = 162.90$) for ^{19}F. Commercially available reagent grade solvents were employed without purification.

Commercially unavailable carbodiimides were prepared according to the literature procedure.[19] β-Alkyl-β-hydroxy-α,α-difluorocarboxylic acids **3d**,**e** were prepared as shown in Scheme 3 and described in the literarure.[25]

Reaction of β-Aryl/alkyl-β-hydroxy-α,α-difluorocarboxylic Acids 3 with Carbodiimides 4; General Procedure

To a 0.1 M solution of **3** in CH_2Cl_2 were added TMP (1 equiv) followed by carbodiimide **4** (1.5 equiv) at r.t. After stirring overnight, aq 1 N HCl was added to acidic pH and the mixture extracted with CH_2Cl_2 (2 × 2 mL). The combined organic layers were dried (Na_2SO_4), concentrated under vacuum, and the crude purified by flash chromatography over silica gel affording NAUs **6**, and eventually DHUs **5** (Tables 1– 3).

Cyclization of *N*-Acylureas 6 to 5,6-Dihydrouracils; General Procedure

To a 0.1 M solution of **6** in CH_2Cl_2, was added Deoxofluor (1.6 equiv) dropwise at r.t. After stirring overnight, sat. aq $NaHCO_3$ was added to basic pH and the mixture extracted with CH_2Cl_2 (2 × 2 mL). The combined organic layers were dried (Na_2SO_4), concentrated under vacuum, and the crude purified by flash chromatography over silica gel affording DHUs **5**.

1,3-Dicyclohexyl-5,5-difluoro-6-(4-methoxyphenyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (5a)

R_f = 0.72 (hexanes–EtOAc, 80:20).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 (d, *J* = 8.6 Hz, 2 H), 6.96 (d, *J* = 8.8 Hz, 2 H), 5.23 (dd, *J* = 18.4, 3.2 Hz, 1 H), 4.58 (t, *J* = 12.1 Hz, 1 H), 3.84 (s, 3 H), 3.65 (m, 1 H), 2.43 (m, 2 H), 1.83 (d, *J* = 12.9 Hz, 2 H), 1.68 (m, 8 H), 1.34 (m, 8 H).

^{13}C NMR (101 MHz, C_6D_{12}): δ = 160.9, 139.3, 129.0, 114.6 (dd, *J* = 1744.5, 283.8 Hz), 114.2, 76.3 (dd, *J* = 29.6, 25.1 Hz), 57.1, 55.3, 53.7, 34.0, 33.6, 28.6, 28.2, 26.3, 25.9, 25.3, 24.2.

^{19}F NMR (235 MHz, $CDCl_3$): δ = –117.7 (dd, *J* = 282.3, 3.2 Hz, 1 F), –124.5 (dd, *J* = 282.3, 18.5 Hz, 1 F).

ESI: *m*/*z* (%) = 443.1 [M$^+$ + Na, 100%].

5,5-Difluoro-1,3-diisopropyl-6-(4-methoxyphenyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (5b)

R_f = 0.52 (hexanes–EtOAc, 90:10).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 (d, *J* = 8.6 Hz, 2 H), 6.96 (d, *J* = 8.8 Hz, 2 H), 5.23 (dd, *J* = 18.9, 3.1 Hz, 1 H), 4.99 (dt, *J* = 13.8, 6.9 Hz, 1 H), 3.93 (dt, *J* = 12.6, 6.3 Hz, 1 H), 3.84 (s, 3 H), 1.48 (d, *J* = 11.6 Hz, 3 H), 1.46 (d, *J* = 11.6 Hz, 3 H), 1.12 (d, *J* = 6.3 Hz, 3 H), 1.09 (d, *J* = 6.3 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.9, 159.8 (dd, *J* = 30.2, 29.2 Hz), 139.6, 129.0, 121.5, 114.2, 114.2, 114.1, 109.6, 107.1, 107.1, 104.6, 76.4 (dd, *J* = 30.1, 23.9 Hz), 55.3, 48.9, 46.4, 24.1, 23.7, 19.2, 18.8.

^{19}F NMR (235 MHz, $CDCl_3$): δ = –118.3 (dt, *J* = 240.2, 30.6 Hz, 1 F), –124.8 (dt, *J* = 151.0, 38.3 Hz, 1 F).

ESI: *m*/*z* (%) = 363.0 [M$^+$ + Na, 100%].

1,3-Dicyclohexyl-5,5-difluoro-6-phenyldihydropyrimidine-2,4(1*H*,3*H*)-dione (5c)

R_f = 0.83 (hexanes–EtOAc, 80:20).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 (m, 5 H), 5.29 (dd, *J* = 18.5, 3.3 Hz, 1 H), 4.58 (m, 1 H), 3.67 (td, *J* = 8.7, 4.4 Hz, 1 H), 2.42 (m, 2 H), 1.83 (d, *J* = 12.8 Hz, 2 H), 1.69 (m, 8 H), 1.35 (m, 8 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 159.7 (t, *J* = 29.5 Hz), 155.7, 139.2, 130.0, 128.7, 127.5, 57.2, 53.7, 33.9, 33.5, 28.5, 28.2, 26.2, 25.9, 25.3, 24.2.

^{19}F NMR (235 MHz, $CDCl_3$): δ = –117.7 (dd, *J* = 282.8, 3.2 Hz, 1 F), –124.2 (dd, *J* = 282.8, 18.6 Hz, 1 F).

ESI: *m*/*z* (%) = 413.1 [M$^+$ + Na, 100%].

5,5-Difluoro-1,3-diisopropyl-6-phenyldihydropyrimidine-2,4(1*H*,3*H*)-dione (5d)

R_f = 0.67 (hexanes–EtOAc, 80:20).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (s, 5 H), 5.29 (dd, *J* = 18.7, 2.7 Hz, 1 H), 5.00 (dt, *J* = 13.8, 6.9 Hz, 1 H), 3.96 (dt, *J* = 12.3, 6.2 Hz, 1 H), 1.48 (d, *J* = 12.0 Hz, 3 H), 1.46 (d, *J* = 12.1 Hz, 3 H), 1.14 (d, *J* = 6.3 Hz, 3 H), 1.10 (d, *J* = 6.3 Hz, 3 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 139.4, 130.0, 129.6, 128.6, 127.9, 127.5, 126.9, 75.7, 49.0, 46.4, 24.0, 23.6, 19.2, 18.8.

^{19}F NMR (235 MHz, $CDCl_3$): δ = –118.1 (dd, *J* = 283.4, 3.1 Hz, 1 F), –124.3 (dd, *J* = 283.4, 18.7 Hz, 1 F).

ESI: *m*/*z* (%) = 343.1 [M$^+$ + Na, 100%].

4-(1,3-Dicyclohexyl-5,5-difluoro-2,6-dioxohexahydropyrimidin-4-yl)benzonitrile (5e)

R_f = 0.50 (hexanes–EtOAc, 80:20).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 8.2 Hz, 2 H), 7.56 (d, *J* = 8.1 Hz, 2 H), 5.35 (d, *J* = 19.3 Hz, 1 H), 4.57 (tt, *J* = 12.1, 3.6 Hz, 1 H), 3.66 (m, 1 H), 2.40 (dqd, *J* = 27.9, 12.3, 3.2 Hz, 2 H), 1.84 (d, *J* = 13.1 Hz, 2 H), 1.70 (m, 8 H), 1.36 (m, 8 H).

^{13}C NMR (101 MHz, C_6D_{12}): δ = 159.1 (t, *J* = 29.3 Hz), 138.3, 134.7, 132.4, 128.8, 128.4, 128.2, 118.0, 114.1, 106.7 (t, *J* = 252.1 Hz), 75.6 (dd, *J* = 29.6, 24.0 Hz), 57.4, 53.9, 33.9, 33.6, 28.6, 28.2, 26.3, 26.2, 25.8, 25.3, 24.2, 24.1.

^{19}F NMR (235 MHz, $CDCl_3$): δ = –118.2 (dd, *J* = 283.9, 1.8 Hz, 1 F), –123.7 (dd, *J* = 283.9, 19.5 Hz, 1 F).

ESI: *m*/*z* (%) = 438.1 [M$^+$ + Na, 100%].

4-(5,5-Difluoro-1,3-diisopropyl-2,6-dioxohexahydropyrimidin-4-yl)benzonitrile (5f)

R_f = 0.71 (hexanes–EtOAc, 70:30).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 8.3 Hz, 2 H), 7.58 (d, *J* = 8.2 Hz, 2 H), 5.36 (dd, *J* = 19.8, 1.8 Hz, 1 H), 4.98 (hept, *J* = 7.0 Hz, 1 H), 3.95 (hept, *J* = 6.3 Hz, 1 H), 1.48 (d, *J* = 12.5 Hz, 3 H), 1.46 (d, *J* = 12.4 Hz, 3 H), 1.16 (d, *J* = 6.3 Hz, 3 H), 1.10 (d, *J* = 6.3 Hz, 3 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 159.0 (t, *J* = 29.3 Hz), 138.6, 134.5, 132.4, 128.2, 118.0, 114.0, 106.5 (dd, *J* = 253.7, 250.1 Hz), 75.6 (dd, *J* = 29.7, 23.9 Hz), 49.3, 46.6, 24.1, 23.6, 19.2, 18.7.

^{19}F NMR (235 MHz, $CDCl_3$): δ = –118.8 (dd, *J* = 284.4, 2.8 Hz, 1 F), –123.9 (dd, *J* = 284.4, 19.8 Hz, 1 F).

ESI: *m*/*z* (%) = 368.1 [M$^+$ + Na, 100%].

5,5-Difluoro-6-(4-methoxyphenyl)-1,3-di-*p*-tolyldihydropyrimidine-2,4(1*H*,3*H*)-dione (5g)

R_f = 0.27 (hexanes–EtOAc, 80:20).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33 (d, *J* = 8.6 Hz, 1 H), 7.25 (d, *J* = 8.6 Hz, 1 H), 7.12 (d, *J* = 8.3 Hz, 1 H), 6.94 (d, *J* = 11.2 Hz, 1 H), 6.92 (d, *J* = 11.2 Hz, 2 H), 6.78 (d, *J* = 8.3 Hz, 1 H), 5.49 (dd, *J* = 16.9, 4.1 Hz, 1 H), 3.78 (s, 2 H), 2.35 (s, 2 H), 2.19 (s, 1 H).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –116.5 (dd, *J* = 285.1, 4.0 Hz, 1 F), –122.3 (dd, *J* = 285.1, 16.9 Hz, 1 F).

ESI: *m*/*z* (%) = 459.1 [M$^+$ + Na, 100%].

5,5-Difluoro-6-phenyl-1,3-di-*p*-tolyldihydropyrimidine-2,4(1*H*,3*H*)-dione (5h)

R_f = 0.46 (hexanes–EtOAc, 80:20).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31 (m, 7 H), 7.14 (d,, *J* = 8.4 Hz, 2 H), 6.97 (d, *J* = 7.7, 2 H), 6.82 (d, *J* = 8.4 Hz, 2 H), 5.56 (dd, *J* = 17.3, 1.9 Hz, 1 H), 2.35 (s, 3 H), 2.20 (s, 3 H).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –116.7 (dd, *J* = 285.5, 3.6 Hz, 1 F), –122.00 (dd, *J* = 285.5, 17.2 Hz, 1 F).

ESI: *m*/*z* (%) = 429.1 [M^+ + Na, 100%].

4-(3-Allyl-1-*tert*-butyl-5,5-difluoro-2,6-dioxohexahydropyrimidin-4-yl)benzonitrile (5k)

R_f = 0.48 (hexanes–EtOAc, 80:20).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 8.4 Hz, 2 H), 7.52 (d, *J* = 8.2 Hz, 2 H), 5.80 (ddt, *J* = 16.4, 10.2, 6.2 Hz, 1 H), 5.26 (m, 2 H), 5.16 (dd, *J* = 10.2, 1.1 Hz, 1 H), 4.43 (d, *J* = 6.0 Hz, 2 H), 1.20 (s, 9 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 157.8 (t, *J* = 36.6 Hz), 139.9, 135.2, 135.1, 132.6, 132.4, 132.2, 132.2, 132.1, 130.1, 129.9, 128.9, 128.5, 116.2 (dd, *J* = 320.4, 99.7 Hz), 116.1, 114.3, 113.0, 43.3, 29.7, 29.4, 28.7, 27.7.

^{19}F NMR (235 MHz, $CDCl_3$): δ = –119.5 (d, *J* = 286.1 Hz, 1 F), –122.8 (dd, *J* = 286.1, 19.7 Hz, 1 F).

ESI: *m*/*z* (%) = 370.1 [M^+ + Na, 100%].

4-(1-*tert*-Butyl-3-cyclohexyl-5,5-difluoro-2,6-dioxohexahydropyrimidin-4-yl)benzonitrile (5l)

R_f = 0.60 (hexanes–EtOAc = 80:20).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (dd, *J* = 70.0, 8.3 Hz, 4 H), 5.25 (dd, *J* = 19.4, 2.2 Hz, 1 H), 4.45 (tt, *J* = 12.0, 3.6 Hz, 1 H), 2.30 (dqd, *J* = 28.7, 12.4, 3.6 Hz, 2 H), 1.76 (d, *J* = 13.2 Hz, 2 H), 1.58 (d, *J* = 12.0 Hz, 3 H), 1.28 (m, 1 H), 1.21 (s, 9 H), 1.11 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.3 (t, *J* = 29.4 Hz), 155.1, 132.5, 128.4, 121.8 (dd, *J* = 2792.5, 228.7 Hz), 117.9, 114.2, 76.0 (dd, *J* = 29.6, 23.8 Hz), 57.6, 53.6, 30.3, 28.6, 28.3, 26.3, 25.3.

^{19}F NMR (235 MHz, $CDCl_3$): δ = –118.1 (d, *J* = 284.0 Hz, 1 F), –123.8 (dd, *J* = 284.1, 19.5 Hz, 1 F).

ESI: *m*/*z* (%) = 390.1 [M^+ + H, 100], 412.2 [M^+ + Na, 25].

6-Benzyl-1,3-dicyclohexyl-5,5-difluorodihydropyrimidine-2,4(1*H*,3*H*)-dione (5m)

R_f = 0.83 (hexanes–EtOAc, 80:20).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27 (m, 3 H), 7.21 (d, *J* = 5.8 Hz, 2 H), 4.44 (dt, *J* = 12.2, 3.7 Hz, 1 H), 4.26 (m, 1 H), 3.22 (dt, *J* = 9.1, 4.7 Hz, 1 H), 3.04 (dd, *J* = 14.4, 2.5 Hz, 1 H), 2.98 (d, *J* = 10.3 Hz, 1 H), 2.28 (m, 2 H), 1.71 (d, *J* = 13.9 Hz, 3 H), 1.54 (m, 5 H), 1.22 (m, 8 H), 1.07 (m, 2 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 159.7 (t, *J* = 29.3 Hz), 139.3, 135.0, 133.8, 129.5, 128.9, 128.7, 128.4, 127.7, 127.3, 127.1, 107.6 (dd, *J* = 252.1, 249.1 Hz), 56.8, 56.7, 55.8, 53.9, 34.9, 33.7, 33.6, 32.8, 32.7, 28.8, 28.4, 28.2, 26.2, 26.0, 25.8, 25.5, 25.3, 24.7, 24.5.

^{19}F NMR (235 MHz, $CDCl_3$): δ = –119.6 (d, *J* = 282.3 Hz, 1 F), –125.3 (dd, *J* = 282.3, 18.4 Hz, 1 F).

ESI: *m*/*z* (%) = 405.1 [M^+ + H, 20], 427.1 [M^+ + Na, 100%].

6-Benzyl-5,5-difluoro-1,3-diisopropyldihydropyrimidine-2,4(1*H*,3*H*)-dione (5n)

R_f = 0.80 (hexanes–EtOAc, 80:20).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 (dd, *J* = 11.2, 4.5 Hz, 2 H), 7.28 (m, 3 H), 4.92 (dt, *J* = 13.8, 6.9 Hz, 1 H), 4.37 (ddt, *J* = 17.9, 10.1, 3.0 Hz, 1 H), 3.64 (dt, *J* = 12.6, 6.3 Hz, 1 H), 3.11 (m, 2 H), 1.41 (t, *J* = 6.8 Hz, 6 H), 1.06 (d, *J* = 6.3 Hz, 3 H), 0.85 (d, *J* = 6.3 Hz, 3 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 159.5 (t, *J* = 29.4 Hz), 139.4, 135.0, 129.4, 128.7, 127.3, 107.6 (dd, *J* = 251.9, 249.6 Hz), 48.7, 46.3, 33.0, 32.9, 23.8, 23.6, 19.1, 18.8.

^{19}F NMR (235 MHz, $CDCl_3$): δ = –119.6 (dd, *J* = 282.7, 3.1 Hz, 1 F), –125.6 (dd, *J* = 282.7, 17.9 Hz, 1 F).

ESI: *m*/*z* (%) = 325.2 [M^+ + H, 15], 347.2 [M^+ + Na, 100].

6-Butyl-5,5-difluoro-1,3-diisopropyldihydropyrimidine-2,4(1*H*,3*H*)-dione (5o)

R_f = 0.84 (hexanes–EtOAc, 80:20).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.95 (dt, *J* = 13.8, 6.9 Hz, 1 H), 4.20 (m, 1 H), 3.89 (dt, *J* = 12.6, 6.3 Hz, 1 H), 1.79 (m, 2 H), 1.47 (m, 4 H), 1.43 (d, *J* = 6.9 Hz, 3 H), 1.42 (d, *J* = 6.9 Hz, 3 H), 1.10 (d, *J* = 6.3 Hz, 6 H), 0.95 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 154.3 (t, *J* = 51.6 Hz), 144.8, 119.3 (dd, *J* = 285.9, 276.5 Hz), 71.8 (dd, *J* = 52.0, 27.5 Hz), 48.7, 44.2, 43.4, 42.0, 31.4, 30.2, 29.7, 27.5, 27.2, 27.0, 22.9, 22.3, 20.8, 13.8, 13.7.

^{19}F NMR (235 MHz, $CDCl_3$): δ = –119.2 (dd, *J* = 282.8, 3.8 Hz, 1 F), –126.0 (dd, *J* = 282.7, 17.0 Hz, 1 F).

ESI: *m*/*z* (%) = 313.1 [M^+ + Na, 100%].

1,6-Dibenzyl-5,5-difluoro-3-phenyldihydropyrimidine-2,4-dione (5p)

R_f = 0.64 (hexanes–EtOAc, 80:20).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (dd, *J* = 7.7, 1.4 Hz, 2 H), 7.33 (ddd, *J* = 10.0, 6.2, 2.7 Hz, 4 H), 7.22 (m, 3 H), 7.10 (dd, *J* = 13.1, 7.3 Hz, 2 H), 6.99 (dd, *J* = 8.7, 4.3 Hz, 2 H), 6.78 (m, 2 H), 5.20 (d, *J* = 4.4 Hz, 2 H), 4.49 (ddt, *J* = 17.8, 10.0, 3.0 Hz, 1 H), 3.04 (ddd, *J* = 24.8, 14.7, 6.4 Hz, 2 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 159.3, 155.3, 143.8, 141.0, 139.0, 136.3, 135.9, 134.1, 129.5, 129.3, 128.7, 128.6, 128.2, 128.0, 127.9, 127.3, 126.3, 124.1, 122.9, 122.8, 46.4, 34.9, 32.7, 32.6.

^{19}F NMR (235 MHz, $CDCl_3$): δ = –120.2 (dd, *J* = 284.7, 3.3 Hz, 1 F), –124.7 (dd, *J* = 284.7, 17.7 Hz, 1 F).

ESI: *m*/*z* (%) = 347.1 [M^+ + Na, 100%].

1-Benzyl-6-butyl-5,5-difluoro-3-phenyldihydropyrimidine-2,4(1*H*,3*H*)-dione (5q)

R_f = 0.74 (hexanes–EtOAc, 80:20).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (m, 7 H), 6.98 (m, 3 H), 5.23 (s, 2 H), 4.31 (m, 1 H), 1.74 (ddd, *J* = 22.9, 11.5, 5.2 Hz, 2 H), 1.31 (m, 4 H), 0.82 (t, *J* = 7.1 Hz, 3 H).

^{19}F NMR (235 MHz, $CDCl_3$): δ = –118.6 (dd, *J* = 285.3, 4.7 Hz, 1 F), –125.1 (dd, *J* = 285.3, 15.6 Hz, 1 F).

ESI: *m*/*z* (%) = 395.1 [M^+ + Na, 100%].

***N*-Cyclohexyl-*N*-(cyclohexylcarbamoyl)-2,2-difluoro-3-hydroxy-3-(4-methoxyphenyl)propanamide (6a)**

R_f = 0.16 (hexanes–EtOAc, 80:20).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 (d, *J* = 8.6 Hz, 2 H), 6.90 (d, *J* = 8.7 Hz, 2 H), 5.73 (br s, 1 H), 5.20 (dd, *J* = 18.9, 6.1 Hz, 1 H), 4.17 (t, *J* = 11.9 Hz, 1 H), 3.81 (s, 3 H), 3.62 (m, 1 H), 1.95 (t, *J* = 10.9 Hz, 2 H), 1.81 (d, *J* = 11.9 Hz, 4 H), 1.72 (m, 2 H), 1.62 (m, 4 H), 1.34 (m, 4 H), 1.16 (m, 4 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 160.1 (t, *J* = 11.8 Hz), 160.1, 151.5, 130.0, 129.2, 127.0, 114.0, 113.7, 73.7 (dd, *J* = 30.0, 23.8 Hz), 56.2, 55.3, 50.5, 32.4, 32.2, 30.8, 30.1, 25.8, 25.4, 25.2, 24.6.

^{19}F NMR (235 MHz, $CDCl_3$): δ = –105.5 (dd, *J* = 265.7, 5.9 Hz, 1 F), –118.2 (dd, *J* = 265.7, 18.8 Hz, 1 F).

ESI: *m*/*z* (%) = 381.1 [M^+ + Na, 100%].

2,2-Difluoro-3-hydroxy-*N*-isopropyl-*N*-(isopropylcarbamoyl)-3-(4-methoxyphenyl)propanamide (6b)
R_f = 0.23 (hexanes–EtOAc, 70:30).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (d, *J* = 8.2 Hz, 2 H), 6.88 (d, *J* = 8.7 Hz, 2 H), 6.11 (d, *J* = 6.7 Hz, 1 H), 5.18 (dt, *J* = 19.7, 5.1 Hz, 1 H), 4.53 (dt, *J* = 13.6, 6.8 Hz, 1 H), 4.34 (d, *J* = 4.2 Hz, 1 H), 3.89 (dq, *J* = 13.4, 6.7 Hz, 1 H), 3.79 (s, 3 H), 1.28 (d, *J* = 12.4 Hz, 3 H), 1.26 (d, *J* = 12.5 Hz, 3 H), 1.18 (d, *J* = 9.6 Hz, 3 H), 1.16 (d, *J* = 9.6 Hz, 3 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 162.9 (t, *J* = 28.8 Hz) 160.0, 151.6, 129.2, 127.0, 115.8 (dd, *J* = 266.4, 253.5 Hz), 113.7, 73.3 (dd, *J* = 30.9, 23.5 Hz), 55.2, 48.7, 43.6, 22.1, 21.7, 20.7, 19.6.

^{19}F NMR (235 MHz, $CDCl_3$): δ = –105.2 (dd, *J* = 263.3, 5.8 Hz, 1 F), –119.0 (dd, *J* = 263.3, 19.7 Hz, 1 F).

ESI: *m*/*z* (%) = 381.0 [M^+ + Na, 100%].

***N*-Cyclohexyl-*N*-(cyclohexylcarbamoyl)-2,2-difluoro-3-hydroxy-3-phenylpropanamide (6c)**
R_f = 0.32 (hexanes–EtOAc, 80:20).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 (d, *J* = 4.2 Hz, 2 H), 7.37 (m, 3 H), 5.63 (d, *J* = 6.2 Hz, 1 H), 5.24 (m, 1 H), 4.17 (t, *J* = 12.1 Hz, 1 H), 4.04 (d, *J* = 4.2 Hz, 1 H), 3.62 (m, 1 H), 1.94 (m, 2 H), 1.83 (t, *J* = 13.8 Hz, 4 H), 1.71 (m, 2 H), 1.60 (m, 4 H), 1.32 (m, 4 H), 1.15 (m, 4 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 162.7, 151.5, 135.0, 128.9, 128.6, 128.5, 128.3, 128.2, 127.9, 127.7, 115.6 (dd, *J* = 266.0, 257.0 Hz), 74.1 (dd, *J* = 29.5, 24.1 Hz), 56.2, 50.6, 32.4, 32.2, 30.7, 30.2, 25.8, 25.4, 25.2, 24.6.

^{19}F NMR (235 MHz, $CDCl_3$): δ = –105.7 (dd, *J* = 267.1, 6.2 Hz, 1 F), –117.4 (dd, *J* = 267.0, 18.5 Hz, 1 F).

ESI: *m*/*z* (%) = 431.1 [M^+ + Na, 100].

2,2-Difluoro-3-hydroxy-*N*-isopropyl-*N*-(isopropylcarbamoyl)-3-phenylpropanamide (6d)
R_f = 0.31 (hexanes–EtOAc, 70:30).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 (m, 5 H), 5.82 (br s, 1 H), 5.26 (dd, *J* = 18.9, 6.0 Hz, 1 H), 4.55 (dt, *J* = 13.4, 6.7 Hz, 1 H), 4.09 (br s, 1 H), 3.91 (td, *J* = 13.4, 6.6 Hz, 1 H), 1.32 (t, *J* = 6.9 Hz, 6 H), 1.17 (t, *J* = 6.9 Hz, 6 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 163.0, 151.6, 151.1, 135.0, 128.9, 128.5, 128.2, 127.9, 127.8, 127.5, 127.3, 74.0 (m), 48.8, 43.7, 22.1, 22.0, 20.6, 19.8.

^{19}F NMR (235 MHz, $CDCl_3$): δ = –105.6 (dd, *J* = 266.6, 6.2 Hz, 1 F), –117.8 (dd, *J* = 266.6, 19.0 Hz, 1 F).

ESI: *m*/*z* (%) = 351.1 [M^+ + Na, 100%].

3-(4-Cyanophenyl)-*N*-cyclohexyl-*N*-(cyclohexylcarbamoyl)-2,2-difluoro-3-hydroxypropanamide (6e)
R_f = 0.10 (hexanes–EtOAc, 80:20).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 8.3 Hz, 2 H), 7.57 (d, *J* = 8.1 Hz, 2 H), 5.74 (d, *J* = 7.1 Hz, 2 H), 5.29 (dd, *J* = 19.4, 5.4 Hz, 1H), 4.60 (br s, 1 H), 4.18 (t, *J* = 11.9 Hz, 1 H), 3.64 (m, 1 H), 1.94 (t, *J* = 8.5 Hz, 2 H), 1.83 (d, *J* = 13.2 Hz, 4 H), 1.65 (m, 6 H), 1.35 (m, 4 H), 1.19 (m, 4 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 162.2 (t, *J* = 28.5 Hz), 151.7, 140.4, 132.4, 131.9, 128.7, 128.2, 118.5, 115.5 (dd, *J* = 267.4, 258.0 Hz), 112.6, 73.4 (dd, *J* = 29.9, 23.9 Hz), 56.4, 50.7, 32.4, 32.3, 30.8, 30.2, 25.8, 25.3, 25.1, 24.6.

^{19}F NMR (235 MHz, $CDCl_3$): δ = –104.0 (dd, *J* = 269.2, 4.6 Hz, 1 F), –117.4 (dd, *J* = 269.2, 19.5 Hz, 1 F).

ESI: *m*/*z* (%) = 434.0 [M^+ + H, 9], 456.1 [M^+ + Na, 100], 471.2 [M^+ + K, 58].

3-(4-Cyanophenyl)-2,2-difluoro-3-hydroxy-*N*-isopropyl-*N*-(isopropylcarbamoyl)propanamide (6f)
R_f = 0.21 (hexanes–EtOAc, 70:30).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 (d, *J* = 8.5 Hz, 2 H), 7.58 (d, *J* = 8.1 Hz, 2 H), 5.69 (br s, 1 H), 5.31 (dt, *J* = 8.4, 5.0 Hz, 1 H), 4.58 (dt, *J* = 13.6, 6.9 Hz, 1 H), 4.37 (d, *J* = 4.6 Hz, 2 H), 3.97 (dq, *J* = 13.2, 6.6 Hz, 1 H), 1.35 (d, *J* = 9.0 Hz, 3 H), 1.33 (d, *J* = 9.1 Hz, 3 H), 1.20 (t, *J* = 6.1 Hz, 6 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 162.7 (t, *J* = 28.7 Hz), 151.8, 140.2, 131.9, 128.7, 118.5, 115.4, 115.3 (dd, *J* = 267.0, 258.1 Hz), 112.8, 111.2, 73.5 (dd, *J* = 29.7, 23.9 Hz), 49.0, 44.0, 22.1, 20.6, 20.1.

^{19}F NMR (235 MHz, $CDCl_3$): δ = –104.1 (dd, *J* = 272.9, 5.4 Hz, 1 F), –117.1 (dd, *J* = 273.0, 19.3 Hz, 1 F).

ESI: *m*/*z* (%) = 376.1 [M^+ + Na, 100%].

***N*-(Allylcarbamoyl)-*N*-*tert*-butyl-2,2-difluoro-3-hydroxy-3-(4-methoxyphenyl)propanamide (6i)**
R_f = 0.28 (hexanes–EtOAc, 80:20).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.11 (br s, 1 H), 7.41 (d, *J* = 8.4 Hz, 2 H), 6.94 (d, *J* = 8.6 Hz, 2 H), 5.86 (qd, *J* = 10.6, 5.3 Hz, 1 H), 5.30 (d, *J* = 3.8 Hz, 1 H), 5.21 (d, *J* = 5.0 Hz, 2 H), 4.45 (d, *J* = 4.9 Hz, 2 H), 3.83 (s, 3 H), 1.40 (s, 9 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 160.2, 151.5, 133.2, 129.9, 129.4, 126.5, 117.3, 113.7, 73.3 (dd, *J* = 29.4, 23.0 Hz), 55.3, 51.9, 46.5, 28.5.

^{19}F NMR (235 MHz, $CDCl_3$): δ = –103.9 (d, *J* = 285.3 Hz, 1 F), –118.7 (dd, *J* = 285.3, 20.5 Hz, 1 F).

ESI: *m*/*z* (%) = 393.1 [M^+ + Na, 100%], 409.0 [M^+ + K, 77%].

***N*-(Allylcarbamoyl)-*N*-*tert*-butyl-2,2-difluoro-3-hydroxy-3-phenylpropanamide (6j)**
R_f = 0.55 (hexanes–EtOAc, 70:30).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (br s, 1 H), 7.42 (m, 5 H), 5.84 (ddd, *J* = 21.8, 10.5, 5.3 Hz, 1 H), 5.30 (dd, *J* = 20.5, 3.5 Hz, 1 H), 5.17 (m, 2 H), 4.43 (d, *J* = 4.6 Hz, 2 H), 3.66 (br s, 1 H), 1.39 (s, 9 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 166.3 (t, *J* = 30.0 Hz), 151.6, 134.5, 133.1, 129.0, 128.2, 127.8, 115.6 (dd, *J* = 268.7, 258.1 Hz), 117.4, 73.6 (dd, *J* = 30.1, 23.1 Hz), 51.9, 46.6, 29.5, 28.5.

^{19}F NMR (235 MHz, $CDCl_3$): δ = –103.9 (d, *J* = 285.8 Hz, 1 F), –118.1 (dd, *J* = 285.6, 20.6 Hz, 1 F).

ESI: *m*/*z* (%) = 363.0 [M^+ + Na, 100%].

***N*-(Allylcarbamoyl)-*N*-*tert*-butyl-3-(4-cyanophenyl)-2,2-difluoro-3-hydroxypropanamide (6k)**
R_f = 0.15 (hexanes–EtOAc, 80:20).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (d, *J* = 8.3 Hz, 2 H), 7.52 (d, *J* = 8.3 Hz, 2 H), 5.77 (m, 1 H), 5.27 (dd, *J* = 20.3, 3.9 Hz, 1 H), 5.10 (ddd, *J* = 6.8, 3.6, 2.1 Hz, 2 H), 4.34 (d, *J* = 5.5 Hz, 2 H), 1.24 (s, 9 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 171.1, 165.6, 157.4, 151.6, 132.9, 132.1, 131.9, 128.9, 117.7, 115.7, 115.6 (dd, *J* = 185.9, 175.1 Hz), 73.0 (dd, *J* = 29.6, 23.4 Hz), 63.6, 43.0, 28.4.

^{19}F NMR (235 MHz, $CDCl_3$): δ = –103.1 (d, *J* = 285.0 Hz, 1 F), –117.8 (dd, *J* = 285.0, 19.4 Hz, 1 F).

ESI: *m*/*z* (%) = 358.1 [M^+ + Na, 100%].

N-Cyclohexyl-N-(cyclohexylcarbamoyl)-2,2-difluoro-3-hydroxy-4-phenylbutanamide (6m)
R_f = 0.37 (hexanes–EtOAc, 80:20).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 6.6 Hz, 2 H), 7.18 (m, 3 H), 5.94 (br d, *J* = 6.8 Hz, 1 H), 4.29 (m, 1 H), 4.12 (tt, *J* = 12.3, 3.5 Hz, 1 H), 3.60 (m, 1 H), 2.99 (d, *J* = 14.0 Hz, 1 H), 2.73 (m, 1 H), 1.91 (m, 2 H), 1.82 (d, *J* = 12.3 Hz, 1 H), 1.74 (d, *J* = 11.8 Hz, 3 H), 1.65 (m, 3 H), 1.57 (m, 4 H), 1.29 (m, 4 H), 1.15 (m, 4 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 151.5, 136.8, 129.5, 128.6, 127.7 (dd, *J* = 724.6, 698.4 Hz), 126.9, 73.3 (dd, *J* = 30.3, 24.3 Hz), 56.1, 50.5, 35.5, 32.5, 32.2, 30.7, 30.1, 25.9, 25.4, 25.2, 24.6.

^{19}F NMR (235 MHz, $CDCl_3$): δ = –107.1 (dd, *J* = 266.8, 5.9 Hz, 1 F), –118.7 (dd, *J* = 266.7, 18.0 Hz, 1 F).

ESI: *m*/*z* (%) = 423.1 [M^+ + H, 5], 445.1 [M^+ + Na, 100].

2,2-Difluoro-3-hydroxy-N-isopropyl-N-(isopropylcarbamoyl)-4-phenylbutanamide (6n)
R_f = 0.20 (hexanes–EtOAc, 80:20).

^{1}H NMR (400 MHz, C_6D_{12}): δ = 7.34 (m, 2 H), 7.26 (m, 3 H), 6.16 (br s, 1 H), 4.57 (dt, *J* = 13.4, 6.7 Hz, 1 H), 4.38 (m, 1 H), 3.99 (td, *J* = 13.4, 6.7 Hz, 1 H), 3.09 (d, *J* = 5.5 Hz, 1 H), 2.82 (dd, *J* = 13.9, 10.6 Hz, 1 H), 1.35 (d, *J* = 6.7 Hz, 3 H), 1.31 (d, *J* = 6.8 Hz, 3 H), 1.23 (d, *J* = 8.3 Hz, 3 H), 1.22 (d, *J* = 8.3 Hz, 3 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 162.5 (t, *J* = 25.8 Hz), 151.6, 136.7, 129.5, 128.6, 128.4, 126.9, 116.5 (t, *J* = 260.7 Hz), 73.2 (dd, *J* = 31.1, 24.4 Hz), 48.6, 43.7, 42.0, 35.5, 22.3, 21.9, 20.6, 19.8.

^{19}F NMR (235 MHz, $CDCl_3$): δ = –107.0 (dd, *J* = 267.9, 6.0 Hz, 1 F), –118.9 (dd, *J* = 267.9, 18.2 Hz, 1 F).

ESI: *m*/*z* (%) = 343.2 [M^+ + H, 10], 365.2 [M^+ + Na, 100].

2,2-Difluoro-3-hydroxy-N-isopropyl-N-(isopropylcarbamoyl)heptanamide (6o)
R_f = 0.23 (hexanes–EtOAc, 80:20).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.05 (br s, 1 H), 4.56 (dt, *J* = 13.6, 6.8 Hz, 1 H), 4.11 (ddt, *J* = 16.0, 12.4, 6.3 Hz, 1 H), 3.97 (dq, *J* = 13.3, 6.7 Hz, 1 H), 3.21 (d, *J* = 6.4 Hz, 1 H), 1.55 (m, 2 H), 1.39 (m, 4 H), 1.34 (d, *J* = 10.1 Hz, 3 H), 1.33 (d, *J* = 10.1 Hz, 3 H), 1.21 (d, *J* = 6.5 Hz, 6 H), 0.92 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.6 (t, *J* = 29.2 Hz), 152.2, 117.2 (dd, *J* = 264.6, 256.8 Hz), 72.6 (dt, *J* = 39.7, 19.8 Hz), 49.0, 44.1, 42.3, 29.1, 27.8, 22.8, 22.6, 22.5, 22.4, 20.9, 20.4, 14.2.

^{19}F NMR (235 MHz, $CDCl_3$): δ = –107.2 (dd, *J* = 270.1, 6.6 Hz, 1 F), –118.7 (dd, *J* = 270.1, 18.2 Hz, 1 F).

ESI: *m*/*z* (%) = 331.2 [M^+ + Na, 100%].

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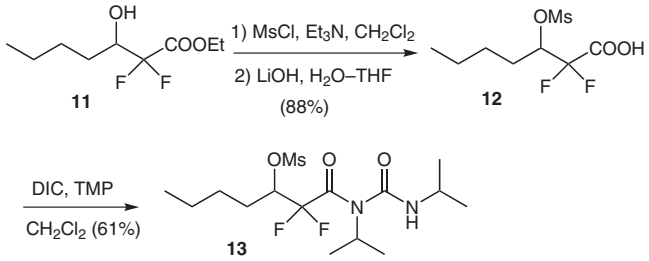

Scheme 7

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