Catalytic Hydrogenation of 3-Amino-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-ones and Its Use in the Synthesis of Trifluoromethyl-Containing Mimetics of Ornithine and Thalidomide

Nataliya A. Tolmachova,[a] Violetta G. Dolovanyuk,[a] Igor I. Gerus,[a] Ivan S. Kondratov,[a] Vitaliy V. Polovinko,[b] Klaus Bergander,[c] Günter Haufe*[c]

[a] Institute of Bioorganic Chemistry and Petrochemistry, National Ukrainian Academy of Science, Murmanska 1, Kiev 94 02660, Ukraine

[b] Enamine Ltd., Alexandra Matrosova str. 23, 01103 Kiev, Ukraine

[c] Organisch-Chemisches Institut der Universität Münster, Corrensstraße 40, 48149 Münster, Germany
Fax +49(251)8339772; E-mail: haufe@uni-muenster.de

Received 8 December 2010; revised 29 January 2011

Abstract: A series of 3-amino-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-ones and 6-hydroxy-5,6-dihydropyridin-2(1*H*)-ones were hydrogenated to give the corresponding piperidinones. These lactams were used for the synthesis of novel trifluoromethyl-containing ornithine analogues and thalidomide mimetics.

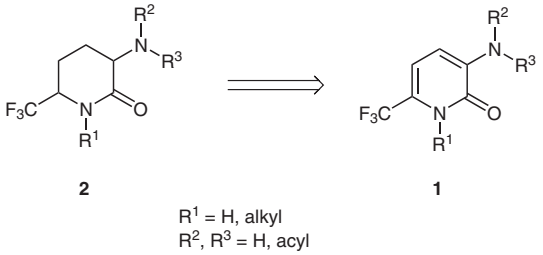
Key words: amino acids, catalysis, halides, heterocycles, hydrogenation, piperidinones

The 3-aminopiperidin-2-one moiety is a relevant motif in numerous biologically active compounds, including conformationally restricted peptidomimetics.[1] Derivatives of 3-amino-6-(trifluoromethyl)piperidin-2-ones are therefore of interest, because the introduction of a trifluoromethyl group[2] into biologically active compounds is frequently an effective strategy for designing new drugs and agrochemicals.[3]

Among the various synthetic approaches to piperidin-2-ones, the heterogeneous catalytic hydrogenation of the 2-pyridinone ring is one of the most common methods.[4] This method has been widely used in alkaloid synthesis[5] and also for the preparation of several biologically active piperidin-2-one derivatives,[6] including some containing a trifluoromethyl group.[6d]

We recently described the hydrogenation of 6-(polyfluoroalkyl)pyrones and the use of this reaction in the synthesis of glutamic acid analogues.[7] As part of our ongoing program for the development of synthetic methods for the preparation of new, potentially active, fluorine-containing amino acids and their derivatives, we therefore attempted the reduction of various 6-(trifluoromethyl)pyridin-2(1*H*)-ones **1** with an amino or *N*-acylamino substituent in the 3-position (Scheme 1).

It is quite obvious that the target transformation will lead to compounds **2**, which contain an α-amino acid motif, and might be useful for the synthesis of new fluorinated amino acids and other potentially bioactive compounds.



Scheme 1 Retrosynthesis of piperidones **2** from pyridinones **1**

We have previously described an effective method for the preparation of benzoyl-containing 6-(trifluoromethyl)pyridinones **1a–d** from pyrones **3** (Scheme 2, first two steps) in one step (synthesis of compounds **1a–c**) or two steps (synthesis of compound **1d**).[8]

We found the two-step method [via the 6-hydroxy-5,6-dihydropyridin-2(1*H*)-ones **4**] was the most suitable for the preparation of pyridinones **1e–g**. Compound **1e** has previously been synthesized in one step,[8] but the two-step method was more convenient for the gram-scale preparation of the compound (Scheme 2). The method was also used to synthesize the pyridinones **4f** and **4g**, each bearing an ester function. In these cases, the yield of the first step was low, probably as a result of polycondensation processes. When compound **1f** was prepared, the side-product **5** was also isolated in 17% yield (Figure 1). This compound is formed as a result of intramolecular lactonization with elimination of methanol. The search for suitable conditions for a selective synthesis of compound **5** is in progress.

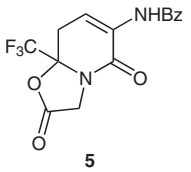
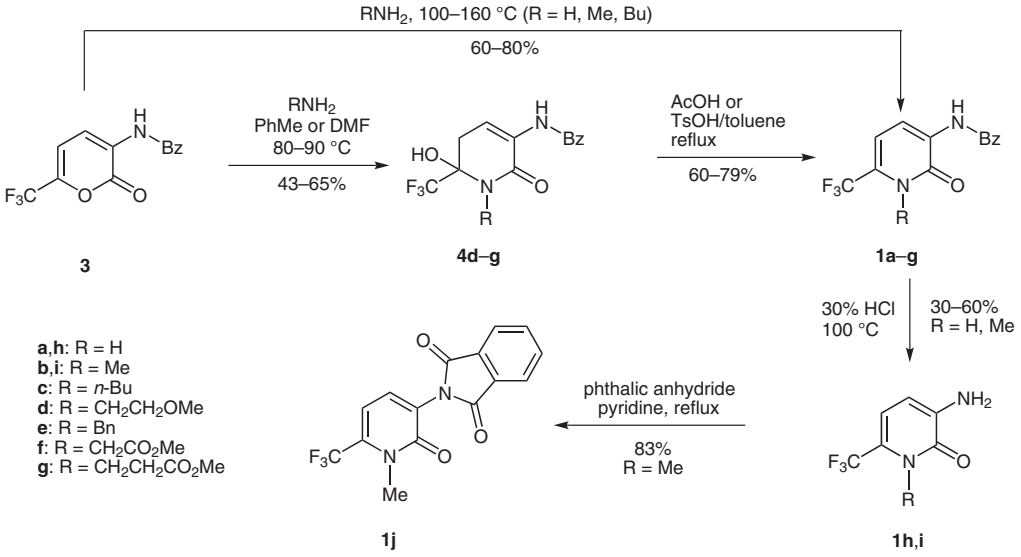


Figure 1 Side-product **5** in the synthesis of compound **1f**

Our attempts to apply the reaction of pyrone **3** with primary amines to the synthesis of pyridinones containing isopropylamino, (1-phenylethyl)amino, or α-alanine methyl

SYNTHESIS 2011, No. 7, pp 1149–1156
Advanced online publication: 01.03.2011
DOI: 10.1055/s-0030-1258448; Art ID: T52310SS



Scheme 2 Synthesis of pyridinones **1a–j**

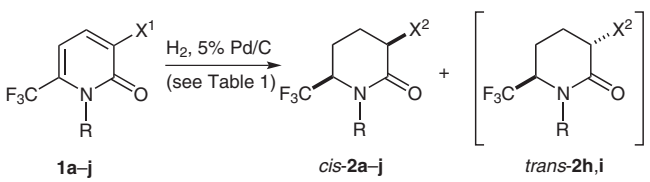
ester groups failed for steric reasons. In all these cases, the starting pyrone **3** was isolated.

The pyridinones **1h–j** were obtained from the corresponding pyridinones **1a** and **1b** (Scheme 2, final two steps) by acidic hydrolysis of the *N*-benzoyl group (**1h** and **1i**), followed by phthalimide ring formation (**1j**).

The pyridinones **1a–j** were hydrogenated by using 5% palladium-on-carbon as a catalyst. The rate and selectivity of the pyridinone ring reduction depend markedly on the substituents adjacent to both the endo- and the exocyclic nitrogen atom (Scheme 3; Table 1). The reduction of the N-unsubstituted pyridinone **1a** required forcing conditions and longer reaction times in comparison with the N-substituted pyridinones **1b–g**. In the case of pyridinones **1a** and **1b**, methanol was found to be the most convenient solvent, whereas the less-soluble pyridinones **1c–g** were hydrogenated in tetrahydrofuran. The reaction proceeded diastereoselectively, and the corresponding *cis*-lactams **1a–g** were obtained in good-to-moderate yields (Scheme 3; Table 1, entries 1–7). Note that in the case of compound **1a**, the phenyl ring of the *N*-benzoyl group was hydrogenated to a form a cyclohexyl group under the reaction conditions. On the other hand, in the case of compound **1e**, no hydrogenolysis of the benzyl group occurred under the reaction conditions.

Pyridinones **1h** and **1i**, bearing an unsubstituted NH_2-group (Table 1, entries 8 and 9), could be reduced under more forcing conditions than required for the reduction of **1a** and **1b** (Table 1, entries 1 and 2). Surprisingly, mixtures of the corresponding *cis*- and *trans*-isomers were obtained (as judged from the ^{19}F NMR spectra of the crude products). The formation of *trans*-isomers under the reaction conditions can be explained in terms of partial epimerization of the initially formed *cis*-**2** isomer to the thermodynamically more stable *trans*-**2** isomer. This assumption was confirmed by the fact that the proportion of the minor diastereomer *trans*-**2i** increased from 5% to 20% (^{19}F NMR) after standing for two days at room temperature. However, compounds *cis*-**2h** and *cis*-**2i** and *trans*-**2** and **-2i** partially decomposed during column chromatography and on standing at room temperature for more than one day. Only the diastereomers *cis*-**2h** and *cis*-**2i** could be isolated in pure form from the reaction mixtures.

The reduction of *N*-methylpyridinone **1j** bearing an *N*-phthalimide protecting group gave the stable compound *cis*-**2j** diastereoselectively (Table 1, entry 10). Along with hydrogenation of the pyridinone ring, one of the phthalimide carbonyl groups was reduced to a methylene group.



Scheme 3 Hydrogenation of pyridinones **1a–i**

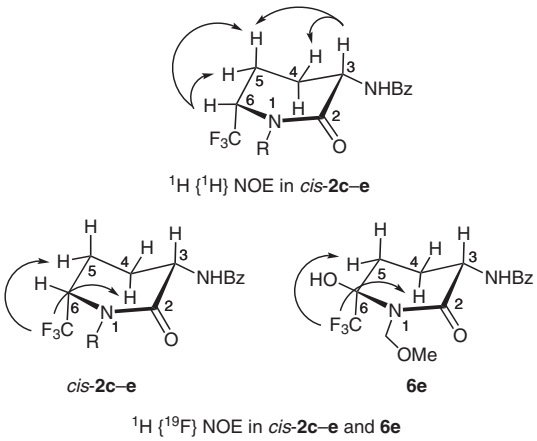
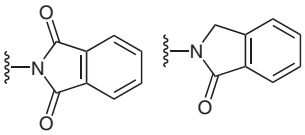


Figure 2 NOE-interactions in compounds *cis*-**2c–e** and **6e**

Table 1 Hydrogenation of Pyridinones **1a–i**: Conditions, Products, and Yields

Entry	Pyridinone	R	X^1	X^2	Conditions	Products (ratio)	Yield (%)
1	**1a**	H	NHBz	NHCOCy	MeOH, 60 °C, 60 atm, 4 d	*cis*-**2a**	75
2	**1b**	Me	NHBz	NHBz	MeOH, 25 °C, 25 atm, 6 h	*cis*-**2b**	88
3	**1c**	Bu	NHBz	NHBz	THF, 25 °C, 40 atm, 8 h	*cis*-**2c**	83
4	**1d**	$(CH_2)_2OMe$	NHBz	NHBz	THF, 25 °C, 40 atm, 8 h	*cis*-**2d**	80
5	**1e**	Bn	NHBz	NHBz	THF, 25 °C, 40 atm, 16 h	*cis*-**2e**	74
6	**1f**	CH_2CO_2Me	NHBz	NHBz	THF, 25 °C, 40 atm, 8 h	*cis*-**2f**	72
7	**1g**	$(CH_2)_2CO_2Me$	NHBz	NHBz	THF, 25 °C, 40 atm, 8 h	*cis*-**2g**	69
8	**1h**	H	NH_2	NH_2	80 °C, 60 atm, 7 d	*cis/trans*-**2h** (85:15)	86 (65)[a]
9	**1i**	Me	NH_2	NH_2	80 °C, 60 atm, 3 d	*cis/trans*-**2i** (95:5)	92 (85)[a]
10	**1j**	Me			r.t., 30 atm, 8 h	*cis*-**2j**	45

[a] Yields of isolated compounds *cis*-**2h** and *cis*-**2i** are given in parentheses.

The relative configurations of stereogenic centers of the products *cis*-**2a–j** were determined by means of nuclear Overhauser effect (NOE) experiments, which indicated a relative *cis*-orientation of hydrogen atoms in the 3- and 6-positions (Figure 2).

On the other hand, a detailed analysis of the NMR data for compounds *cis*-**2c–e** indicated that the 3-H atom occupies the axial position ($J_{3\text{-Ha/4-Ha}}$ = 11.3–12.0 Hz, $J_{3\text{-Ha/4-He}}$ = 6.6–6.7 Hz; 1,3-diaxial NOE between 3-H_a and 5-H_a), whereas the 6-H atom occupies the equatorial position ($J_{6\text{-He/5-He}}$ = 0–2.4 Hz, $J_{6\text{-He/5-Ha}}$ = 5.9–7.0 Hz, NOE of 6-H_a to both 5-H_a and 5-H_e). Additional confirmation was provided by a hetero-NOE analysis, which showed the presence of an interaction between the trifluoromethyl group and 5-H_e, as well as between the trifluoromethyl group and 4-H_a (Figure 2).

For compounds *cis*-**2a** and *cis*-**2h** the results of NMR experiments are ambiguous. The structure of *cis*-**2a** was therefore confirmed by X-ray crystal structure analysis (Figure 3).[9] The structure of compound *cis*-**2h** was confirmed by the identity with the products obtained by hydrolysis of *cis*-**2a** and *cis*-**2h** (see below). The structures of compounds *cis*-**2a–i** were additionally confirmed by the results of ^1H–^1H COSY experiments.

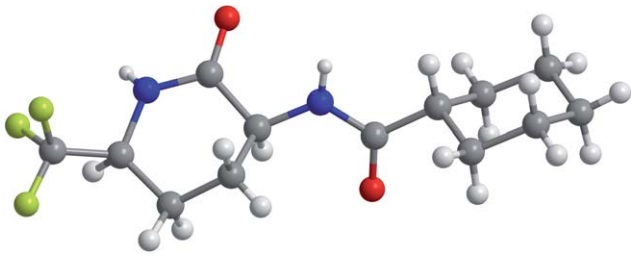
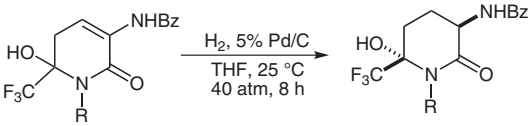


Figure 3 Molecular structure of compound *cis*-**2a** as obtained by X-ray crystal structure analysis

6-Hydroxydihydropyridinones **4d–f**, which are stable intermediates in the synthesis of the corresponding pyridinones **1d–f**, were also hydrogenated by using 5% palladium-on-carbon to give the corresponding 6-hydroxypiperidones **6d–f**. Partial reduction of compounds **4** occurred under 2–3 atm pressure. For example, the conversion of compound **4e** under H_2 at 3 atm was ~40% after two days, and this did not increase significantly within the next day, even when additional portions of the catalyst were added. Under more forcing conditions (tetrahydrofuran, 25 °C, 40 atm, 8 h), the reduction was complete and the 6-hydroxypiperidones **6d–f** were obtained in moderate-to-good yields (Scheme 4; Table 2)



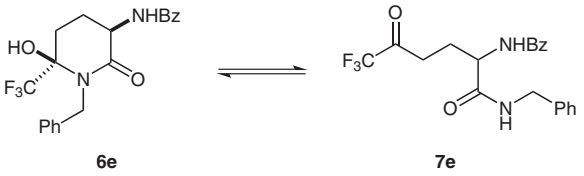
4d–g **6d–g**

Scheme 4 Hydrogenation of pyridinones **4d–g**

Table 2 Hydrogenation of Pyridinones **4d–g**

Entry	Pyridinone	R	Product	Yield (%)
1	**4d**	$(CH_2)_2OMe$	**6d**	74
2	**4e**	Bn	**6e**	64
3	**4f**	CH_2CO_2Me	**6f**	81
4	**4g**	$(CH_2)_2CO_2Me$	**6g**	79

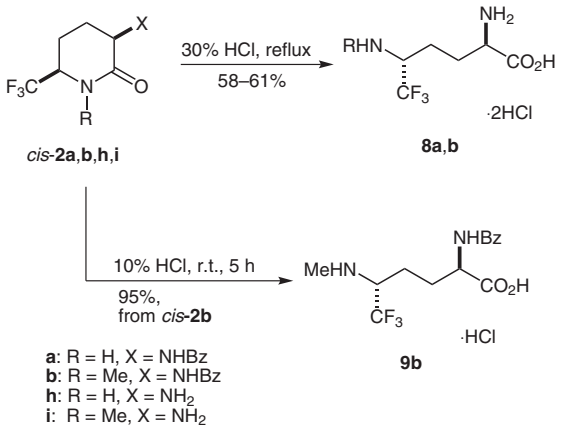
Compounds **6** generally exist as single epimers in chloroform solution; only in the case of compound **6e** was an equilibrium observed between the open form **7e** and the cyclic form **6e** (ratio 1:17; ^{19}F NMR) (Scheme 5). No other form was observed in the cases of compounds **6d**, **6f**, and **6g** in chloroform solutions. An intramolecular hydrogen bond between the hydroxy group and the oxygen atom in the *N*-substituent could play an important role in the configurational stability of these compounds.



6e **7e**

Scheme 5 Equilibrium between compounds **6e** and **7e** in chloroform solution

The piperidones **2** prepared as described above can be used for the synthesis of some potentially bioactive compounds. Thus, hydrolysis of compounds *cis*-**2a** and -**2b** (or *cis*-**2h** and -**2i**) under acidic conditions gave the diastereomerically pure amino acids **8a** and **8b** in 58–61% yield after purification by ion-exchange chromatography. These compounds are new δ-trifluoromethyl group containing analogues of ornithine (Scheme 6). They can also be considered as analogues of glutamine, according to the concept of bioisosteric replacement of a CONH group by a $CH(CF_3)NH$ fragment, as proposed by Zanda.[10a–c] This type of replacement has been used for the synthesis of new



cis-**2a**,**b**,**h**,**i** **8a**,**b** **9b**

Scheme 6 Synthesis of amino acids **8a** and **8b**, and the α-*N*-benzoyl amino acid **9b**

hydrolytically stable selective inhibitors of cathepsin K.[10d,e] Also, in the case of compound **2b** (R = Me), hydrolysis under mild conditions gave the *N*-benzoyl amino acid **9b** in 95% yield.

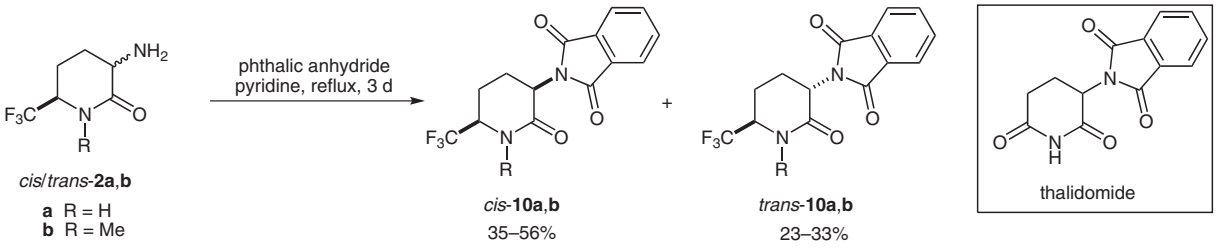
A detailed analysis of the NMR spectra of compounds **6** showed that the 3-H atom occupies an axial position ($J_{3\text{-Ha/4-Ha}}$ = 11.9–12.1 Hz, $J_{3\text{-Ha/4-He}}$ = 5.8–6.4 Hz; 1,3-diaxial NOE between 3-H_a and 5-H_a). The relative configuration of compound **6d** was established by hetero-NOE analysis, which showed the presence of an interaction between the trifluoromethyl group and 5-H_e, as well as between the trifluoromethyl group and 4-H_a (Figure 2). The NMR data for compounds **6e–g** are very similar to those for **6d**. Therefore, the relative configuration of compounds **6e–g** is assumed to be the same as that of compound **6d**.

The reaction of the *cis/trans* mixtures of **2a** (85:15) or **2b** (95:5) (or of the diastereomerically pure *cis*-**2b**) with phthalic anhydride led to corresponding diastereomeric mixtures of *cis/trans*-**10a** or *cis/trans*-**10b** (Scheme 7). Under the reaction conditions, partial epimerization occurred to give a 55:45 ratio for *cis/trans*-**10a** and a 70:30 ratio for *cis/trans*-**10b**. We were unable to find any conditions that caused the transformation to occur without epimerization. The resulting mixtures were separated by column chromatography to give the pure diastereomers *cis*-**10a** and *trans*-**10a** and *cis*-**10b** and *trans*-**10b**.

According to Zanda's principle,[10] these compounds can be considered as analogues of thalidomide, a well-known sedative and hypnotic that was withdrawn from the market in 1962 because of its teratogenicity. It is currently used in the treatment of a number of diseases, and several analogues have been developed based on thalidomide as a lead structure [e.g., Actimid (CC-4047) and Revlimid (lenalidomide)].[11]

The relative configuration of the stereogenic centers of the products *cis*-**10a** and **-10b** (as well as *cis*-**2j**) were determined by NOESY experiments, which showed a *cis*-orientation of the hydrogen atoms in positions 3 and 6. In case of compounds *trans*-**10** and -**10b**, interactions between hydrogen atoms in positions 3, 4, 5, and 6 indicate a *trans*-configuration (Figure 4, see also Scheme 7).

The structures of compounds *cis*-**10b**, *trans*-**10b** and *cis*-**2j** were further confirmed by ^{1}H–^{1}H COSY experiments, and the structure of compound *cis*-**10a** was established unambiguously by X-ray crystal structure analysis (Figure 5).[9]

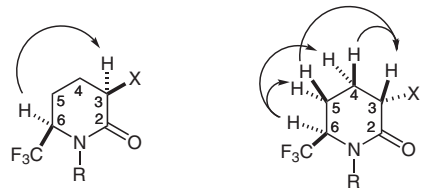


cis/*trans*-**2a**,**b**
a R = H
b R = Me

cis-**10a**,**b**
35–56%

trans-**10a**,**b**
23–33%

Scheme 7 Synthesis of compounds *cis/trans*-**10a**,**b**



cis-**10a**,**b** and *cis*-**2j** *trans*-**10a**,**b**

Figure 4 NOESY experiments confirm the relative configurations of compounds *cis*-**10a, -10b**, *cis*-**2j**, and *trans*-**10a** and -**10b**

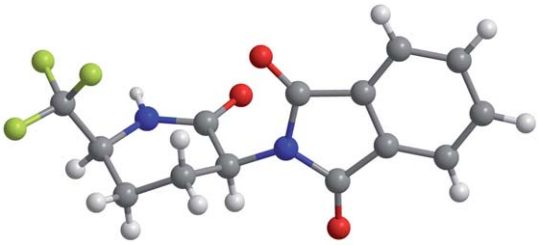


Figure 5 Molecular structure of compound *cis*-**10a** obtained by X-ray crystal structure analysis

Initial tests of the bioactivity of compounds **8b** and **9b** and the thalidomide analogues **10** were carried out. Compound **8b** was found to be a defined stimulator of cellular immunity and does not significantly influence the humoral immunity or nonspecific resistance of mice. In contrast, compound **9b** modulated all three types of immunity in mice (see Supporting Information). Moreover, compounds **10** showed antimicrobial activity against *Staphylococcus aureus* (St. 209). Preliminary results showed that compounds *cis*-**10a** and -**10b** and *trans*-**10a** possess visible activity in comparison to thalidomide, whereas compound *trans*-**10b** does not have any activity at all (see supporting information). Further investigations of compounds **8a** and **8b** as mimetics of natural amino acids are in progress.

In conclusion, the hydrogenation of 6-(trifluoromethyl)pyridinones **1** and the 6-hydroxydihydropyridinones **4** gave the corresponding piperidones **2a–j** and **6d–g** in moderate-to-excellent yields. The new pyridinones **1e–j** and 6-hydroxydihydropyridinones **4e–j** were also prepared.

The products **2f**, **2g**, **6f**, and **6g** are of interest as building blocks for conformationally restricted peptidomimetics because of the presence of a dipeptide motif in their structures. The hydrogenation products were used in the synthesis of amino acids **8a** and **8b** and the phthalimide analogues *cis/trans*-**10a** and **-10b**.

Melting points are uncorrected. NMR spectra were recorded on Bruker Avance DRX and Varian INOVA spectrometers at 500 MHz (^{1}H), 126 MHz (^{13}C), or 470 MHz (^{19}F), and on a Varian Unity Plus spectrometer at 600 MHz (^{1}H) at 25 °C. TMS (for ^{1}H and ^{13}C NMR) and CCl_3F (for ^{19}F NMR) were used as internal standards. IR spectra were recorded on a Bruker Vertex 70 spectrometer. The progress of reactions was monitored by TLC (silica gel 60 F254, Merck). Column chromatography was carried out on silica gel 60 (Merck, particle size 0.040–0.063 mm). Ion-exchange chromatography was performed on Amberlite IR-120 by standard techniques.[12] Elemental analyses were correct within ±0.3% for C, H, and N. Spectroscopic data are presented here for typical compounds only; data for all other compounds can be found in the supporting information.

All starting materials were of the highest commercial quality and were used without further purification. The pyridinones **1a–d** and **4d** were prepared according to our earlier published procedures.[8] The previously prepared pyridinone **1e** was synthesized by an improved procedure (see below).

N-[1-Benzyl-6-hydroxy-2-oxo-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridin-3-yl]benzamide (4e)

Pyrone **3** (2.83 g, 10 mmol) and $BzNH_2$ (1.60g, 15 mmol) were heated in DMF at 80–90 °C for 8 h, while the progress of the reaction was monitored by TLC. The reaction mixture was then cooled to r.t., poured into H_2O, and extracted with EtOAc (3 × 20 mL). The organic layer was washed with water (3 × 10 mL) and brine (1 × 10 mL), dried ($MgSO_4$), and concentrated. The ^{19}F NMR spectrum of the crude product showed ~80% conversion. The residue was purified by column chromatography [EtOAc–cyclohexane (1:2)] to give a colorless oil; yield: 2.55 g (65%); R_f = 0.56.

IR (CH_2Cl_2): 1030, 1186, 1362, 1413, 1439, 1524, 1648, 1733, 2855, 2928, 3034, 3066, 3383, 3563 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): 2.93 (d, J = 18.8 Hz, 1 H, H_a of CH_2), 3.11 (dd, J_1 = 6.4 Hz, J_2 = 18.8 Hz, 1 H, H_b of CH_2), 4.69 (d, J = 15.3 Hz, 1 H, H_a of CH_2Ph), 4.98 (d, J = 15.3 Hz, 1 H, H_b of CH_2Ph), 5.42 (br s, OH), 7.13–7.55 (m, 9 H, Ph, CH), 7.76 (d, J = 7.3 Hz, 2 H, 1 H, Ph), 8.85 (s, 1 H, NH).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 32.0, 45.2, 84.1 (q, J = 31.0 Hz), 112.6, 126.7, 127.0, 127.3, 127.4, 128.5, 128.8, 132.3, 133.7, 138.2, 162.0, 166.3. Peaks of the CF_3-carbon signal were overlapped by the signals of the aromatic carbon atoms.

^{19}F NMR (470 MHz, $CDCl_3$): δ = –81.9 (s, CF_3).

MS (ESI): *m/z* calcd for $C_{20}H_{17}F_3N_2O_3Na$: 413.1089; found: 413.1086.

6-Hydroxydihydropyridinones (4f and 4g); General Procedure

A soln of the appropriate amino acid ester hydrochloride (35 mmol) and Et_3N (1.82 g, 18 mmol) in DMF was stirred at r.t. for 30 min. Pyrone **3** (2.83 g, 10 mmol) was then added and the mixture was stirred at 80–90 °C for 6 h while the progress of the reaction was monitored by TLC. The mixture was then cooled to r.t., poured into H_2O, and extracted with EtOAc (3 × 20 mL). The organic layer was washed with water (3 × 10 mL) and brine (1 × 10 mL), dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography.

Methyl [5-(Benzoylamino)-2-hydroxy-6-oxo-2-(trifluoromethyl)-3,6-dihydropyridin-1(2*H*)-yl]acetate (4f)

The product was obtained from methyl glycinate hydrochloride (4.4 g) and purified by column chromatography [EtOAc–cyclohexane (1:2)]; yield: 1.71 g (46%); mp 143–145 °C; R_f = 0.24.

IR (CH_2Cl_2): 1039, 1188, 1398, 1430, 1525, 1654, 1741, 2958, 3062, 3391 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.01 (dd, J_1 = 18.6 Hz, J_2 = 4.2 Hz, 1 H, H_a of CH_2), 3.15 (dd, J_1 = 18.6 Hz, J_2 = 5.3 Hz, 1 H, H_b of CH_2), 3.80 (s, 3 H, CH_3), 4.16 (d, J_1 = 17.6 Hz, 1 H, H_a of CH_2CO_2Me), 4.79 (d, J_1 = 17.6 Hz, 1 H, H_b of CH_2CO_2Me), 5.53 (br s, 1 H, OH), 7.43–7.58 (m, 4 H, Ar and CH), 7.80–7.85 (m, 2 H, Ar), 8.75 (s, 1 H, NH).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 31.3, 43.9, 53.1, 84.2 (q, J = 30.9 Hz), 114.1, 123.4 (q, J = 290.0 Hz), 126.1, 127.0, 128.9, 132.2, 134.0, 162.2, 166.0, 172.3.

^{19}F NMR (470 MHz, $CDCl_3$): δ = –81.8 (s, CF_3).

MS (ESI): *m/z* calcd for $C_{16}H_{15}F_3N_2O_5Na$: 395.0831; found: 395.0827.

Pyridinones 1e–g; General Procedure

A soln of corresponding dihydropyridinone **4e–g** (1 mmol) and TsOH in toluene (25 mL) was refluxed with simultaneous water/toluene azeotrope removal while the progress of the reaction was monitored by TLC. When conversion was complete, toluene was evaporated off under low pressure, and the resulting crude product was purified by crystallization or by column chromatography.

Methyl [3-(Benzoylamino)-2-oxo-6-(trifluoromethyl)pyridin-1(2*H*)-yl]acetate (1f)

The product was obtained from compound **4f** (372 mg) as a mixture with compound **5** and isolated by column chromatography [EtOAc–cyclohexane (1:2)]; yield: 216 mg (61%); mp 157–159 °C; R_f = 0.24.

IR (CH_2Cl_2): 1130, 1192, 1225, 1306, 1378, 1522, 1621, 1660, 1761, 3375 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.81 (s, 3 H, Me), 4.93 (s, 2 H, CH_2), 6.89 (d, *J* = 7.7 Hz, 1 H, CH), 7.47–7.62 (m, 3 H, Ph), 7.90–7.95 (m, 2 H, Ph), 7.58 (d, *J* = 7.7 Hz, 1 H, CH), 9.27 (br s, 1 H, NH).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 47.0 (q, *J* = 2.7 Hz), 53.0, 108.8 (q, *J* = 6.4 Hz), 110.1, 118.9, 120.2 (q, *J* = 275.0 Hz), 126.8 (q, *J* = 33.5 Hz), 127.4, 129.4, 132.7, 133.6, 157.9, 166.1, 167.1.

^{19}F NMR (470 MHz, $CDCl_3$): δ = –63.16 (s, CF_3).

MS (ESI): *m/z* calcd for $C_{16}H_{13}F_3N_2O_4Na$: 377.0725; found: 377.0722.

***N*-[2,5-Dioxo-8a-(trifluoromethyl)-2,3,8,8a-tetrahydro-5*H*-[1,3]oxazolo[3,2-*a*]pyridin-6-yl]benzamide (5)**

The product was obtained from compound **4f** as a mixture with compound **1f** and isolated by column chromatography [EtOAc–cyclohexane (1:2)] as a colorless oil; yield 58 mg (17%); R_f = 0.64.

IR (CH_2Cl_2): 1200, 1426, 1525, 1672, 1836, 2926, 3055, 3401 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.10 (d, *J* = 18.7 Hz, 1 H, H_a of CH_2), 3.36 (dd, J_1 = 18.7 Hz, J_2 = 6.5 Hz, 1 H, H_b of CH_2), 4.14 (d, *J* = 17.5 Hz, 1 H, H_a of CH_2N), 4.53 (d, *J* = 17.5 Hz, 1 H, H_b of CH_2N), 7.47–7.61 (m, 4 H, Ar and CH), 7.85–7.88 (m, 2 H, Ar), 8.56 (s, 1 H, NH).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 27.3, 43.5, 89.9 (q, *J* = 33.9 Hz), 112.1, 122.9 (q, *J* = 286.0 Hz), 126.7, 127.0, 128.9, 132.4, 133.8, 158.2, 165.8, 166.3.

^{19}F NMR (470 MHz, $CDCl_3$): δ = –84.5 (s, CF_3).

MS (ESI): *m/z* calcd for $C_{15}H_{11}F_3N_2O_4Na$: 363.0569; found: 363.0563.

Amines 1h and 1i: General Procedure

A soln of pyridinone **1a** or **1b** (1 mmol) in 30% aq HCl (15 mL) was refluxed for 12 h while the progress of the reaction was monitored by ^{19}F NMR spectroscopy. After complete hydrolysis, the mixture was cooled and the precipitated BzOH was filtered off. The filtrate was evaporated at 30–40 °C (30–60 mmHg) to give the amine hydrochloride, which was purified by washing with MeCN. The salt was dissolved in H_2O (2 mL), and sat. aq $KHCO_3$ was added dropwise until the pH was about 7. The soln was then extracted with EtOAc (3 × 25 mL), and the organic layer was dried ($MgSO_4$) and concentrated at 20–30 °C (30–60 mmHg) to give a residue that was crystallized (hexane).

3-Amino-6-(trifluoromethyl)pyridin-2(1*H*)-one (1h)

The product was obtained from **1a** (282 mg).

Yield: 53 mg (30%), mp 110–111 °C; the hydrochloride could be isolated in 55% yield (118 mg).

IR (KBr): 835, 953, 1091, 1128, 1178, 1195, 1285, 1320, 1605, 1639, 1864, 2749, 2838, 2903, 3078, 3165, 3308, 3425 cm^{-1}.

^{1}H NMR (500 MHz, CD_3OD): δ = 4.61 (s, 2 H, NH_2), 6.52 (d, *J* = 7.2 Hz, 1 H, CH), 6.56 (d, *J* = 7.2 Hz, 1 H, CH), 12.21 (s, 1 H, NH).

^{13}C NMR (126 MHz, CD_3OD): δ = 108.7 (q, *J* = 6.6 Hz), 109.7, 120.9 (q, *J* = 271.9 Hz), 120.6 (q, *J* = 31.8 Hz), 141.30, 157.1.

^{19}F NMR (470 MHz, CD_3OD): δ = –67.0 (s, CF_3).

2-[1-Methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydropyridin-3-yl]-1*H*-isoindole-1,3(2*H*)-dione (1j)

A solution of amine **1i** (192 mg, 1 mmol) and phthalic anhydride (222 mg, 1.5 mmol) in pyridine (10 mL) was heated at 60 °C for 3 h, and then refluxed for 50–70 h while the progress of the reaction was followed by ^{19}F NMR spectroscopy. After completion of the reaction, pyridine was evaporated at 30–40 °C (30–60 mmHg) and the residue was purified by crystallization [hexane–toluene (4:1)]; yield: 267 mg (83%); mp 149–151 °C.

IR (KBr): 691, 722, 820, 882, 944, 972, 1057, 1083, 1111, 1141, 1183, 1199, 1256, 1301, 1375, 1405, 1465, 1543, 1622, 1668, 1725, 1762, 1786, 1885 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.70 (s, 3 H, CH_3), 6.81 (d, *J* = 7.5 Hz, 1 H, CH), 7.52 (d, *J* = 7.5 Hz, 1 H, CH) 7.79 (m, 2 H, phthalimide), 7.95 (m, 2 H, phthalimide).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 32.7, 105.1 (q, *J* = 6.5 Hz) 119.7 (q, *J* = 275.4 Hz), 124.0, 126.6, 132.0, 134.5, 136.1 (q, *J* = 33.7 Hz), 137.2, 158.6, 166.3.

^{19}F NMR (470 MHz, $CDCl_3$): δ = –65.0 (s, CF_3).

MS (ESI): *m/z* calcd for $C_{15}H_9F_3N_2O_3Na$: 345.0463; found: 345.0457.

Hydrogenation of Compounds 1a–j or 4d–f; General Procedure

A mixture of a pyridinone **1a–j** or **4d–f** (1 mmol) and 5% Pd/C (20–60 mg) in an appropriate solvent (10 mL) was stirred in an autoclave under appropriate conditions (for **1a–i**: see Table 1; for **4d–f**: THF, 25 °C, 40 atm, 8 h) while the progress was monitored by ^{19}F NMR spectroscopy and TLC. When hydrogenation was complete, the mixture was filtered and the solvent was evaporated at 20–30 °C (30–60 mmHg) to give a residue that was purified by crystallization or column chromatography.

***cis*-*N*-[2-Oxo-6-(trifluoromethyl)piperidin-3-yl]cyclohexanecarboxamide (*cis*-2a)**

The product was obtained from **1a** (281 mg) and purified by crystallization [$CHCl_3$–MeCN (2:1)]; yield: 219 mg (75%); mp 181–182 °C.

IR (KBr): 1128, 1167, 1209, 1264, 1422, 1530, 1638, 1688, 3211, 3303 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.07–1.37 (m, 5 H, *c*-hex), 1.54–1.87 (m, 7 H, *c*-hex and CH_2), 1.92–2.14 (m, 3 H, *c*-hex and CH_2), 4.02 (m, 1 H, CH), 4.21 (m, 1 H, CH), 7.94 (d, *J* = 8.5 Hz, 1 H, NH), 8.19 (s, 1 H, NH).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 19.6, 23.9, 25.4, 25.5, 25.6, 29.1, 29.3 44.8, 48.8, 52.1 (q, *J* = 31.3 Hz), 125.2 (q, *J* = 279.5 Hz), 171.8, 177.8.

^{19}F NMR (470 MHz, DMSO-d_6): δ = –76.57 (d, *J* = 7.4 Hz, CF_3).

MS (ESI): *m/z* calcd for $C_{13}H_{19}F_3N_2O_2Na$: 315.1296; found: 315.1291.

***trans*-*N*-[6-Hydroxy-1-(2-methoxyethyl)-2-oxo-6-(trifluoromethyl)piperidin-3-yl]benzamide (*trans*-6d)**

The product was obtained from **4d** (358 mg) and purified by column chromatography [EtOAc–cyclohexane (3:2)]; yield: 266 mg (74%); mp 144–146 °C; R_f = 0.38.

IR (KBr): 710, 1090, 1116, 1156, 1550, 1589, 1631, 2885, 2975, 3149, 3298 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.80–1.97 (m, 1 H, H_a of CH_2), 2.00–2.16 (m, 1 H, H_b of CH_2), 2.49–2.61 (m, 1 H, H_a of CH_2), 2.61–2.71 (m, 1 H, H_b of CH_2), 3.42 (s, 3 H, CH_3), 3.45 (ddd, J_1 = 9.6 Hz, J_2 = 3.6 Hz, J_3 = 1.7 Hz, 1 H, H_a of CH_2N), 3.51 (ddd, J_1 = 10.7 Hz, J_2 = 9.6 Hz J_3 = 1.8 Hz, 1 H, H_a of CH_2N), 3.64 (ddd, J_1 = 14.4 Hz, J_2 = 10.7 Hz, J_3 = 3.6 Hz, 1 H, H_a of CH_2O), 4.19 (dt, J_1 = 14.4 Hz, J_2 = 1.7 Hz, 1 H, H_b of CH_2O), 4.64 (dt, J_1 = 11.9, J_2 = 6.0, 1 H, CHN), 5.81 (br s, 1 H, OH), 7.05 (d, J = 6.0 Hz, 1 H, NH), 7.37–7.55 (m, 3 H, Ph), 7.77–7.84 (m, 2 H, Ph).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 23.9 (q, J = 2.3 Hz), 31.8, 42.1 (q, J = 2.4 Hz), 51.5, 59.2, 69.2, 83.9 (q, J = 30.2 Hz), 124.2 (q, J = 290.7 Hz), 127.1, 128.6, 131.8, 133.8, 167.9, 170.5.

^{19}F NMR (470 MHz, $CDCl_3$): δ = –77.6 (s, CF_3).

Amino Acids 8a and 8b; General Procedure

A soln of lactam *cis*-**2a**,**b** or *cis*-**2h**,**i** (1 mmol) in 30% aq HCl (25 mL) was stirred at 100 °C while the reaction was monitored by ^{19}F NMR. When the reaction was complete (5–7 h), the soln was filtered and the H_2O was evaporated at 30–40 °C and 30–60 mmHg. The residue was purified by ion-exchange chromatography to give an ammonia soln that was concentrated. The residue was dissolved in H_2O and concentrated again in vacuo to remove traces of NH_3. Hydrochlorides of **8a** and **8b** were obtained by dissolving the free diamino acids in 15% aq HCl and evaporating the resulting soln at 30–40 °C and 30–60 mmHg.

(2*R*,5*R*/2*S*,5*S*)-2,5-Diamino-6,6,6-trifluorohexanoic Acid Dihydrochloride (8a)

The product was obtained as a white solid from *cis*-**2a** (292 mg) or *cis*-**2h** (182 mg); yield: 167 mg (61%) or 123 mg (45%), respectively; mp > 300 °C (dec.).

IR (KBr): 1126, 1269, 1415, 1504, 1600, 1664, 2968 cm^{-1}.

^1H NMR (500 MHz, D_2O): δ = 1.88 (m, 1 H, H_a of CH_2), 2.06 (m, 2 H, CH_2), 2.15 (m, 1 H, H_b of CH_2), 3.95 (m, 1 H, CH), 4.12 (m, 1 H, CH).

^{13}C NMR (126 MHz, D_2O): δ = 22.7, 25.0, 51.8 (q, J = 32.0 Hz), 52.5, 123.5 (q, J = 285.3 Hz), 171.5.

^{19}F NMR (470 MHz, D_2O): δ = –74.3 (d, J = 7.6 Hz, CF_3).

(2*R*,5*R*/2*S*,5*S*)-2-(Benzoylamino)-6,6,6-trifluoro-5-(methylamino)hexanoic Acid Hydrochloride (9b)

A soln of lactam *cis*-**2b** (300 mg, 1 mmol) was dissolved in 10% aq HCl (10 mL). After 5 h, the soln was evaporated at r.t. and 30–60 mmHg to give a residue that was washed with Et_2O and dried under vacuum; yield: 305 mg (95%). mp 40 °C (dec.).

IR (KBr): 1040, 1096, 1132, 1168, 1192, 1264, 1312, 1336, 1408, 1488, 1534, 1638, 1666, 3007 cm^{-1}.

^1H NMR (500 MHz, acetone-d_6): δ = 1.96 (m, 1 H, H_a of CH_2), 2.14 (m, 2 H, CH_2), 2.28 (m, 1 H, H_b of CH_2) (m, 2 H), 2.87 (s, 3 H, Me), 4.14 (m, 1 H, CH), 4.56 (m, 1 H, CH), 7.32 (m, 2 H, aryl), 7.38 (m, 1 H, aryl), 7.79 (m, 2 H, aryl).

^{13}C NMR (126 MHz, acetone-d_6): δ = 21.4, 24.5, 36.5, 50.1, 59.1 (q, J = 28.3 Hz), 126.3 (q, J = 287.9 Hz), 127.8, 128.6, 131.7, 134.6, 166.5, 170.2.

^{19}F NMR (470 MHz, acetone-d_6): δ = –71.3 (d, J = 7.3 Hz, CF_3).

***cis/trans*-10a and -10b; General Procedure**

A soln of a mixture of diastereomers *cis/trans*-**2a** or *cis/trans*-**2b** (1 mmol) and phthalic anhydride (0.15 mmol) in pyridine (20 mL) was heated at 60 °C for 3 h and then refluxed for 50–70 h while the progress of the reaction was monitored by ^{19}F NMR spectroscopy. When the reaction was complete, pyridine was evaporated at 30–40 °C (30–60 mmHg) and the residue was purified by column chromatography.

***cis*-2-[2-Oxo-6-(trifluoromethyl)piperidin-3-yl]-1*H*-isoindole-1,3(2*H*)-dione (*cis*-10a)**

The product was obtained from an 85:15 mixture of *cis*- and *trans*-**2a** (182 mg) and purified by column chromatography [EtOAc–hexane (1:4)]; yield: 109 mg (35%); mp > 200 °C (dec.); R_f = 0.3.

IR (KBr): 888, 1022, 1142, 1171, 1195, 1305, 1680, 1718, 1769, 1784, 2904, 3101, 3210 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 1.91 (m, 1 H, H_a of CH_2), 2.11 (m, 1 H, H_b of CH_2), 2.32 (m, 1 H, H_a of CH_2), 2.51 (m, 1 H, H_b of CH_2), 4.13 (m, 1 H, CH), 4.74 (s, 1 H, CH), 7.84–7.92 (m, 4 H, Ar), 8.59 (s, 1 H, NH).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 20.3, 22.1, 49.1, 51.8 (q, J = 29.5 Hz), 123.7, 126.0 (q, J = 268.5 Hz), 131.9, 135.2, 167.7, 168.1.

^{19}F NMR (470 MHz, DMSO-d_6): δ = –80.3 (br s, CF_3).

***trans*-2-[2-Oxo-6-(trifluoromethyl)piperidin-3-yl]-1*H*-isoindole-1,3(2*H*)-dione (*trans*-10a)**

The product was obtained from an 85:15 mixture of *cis*- and *trans*-**2a** (182 mg) and purified by column chromatography [EtOAc–hexane (1:4)]; yield: 103 mg (33%); mp 179–181 °C; R_f = 0.2.

IR (KBr): 718, 1112, 1393, 1467, 1688, 1717, 1770, 2967 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 2.01 (m, 1 H, H_a of CH_2), 2.20 (m, 1 H, H_a of CH_2), 2.34 (m, 1 H, H_b of CH_2), 2.54 (m, 1 H, H_b of CH_2), 4.18 (m, 1 H, CH), 4.80 (m, 1 H, CH), 6.16 (s, 1 H, NH), 7.74 (m, 2 H, Ar), 7.86 (m, 2 H, Ar).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 21.1, 24.1, 48.6, 54.8 (q, J = 31.0 Hz), 123.6, 124.0 (q, J = 279.5 Hz), 132.0, 134.3, 167.6, 167.7.

^{19}F NMR (470 MHz, $CDCl_3$): δ = –79.3 (br s, CF_3).

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

Acknowledgment

This work was supported by the Deutsche Forschungsgemeinschaft (Ha 2145/9-1; AOBJ: 560896). We thank Enamine Ltd (Kiev) for technical and financial supports, and we wish to express our gratitude to Mrs. S. V. Shishkina and Dr O. V. Shishkin (STC 'Institute for Single Crystals', Kharkov, Ukraine) for performing the X-ray diffraction study and to Drs S. I. Vdovenko and L. A. Metelitsa (Institute of Bioorganic Chemistry and Petrochemistry, National Ukrainian Academy of Sciences, Kiev, Ukraine) for performing the IR experiments and the biological tests, respectively.

References

(1) For some recent examples, see: (a) Boeglin, D.; Hamdan, F. F.; Melendez, R. E.; Cluzeau, J.; Laperriere, A.; Héroux, M.; Bouvier, M.; Lubell, W. D. *J. Med. Chem.* **2007**, *50*, 1401. (b) Manzoni, L.; Bassanini, M.; Belvisi, L.; Motto, I.; Scolastico, C.; Castorina, M.; Pisano, C. *Eur. J. Org. Chem.* **2007**, 1309. (c) Smallheer, J. M.; Wang, S.; Laws, M. L.; Nakajima, S.; Hu, Z.; Han, W.; Jacobson, I.; Luettgen, J. M.;

Rossi, K. A.; Rendina, A. R.; Knabb, R. M.; Wexler, R. R.; Lam, P. Y. S.; Quan, M. L. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2428. (d) Mezo, A. R.; McDonnell, K. A.; Castro, A.; Fraley, C. *Bioorg. Med. Chem.* **2008**, *16*, 6394. (e) Lewis, J. A.; Daniels, R. N.; Lindsley, C. W. *Org. Lett.* **2008**, *10*, 4545.

(2) (a) Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*; Wiley-VCH: Weinheim, **2004**. (b) Uneyama, K. *Organofluorine Chemistry*; Blackwell: Oxford, **2006**.

(3) (a) Bégué, J.-P.; Bonnet-Delpon, D. *Bioorganic and Medicinal Chemistry of Fluorine*; John Wiley: Hoboken, **2008**, 365. (b) *Fluorine in Medicinal Chemistry and Chemical Biology*; Ojima, I., Ed.; Wiley: Chichester, **2009**. (c) *Fluorinated Heterocyclic Compounds: Synthesis, Chemistry, and Applications*; Petrov, V. A., Ed.; John Wiley: Hoboken, **2009**, 399–507. (d) Theodoridis, G. *Adv. Fluorine Sci.* **2006**, *2*, 121.

(4) Nishimura, S. *Handbook of Heterogeneous Catalytic Hydrogenation for Organic Synthesis*; Wiley-Interscience: New York, **2001**, 511–513.

(5) For some recent examples, see: (a) Shi, G.-F.; Li, J.-Q.; Jiang, X.-P.; Cheng, Y. *Tetrahedron* **2008**, *64*, 5005. (b) Jiang, X.-P.; Cheng, Y.; Shi, G.-F.; Kang, Z.-M. *J. Org. Chem.* **2007**, *72*, 2212. (c) Padwa, A.; Heidelbaugh, T. M.; Kuethe, J. T. *J. Org. Chem.* **2000**, *65*, 2368.

(6) For some recent examples, see: (a) Liang, G.-B.; Qian, X.; Biftu, T.; Singh, S.; Gao, Y.-D.; Scapin, G.; Patel, S.; Leiting, B.; Patel, R.; Wu, J.; Zhang, X.; Thornberry, N. A.; Weber, A. E. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3706. (b) McCarthy, A. R.; Hartmann, R. W.; Abell, A. D. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3603. (c) Guthikonda, R. N.; Shah, S. K.; Pacholok, S. G.; Humes, J. L.; Mumford, R. A.; Grant, S. K.; Chabin, R. M.; Green, B. G.; Tsou, N.; Ball, R.; Fletcher, D. S.; Luell, S.; MacIntyre, D. E.; MacCoss, M. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1997. (d) Fischer, C.; Munoz, B.; Zultanski, S.; Methot, J.; Zhou, H.; Brown, W. C. WO 2008156580, **2008**; *Chem Abstr.* **2008**, *150*, 77691.

(7) Tolmacheva, N. A.; Gerus, I. I.; Dolovanyuk, V. G.; Kondratov, I. S.; Haufe, G. *Eur. J. Org. Chem.* **2009**, 5012.

(8) Gerus, I. I.; Tolmachova, N. A.; Vdovenko, S. I.; Fröhlich, R.; Haufe, G. *Synthesis* **2005**, 1269.

(9) Crystallographic data for compounds *cis*-**10a** and *cis*-**2a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications CCDC 756799 and CCDC 798421, respectively; copies can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(1223)336033 or email: deposit@ccdc.cam.ac.uk].

(10) (a) Molteni, M.; Pesenti, C.; Sani, M.; Volonterio, A.; Zanda, M. *J. Fluorine Chem.* **2004**, *125*, 1735. (b) Bigotti, S.; Meille, S. V.; Volonterio, A.; Zanda, M. *J. Fluorine Chem.* **2008**, *129*, 767. (c) Molteni, M.; Bellucci, M. C.; Bigotti, S.; Mazzini, S.; Volonterio, A.; Zanda, M. *Org. Biomol. Chem.* **2009**, *7*, 2286. (d) Black, W. C.; Bayly, C. I.; Davis, D. E.; Desmarais, S.; Falgueyret, J.-P.; Leger, S.; Li, C. S.; Masse, F.; McKay, D. J.; Palmer, J. T.; Percival, M. D.; Robichaud, J.; Tsoub, N.; Zambonia, R. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4741. (e) Li, C. S.; Deschenes, D.; Desmarais, S.; Falgueyret, J.-P.; Gauthier, J. Y.; Kimmel, D. B.; Leger, S.; Masse, F.; McGrath, M. E.; McKay, D. J.; Percival, M. D.; Riendeau, D.; Rodan, S. B.; Therien, M.; Truong, V. L.; Weslowski, G.; Zamboni, R.; Black, W. C. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1985.

(11) For recent reviews, see (a) Melchert, M.; List, A. *Int. J. Biochem. Cell Biol.* **2007**, *39*, 1489. (b) Huang, Y.-T.; Hsu, C. W.; Chiu, T. H. *Tzu Chi Med. J.* **2008**, *20*, 188.

(12) Weiss, J.; Weiss, T. *Handbook of Ion Chromatography*, 3rd ed.; Wiley-VCH: Weinheim, **2004**.