EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201403495

Synthesis of Trifluoromethylated Analogues of 4,5-Dihydroorotic Acid

Volodymyr A. Sukach,*[a] Anastasia A. Resetnic,[b] Viktor M. Tkachuk,[a] Zhengguo Lin,[b] Ulrich Kortz,[b] Mykhailo V. Vovk,[a] and Gerd-Volker Röschenthaler[b]

Keywords: Nitrogen heterocycles / Fluorine / Cyanides / Noncovalent interactions

4-(Trifluoromethyl)pyrimidin-2(1*H*)-ones react with trimethylsilyl cyanide in the presence of a tertiary amine catalyst to give Michael-like 1,4-conjugate hydrocyanation adducts exclusively at the 3,6-positions. The resulting 2-oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-4-carbonitriles have been used to synthesize new trifluoromethylated 4,5-dihydroorotic acid analogues and their esters in racemic as well as enantiopure forms by a chiral auxiliary approach. The orthogonal intramolecular C–F···C=O interaction between the fluorine atom of the CF_3 group and the carbon atom of the ester group observed in the crystal state may stabilize the sterically unfavourable conformation of the methyl 2-oxo-6-(trifluoromethyl)hexahydropyrimidine-4-carboxylate molecule with axially oriented substituents.

Introduction

Organofluorine compounds are of paramount importance in the modern chemical industry, and they have also found widespread application in crop protection, medicine, and materials science.[1] There is an ever-growing variety of synthetic fluorinated molecules, including approved and investigational drug substances containing one or more single fluorine atoms or fluorinated functional groups (CHF_2, CF_3, OCF_3, and SCF_3 are common).[2] The persistent interest in such compounds may be attributed to the advantageous chemical, physicochemical, and biological properties imparted by fluorine incorporation.

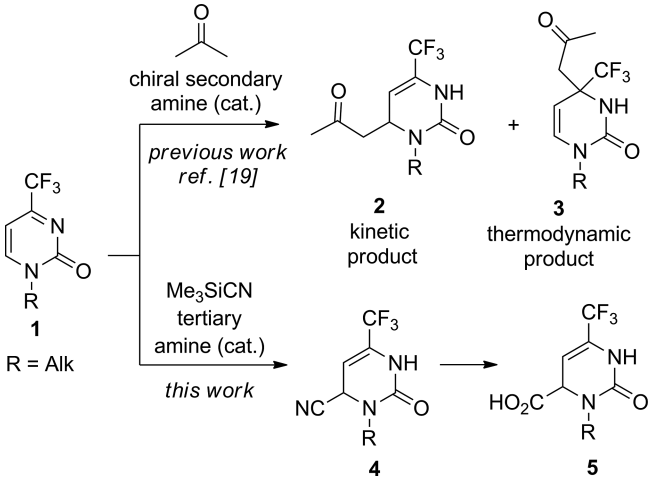
Fluorination has become a powerful tool for the modulation of crucial parameters of drug-candidate molecules. This approach is often used to influence metabolic stability and cell permeability, and to control the conformation of biologically active molecules.[3] There are numerous examples showing that fluorine atoms can significantly contribute to ligand binding affinity and selectivity through different types of positive nonbonding interactions within the active site of the corresponding protein target.[4] Fluorophilic environments in proteins include the peptide bonds, which can be involved in C–F···H–N, C–F···C=O, and C–F···H–C_α interactions, as well as the side-chain amide residues of Asn and Glu, and the positively charged guanidinium side-chain of Arg.[4,5] Additionally, coordination to the metal ion Zn^{2+} is sometimes observed.[6] Such electropositive regions are strongly attractive to hydrogen-bond accepting C=O, OH, thiol, and carboxylate groups. The question of how efficiently they can be replaced by fluorine-containing moieties as bioisosteres is being actively researched.[7] Therefore, the synthesis of new fluorinated analogues of biologically active small molecules is of great interest in organofluorine and medicinal chemistry.

Trifluoromethyl ketimines are an important class of fluorinated compounds that have generated considerable recent research interest.[8] The electron-accepting properties of the trifluoromethyl group make the typically deactivated ketimine C=N double bond readily susceptible to the addition of various C-nucleophiles. As a result, plenty of synthetic methods for the preparation of trifluoromethylated amines,[9] α- and β-amino ketones,[10] β-aminonitroalkanes,[11] and α-aminonitriles,[12] as well as α- and β-amino acids[13,14] have been developed over the past few decades. Much research has focussed on the chemistry of trifluoromethyl ketimines containing a reactive *endo* heterocyclic C=N bond.[15] Compounds of this type have found widespread application as starting materials in the synthesis of new fluorinated cyclic amine derivatives[15c,16] and 3,4-dihydroquinazolin-2-ones (including asymmetric versions).[17] 4-(Trifluoromethyl)pyrimidin-2(1*H*)-ones **1** (Scheme 1), which also belong to the class of cyclic ketimines, stand out due to their ambident electrophilic nature.[18] They have been much less studied until now, despite their synthetic availability[15d–15f] and the fact that they are original fluorinated derivatives of pyrimidin-2-one, a key heterocyclic component of nucleic acids. A first insight into the reactivity of compounds **1** with nucleophiles was recently provided by our group.[19] We demonstrated that compounds **1** reversibly react with acetone at the endocyclic C=N or C=C

[a] Department of Organic Reactions Mechanisms, Institute of Organic Chemistry, National Academy of Sciences of Ukraine, Murmans'ka 5, Kyiv 02660, Ukraine
E-mail: vsukach@gmail.com
http://www.ioch.kiev.ua
[b] School of Engineering and Science, Jacobs University Bremen, Campus Ring 1, 28759 Bremen, Germany
E-mail: g.roeschenthaler@jacobs-university.de
http://www.jacobs-university.de

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201403495.

bond, depending on the catalyst used, and also on whether thermodynamic or kinetic control is operative (Scheme 1). In the reaction catalysed by secondary amines, the formation of Michael-like adduct **2** is preferred under kinetically controlled conditions. Mannich-like adducts **3** are thermodynamically stable, and are formed after a prolonged reaction time. Unfortunately, because of the pronounced reversibility of these conversions, both products were isolated in racemic form. Another drawback was the very limited scope of ketone nucleophiles (only acetone was suitable).



Scheme 1. Summary of previous and present studies.

To further illustrate the reactivity and synthetic potential of pyrimidones **1**, we have used hydrogen cyanide as a different type of C-nucleophile. In this case, the formation of the analogous kinetic product (i.e., **4**) provides easy access to compounds **5**, new trifluoromethylated derivatives of dihydroorotic acid (DHO, Scheme 1). DHO is a crucial component of pyrimidine nucleotide biosynthesis. It is formed in the cyclization of *N*-carbamoyl-L-aspartic acid catalysed by the zinc metalloenzyme dihydroorotase (DHOase; Scheme 2).[20]

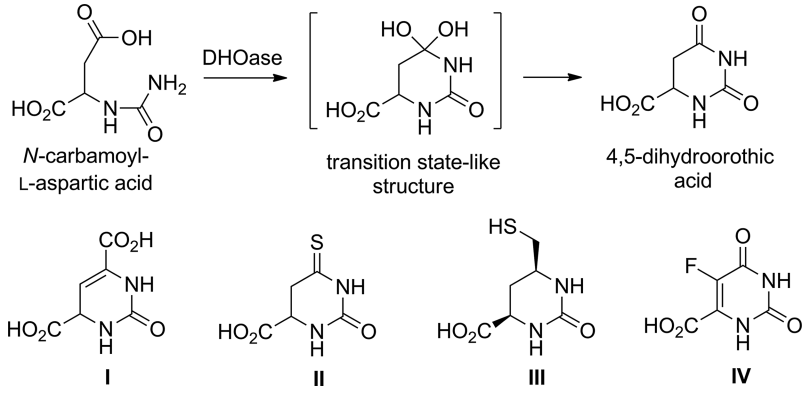
DHOase has long been known as a target for antimalarial and anticancer drug development. Its most potent inhibitors (structures **I**–**IV**, Scheme 2) exert their action through mimicry of the transition state of the enzymatic reaction through interactions of carboxylate, carbonyl, and thiol groups or fluorine atom(s) with the Zn^{2+} cofactor and hydrogen-bond donating regions.[21] The synthesis of new fluorinated analogues of DHO is a promising research field from both theoretical and practical points of view, taking into account, on the one hand, a call to clarify the fluorine effect on molecular binding to the protein active sites,[22] and, on the other hand, the urgent need for new medications in the relevant therapeutic areas.[23]

In this paper, we report the first catalytic hydrocyanation reaction of 4-(trifluoromethyl)pyrimidin-2(1*H*)-ones **1**. This conversion has opened up a synthetic route to several racemic and enantiopure trifluoromethylated DHO analogues that could mimic the transition state of the DHOase enzymatic reaction.

Results and Discussion

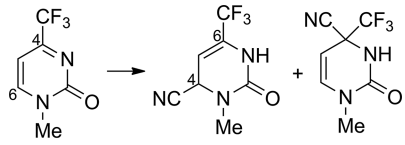
The 4-(trifluoromethyl)pyrimidin-2(1*H*)-ones (i.e., **1**) used in this study were prepared by the procedure of Gerus and Zanatta starting from 4-ethoxy-1,1,1-trifluoro-3-buten-2-one and ureas.[15f,15g] Simple N^1-methyl-substituted compound **1a** was used to screen cyanide sources and solvents for the hydrocyanation reaction (Table 1). As cyanide sources, we tested TMSCN (TMS = trimethylsilyl; in combination with *i*PrOH as the trimethylsilyl group acceptor), acetone cyanohydrin, and HCN.

An initial experiment was carried out using TMSCN in toluene. We found that a catalytic amount of organic base (triethylamine) was necessary for the reaction to take place. After as little as 3–5 min of stirring the reaction mixture at room temperature, the sparingly soluble starting pyrimidone (i.e., **1a**) had completely dissolved, and this was followed by the rapid precipitation of 3-methyl-2-oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-4-carbonitrile (**4a**) as a white bulky solid. The isolated yield after filtration and washing with hexane was 72% (Table 1, entry 1). We also found that a toluene/hexane mixture (2:1) gave a higher yield (93%) of **4a** (Table 1, entry 2). The material obtained was >95% pure according to ^{1}H NMR spectroscopy. The formation of the 3,6-adduct was initially confirmed by ^{19}F and ^{13}C NMR spectroscopy. The chemical shift of the



Scheme 2. Enzymatic reaction catalysed by dihydroorotase (DHOase) and structures of its inhibitors.

Table 1. Screening of the cyanide source, solvent, and time for the hydrocyanation reaction of 1-methyl-4-(trifluoromethyl)pyrimidin-2(1*H*)-one (**1a**).[a]



1a **4a** **6**

Entry[a]	Cyanide source	Solvent	Time [h]	Yield of **4a** [%][b]
1	TMSCN	toluene	1	72
2	TMSCN	toluene/hexane, 2:1	1	93
3	$Me_2C(OH)CN$[c]	toluene	1	–[d]
4	HCN[c]	toluene	1	–[d]
5	TMSCN, 1.2 equiv.	toluene/hexane, 2:1	1	–[e]
6	TMSCN	toluene	24	–[f]
7	TMSCN	MTBE	24	–[d]
8	TMSCN	CH_2Cl_2	1	–[g]
9	TMSCN	CH_2Cl_2	24	–[f]
10	TMSCN	*i*PrOH	24	–[f]

[a] Reaction conditions: compound **1a** (1.5 mmol), cyanide source (3 mmol), *i*PrOH (3 mmol), Et_3N (0.3 mmol), solvent (5 mL), 20 °C. [b] Yields of pure isolated product. [c] Without *i*PrOH. [d] No reaction. [e] 1.8 mmol of TMSCN and *i*PrOH were used, a **4a/1a** mixture (5:1) was isolated. [f] Not isolated, decomposition. [g] Conversion 71%, formation of a **4a/6** mixture (4:1).

fluorine nuclei was observed at δ = –71.00 ppm. The signal of the C-6 carbon was detected at δ = 131.58 ppm (quartet, $^2J_{C,F}$ = 37.4 Hz). All these measurements were recorded in $CDCl_3$. These data rule out structure **6** in which the fluorine and corresponding C-4 carbon atoms would be more shielded, and so have smaller chemical shifts of $\delta \approx$ –82 and 60 ppm, respectively.[19]

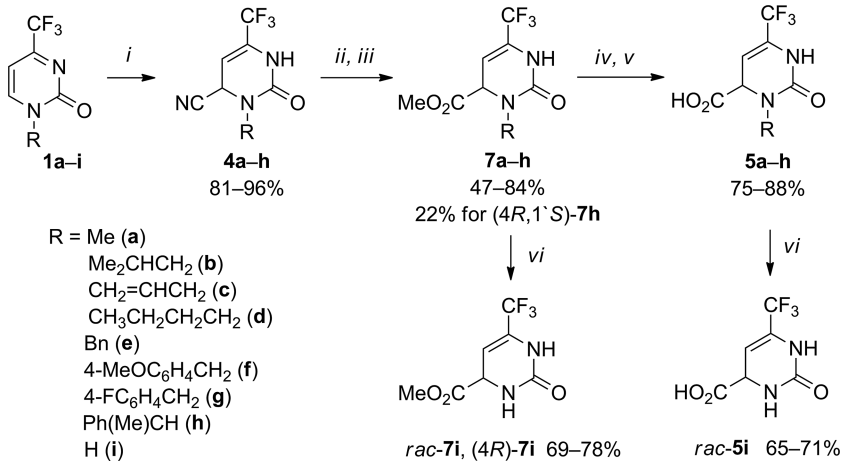
The use of acetone cyanohydrin and HCN instead of TMSCN in toluene did not result in any noticeable formation of **4a** (Table 1, entries 3 and 4). The efficiency of hydrocyanation with TMSCN could be explained by a mechanism involving initial trimethylsilylation of the oxygen atom and activation of the electrophilic centres for attack by the cyanide anion. The *O*-silylated intermediate is then cleaved by 2-propanol to give the final product (i.e., **4a**). The use of 1.2 equiv. of TMSCN led to incomplete conversion of **1a** (Table 1, entry 5). *i*PrOH can be replaced by methanol.

Prolongation of the reaction time to 24 h resulted in the gradual dissolution of the initially formed precipitate, a darkening of the reaction mixture, and, finally, tar formation on the flask walls (Table 1, entry 6). ^{19}F NMR analysis of the reaction mixture always indicated the presence of the starting material (up to 20%), along with regioisomeric product **6** having a chemical shift of δ = –81.90 ppm (in toluene). A large number of unidentified signals were observed after the reaction was run for 24 h. This behaviour points to the reversibility of the hydrogen cyanide addition. Clear evidence for an equilibrium between **4a**, **1a**, and HCN was provided by ^1H NMR spectra of supposedly pure **4a** recorded in [D_6]DMSO, which, however, showed the signals of the three components (including the HCN proton at δ = 6.33 ppm) as a result of the reverse reaction. Interestingly, compound **4a**, which is stable for weeks in $CDCl_3$ solution, decomposes upon addition of a catalytic amount of triethylamine to form a mixture of **1a**, **4a**, and **6**. This suggests that the exclusive formation of **4a** under conditions of kinetic control is due to displacement of the equilibrium through product precipitation. The choice of reaction solvent is therefore crucial, as demonstrated by the unsatisfactory results with CH_2Cl_2, *i*PrOH, and MTBE (methyl *tert*-butyl ether; Table 1, entries 7–10). The complex degradation processes observed after a prolonged reaction time (Table 1, entries 6, 9, and 10) are presumably due to the increased acidity of the C-4 proton in the **4a** molecule; the resulting carbanion species can lead to unidentified side-reactions.

Using the optimized conditions for the hydrocyanation of **1a** (Table 1, entry 2), we went on to study the scope of the reaction using various N^1-substituted 4-(trifluoromethyl)pyrimidin-2(1*H*)-ones (i.e., **1b**–**1i**). As expected, simple primary alkyl substituents were well tolerated (compounds **4b**–**4g**, Scheme 3). To explore secondary N^1-alkyl derivatives, we synthesized previously unknown compound **1h** in both racemic and enantiopure form [using (1*S*)-1-phenylethanamine as a chiral pool starting material]. The yield of the corresponding racemic nitrile (i.e., **4h**) was almost quantitative. A diastereomeric ratio of 5:1, determined by ^1H and ^{19}F NMR spectroscopy, represented a high diastereoselectivity. The racemic major isomer was purified after the next step (Scheme 3, see below for detailed description). Unfortunately, optically pure (*S*)-**1h** gave no crystalline product **4h** with any of the solvents and temperatures tested. Finally, the reaction was carried out in toluene at 0–5 °C, and quenched after 1 h with acetic acid (0.5 equiv.). After washing the clear toluene solution with water, a mixture of enantiopure diastereomers **4h** (5:1 ratio, total 73%), starting pyrimidone (7%), and regioisomeric product **6h** (20%) was isolated, and was used in the next step in an attempt to separate a more stable enantiopure compound (4*R*,1′*S*)-**4h** derivative by preparative chromatography (see below for details). As N^1-*tert*-alkyl and N^1-aryl pyrimidones **1** are not available by any known methods, we could not study the effect of these substituents on the course of the reaction. N^1-Unsubstituted pyrimidone **1i** reacted differently to give mainly the *O*-silylated derivative under a variety of tested conditions.

Compounds **4a**–**4h** are white solids with a faint almond smell, and they can be crystallized from nonpolar solvents ($CHCl_3$, toluene) and stored for a few months without noticeable decomposition. On heating to the melting point, they rapidly release HCN, which causes the sample to solidify (a "double melting point" effect). Derivative **4g** produced fine single crystals from $CDCl_3$ solution that were analysed by X-ray crystallography in order to unambiguously prove the 3,6-adduct structure of compounds **4** (Figure 1, see Supporting Information for details).

To prepare trifluoromethylated dihydroorotic acid analogues from nitriles **4a**–**4h**, we first developed a preparatively convenient method for cyano group methanolysis. This used HCl (4 M solution in dioxane), and the reaction



Scheme 3. Synthesis of 3-alkyl-2-oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-4-carbonitriles **4a**–**4h** and their derivatives, viz., methyl 3-alkyl-2-oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-4-carboxylates **7a**–**7i** and 3-alkyl-2-oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-4-carboxylic acids **5a**–**5i**. Reaction conditions: i) Compound **1a**–**1h** (1.5 mmol), TMSCN (3 mmol), *i*PrOH (3 mmol), Et_3N (0.3 mmol), toluene/hexane (2:1; 5 mL), 20 °C, 1 h; ii) Compound **4a**–**4h** (1.5 mmol), MeOH (6 mmol), HCl (4 M in anhydrous dioxane; 6 mL), 0–5 °C, 6 h; iii) H_2O (10 mL), 20 °C, 1 h; iv) Compound **7a**–**7h** (1 mmol), LiOH (0.95 mmol), THF/H_2O (1:1; 5 mL), 20 °C, 16 h; v) HCl (conc.), pH 2; vi) Compound **5f**, **5h**, **7f**, or **7h** (1 mmol), CF_3CO_2H (5 mL), reflux, 30 min, yields of pure isolated products.

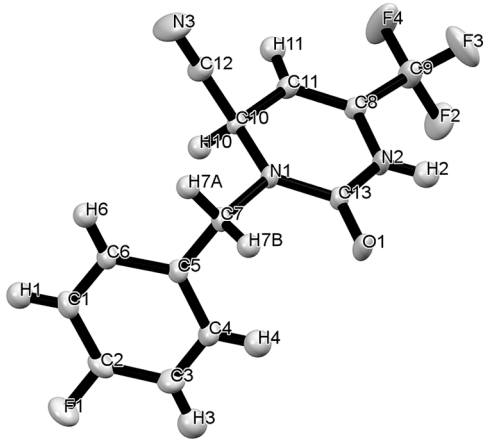


Figure 1. X-ray crystal structure of compound **4g**.

proceeded through the formation of the corresponding imino ester hydrochlorides. Taking into account the intrinsic instability of the starting nitriles (i.e., **4**), it was quite inappropriate to directly hydrolyse them to carboxylic acids under the commonly used harsh alkaline or acidic conditions.

The proposed method gave methyl 3-alkyl-2-oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-4-carboxylates **7a**–**7h** in high yields without chromatographic purification (Scheme 3). The major diastereomer of racemic **7h** was easily isolated by a single crystallization from MeOH/H_2O (3:1) in 47% overall yield (starting from racemic **4h** as a mixture of two diastereomers). The relative configuration of its stereogenic centres was determined by X-ray crystallography to be (4*RS*,1′*SR*). In the crystalline state, the molecules of this compound are assembled into heterochiral dimers by hydrogen bonds (Figure 2, see Supporting Information for details). From the X-ray crystallographic data we concluded that the corresponding enantiopure ester **7h** prepared from (*S*)-**1h** has an *R* configuration at its newly formed endocyclic chiral centre.

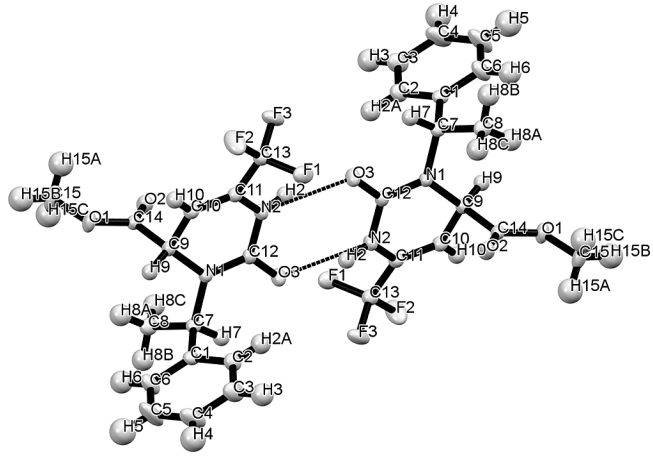


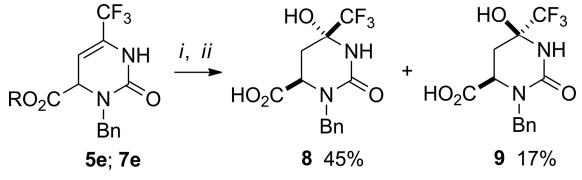
Figure 2. X-ray crystal structure of racemic compound (1′*SR*,4*RS*)-**7h**. Molecules are assembled into heterochiral dimers by hydrogen bonds.

Subsequent hydrolysis of the ester group with a sub stoichiometric amount of LiOH in THF/H_2O (1:1) provided the corresponding target acids (i.e., **5a**–**5h**) in excellent yields. Unfortunately, acid **5h** was obtained as a 2:1 inseparable mixture of two isomers owing to isomerization at the C-4 atom of **5h** during the hydrolysis of the ester group. Moreover, ^1H NMR analysis of the isolated sample of unreacted ester **7h** clearly indicated that the starting material had also isomerized under the conditions used. This process is likely to be induced by the increased acidity of the H-4 proton due to the effect of the trifluoromethyl group.

A series of N^3-alkyl-substituted trifluoromethylated analogues of dihydroorotic acid was prepared by the reactions

described above. The N^3-unsubstituted racemic compounds **5i** and **7i**, which are not accessible through direct hydrocyanation of **1i**, were readily obtained by removal of the 4-methoxybenzyl or 1-(1-phenylethyl) substituents after a short time at reflux in trifluoroacetic acid (TFA; Scheme 3). Likewise, the developed approach provides easy access to an enantiopure (*R*) form of **7i**, which is configurationally stable under the relatively drastic conditions of refluxing TFA, but which rapidly decomposes in basic media, such as a dilute LiOH solution. The enantiomeric composition was confirmed by its transformation into optically pure derivative (4*R*,6*S*)-**10d** (see below). Carboxylic acid **5i** is a dihydroorotic acid analogue, with the endocyclic $–CH_2(C=O)–$ moiety replaced by the structurally similar $–CH=C(CF_3)–$ moiety. This compound is of potential interest in medicinal chemistry as a new fluorinated building block and as a mimic of dihydroorotase inhibitor **I** (see Scheme 2).

The use of excess LiOH in the hydrolysis led to the simultaneous hydration of the endocyclic double bond to form a cyclic hydroxyaminal (at a much slower rate than the normal hydrolytic process). Compound **5e** or **7e**, when treated with 4 equiv. of LiOH at room temperature for 16 h, was converted into a mixture of diastereomeric salts of 3-benzyl-6-hydroxy-2-oxo-6-(trifluoromethyl)hexahydropyrimidine-4-carboxylic acids **8** and **9** in a ratio of 1.9:1, as shown by the ^{19}F NMR spectra of the reaction mixture. Acidification to pH 2 resulted in the precipitation of the nearly pure major diastereomer (i.e., **8**), and this was followed by crystallization from aqueous MeOH to give a 45% yield of the isolated material (Scheme 4).



Scheme 4. Cyclic hydroxyaminal formation from compounds **5e** and **7e**. Reaction conditions: i) Compound **5e** or **7e** (1 mmol), LiOH (4 mmol), THF/H_2O (1:1; 6 mL), 20 °C, 16 h; ii) HCl (aq.), pH 2, yields of pure isolated products.

The structure of **8** was determined by X-ray crystallographic analysis, and it was shown to be the (4*RS*,6*RS*) isomer with the CF_3 and COOH groups in equatorial orientations (Figure 3, see Supporting Information for details). In contrast to the crystal structures of compounds **4g** and **7h**, the molecules of **8** are assembled into homochiral associations by hydrogen bonds between the OH, COOH, and endocyclic CONH groups. The minor diastereomer (i.e., **9**) was isolated in a pure state in 17% yield from the mother liquor remaining after the filtration of **8**.

As previously reported, the C=C double bond of *N*-acylated α-trifluoromethyl-substituted enamines can be reduced by treatment with sodium borohydride in THF/H_2O.[24] Compounds **5** and **7**, which have a similar structural motif, proved almost completely unreactive under such conditions.

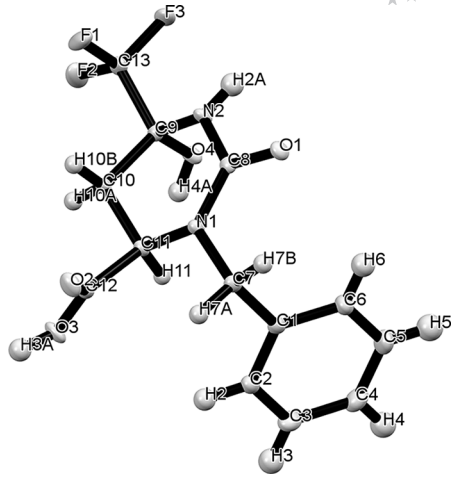
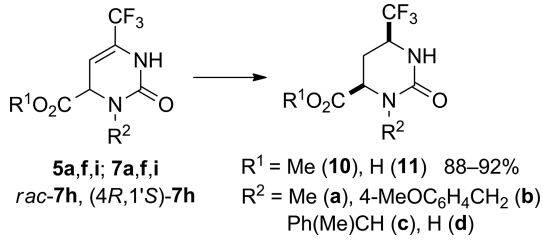


Figure 3. X-ray crystal structure of compound **8**. The CF_3 and COOH groups were found in equatorial positions.

It has been demonstrated that an efficient and highly regioselective hydrogenation leading to methyl 2-oxo-6-(trifluoromethyl)hexahydropyrimidine-4-carboxylates **10** and the corresponding acids (i.e., **11**) is readily achievable under mild conditions with hydrogen gas (1 atm) in the presence of a Pd/C catalyst at room temperature (Scheme 5).



Scheme 5. Diastereoselective hydrogenation of acids **5a**, **5f**, **5i** and their methyl esters **7a**, **7f**, **7h**, **7i**. Reaction conditions (1 mmol of the corresponding substrate was used): MeOH (5 mL), H_2 (1 atm), Pd/C (cat.), 1 h, 20 °C, yields of pure isolated products.

The relative configuration of the two endocyclic stereogenic centres in the molecules of the obtained single diastereomers was assigned as (4*RS*,6*SR*), i.e., *cis*, based on the X-ray crystallographic data for compound **10a** (Figure 4, see Supporting Information for details). Thus, the enantiopure **10d** that was obtained from (*R*)-**7i** has an (4*R*,6*S*) configuration. The enantiomeric composition of enantiopure (4*R*,6*S*,1′*S*)-**10c** was confirmed by ^{19}F NMR spectroscopy using quinine as a chiral solvating agent (see Supporting Information for details). The structure of acid **11a** was confirmed by its esterification with methanol to give **10a**. These results allowed us to conclude that the diastereoselective hydrogenation gave *cis* products for all the described examples.

A particular feature of the crystal structure of **10a** is the sterically unfavourable axial orientation of both the CF_3 and COOMe groups. Even though crystal packing forces may be a key structural determinant in the solid state,[25]

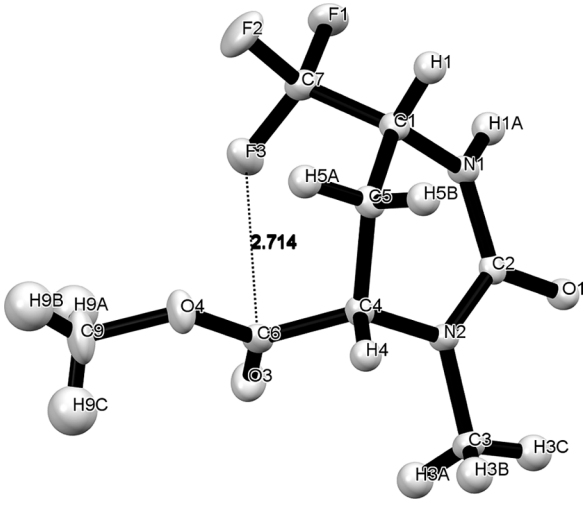
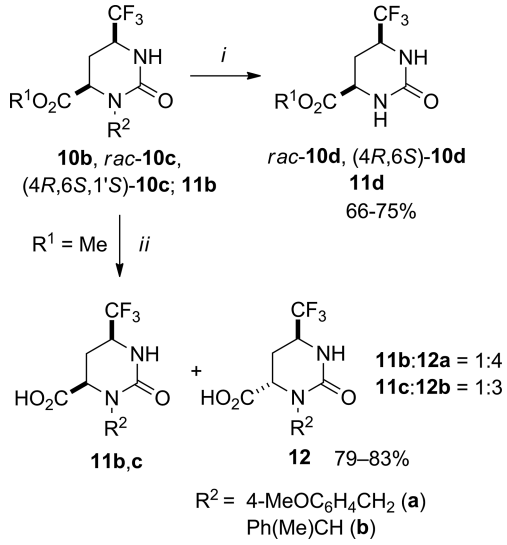


Figure 4. X-ray crystal structure of compound **10a**. The molecule has a conformation with axially oriented CF_3 and COOMe groups. The dashed line shows the short orthogonal intramolecular C–F···C=O contact. The label indicates the distance between the corresponding fluorine and carbon atoms.



Scheme 6. Synthesis of N^3-unsubstituted compounds **10d** and **11d** by acidic cleavage of 4-methoxybenzyl and 1-(1-phenylethyl) substituents and hydrolysis of esters **10b** and **10c** with the formation of diastereomeric acids **11b/12a** and **11c/12b** mixtures. Reaction conditions (1 mmol of the corresponding substrate was used): i) CF_3CO_2H (5 mL), reflux, 30 min; ii) LiOH (0.95 mmol), THF/H_2O (1:1, 6 mL), 20 °C, 16 h, then aq. HCl, pH 2, yields of pure isolated products.

the observed conformational preference can also be explained by the attractive intramolecular orthogonal multipolar C–F···C=O interaction.[5a,26] A short contact between one of the fluorine atoms and the carbon atom of the ester group (2.714 Å distance) with an apparent orthogonal geometry supports this hypothesis (Figure 4). Similar intermolecular interactions are typical of protein–ligand complexes, and they affect the binding mode and biological properties of many fluorine-containing drugs.[1,4] We believe that the described fluorine effect can control the conformation of other trifluoromethylated hetero- and carbocyclic small molecules, and that it therefore has potential as a new conformational tool in the rational design of organocatalysts and biologically active compounds.[27]

Surprisingly, the 4-methoxybenzyl and 1-(1-phenylethyl) N^3-substituents tolerated mild hydrogenation conditions without undergoing reductive cleavage. It was possible to subsequently remove them by heating the corresponding reduced products (i.e., **10b**, **10c**, and **11b**) in refluxing TFA without isomerization at the endocyclic chiral centre at C-4 (Scheme 6).

This approach has provided an alternative route to racemic and enantiopure (4*R*,6*S*) ester **10d** and racemic acid **11d**, which are interesting as a new low-molecular weight fluorinated heterocyclic building block and a trifluoromethyl-containing mimic of dihydroorotase inhibitor **III** (see Scheme 2). However, the aforementioned isomerization did occur during the hydrolysis of the ester group in compounds **10b** and **10c** (even though substoichiometric amounts of LiOH were used). Unexpectedly, isomers **12a** and **12b** were the major components in the resulting inseparable mixture of diastereomeric acids (Scheme 6). Therefore, such a route could not be used for the preparation of diastereomerically pure **11d** by subsequent acidic cleavage of the N^3-substituent.

Conclusions

We have shown that the reaction of N^1-alkyl-4-(trifluoromethyl)pyrimidin-2(1*H*)-ones **1** with TMSCN in the presence of a tertiary amine catalyst and an alcohol results in the selective and highly efficient 1,4-conjugate addition of HCN to the endocyclic C=C bond of the pyrimidine ring. Using a chiral auxiliary approach, an asymmetric version of this transformation was also accomplished. The resulting nitriles (i.e., **4a**–**4h**) appear to be versatile starting compounds for the synthesis of racemic trifluoromethylated dihydroorotic acid analogues **5a**–**5i** as well as their methyl esters **7a**–**7i**. Esters **7h** and **7i** were prepared in enantiopure forms. A highly diastereoselective reduction of the 2-oxo-1,2,3,4-tetrahydropyrimidine ring of compounds **5** and **7** into the 2-oxohexahydropyrimidine moiety of compounds **10** and **11** was easily achieved by straightforward hydrogenation with hydrogen gas in the presence of a Pd/C catalyst under mild conditions. The developed method allowed the preparation of racemic 2-oxo-6-(trifluoromethyl)hexahydropyrimidine-4-carboxylic acids **11** and their methyl esters **10**. Enantiopure forms of esters **10c** and **10d** were isolated. The X-ray crystallographic study of compound **10a** revealed a hitherto unknown example of an intramolecular orthogonal C–F···C=O interaction that may stabilize the molecule in a sterically unfavourable conformation. The compounds prepared in this study show promise as new fluorinated building blocks and mimics of dihydroorotase enzyme inhibitors that could be of particular interest in medicinal chemistry.

Experimental Section

General Details: All chemicals were obtained from commercial suppliers (Sigma–Aldrich, Enamine Ltd.), and were used without further purification. Solvents were purified by standard methods. ^{1}H (399.78 or 299.94 MHz), ^{13}C (100.53 or 125.71 MHz), and ^{19}F (188.14 or 376.17 MHz) NMR spectra were recorded with Jeol ECX 400, Varian VXR-300, and Varian Mercury 400 instruments using tetramethylsilane or CCl_3F as an internal standard. ^{1}H NMR spectroscopic data are reported as chemical shifts (ppm) followed by relative integrals, multiplicities ("s" singlet, "d" doublet, "t" triplet, "q" quartet, "dd" doublet of doublets, "dt" doublet of triplets, "dq" doublet of quartets, "sext" sextet, "m" multiplet, "br." broad), and coupling constants (Hz). LCMS spectra were recorded with an Agilent 1100 Series high-performance liquid chromatograph equipped with a diode matrix with an Agilent LCMSD SL mass-selective detector. Crystal data for all compounds were collected with a Bruker APEX-II CCD detector. Optical rotations were measured with an Anton Paar MCP 300 polarimeter (sample-cell path length 100 mm, wavelength 589 nm). Preparative chromatography was carried out using a low-pressure (up to 3 atm) CombiFlash Companion apparatus equipped with a UV detector (eluent hexane/methyl *tert*-butyl ether). Microanalyses were performed in the Microanalytical Laboratory of the Institute of Organic Chemistry, National Academy of Sciences of Ukraine. Compounds **1a**–**1i** were prepared according to literature procedures (see Supporting Information for the general procedure and characterization data for new compounds).

General Procedure for the Synthesis of 2-Oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-4-carbonitriles 4a–4g: Compound **1a**–**1g** (1.5 mmol), 2-propanol (0.18 g, 3 mmol), and triethylamine (0.03 g, 0.3 mmol) were mixed in a toluene/hexane mixture (2:1; 5 mL), and then TMSCN (0.75 mL, 3 mmol) was added at 20 °C. The mixture was stirred for 1 h. The resulting white precipitate was collected by filtration, washed with hexane (10 mL), and dried in air. The resulting products were >95% pure, and were used in the next stage without further purification.

In the case of enantiopure compound *S*-**1h**, the reaction mixture was kept for 30 min at 5 °C. The clear solution was quenched with acetic acid (0.036 g, 0.9 mmol), the mixture was washed with distilled water (2 × 10 mL), the organic phase was dried with sodium sulfate, and the solvent was evaporated. The residue, which contained (1′*S*,4*R*)-**4h** (61%) and (1′*S*,4*S*)-**4h** (12%) along with regioisomer **6h** (20%) and starting material *S*-**1h** (7%), was used in the next step without further purification.

3-Methyl-2-oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-4-carbonitrile (4a): Yield 0.29 g (93%), m.p. 120–122 °C. ^{1}H NMR ($CDCl_3$): δ = 3.09 (s, 3 H), 5.02–5.06 (m, 1 H), 5.37–5.41 (m, 1 H), 8.50 (br. s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 33.5, 49.4, 93.1 (q, $^3J_{C,F}$ = 4.79 Hz), 114.5, 119.0 (q, $^1J_{C,F}$ = 273.17 Hz), 131.5 (q, $^2J_{C,F}$ = 37.38 Hz), 151.8 ppm. ^{19}F NMR ($CDCl_3$): δ = –71.0 ppm. $C_7H_6F_3N_3O$ (205.14): calcd. C 40.98, H 2.95, N 20.48; found C 40.92, H 2.90, N 20.50. LCMS: $[M + H]^+$ 206, $[M – CN]^+$ 179.

3-(2-Methylpropyl)-2-oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-4-carbonitrile (4b): Yield 0.30 g (81%), m.p. 134–136 °C. ^{1}H NMR ($CDCl_3$): δ = 0.89 (d, J = 6.65 Hz, 3 H), 0.96 (d, J = 6.66 Hz, 3 H), 1.98–2.01 (m, 1 H), 2.90 (dd, J = 13.74, 9.29 Hz, 1 H), 3.73 (dd, J = 14.18, 9.30 Hz, 1 H), 4.98 (d, J = 3.99 Hz, 1 H), 5.36 (d, J = 4.02 Hz, 1 H), 9.02 (br. s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.2, 19.4, 25.7, 46.9, 52.8, 92.8 (q, $^3J_{C,F}$ = 4.99 Hz), 114.6, 118.5 (q, $^1J_{C,F}$ = 273.26 Hz), 131.5 (q, $^2J_{C,F}$ = 36.40 Hz), 151.9 ppm. ^{19}F NMR ($CDCl_3$): δ = –71.4 ppm. $C_{10}H_{12}F_3N_3O$ (247.22): calcd. C 58.58, H 4.89, N 17.00; found C 58.65, H 4.90, N 16.91. LCMS: $[M + H]^+$ 248, $[M – CN]^+$ 221.

2-Oxo-3-(prop-2-en-1-yl)-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-4-carbonitrile (4c): Yield 0.29 g (85%), m.p. 125–127 °C. ^{1}H NMR ($CDCl_3$): δ = 3.58 (dd, J = 15.07, 8.35 Hz, 1 H), 4.72 (d, J = 15.51 Hz, 1 H), 5.03 (s, 1 H), 5.37–5.40 (m, 3 H), 5.71 (s, 1 H), 9.11 (br. s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 45.3, 47.4, 93.1 (q, $^3J_{C,F}$ = 4.99 Hz), 114.3, 118.4 (q, $^1J_{C,F}$ = 273.76 Hz), 120.7, 129.8, 131.1 (q, $^2J_{C,F}$ = 36.90 Hz), 151.3 ppm. ^{19}F NMR ($CDCl_3$): δ = –71.5 ppm. $C_9H_8F_3N_3O$ (231.17): calcd. C 46.76, H 3.49, N 18.18; found C 46.80, H 3.41, N 18.15. LCMS: $[M + H]^+$ 232, $[M – CN]^+$ 205.

3-Butyl-2-oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-4-carbonitrile (4d): Yield 0.32 g (86%), m.p. 102–104 °C. ^{1}H NMR ($CDCl_3$): δ = 0.95 (t, J = 7.68 Hz, 3 H), 1.35 (sext, J = 7.68 Hz, 2 H), 1.58–1.62 (m, 2 H), 3.17–3.21 (m, 1 H), 3.80–3.85 (m, 1 H), 5.05 (s, 1 H), 5.36 (s, 1 H), 9.15 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.1, 19.3, 28.1, 45.7, 46.6, 92.8, 114.8, 118.5 (q, $^1J_{C,F}$ = 273.76 Hz), 131.3 (q, $^2J_{C,F}$ = 36.90 Hz), 151.6 ppm. ^{19}F NMR ($CDCl_3$): δ = –71.6 ppm. $C_{10}H_{12}F_3N_3O$ (247.22): calcd. C 48.58, H 4.89, N 17.00; found C 48.44, H 3.80, N 17.09. LCMS: $[M + H]^+$ 248, $[M – CN]^+$ 221.

3-Benzyl-2-oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-4-carbonitrile (4e): Yield 0.38 g (91%), m.p. 131–133 °C. ^{1}H NMR ($CDCl_3$): δ = 4.02 (d, J = 14.88 Hz, 1 H), 4.83–4.86 (m, 1 H), 5.31–5.35 (m, 1 H), 5.50 (d, J = 14.90 Hz, 1 H), 7.30–7.45 (m, 5 H), 8.45 (br. s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 45.7, 48.6, 93.5 (q, $^3J_{C,F}$ = 4.82 Hz), 114.5, 118.9 (q, $^1J_{C,F}$ = 273.59 Hz), 128.8, 129.3, 131.4 (q, $^2J_{C,F}$ = 36.61 Hz), 133.8, 152.1 ppm. ^{19}F NMR ($CDCl_3$): δ = –70.8 ppm. $C_{13}H_{10}F_3N_3O$ (281.23): calcd. C 55.52, H 3.58, N 14.94; found C 50.55, H 3.54, N 14.95. LCMS: $[M + H]^+$ 282, $[M – CN]^+$ 255.

3-(4-Methoxybenzyl)-2-oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-4-carbonitrile (4f): Yield 0.45 g (96%), m.p. 135–137 °C. ^{1}H NMR ($CDCl_3$): δ = 3.81 (s, 3 H), 3.96 (d, J = 14.88 Hz, 1 H), 4.83 (d, J = 5.04 Hz, 1 H), 5.30 (d, J = 5.02 Hz, 1 H), 5.42 (d, J = 14.86 Hz, 1 H), 6.90 (dd, J = 8.47, 1.83 Hz, 2 H), 7.26 (dd, J = 8.46, 1.84 Hz, 2 H), 8.58 (br. s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 45.4, 48.1, 55.4, 93.6 (q, $^3J_{C,F}$ = 4.79 Hz), 114.5, 114.6, 119.0 (q, $^1J_{C,F}$ = 273.65 Hz), 125.5, 130.3, 131.3 (q, $^2J_{C,F}$ = 36.90 Hz), 151.6, 160.1 ppm. ^{19}F NMR ($CDCl_3$): δ = –70.8 ppm. $C_{14}H_{12}F_3N_3O_2$ (311.26): calcd. C 54.02, H 3.89, N 13.50; found C 54.15, H 3.90, N 13.44. LCMS: $[M + H]^+$ 312, $[M – CN]^+$ 285.

3-(4-Fluorobenzyl)-2-oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-4-carbonitrile (4g): Yield 0.40 g (90%), m.p. 148–150 °C. ^{1}H NMR ($CDCl_3$): δ = 4.06 (d, J = 15.11 Hz, 1 H), 4.84 (d, J = 5.04 Hz, 1 H), 5.33 (d, J = 5.04 Hz, 1 H), 5.39 (d, J = 15.12 Hz, 1 H), 7.08–7.13 (m, 2 H), 7.33–7.40 (m, 2 H), 8.99 (br. s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 45.8, 48.1, 93.5 (q, $^3J_{C,F}$ = 4.82 Hz), 114.4, 116.3 (d, $^2J_{C,F}$ = 22.16 Hz), 118.9 (q, $^1J_{C,F}$ = 273.59 Hz), 129.6 (d, $^4J_{C,F}$ = 2.89 Hz), 130.6 (d, $^3J_{C,F}$ = 7.71 Hz), 131.4 (q, $^2J_{C,F}$ = 36.61 Hz), 151.9, 161.5 (d, $^1J_{C,F}$ = 248.54 Hz) ppm. ^{19}F NMR ($CDCl_3$): δ = –112.5 (s, 1 F), –70.8 (s, 3 F) ppm. $C_{13}H_9F_4N_3O$ (299.22): calcd. C 52.18, H 3.03, N 14.04; found C 52.19, H 2.97, N 14.10. LCMS: $[M + H]^+$ 300, $[M – CN]^+$ 273.

2-Oxo-3-(1-phenylethyl)-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-4-carbonitrile (4h): Mixture of racemic diastereomers (5:1, 1′*SR*,6*RS*:1′*SR*,6*SR*), yield 0.39 g (88%), m.p. 121–123 °C. ^{1}H NMR ($CDCl_3$): δ = 1.62 (d, J = 7.10 Hz, 0.6 H), 1.81 (d, J = 7.10 Hz, 3 H), 4.50 (d, J = 6.18 Hz, 1 H), 4.86 (d, J = 6.18 Hz, 0.2 H), 5.27 (d, J = 5.95 Hz, 1 H), 5.45 (d, J = 5.95 Hz, 0.2 H), 5.83

(q, J = 7.10 Hz, 1 H), 5.89 (q, J = 7.10 Hz, 0.2 H), 7.35–7.49 (m, 6 H), 8.44 (br. s, 1 H), 8.53 (br. s, 0.2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 15.74, 15.78, 40.9, 41.7, 52.8, 53.5, 94.6 (q, $^3J_{C,F}$ = 4.82 Hz), 116.7, 119.0 (q, $^1J_{C,F}$ = 273.59 Hz), 127.9, 128.8, 129.1, 129.3, 131.8 (q, $^2J_{C,F}$ = 36.61 Hz), 137.4, 152.4, 152.5 ppm. ^{19}F NMR ($CDCl_3$): δ = –70.5 (s, 1 F), –70.4 (s, 0.2 F) ppm. $C_{14}H_{12}F_3N_3O$ (295.26): calcd. C 56.95, H 4.10, N 14.23; found C 57.13, H 4.17, N 14.15. LCMS: $[M + H]^+$ 296, $[M – CN]^+$ 269.

General Procedure for the Synthesis of Methyl 2-Oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-4-carboxylates (7a–7h): Compound **4a**–**4h** (1.5 mmol) was added to a mixture of anhydrous methanol (0.192 g, 6 mmol) and HCl (4 M in anhydrous dioxane; 6 mL) at 5 °C. The reaction mixture was stirred at this temperature for 6 h. Then water (10 mL) was added, and the mixture was stirred for 1 h at 22 °C. The resulting precipitate formed was collected by filtration, washed with water (10 mL), and dried in air. For the preparation of enantiopure (4*R*,1′*S*)-**7h**, the mixture obtained after stirring in water was extracted with dichloromethane (20 mL), the organic layer was washed with water (20 mL), and dried with sodium sulfate, and the solvent was evaporated. The residue was subjected to preparative chromatography.

Methyl 3-Methyl-2-oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-4-carboxylate (7a): Yield 0.26 g (74%), m.p. 128–130 °C (toluene). ^{1}H NMR ([D$_6$]DMSO): δ = 2.76 (s, 3 H), 3.67 (s, 3 H), 4.87 (d, J = 5.04 Hz, 1 H), 5.52 (d, J = 5.04 Hz, 1 H), 9.66 (s, 1 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 33.8, 53.1, 59.7, 97.7 (q, $^3J_{C,F}$ = 4.79 Hz), 119.9 (q, $^1J_{C,F}$ = 272.69 Hz), 129.4 (q, $^2J_{C,F}$ = 34.98 Hz), 152.6, 169.9 ppm. ^{19}F NMR ([D$_6$]DMSO): δ = –69.0 ppm. $C_8H_9F_3N_2O_3$ (238.16): calcd. C 40.34, H 3.81, N 11.76; found C 40.30, H 3.83, N 11.71. LCMS: $[M + H]^+$ 239.

Methyl 3-(2-Methylpropyl)-2-oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-4-carboxylate (7b): Yield 0.32 g (77%), m.p. 140–142 °C (toluene). ^{1}H NMR ([D$_6$]DMSO): δ = 0.77 (d, J = 6.57 Hz, 3 H), 0.84 (d, J = 6.57 Hz, 3 H), 1.76–1.90 (m, 1 H), 3.55–3.72 (m, 4 H), 4.84 (d, J = 5.69 Hz, 1 H), 5.58 (d, J = 5.69 Hz, 1 H), 9.65 (s, 1 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 19.7, 26.0, 52.6, 52.9, 57.7, 97.6 (q, $^3J_{C,F}$ = 3.99 Hz), 119.5 (q, $^1J_{C,F}$ = 272.26 Hz), 129.1 (q, $^2J_{C,F}$ = 34.90 Hz), 152.4, 169.9 ppm. ^{19}F NMR ([D$_6$]DMSO): δ = –69.0 ppm. $C_{11}H_{15}F_3N_2O_3$ (280.24): calcd. C 47.14, H 5.39, N 10.00; found C 47.21, H 5.41, N 10.12. LCMS: $[M + H]^+$ 281.

Methyl 2-Oxo-3-(prop-2-en-1-yl)-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-4-carboxylate (7c): Yield 0.29 g (73%), m.p. 102–104 °C (toluene). ^{1}H NMR ([D$_6$]DMSO): δ = 3.50 (dd, J = 15.15, 8.10 Hz, 1 H), 3.68 (s, 3 H), 4.29 (dd, J = 15.15, 4.24 Hz, 1 H), 4.76 (d, J = 5.60 Hz, 1 H), 5.12 (s, 1 H), 5.17 (d, J = 8.70 Hz, 1 H), 5.58 (d, J = 5.60 Hz, 1 H), 5.69–7.75 (m, 1 H), 9.76 (s, 1 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 47.8, 52.6, 56.8, 97.6 (q, $^3J_{C,F}$ = 5.49 Hz), 117.7. 119.5 (q, $^1J_{C,F}$ = 272.76 Hz), 129.0 (q, $^2J_{C,F}$ = 34.91 Hz), 132.9, 151.8, 169.7 ppm. ^{19}F NMR ([D$_6$]DMSO): δ = –69.0 ppm. $C_{10}H_{11}F_3N_2O_3$ (264.20): calcd. C 45.46, H 4.20, N 10.60; found C 45.37, H 4.13, N 10.62. LCMS: $[M + H]^+$ 265.

Methyl 3-Butyl-2-oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-4-carboxylate (7d): Yield 0.31 g (74%), m.p. 108–110 °C (toluene). ^{1}H NMR ([D$_6$]DMSO): δ = 0.86 (t, J = 7.14 Hz, 3 H), 1.22 (sext, J = 7.14 Hz, 2 H), 1.35–1.50 (m, 2 H), 2.72–2.80 (m, 1 H), 3.65–3.73 (m, 4 H), 4.89 (d, J = 4.39 Hz, 1 H), 5.55 (d, J = 4.39 Hz, 1 H), 9.64 (s, 1 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 13.7, 19.4, 28.9, 45.5, 52.6, 57.3, 97.5 (q, $^3J_{C,F}$ = 4.49 Hz), 119.5 (q, $^1J_{C,F}$ = 272.26 Hz), 129.0 (q, $^2J_{C,F}$ = 35.40 Hz), 152.0, 170.0 ppm. ^{19}F NMR ([D$_6$]DMSO): δ = –69.1 ppm. $C_{11}H_{15}F_3N_2O_3$ (280.24): calcd. C 47.14, H 5.39, N 10.00; found C 47.10, H 5.33, N 10.03. LCMS: $[M + H]^+$ 281.

Methyl 3-Benzyl-2-oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-4-carboxylate (7e): Yield 0.38 g (81%), m.p. 155–157 °C (toluene). ^{1}H NMR ($CDCl_3$): δ = 3.71 (s, 3 H), 3.95 (d, J = 15.11 Hz, 1 H), 4.51–4.55 (m, 1 H), 5.29 (d, J = 15.11 Hz, 1 H), 5.32–5.36 (m, 1 H), 7.23–7.37 (m, 5 H), 8.26 (s, 1 H) ppm. ^{13}C NMR ([D$_6$]-DMSO): δ = 49.2, 53.1, 57.7, 98.2 (q, $^3J_{C,F}$ = 4.79 Hz), 120.0 (q, $^1J_{C,F}$ = 272.69 Hz), 127.9, 128.3, 129.0, 129.4 (q, $^2J_{C,F}$ = 34.98 Hz), 137.2, 152.6, 170.0 ppm. ^{19}F NMR ([D$_6$]DMSO): δ = –69.1 ppm. $C_{14}H_{13}F_3N_2O_3$ (314.26): calcd. C 53.51, H 4.17, N 8.91; found C 53.55, H 4.09, N 10.56. LCMS: $[M + H]^+$ 315.

Methyl 3-(4-Methoxybenzyl)-2-oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-4-carboxylate (7f): Yield 0.41 g (79%), m.p. 123–125 °C (toluene). ^{1}H NMR ([D$_6$]DMSO): δ = 3.58 (s, 3 H), 3.69 (s, 3 H), 3.90 (d, J = 14.88 Hz, 1 H), 4.60–4.65 (m, 1 H), 4.85 (d, J = 14.88 Hz, 1 H), 5.53–5.57 (m, 1 H), 6.86 (d, J = 8.70 Hz, 2 H), 7.16 (d, J = 8.70 Hz, 2 H), 9.77 (s, 1 H) ppm. ^{13}C NMR ([D$_6$] DMSO): δ = 48.5, 53.1, 55.5, 57.3, 98.1 (q, $^3J_{C,F}$ = 4.79 Hz), 114.4, 120.0 (q, $^1J_{C,F}$ = 272.69 Hz), 128.9, 129.4 (q, $^2J_{C,F}$ = 34.99 Hz), 130.0, 152.6, 159.2, 170.1 ppm. ^{19}F NMR ([D$_6$]DMSO): δ = –69.1 ppm. $C_{15}H_{15}F_3N_2O_4$ (344.29): calcd. C 52.33, H 4.39, N 8.14; found C 53.21, H 4.40, N 8.13. LCMS: $[M + H]^+$ 345.

Methyl 3-(4-Fluorobenzyl)-2-oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-4-carboxylate (7g): Yield 0.42 g (84%), m.p. 132–134 °C (toluene). ^{1}H NMR ([D$_6$]DMSO): δ = 3.58 (s, 3 H), 4.03 (d, J = 15.11 Hz, 1 H), 4.71–4.74 (m, 1 H), 4.83 (d, J = 15.11 Hz, 1 H), 5.55–5.59 (m, 1 H), 7.09–7.16 (m, 2 H), 7.25–7.31 (m, 1 H), 9.81 (s, 1 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 48.5, 53.1, 57.7, 98.2 (q, $^3J_{C,F}$ = 4.82 Hz), 115.7 (d, $^2J_{C,F}$ = 21.19 Hz), 119.9 (q, $^1J_{C,F}$ = 272.62 Hz), 129.4 (q, $^2J_{C,F}$ = 34.68 Hz), 130.5 (d, $^3J_{C,F}$ = 8.67 Hz), 133.5 (d, $^4J_{C,F}$ = 2.89 Hz), 152.6, 162.0 (d, $^1J_{C,F}$ = 242.76 Hz), 170.1 ppm. ^{19}F NMR ([D$_6$]DMSO): δ = –68.3 (s, 3 F), –114.6 (s, 1 F) ppm. $C_{14}H_{12}F_4N_2O_3$ (332.25): calcd. C 50.61, H 3.64, N 8.43; found C 50.67, H 3.58, N 8.44. LCMS: $[M + H]^+$ 333.

Methyl (4*RS*)-2-Oxo-3-[(1*SR*)-1-phenylethyl]-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-4-carboxylate (7h): Yield 0.23 g (47%), m.p. 150–152 °C (MeOH/H_2O, 2:1). ^{1}H NMR ([D$_6$]DMSO): δ = 1.34 (d, J = 7.10 Hz, 6 H), 3.66 (s, 3 H), 4.39–4.44 (m, 1 H), 5.56 (d, J = 6.41 Hz, 1 H), 5.59 (d, J = 7.10 Hz, 1 H), 7.22–7.37 (m, 5 H), 9.81 (s, 1 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 17.1, 52.3, 53.3, 53.5, 98.5 (q, $^3J_{C,F}$ = 4.82 Hz), 120.0 (q, $^1J_{C,F}$ = 272.62 Hz), 127.2, 128.0, 129.1, 129.9 (q, $^2J_{C,F}$ = 35.16 Hz), 141.1, 152.8, 171.3 ppm. ^{19}F NMR ([D$_6$]DMSO): δ = –68.6 ppm. $C_{15}H_{15}F_3N_2O_3$ (328.29): calcd. C 54.88, H 4.61, N 8.53; found C 54.70, H 4.69, N 8.50. LCMS: $[M + H]^+$ 329.

Methyl (4*R*)-2-Oxo-3-[(1*S*)-1-phenylethyl]-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-4-carboxylate (7h): Yield 0.1 g (22%), oily colourless substance. $[\alpha]_D^{20}$ = +273.6 (c = 0.75, MeOH).

General Procedure for the Synthesis of 2-Oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-4-carboxylic Acids (5a–5h): Compound **7a**–**7h** (1 mmol) was dissolved in tetrahydrofuran (3 mL), and a solution of LiOH (0.0228 g, 0.95 mmol) in water (3 mL) was added at 20 °C. The reaction mixture was stirred at this temperature for 16 h. The solvent was evaporated, and water (10 mL) was added. The mixture was washed with dichloromethane (2 × 10 mL). The aqueous layer was stirred under vacuum for 20 min to completely remove the organic solvent, and then it was acidified with concentrated hydrochloric acid to pH 2. The white precipitate formed was collected by filtration, washed with water (2 × 5 mL), and dried in air.

3-Methyl-2-oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-4-carboxylic Acid (5a): Yield 0.17 g (77%), m.p. 197–199 °C (ethanol/

water, 1:2). ^{1}H NMR ([D$_6$]DMSO): δ = 4.69 (dq, J = 5.72, 1.60 Hz, 1 H), 5.50–5.54 (m, 1 H), 9.55 (d, J = 1.37 Hz, 1 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 33.8, 59.8, 98.3 (q, $^3J_{C,F}$ = 4.80 Hz), 120.0 (q, $^1J_{C,F}$ = 272.62 Hz), 131.8 (q, $^2J_{C,F}$ = 35.16 Hz), 152.7, 170.8 ppm. ^{19}F NMR ([D$_6$]DMSO): δ = –68.6 ppm. $C_7H_7F_3N_2O_3$ (224.14): calcd. C 37.51, H 3.15, N 12.50; found C 37.55, H 3.14, N 12.40. LCMS: [M + H]$^+$ 225.

3-(2-Methylpropyl)-2-oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-4-carboxylic Acid (5b): Yield 0.2 g (75%), m.p. 210–212 °C (ethanol/water, 1:2). ^{1}H NMR ([D$_6$]DMSO): δ = 0.77 (d, J = 6.57 Hz, 3 H), 0.84 (d, J = 6.57 Hz, 3 H), 1.78–1.90 (m, 1 H), 2.42–2.53 (m, 1 H), 3.63 (dd, J = 14.05, 7.88 Hz, 1 H), 4.67 (d, J = 5.26 Hz, 1 H), 5.57 (d, J = 5.26 Hz, 1 H), 9.53 (s, 1 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 19.8, 26.0, 53.0, 57.9, 98.3 (q, $^3J_{C,F}$ = 4.99 Hz), 119.6 (q, $^1J_{C,F}$ = 272.26 Hz), 128.7 (q, $^2J_{C,F}$ = 35.40 Hz), 152.5, 170.7 ppm. ^{19}F NMR ([D$_6$]DMSO): δ = –68.6 ppm. $C_{10}H_{13}F_3N_2O_3$ (266.22): calcd. C 45.12, H 4.92, N 10.52; found C 45.14, H 4.80, N 10.44. LCMS: [M + H]$^+$ 267.

2-Oxo-3-(prop-2-en-1-yl)-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-4-carboxylic Acid (5c): Yield 0.19 g (76%), m.p. 201–202 °C (ethanol/water, 1:2). ^{1}H NMR ([D$_6$]DMSO): δ = 3.41 (dd, J = 15.39, 6.59 Hz, 1 H), 4.38 (dd, J = 15.39, 4.39 Hz, 1 H), 4.60 (d, J = 4.94 Hz, 1 H), 5.11–5.20 (m, 2 H), 5.59 (d, J = 5.49 Hz, 1 H), 5.69–5.79 (m, 1 H), 9.65 (s, 1 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 47.8, 56.8, 98.3 (q, $^3J_{C,F}$ = 4.49 Hz), 117.7, 119.6 (q, $^1J_{C,F}$ = 272.26 Hz), 128.6 (q, $^2J_{C,F}$ = 34.91 Hz), 133.1, 151.9, 170.5 ppm. ^{19}F NMR ([D$_6$]DMSO): δ = –68.6 ppm. $C_9H_9F_3N_2O_3$ (250.17): calcd. C 43.21, H 3.63, N 11.20; found C 43.32, H 3.60, N 11.25. LCMS: [M + H]$^+$ 251.

3-Butyl-2-oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-4-carboxylic Acid (5d): Yield 0.2 g (75%), m.p. 216–218 °C (ethanol/water, 2:1). ^{1}H NMR ([D$_6$]DMSO): δ = 0.86 (t, J = 7.14 Hz, 3 H), 1.22 (sext, J = 7.14 Hz, 2 H), 1.35–1.50 (m, 2 H), 2.70–2.75 (m, 1 H), 3.66–3.73 (m, 1 H), 4.72 (d, J = 4.39 Hz, 1 H), 4.72 (d, J = 4.39 Hz, 1 H), 5.54 (d, J = 4.39 Hz, 1 H), 9.52 (s, 1 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 13.7, 19.5, 28.9, 45.6, 57.4, 98.2 (q, $^3J_{C,F}$ = 4.49 Hz), 119.6 (q, $^1J_{C,F}$ = 272.26 Hz), 128.6 (q, $^2J_{C,F}$ = 35.40 Hz), 152.1, 170.8 ppm. ^{19}F NMR ([D$_6$]DMSO): δ = –68.5 ppm. $C_{10}H_{13}F_3N_2O_3$ (266.22): calcd. C 45.12, H 4.92, N 10.52; found C 45.13, H 4.99, N 10.55. LCMS: [M + H]$^+$ 267.

3-Benzyl-2-oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-4-carboxylic Acid (5e): Yield 0.25 g (83%), m.p. 165–167 °C (ethanol/water, 2:1). ^{1}H NMR ([D$_6$]DMSO): δ = 3.82 (d, J = 15.34 Hz, 1 H), 4.51 (d, J = 4.58 Hz, 1 H), 5.07 (d, J = 15.34 Hz, 1 H), 5.55 (d, J = 15.34 Hz, 1 H), 7.18–7.36 (m, 5 H), 9.72 (d, J = 1.60 Hz, 1 H), 13.05 (br. s, 1 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 49.1, 57.6, 98.8 (q, $^3J_{C,F}$ = 4.79 Hz), 120.1 (q, $^1J_{C,F}$ = 272.69 Hz), 127.9, 128.2, 129.0 (q, $^2J_{C,F}$ = 34.99 Hz), 129.1, 137.3, 152.8, 170.8 ppm. ^{19}F NMR ([D$_6$]DMSO): δ = –68.7 ppm. $C_{13}H_{11}F_3N_2O_3$ (300.23): calcd. C 52.01, H 3.69, N 9.33; found C 51.91, H 3.65, N 9.37. LCMS: [M + H]$^+$ 301.

3-(4-Methoxybenzyl)-2-oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-4-carboxylic Acid (5f): Yield 0.28 g (85%), m.p. 181–183 °C (ethanol/water, 2:1). ^{1}H NMR ([D$_6$]DMSO): δ = 3.69 (s, 3 H), 3.76 (d, J = 15.11 Hz, 1 H), 4.46 (d, J = 5.04 Hz, 1 H), 4.99 (d, J = 15.11 Hz, 1 H), 5.52 (d, J = 5.04 Hz, 1 H), 6.86 (d, J = 8.47 Hz, 2 H), 7.15 (d, J = 8.47 Hz, 2 H), 9.69 (s, 1 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 48.4, 55.5, 57.2, 98.7 (q, $^3J_{C,F}$ = 4.79 Hz), 114.4, 120.0 (q, $^1J_{C,F}$ = 272.14 Hz), 129.0, 129.0 (q, $^2J_{C,F}$ = 35.16 Hz), 129.9, 152.7, 159.2, 170.8 ppm. ^{19}F NMR ([D$_6$]DMSO): δ = –68.7 ppm. $C_{14}H_{13}F_3N_2O_4$ (330.26): calcd. C 50.91, H 3.97, N 8.48; found C 50.93, H 4.01, N 8.45. LCMS: [M + H]$^+$ 331.

3-(4-Fluorobenzyl)-2-oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-4-carboxylic Acid (5g): Yield 0.28 g (88%), m.p. 185–187 °C (ethanol/water, 2:1). ^{1}H NMR ([D$_6$]DMSO): δ = 3.89 (d, J = 15.34 Hz, 1 H), 4.56 (d, J = 4.58 Hz, 1 H), 4.96 (d, J = 15.34 Hz, 1 H), 5.55 (d, J = 4.58 Hz, 1 H), 7.08–7.16 (m, 2 H), 7.25–7.31 (m, 2 H), 9.72 (s, 1 H), 12.50 (br. s, 1 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 48.5, 57.7, 98.9 (q, $^3J_{C,F}$ = 4.79 Hz), 115.7 (d, $^2J_{C,F}$ = 35.16 Hz), 120.1 (q, $^1J_{C,F}$ = 272.62 Hz), 128.9 (q, $^2J_{C,F}$ = 35.64 Hz), 130.4 (d, $^3J_{C,F}$ = 8.67 Hz), 133.7 (d, $^4J_{C,F}$ = 2.89 Hz), 152.8, 162.0 (q, $^1J_{C,F}$ = 242.76 Hz), 170.8 ppm. ^{19}F NMR ([D$_6$]DMSO): δ = –68.6 ppm. $C_{13}H_{10}F_4N_2O_3$ (318.22): calcd. C 49.07, H 3.17, N 8.80; found C 59.20, H 3.11, N 8.88. LCMS: [M + H]$^+$ 319.

2-Oxo-3-(1-phenylethyl)-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-4-carboxylic Acid (5h): Mixture of two diastereomers (2:1), yield 0.26 g (83%), m.p. 158–160 °C (ethanol/water, 2:1). ^{1}H NMR ([D$_6$]DMSO): δ = 1.37 (d, J = 7.10 Hz, 3 H), 1.49 (d, J = 7.10 Hz, 1.5 H), 4.25–4.30 (m, 1 H), 4.65–4.69 (m, 0.5 H), 5.41 (q, J = 7.10 Hz, 0.5 H), 5.50–5.64 (m, 2.5 H), 7.17–7.37 (m, 7.5 H), 9.54 (d, J = 2.06 Hz, 0.5 H), 9.70 (d, J = 2.06 Hz, 1 H), 12.52 (br. s, 0.5 H), 13.16 (br. s, 1 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 17.2, 17.5, 52.1, 53.5, 53.6, 54.8, 99.2 (q, $^3J_{C,F}$ = 4.79 Hz), 99.5 (q, $^3J_{C,F}$ = 4.79 Hz), 120.1 (q, $^1J_{C,F}$ = 272.21 Hz), 127.1, 127.9, 128.7 (q, $^2J_{C,F}$ = 35.40 Hz), 129.1, 139.8, 141.4, 152.7, 153.0, 170.9, 172.2 ppm. ^{19}F NMR ([D$_6$]DMSO): δ = –68.60 (s, 1 F), –68.69 (s, 2 F) ppm. $C_{14}H_{13}F_3N_2O_3$ (314.26): calcd. C 53.51, H 4.17, N 8.91; found C 53.57, H 4.15, N 8.82. LCMS: [M + H]$^+$ 315.

General Procedure for the Synthesis of Compounds (5i) and (7i): Compound **5f**, **5h**, **7f**, or **7h** (1 mmol) was dissolved in CF_3CO_2H (5 mL) and heated at reflux for 30 min. The solvent was evaporated, and the residue was treated with diethyl ether (20 mL). The solid was collected by filtration and then recrystallized.

Methyl 2-Oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-4-carboxylate (7i): Starting from **7f**, yield 0.15 g (69%); starting from (4*RS*,1′*SR*)-**7h**, yield 0.17 g (78%), m.p. 163–165 °C (racemic, acetonitrile). ^{1}H NMR ([D$_6$]DMSO): δ = 3.65 (s, 3 H), 4.70 (s, 1 H), 5.44 (d, J = 3.90 Hz, 1 H), 7.29 (s, 1 H), 9.46 (s, 1 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 53.0, 53.4, 97.9 (q, $^3J_{C,F}$ = 3.85 Hz), 120.1 (q, $^1J_{C,F}$ = 272.62 Hz), 129.3 (q, $^2J_{C,F}$ = 34.68 Hz), 152.5, 171.3 ppm. ^{19}F NMR ([D$_6$]DMSO): δ = –69.0 ppm. $C_7H_7F_3N_2O_3$ (224.14): calcd. C 37.51, H 3.15, N 12.50; found C 37.42, H 3.10, N 12.48. LCMS: [M + H]$^+$ 225.

Methyl (4*R*)-2-Oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-4-carboxylate (7i): Starting from (4*R*,1′*S*)-**7h**, yield 0.17 g (77%), m.p. 168–170 °C (chloroform/hexane, 9:1). $[a]_D^{20}$ = +54.0 (c = 0.5, MeOH).

2-Oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-4-carboxylic Acid (5i): Starting from **5f**, yield 0.14 g (65%); starting from **5h** (as a mixture of diastereomers), yield 0.15 g (71%), m.p. 205–207 °C (2-propanol). ^{1}H NMR ([D$_6$]DMSO): δ = 4.54–4.58 (m, 1 H), 5.43 (d, J = 3.90 Hz, 1 H), 7.18 (s, 1 H), 9.36 (s, 1 H), 12.5 (br. s, 1 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 53.5, 98.5 (q, $^3J_{C,F}$ = 4.82 Hz), 120.2 (q, $^1J_{C,F}$ = 272.62 Hz), 128.8 (q, $^2J_{C,F}$ = 34.68 Hz), 152.6, 172.1 ppm. ^{19}F NMR ([D$_6$]DMSO): δ = –68.7 ppm. $C_6H_5F_3N_2O_3$ (210.11): calcd. C 34.30, H 2.40, N 13.33; found C 34.37, H 2.38, N 13.33. LCMS: [M + H]$^+$ 211.

(4*RS*,6*RS*)-3-Benzyl-6-hydroxy-2-oxo-6-(trifluoromethyl)hexahydropyrimidine-4-carboxylic Acid (8): Compound **5e** or **7e** (1 mmol) was dissolved in tetrahydrofuran (3 mL), and a solution of LiOH (4 mmol) in water (3 mL) was added. The reaction mixture was stirred at 20 °C for 16 h. The solvent was evaporated, and water (10 mL) was added. The resulting solution was acidified with con-

centrated hydrochloric acid to pH 2. The resulting white precipitate was collected by filtration, washed with water (2× 5 mL), dried in air, and recrystallized from MeOH/H_2O (1:1), yield 0.14 g (45%), m.p. 180–182 °C. ^{1}H NMR ([D$_6$]DMSO): δ = 2.22 (dd, J = 14.51, 5.95 Hz, 1 H), 2.33 (dd, J = 14.51, 7.56 Hz, 1 H), 3.83 (d, J = 16.03 Hz, 1 H), 3.95 (t, J = 6.87 Hz, 1 H), 5.17 (d, J = 15.80 Hz, 1 H), 7.17–7.32 (m, 6 H), 7.61 (s, 1 H), 12.76 (br. s, 1 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 31.8, 48.5, 54.0, 79.6 (q, $^2J_{C,F}$ = 31.79 Hz), 123.9 (q, $^1J_{C,F}$ = 286.11 Hz), 127.5, 127.9, 128.9, 138.0, 154.6, 172.1 ppm. ^{19}F NMR ([D$_6$]DMSO): δ = –83.1 ppm. $C_{13}H_{13}F_3N_2O_4$ (318.25): calcd. C 49.06, H 4.12, N 8.80; found C 49.09, H 4.07, N 8.83. LCMS: [M + H]$^+$ 319.

(4*RS*,6*SR*)-3-Benzyl-6-hydroxy-2-oxo-6-(trifluoromethyl)hexahydropyrimidine-4-carboxylic Acid (9): The remaining acidic filtrate from the synthesis of compound **8** described above was evaporated to dryness, and the residue was treated with methanol. The insoluble material was removed by filtration, and the solvent was evaporated from the filtrate. The resulting residue was recrystallized from acetonitrile, yield 0.054 g (17%), m.p. 171–173 °C. ^{1}H NMR ([D$_6$]DMSO): δ = 2.05 (dd, J = 13.57, 6.53 Hz, 1 H), 2.33 (d, J = 13.34 Hz, 1 H), 3.80 (d, J = 15.68 Hz, 1 H), 3.93 (dd, J = 6.18, 2.18 Hz, 1 H), 5.12 (d, J = 15.68 Hz, 1 H), 7.04 (br. s, 1 H), 7.17–7.30 (m, 5 H), 7.42 (s, 1 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 30.3, 49.6, 53.6, 79.9 (q, $^2J_{C,F}$ = 31.79 Hz), 124.0 (q, $^1J_{C,F}$ = 287.07 Hz), 127.5, 127.8, 128.9, 138.5, 153.9, 172.0 ppm. ^{19}F NMR ([D$_6$]DMSO): δ = –83.4 ppm. $C_{13}H_{13}F_3N_2O_4$ (318.25): calcd. C 49.06, H 4.12, N 8.80; found C 49.15, H 4.13, N 8.72. LCMS: [M + H]$^+$ 319.

General Procedure for the Synthesis of Methyl (4*RS*,6*SR*)-2-Oxo-6-(trifluoromethyl)hexahydropyrimidine-4-carboxylates 10a–10d and (4*RS*,6*SR*)-2-Oxo-6-(trifluoromethyl)hexahydropyrimidine-4-carboxylic Acids (11a, 11b, and 11d): Compound **5a**, **5f**, **5i**, **7a**, **7f**, **7h**, or **7i** (1 mmol) was dissolved in MeOH (5 mL), and Pd/C catalyst (10%; 100 mg) was added. Hydrogen gas was bubbled into the resulting suspension while stirring. The reaction was monitored by TLC or ^{19}F NMR spectroscopy. After the starting material had completely disappeared (about 1 h), the mixture was filtered, and the solvent was evaporated. The resulting white solid residue was recrystallized.

Compounds **10d** and **11d** were also obtained according to the general procedure for the synthesis of compounds **5i** and **7i**, starting from compounds **10b**, **10c**, or **11b** as appropriate.

Methyl (4*RS*,6*SR*)-3-Methyl-2-oxo-6-(trifluoromethyl)hexahydropyrimidine-4-carboxylate (10a): Yield 0.22 g (92%), m.p. 157–159 °C (toluene). ^{1}H NMR ([D$_6$]DMSO): δ = 2.25–2.31 (m, 1 H), 2.40 (dt, J = 15.11, 7.33 Hz, 1 H), 2.79 (s, 3 H), 3.61 (s, 3 H), 3.99–4.10 (m, 1 H), 4.28 (dd, J = 7.33, 2.75 Hz, 1 H), 7.11 (d, J = 3.89 Hz, 1 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 22.0, 35.1, 50.2 (q, $^2J_{C,F}$ = 30.67 Hz), 52.6, 56.7, 125.6 (q, $^1J_{C,F}$ = 282.76 Hz), 154.3, 171.3 ppm. ^{19}F NMR ([D$_6$]DMSO): δ = –75.7 (d, J = 8.67 Hz) ppm. $C_8H_{11}F_3N_2O_3$ (240.18): calcd. C 40.01, H 4.62, N 11.66; found C 40.04, H 4.53, N 11.62. LCMS: [M + H]$^+$ 241.

Methyl (4*RS*,6*SR*)-3-(4-Methoxybenzyl)-2-oxo-6-(trifluoromethyl)-hexahydropyrimidine-4-carboxylates (10b): Yield 0.31 g (90%), m.p. 167–169 °C (toluene). ^{1}H NMR ([D$_6$]DMSO): δ = 2.20–2.36 (m, 2 H), 3.60 (s, 3 H), 3.69 (s, 3 H), 3.75 (d, J = 15.34 Hz, 1 H), 4.02–4.14 (m, 2 H), 5.06 (d, J = 15.34 Hz, 1 H), 6.84 (d, J = 8.70 Hz, 2 H), 7.13 (d, J = 8.70 Hz, 2 H), 7.25 (d, J = 4.12 Hz, 1 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 22.4, 48.9, 50.2 (q, $^2J_{C,F}$ = 31.63 Hz), 52.6, 54.1, 55.5, 114.3, 125.5 (q, $^1J_{C,F}$ = 282.76 Hz), 129.5, 130.2, 154.3, 158.9, 171.1 ppm. ^{19}F NMR ([D$_6$]DMSO): δ = –75.6 (d, J = 8.67 Hz) ppm. $C_{15}H_{17}F_3N_2O_4$ (346.30): calcd. C 52.02, H 4.95, N 8.09; found C 51.99, H 4.97, N 8.20. LCMS: [M + H]$^+$ 347.

Methyl (4*RS*,6*SR*)-2-Oxo-3-[(1*SR*)-1-phenylethyl]-6-(trifluoromethyl)hexahydropyrimidine-4-carboxylate (10c): Yield 0.29 g (89%), m.p. 162–164 °C (toluene). ^{1}H NMR ([D$_6$]DMSO): δ = 1.33 (d, J = 7.33 Hz, 3 H), 2.01–2.10 (m, 1 H), 2.26 (d, J = 15.57 Hz, 1 H), 3.59 (s, 3 H), 4.02 (dd, J = 7.10, 2.06 Hz, 1 H), 4.04–4.12 (m, 1 H), 5.55 (q, J = 7.10 Hz, 1 H), 7.08 (d, J = 4.12 Hz, 1 H), 7.20–7.33 (m, 5 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 17.1, 23.5, 49.9 (q, $^2J_{C,F}$ = 31.63 Hz), 51.0, 52.4, 52.6, 125.5 (q, $^1J_{C,F}$ = 281.80 Hz), 127.2, 127.6, 128.9, 142.5, 154.9, 171.9 ppm. ^{19}F NMR ([D$_6$]-DMSO): δ = –75.7 (d, J = 8.67 Hz) ppm. $C_{15}H_{17}F_3N_2O_3$ (330.30): calcd. C 54.54, H 5.19, N 8.48; found C 54.59, H 5.09, N 8.50. LCMS: [M + H]$^+$ 331.

Methyl (4*R*,6*S*)-2-Oxo-3-[(1*S*)-1-phenylethyl]-6-(trifluoromethyl)-hexahydropyrimidine-4-carboxylate (10c): Yield 0.30 g (90%), m.p. 158–160 °C (toluene). $[\alpha]_D^{20}$ = +36.7 (c = 0.72, MeOH).

Methyl (4*RS*,6*SR*)-2-Oxo-6-(trifluoromethyl)hexahydropyrimidine-4-carboxylate (10d): Starting from **5i**, yield 0.20 g (89%); starting from **10b**, yield 0.17 g (75%), m.p. 178–180 °C (chloroform). ^{1}H NMR ([D$_6$]DMSO): δ = 2.04 (dt, J = 13.97, 5.84 Hz, 1 H), 2.27 (dt, J = 13.97, 5.84 Hz, 1 H), 4.04–4.17 (m, 2 H), 6.73 (s, 1 H), 7.06 (s, 1 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 21.9, 49.9 (q, $^2J_{C,F}$ = 30.92 Hz), 49.9, 125.0 (q, $^1J_{C,F}$ = 280.74 Hz), 154.1, 171.4 ppm. ^{19}F NMR ([D$_6$]DMSO): δ = –75.7 (d, J = 7.22 Hz) ppm. $C_7H_9F_3N_2O_3$ (226.15): calcd. C 37.18, H 4.01, N 12.39; found C 37.17, H 4.07, N 12.30. LCMS: [M + H]$^+$ 227.

Methyl (4*R*,6*S*)-2-Oxo-6-(trifluoromethyl)hexahydropyrimidine-4-carboxylate (10d): Starting from (4*R*,6*S*)-**7i**, yield 0.2 g (88%); starting from (4*R*,6*S*,1′*S*)-**10c**, yield 0.16 g (71%), m.p. 170–172 °C (2-propanol/hexane, 1:9). $[\alpha]_D^{20}$ = +3.92 (c = 1.2, MeOH).

(4*RS*,6*SR*)-3-Methyl-2-oxo-6-(trifluoromethyl)hexahydropyrimidine-4-carboxylic Acid (11a): Yield 0.20 g (88%), m.p. 220–222 °C (acetonitrile). ^{1}H NMR ([D$_6$]DMSO): δ = 2.25 (dt, J = 14.68, 3.21 Hz, 1 H), 2.31–2.38 (m, 1 H), 2.78 (s, 3 H), 3.97–4.06 (m, 1 H), 4.08 (dd, J = 7.12, 3.43 Hz, 1 H), 7.02 (d, J = 3.89 Hz, 1 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 22.1, 35.0, 50.3 (q, $^2J_{C,F}$ = 30.67 Hz), 56.9, 125.5 (q, $^1J_{C,F}$ = 281.80 Hz), 154.5, 172.4 ppm. ^{19}F NMR ([D$_6$]DMSO): δ = –75.2 (d, J = 8.67 Hz) ppm. $C_7H_9F_3N_2O_3$ (226.15): calcd. C 37.18, H 4.01, N 12.39; found C 37.20, H 3.90, N 12.32. LCMS: [M + H]$^+$ 227.

(4*RS*,6*SR*)-3-(4-Methoxybenzyl)-2-oxo-6-(trifluoromethyl)hexahydropyrimidine-4-carboxylic Acid (11b): Yield 0.30 g (90%), m.p. 215–217 °C (acetonitrile). ^{1}H NMR ([D$_6$]DMSO): δ = 2.17–2.27 (m, 1 H), 2.30–2.34 (m, 1 H), 3.65–3.74 (m, 4 H), 4.02–4.08 (m, 1 H), 6.84 (d, J = 8.70 Hz, 2 H), 7.13 (d, J = 8.24 Hz, 2 H), 7.19 (d, J = 3.89 Hz, 1 H), 12.98 (br. s, 1 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 22.2, 48.7, 50.2 (q, $^2J_{C,F}$ = 30.67 Hz), 53.8, 55.5, 114.3, 125.5 (q, $^1J_{C,F}$ = 282.76 Hz), 129.4, 130.3, 154.5, 158.9, 172.1 ppm. ^{19}F NMR ([D$_6$]DMSO): δ = –77.2 (d, J = 8.67 Hz) ppm. $C_{14}H_{15}F_3N_2O_4$ (332.27): calcd. C 50.61, H 4.55, N 8.43; found C 50.65, H 4.61, N 8.35. LCMS: [M + H]$^+$ 333.

(4*RS*,6*SR*)-2-Oxo-6-(trifluoromethyl)hexahydropyrimidine-4-carboxylic Acid (11d): Starting from **5i**, yield 0.19 g (90%); starting from **11b**, yield 0.14 g (66%), m.p. 248–250 °C (acetonitrile). ^{1}H NMR ([D$_6$]DMSO): δ = 1.93 (dt, J = 13.74, 7.10 Hz, 1 H), 2.26 (dt, J = 13.74, 5.72 Hz, 1 H), 3.98–4.02 (m, 1 H), 4.07–4.16 (m, 1 H), 6.46 (s, 1 H), 7.02 (s, 1 H), 12.00 (br. s, 1 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 22.9, 50.5, 50.6 (q, $^2J_{C,F}$ = 30.67 Hz), 125.5 (q, $^1J_{C,F}$ = 280.84 Hz), 154.8, 172.7 ppm. ^{19}F NMR ([D$_6$]DMSO): δ = –75.7 (d, J = 7.22 Hz) ppm. $C_6H_7F_3N_2O_3$ (212.3): calcd. C 33.97,

H 3.33, N 13.21; found C 34.11, H 3.30, N 13.21. LCMS: $[M + H]^+$ 213.

CCDC-1008782 (for **4g**), -1008783 (for **7h**), 1008785 (for **8**), and 1008784 (for **10a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): experimental data for compounds **1c**, **1d**, **1f**–**1h**, copies of ^1H and ^{13}C spectra of all new compounds, ^{19}F NMR spectra with quinine additive as a chiral solvating agent, detailed X-ray structure analysis of **4g**, **7h**, **8** and **10a**.

Acknowledgments

V. A. S. is grateful to the Deutsche Forschungsgemeinschaft (DFG) for financial support (grant number RO 362/56-1), and thanks Dr. Maxim Ponomarenko for helpful discussions, and Dr. Andriy Potaman for valuable assistance in the chromatographic purification of enantiopure compounds.

[1] a) P. Kirsch, *Modern Fluoroorganic Chemistry – Synthesis Reactivity, Applications*, 2nd ed., Wiley-VCH, Weinheim, Germany, **2013**; b) V. Gouverneur, K. Müller (Eds.), *Molecular Medicine and Medicinal Chemistry*, vol. 6: *Fluorine in Pharmaceutical and Medicinal Chemistry – From Biophysical Aspects to Clinical Applications*, Imperial College Press, London, **2012**.

[2] J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432–2506.

[3] a) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320–330; b) V. A. Soloshonok, K. Mikami, T. Yamazaki, J. T. Welch, J. F. Honek (Eds.), *Current Fluoroorganic Chemistry – New Synthetic Directions, Technologies, Materials, and Biological Applications*, vol. 949, American Chemical Society, Washington, **2007**; c) K. L. Kirk, *J. Fluorine Chem.* **2006**, *127*, 1013–1039; d) R. Filler, R. Saha, *Future Med. Chem.* **2009**, *1*, 777–791; e) D. O'Hagan, *Chem. Soc. Rev.* **2008**, *37*, 308–319.

[4] a) C. Bissantz, B. Kuhn, M. Stahl, *J. Med. Chem.* **2010**, *53*, 5061–5084; b) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881–1886.

[5] a) F. Hof, D. M. Scofield, W. B. Schweizer, F. Diederich, *Angew. Chem. Int. Ed.* **2004**, *43*, 5056–5059; *Angew. Chem.* **2004**, *116*, 5166–5169; b) G.-F. Hao, F. Wang, H. Li, X.-L. Zhu, W.-C. Yang, L.-S. Huang, J.-W. Wu, E. A. Berry, G.-F. Yang, *J. Am. Chem. Soc.* **2012**, *134*, 11168–11176; c) C. Dalvit, A. Vulpetti, *ChemMedChem* **2011**, *6*, 104–114; d) H.-J. Schneider, *Chem. Sci.* **2012**, *3*, 1381–1394; e) C. Dalvit, A. Vulpetti, *ChemMedChem* **2012**, *7*, 262–272.

[6] a) L. R. Scolnick, A. M. Clements, J. Liao, L. Crenshaw, M. Hellberg, J. May, T. R. Dean, D. W. Christianson, *J. Am. Chem. Soc.* **1997**, *119*, 850–851; b) M. Lee, C. W. Chan, S. C. Graham, R. I. Christopherson, J. M. Guss, M. J. Maher, *J. Mol. Biol.* **2007**, *370*, 812–825.

[7] N. A. Meanwell, *J. Med. Chem.* **2011**, *54*, 2529–2591.

[8] J. Nie, H.-C. Guo, D. Cahard, J.-A. Ma, *Chem. Rev.* **2011**, *111*, 455–529.

[9] a) T. Guo, R. Song, B.-H. Yuan, X.-Y. Chen, X.-W. Sun, G.-Q. Lin, *Chem. Commun.* **2013**, *49*, 5402–5404; b) G. Huang, Z. Yin, X. Zhang, *Chem. Eur. J.* **2013**, *19*, 11992–11998; c) H. Xiao, Y. Huang, F.-L. Qing, *Tetrahedron: Asymmetry* **2010**, *21*, 2949–2955.

[10] a) L.-H. Sun, Z.-Q. Liang, W.-Q. Jia, S. Ye, *Angew. Chem. Int. Ed.* **2013**, *52*, 5803–5806; *Angew. Chem.* **2013**, *125*, 5915–5918; b) Y. Liu, Y. Huang, F.-L. Qing, *Tetrahedron* **2012**, *68*, 4955–4961; c) N. M. Golovach, V. N. Tkachuk, V. A. Sukach, M. V. Vovk, *Russ. J. Org. Chem.* **2012**, *48*, 1187–1190.

[11] F. Zhang, Z.-J. Liu, J.-T. Liu, *Org. Biomol. Chem.* **2011**, *9*, 3625–3628.

[12] a) Y.-L. Liu, X.-P. Zeng, J. Zhou, *Chem. Asian J.* **2012**, *7*, 1759–1763; b) X.-M. Yuan, J. Xu, Z.-J. Liu, X.-J. Yang, L.-M. Wang, Y. Zhang, X.-Y. Yang, X.-P. He, J.-T. Liu, *J. Fluorine Chem.* **2012**, *144*, 102–107; c) F. Palacios, A. M. Ochoa de Retana, S. Pascual, G. F. De Troconiz, *Tetrahedron* **2011**, *67*, 1575–1579; d) Y.-L. Liu, T.-D. Shi, F. Zhou, X.-L. Zhao, X. Wang, J. Zhou, *Org. Lett.* **2011**, *13*, 3826–3829.

[13] a) S. Fustero, P. Bello, J. Miró, M. Sánchez-Roselló, M. A. Maestro, J. González, C. del Pozo, *Chem. Commun.* **2013**, *49*, 1336–1338; b) K. Morisaki, M. Sawa, J.-Y. Nomaguchi, H. Morimoto, Y. Takeuchi, K. Mashima, T. Ohshima, *Chem. Eur. J.* **2013**, *19*, 8417–8420; c) D. Enders, K. Gottfried, G. Raabe, *Adv. Synth. Catal.* **2010**, *352*, 3147–3152; d) R. Husmann, E. Sugiono, S. Mersmann, G. Raabe, M. Rueping, G. Bolm, *Org. Lett.* **2011**, *13*, 1044–1047; e) J. Yang, Q.-Q. Min, Y. He, X. Zhang, *Tetrahedron Lett.* **2011**, *52*, 4675–4677; f) S. Fustero, M. Sánchez-Roselló, C. Báez, C. del Pozo, J. L. García Ruano, J. Alemán, L. Marzo, A. Parra, *Amino Acids* **2011**, *41*, 559–573; g) G. T. Shchetnikov, M. A. Zotova, C. Bruneau, P. H. Dixneuf, S. N. Osipov, *Eur. J. Org. Chem.* **2010**, 1587–1592.

[14] a) F. Grellepois, *J. Org. Chem.* **2013**, *78*, 1127–1137; b) F. Palacios, A. M. Ochoa de Retana, S. Pascual, G. Fernández de Trocóniz, J. M. Ezpeleta, *Eur. J. Org. Chem.* **2010**, 6618–6626.

[15] a) A. V. Gulevich, N. E. Shevchenko, E. S. Balenkova, G.-V. Röschenthaler, V. G. Nenajdenko, *Synlett* **2009**, 403–406; b) N. E. Shevchenko, E. S. Balenkova, G.-V. Röschenthaler, V. G. Nenajdenko, *Synthesis* **2010**, 120–126; c) O. I. Shmatova, N. E. Shevchenko, E. S. Balenkova, G.-V. Röschenthaler, V. G. Nenajdenko, *Mendeleev Commun.* **2013**, *23*, 92–93; d) V. A. Sukach, V. M. Tkachuk, E. B. Rusanov, G.-V. Roeschenthaler, M. V. Vovk, *Tetrahedron* **2012**, *68*, 8408–8415; e) H. Berber, M. Soufyane, C. Mirand, S. Schmidt, A.-M. Aubertin, *Tetrahedron* **2001**, *57*, 7369–7375; f) N. Zanatta, D. Faoro, L. da. S. Fernandes, P. B. Brondani, D. C. Flores, A. F. C. Flores, H. G. Bonacorso, M. A. P. Martins, *Eur. J. Org. Chem.* **2008**, 5832–5838; g) I. I. Gerus, S. I. Vdovenko, M. G. Gorbunova, V. P. Kukhar', *Chem. Heterocycl. Compd.* **1991**, *27*, 398–406; h) J. W. Corbett, S. S. Ko, J. D. Rodgers, L. A. Gearhart, N. A. Magnus, L. T. Bacheler, S. Diamond, S. Jeffrey, R. M. Klabe, B. C. Cordova, S. Garber, K. Logue, G. L. Trainor, P. S. Anderson, S. K. Erickson-Viitanen, *J. Med. Chem.* **2000**, *43*, 2019–2030; i) N. A. Magnus, P. N. Confalone, L. Storace, M. Patel, C. C. Wood, W. P. Davis, R. L. Parsons Jr., *J. Org. Chem.* **2003**, *68*, 754–761.

[16] a) O. I. Shmatova, N. E. Shevchenko, E. S. Balenkova, G.-V. Röschenthaler, V. G. Nenajdenko, *Eur. J. Org. Chem.* **2013**, 3049–3058; b) I. L. Odinets, O. I. Artyushin, K. A. Lyssenko, N. E. Shevchenko, V. G. Nenajdenko, G.-V. Röschenthaler, *J. Fluorine Chem.* **2009**, *130*, 662–666; c) A. V. Gulevich, N. E. Shevchenko, E. S. Balenkova, G.-V. Röschenthaler, V. G. Nenajdenko, *Synlett* **2009**, 403–406; d) O. I. Shmatova, V. G. Nenajdenko, *Eur. J. Org. Chem.* **2013**, 6397–6403.

[17] a) B. Jiang, J. J. Dong, Y. G. Si, X. L. Zhao, Z. G. Huang, M. Xu, *Adv. Synth. Catal.* **2008**, *350*, 1360–1366; b) H. Xie, Y. Zhang, S. Zhang, X. Chen, W. Wang, *Angew. Chem. Int. Ed.* **2011**, *50*, 11773–11776; *Angew. Chem.* **2011**, *123*, 11977–11980; c) H.-N. Yuan, S. Wang, J. Nie, W. Meng, Q. Yao, J.-A. Ma, *Angew. Chem. Int. Ed.* **2013**, *52*, 3869–3873; *Angew. Chem.* **2013**, *125*, 3961–3965; d) F.-G. Zhang, X.-Y. Zhu, S. Li, J. Nie, J.-A. Ma, *Chem. Commun.* **2012**, *48*, 11552–11554; e) H.-N. Yuan, S. Li, J. Nie, Y. Zheng, J.-A. Ma, *Chem. Eur. J.* **2013**, *19*, 15856–15860.

[18] a) F. Rise, D. Grace, K. Undheim, *J. Organomet. Chem.* **1988**, *338*, 341–346; b) J. J. Fox, T.-L. Su, L. M. Stempel, K. A. Watanabe, *J. Org. Chem.* **1982**, *47*, 1081–1084; c) A. Katoh, Y. Om-

ote, C. Kashima, *J. Heterocycl. Chem.* **1984**, *21*, 53–55; d) F. Rise, K. Undheim, *J. Organomet. Chem.* **1985**, *291*, 139–144; e) C. Kashima, A. Katoh, Y. Yokota, Y. Omote, *J. Chem. Soc. Perkin Trans. 1* **1981**, 489–492; f) F. Rise, C. Romming, K. Undheim, *Acta Chem. Scand., Ser. B* **1985**, *39*, 459–468.

[19] V. A. Sukach, V. M. Tkachuk, V. M. Shoba, V. V. Pirozhenko, E. B. Rusanov, A. A. Chekotilo, G.-V. Röschenthaler, M. V. Vovk, *Eur. J. Org. Chem.* **2014**, 1452–1460.

[20] I. Lieberman, A. Kornberg, *J. Biol. Chem.* **1954**, *207*, 911–924.

[21] Y. Li, F. M. Raushel, *Bioorg. Chem.* **2005**, *33*, 470–483.

[22] D. B. Berkowitz, K. R. Karukurichi, R. de la Salud-Bea, D. L. Nelson, C. D. McCune, *J. Fluorine Chem.* **2008**, *129*, 731–742.

[23] a) J. L. Adams, T. D. Meek, S.-M. Mong, R. K. Johnson, B. W. Metcalf, *J. Med. Chem.* **1988**, *31*, 1355–1359; b) F. W. Muregi, S. Kanoc, H. Kinoa, A. Ishih, *Exp. Parasitol.* **2009**, *121*, 376–380.

[24] a) A. Arnone, P. Bravo, S. Capelli, G. Fronza, S. V. Meille, M. Zanda, *J. Org. Chem.* **1996**, *61*, 3375–3387; b) P. Bravo, *Tetrahedron Lett.* **1995**, *36*, 3043–3046.

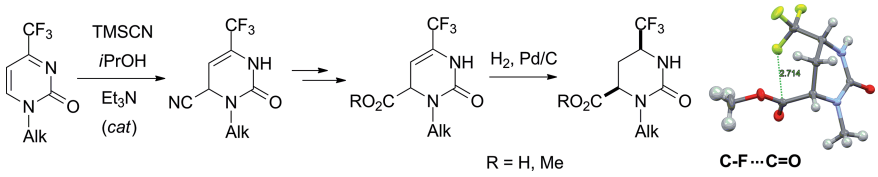
[25] H. P. G. Thompson, G. M. Day, *Chem. Sci.* **2014**, DOI: 10.1039/C4SC01132E.

[26] a) R. Paulini, K. Müller, F. Diederich, *Angew. Chem. Int. Ed.* **2005**, *44*, 1788–1805; *Angew. Chem.* **2005**, *117*, 1820–1839; b) K. Nishide, Y. Hagimoto, H. Hasegawa, M. Shiro, M. Node, *Chem. Commun.* **2001**, 2394–2395.

[27] a) L. E. Zimmer, C. Sparr, R. Gilmour, *Angew. Chem. Int. Ed.* **2011**, *50*, 11860–11871; *Angew. Chem.* **2011**, *123*, 12062–12075; b) L. Hunter, *Beilstein J. Org. Chem.* **2010**, *6*, 38–52.

Received: November 19, 2014
Published Online: ■

EurJOC European Journal of Organic Chemistry



A preparatively convenient route to trifluoromethylated analogues of 4,5-dihydroorotic acid and their esters featuring intramolecular orthogonal dipolar C–F···C=O interactions in the crystal state is presented.

V. A. Sukach,* A. A. Resetnic, V. M. Tkachuk, Z. Lin, U. Kortz, M. V. Vovk, G.-V. Röschenthaler 1–13

Synthesis of Trifluoromethylated Analogues of 4,5-Dihydroorotic Acid

Keywords: Nitrogen heterocycles / Fluorine / Cyanides / Noncovalent interactions

