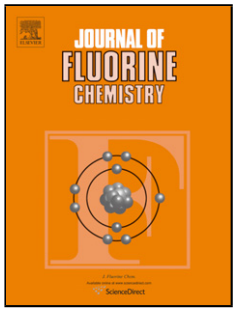

Title: Synthesis of *gem*-difluorocyclopentane/hexane building blocks

Authors: Kostiantyn P. Melnykov, Pavel S. Nosik, Bohdan B. Kurpil, Dmitriy A. Sibgatulin, Dmitriy M. Volochnyuk, Sergey V. Ryabukhin, Oleksandr O. Grygorenko

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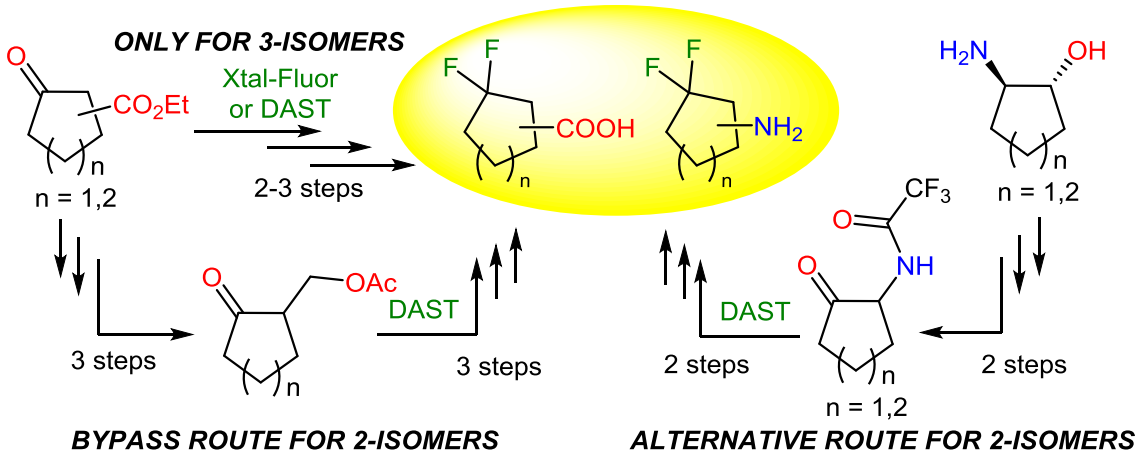
Graphical Abstract

Synthesis of gem-difluorocycloalkane building blocks is described.



Highlights

- An approach to *gem*-difluorocyclopentane/hexane carboxylic acids and amines is developed.
- Straightforward fluorination of 3-ketocycloalkanecarboxylates leads to the target 3,3-difluoro-substitited cycloalkanes.
- For the 2,2-difluorocycloalkanecarboxylic acids, the bypass route *via* (2-oxocycloalkyl)methyl acetates is necessary.
- 2,2-Difluorocycloalkylamines can be obtained *via* deoxofluorination of 2-(trifluoroacetylamino)cycloalkanones.

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Synthesis of *gem*-difluorocyclopentane/hexane building blocks

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ABSTRACT

An approach to the preparation of *gem*-difluorocyclopentane/hexane-derived carboxylic acids and amines is described. Whereas for 3,3-difluoro-substituted cycloalkanones, straightforward deoxofluorination of the corresponding ketoesters led to the target compounds, in the case of 2,2-difluoro isomers, the bypass or alternative routes were necessary.

1. Introduction

Fluorinated cycloalkane building blocks are important structural motifs which become increasingly important in various areas, and most of all in drug discovery and agrochemistry [1]. One of the most prominent examples of this concept is related to development of Maraviroc (**1**), an antiretroviral drug approved by FDA in 2007 [2]. In this case, using 4,4-diflurocyclohexanecarboxylic acid (**2**) as a ~~building~~ block for the modification of optimized substance resulted in the compound with unique antiviral profile and lack of affinity

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for the hERG channel [3]. It is not surprising therefore that compound **2** and other building blocks bearing 4,4-difluorocyclohexyl moiety were widely used in medicinal chemistry since then [4]. On the contrary, isomeric and homologous *gem*-difluorocycloalkanes **3**–**6** were much less explored to date. Derivatives of these building blocks were evaluated as potent and selective cathepsin inhibitors [5], cholesteryl ester transfer protein (CETP) inhibitors [6], antibacterial agents [7], muscarinic M_3 receptor antagonists [8], bradykinin B_1 receptor antagonists [9], and opioid receptor-like 1 (ORL1) antagonists [10].

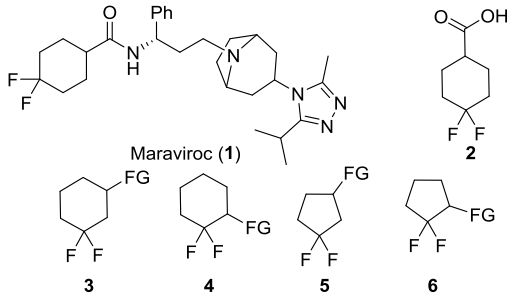
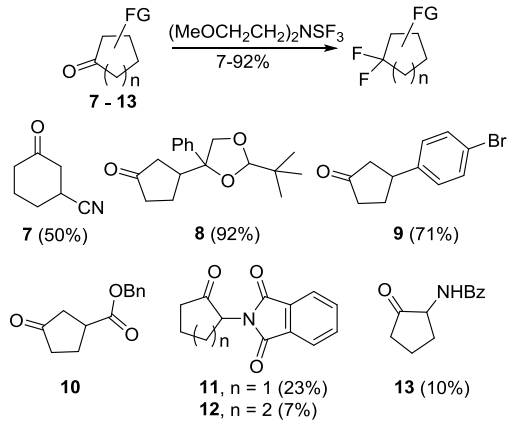


Figure 1. *gem*-Difluorocycloalkane building blocks

Most of the methods for the preparation of building blocks of the type **3**–**6** relied on deoxofluorination of appropriate ketones with (bis-(2-methoxyethyl)amino)sulfur trifluoride (Deoxo-Fluor®) (*e. g.*, for the substrates **7** [11], **8** [12], **9** [13], **10** [9], **11**–**13** [14]) (Scheme 1). In some cases, this procedure gave complex mixtures of the products, with less than 25% yield of the target compounds (*e. g.*, for **11**–**13**). Other known methods included deoxofluorination of α-haloketones with SF_4 [15], reaction of α-diazoketones with F_2 [16], ring-opening of 1-fluoro-2-cyanoepoxides [17], electrochemical ring expansion of cyclic α,β-unsaturated esters [18] or reaction of the corresponding dithiane derivatives with BrF_3 [19]. Notably, synthetic approaches to amines and carboxylic acids of the type **3**–**6** (*i. e.* FG = COOH, NH_2), which might be especially useful as building blocks for early drug discovery, were not documented in the literature.



Scheme 1. Synthesis of *gem*-difluorocycloalkane building blocks *via* deoxofluorination with Deoxo-Fluor®

2. Results and discussion

Herein, we describe a practical approach to *gem*-difluorocyclopentane/hexane building blocks **14**–**21** (Figure 2). For the synthesis of building blocks **14**–**17**, we relied on deoxofluorination of esters **22** and **23**, which were prepared using slightly modified literature methods (Scheme 2) [20, 21]. For the key step, we have chosen conditions described by Couturier and co-workers [22], which involved

using XtalFluor-E (**24**) – $Et_3N{\cdot}3HF$ as the deoxofluorination reagent; this system showed high efficiency the preparation for various *gem*-difluorocycloalkanes, including ethyl ester of the compound **2**. In the case of **22**, the reaction gave no by-products but was very slow: after a week at 80 °C, only 60% conversion to **25** was achieved. Ester **23** was more reactive, and the corresponding *gem*-difluoro derivative **26** was obtained in 68% yield. We have also checked if more reactive (and less expensive) diethylaminosulfur trifluoride (DAST) can be used in this transformation instead of XtalFluor-E – $Et_3N{\cdot}3HF$. In the case of **25**, this was true, and ester **25** was obtained in 61% yield. In the case of **26**, however, formation of the elimination by-products was observed to a great extent. Hydrolysis of **25** and **26** gave the target carboxylic acids **14** and **15** (92–99%), which were transformed to amines **16** and **17** (isolated as hydrochlorides) in 52–62% yields *via* Schmidt rearrangement.

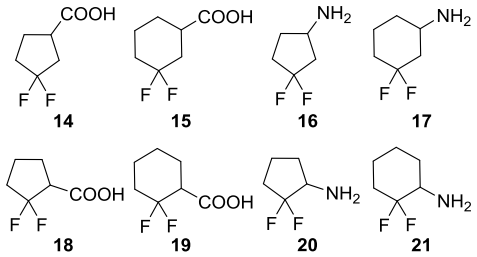
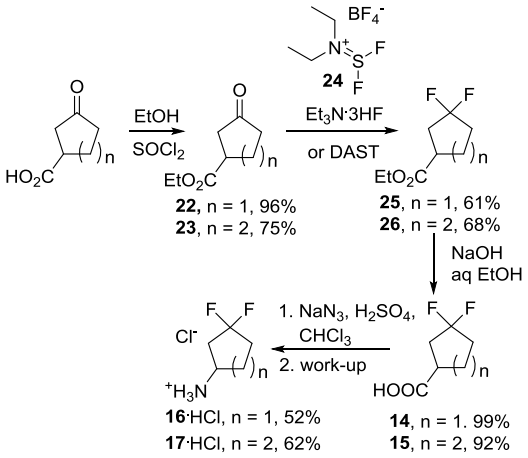
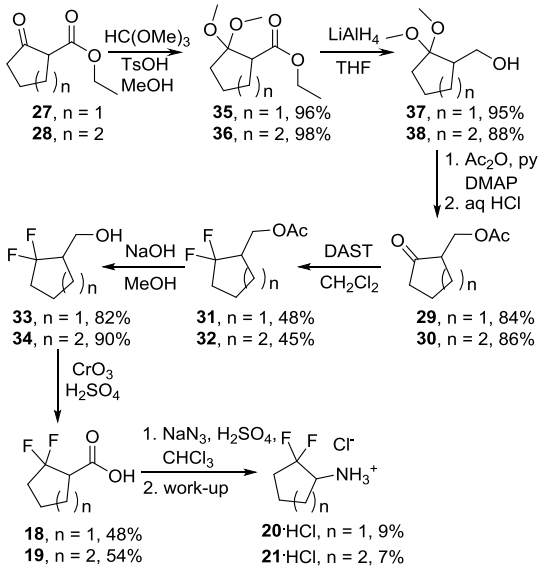


Figure 2. Building blocks **14**–**21** reported in this paper



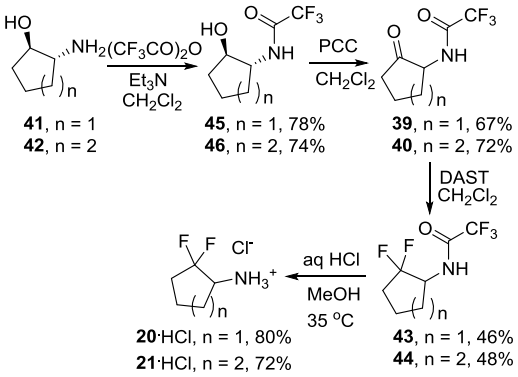
Scheme 2. Synthesis of building blocks **14**–**17**

This method did not work with ketoesters **27** and **28** – complex mixtures of products were obtained under the conditions described above. For the preparation of building blocks **18**–**21**, a bypass route was used (Scheme 3). First, compounds **27** and **28** were transformed to acetates **29** and **30** in four steps, including protection of the carbonyl group, reduction of the ester moiety, acetylation and deprotection (74–77% overall yield). It was found that XtalFluor-E did not give any advantage over less expensive DAST for deoxofluorination of the esters **29** and **30**. The corresponding *gem*-difluorocycloalkanes **31** and **32** were obtained using DAST in 48% and 45% yields, respectively. Hydrolysis of **31** and **32** gave alcohols **33** and **34** (82–90%), which are themselves promising key intermediates for synthesis. Oxidation of **33** and **34** with Jones reagent led to the target carboxylic acids **18** and **19** (48–54%).



Scheme 3. Synthesis of building blocks **18**–**21**

Unfortunately, Schmidt reaction of **18** and **19** under conditions analogous to those used for **14** and **15** gave amine hydrochlorides **20**·HCl and **21**·HCl in low yields (7–9%). Therefore, we considered deoxofluorination of 2-aminocycloalkanone derivatives as an alternative key step for the preparation of **20** and **21**. Although deoxofluorination of the substrates **11**–**13** bearing phtalimide or benzoyl protective groups was described in the literature (with 7–23% yields),[14] deprotection of the corresponding products was not fruitful in our hands. In our approach, we have used trifluoroacetyl derivatives **39** and **40**, prepared in two steps from the corresponding amino alcohols **41** and **42** (Scheme 4). Deoxofluorination of **39** and **40** led to isolation of the products **43** and **44** in 46% and 48% yields, respectively. Deprotection of **43** and **44** occurred upon mild acidic hydrolysis and gave **20**·HCl and **21**·HCl in good yields (72–80%).



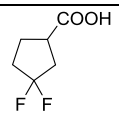
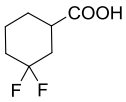
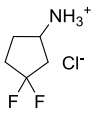
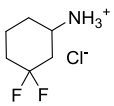
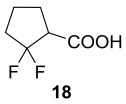
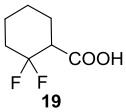
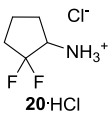
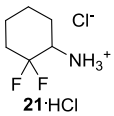
Scheme 4. Alternative approach to the synthesis of building blocks **20** and **21** (relative configurations are shown)

3. Conclusions

Deoxofluorination of appropriate substrates proved to be an efficient method for the preparation of *gem*-difluorocyclopentane/hexane building blocks (*i. e.*, carboxylic acids and primary amines) (Table 1). It was shown that less expensive DAST can be used for the deoxofluorination step instead of Deoxo-Fluor® reported in the previous works for most of the building blocks discussed. In the case of 3,3-difluoro-substitited cycloalkane derivatives, straightforward fluorination of the corresponding 3-ketocycloalkanecarboxylates led to the target compounds. For the 2,2-difluoro isomers, the bypass route *via* (2-oxocycloalkyl)methyl acetates was necessary, which allowed for the preparation of the corresponding carboxylic acids. 2,2-Difluorocycloalkylamines were obtained by alternative route,

including deoxofluorination of the corresponding 2-(trifluoroacetylamino)cycloalkanones. The use of trifluoroacetyl protective group allowed improving the yield of the deoxofluorination step as compared to the literature precedents. The procedures developed were used at up to 10 g scale, and in our opinion, have potential for further scale-up.

Table 1. An overview of the synthetic methods developed in this work for the synthesis of building blocks **14–21.**

Compound	No. of steps	Overall yield (%)	Deoxofluorination reagent
 **14**	3	58	DAST
 **15**	3	40	XTal-Fluor-E – $Et_3N{\cdot}3HF$
 **16**·HCl	4	30	DAST
 **17**·HCl	4	29	XTal-Fluor-E – $Et_3N{\cdot}3HF$
 **18**	6	14	DAST
 **19**	6	16	DAST
 **20**·HCl	4	19	DAST
 **21**·HCl	4	18	DAST

4. Experimental

4.1. General

The solvents were purified according to the standard procedures [23]. 3-Oxocyclopentane-3-carboxylic acid [20a] and 3-oxocyclohexanecarboxylic acid [21a] were prepared using reported methods. All other starting materials were purchased from commercial sources. Analytical TLC was performed using Polychrom SI F254 plates. Column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) as the stationary phase. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a Varian Gemini 2000

spectrometer (at 400 MHz for Protons, 101 MHz for Carbon-13, and 376 MHz for Fluorine-19). Chemical shifts are reported in ppm downfield from TMS (^{1}H, ^{13}C) as an internal standard. Elemental analyses were performed at the Laboratory of Organic Analysis, Institute of Organic Chemistry, National Academy of Sciences of Ukraine, their results were found to be in good agreement (±0.4%) with the calculated values. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization (APCI).

*4.2. Ethyl 3-oxocyclopentane carboxylate (**22**)*

Ester **22** was prepared from 3-oxocyclopentane-3-carboxylic acid using the procedure described below for the compound **23**. The crude product was purified by column chromatography (hexanes – EtOAc (4:1) as eluent). All the spectral and physical data are in accordance with the literature data [24]. Yield 15.3 g, 96%. Colorless oil. R_f = 0.27 (hexanes – EtOAc (4:1)). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.19 (q, *J* = 7.1 Hz, 2H), 3.17 – 3.07 (m, 1H), 2.57 – 2.08 (m, 6H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 215.4, 173.5, 60.5, 40.8, 40.6, 37.0, 26.2, 13.9. MS (EI): *m*/z = 156 (M^+), 128 (M^+–C_2H_4), 111 (M^+–COOH). Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.12; H, 7.99.

*4.3. Ethyl 3-oxocyclohexane carboxylate (**23**)*

To a solution of 3-oxocyclohexane carboxylic acid (63.0 g, 0.443 mol) in ethanol (950 mL), $SOCl_2$ (38.8 mL, 0.532 mol) was added at 15 °C. The reaction mixture was stirred at rt overnight, and then evaporated under reduced pressure. The residue was dissolved in $CHCl_3$ (500 mL) and stirred with saturated aq $NaHCO_3$ (200 mL) for 30 min. The layers were separated, and the aqueous layer was extracted with $CHCl_3$ (2×50 mL). The combined organic phases were dried over Na_2SO_4 and evaporated in vacuo. The residue was distilled under reduced pressure to give **23**. Yield 56.3 g, 75%. Colorless oil. Bp 90 °C / 1.8 mbar (lit. [21c] Bp 80–83 °C / 0.6 Torr). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.14 (q, *J* = 7.1 Hz, 2H), 2.83 – 2.72 (m, 1H), 2.53 (d, *J* = 8.2 Hz, 2H), 2.41 – 2.26 (m, 2H), 2.16 – 2.01 (m, 2H), 1.89 – 1.66 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 208.6, 173.1, 60.6, 43.0, 42.9, 40.7, 27.5, 24.3, 14.0. MS (EI): *m*/z = 170 (M^+), 97(M^+–CO_2Et). Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.14; H, 8.12.

*4.4. Ethyl 3,3-difluorocyclopentane carboxylate (**25**)*

To a solution of DAST (45.1 g, 37.0 mL, 282 mmol) in CH_2Cl_2 (450 mL) a solution of **22** (11.0 g, 70.4 mmol) in CH_2Cl_2 (150 mL) was added at rt. The reaction mixture was refluxed until the starting material had disappeared (*ca.* 72 h, monitored by ^{1}H NMR probe), then cooled, and saturated aq $NaHCO_3$ was added to pH = 7. The aqueous phase was extracted with CH_2Cl_2 (2×100 mL), the combined organic extracts were dried over Na_2SO_4 and evaporated in vacuo. The residue was distilled under reduced pressure. Yield 7.71 g, 61%. Colorless oil. Bp 31–32°C / 1.8 mbar. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.17 (q, *J* = 7.1 Hz, 2H), 3.05 – 2.93 (m, 1H), 2.47 – 2.31 (m, 2H), 2.28 – 1.97 (m, 4H), 1.27 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (CDCl3, 101 MHz): δ = 173.3, 131.2 (dd, *J* = 250, 246 Hz), 60.6, 40.6 (dd, *J* = 5.4, 2.9 Hz), 38.1 (t, *J* = 26.6 Hz), 34.7 (t, *J* = 25.2 Hz), 26.2 (dd, *J* = 4.4, 3.5 Hz), 13.9. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = –92.0 (dquint, *J* = 229, 16.4 Hz), –93.2 (dquint, *J* = 229, 16.4 Hz). MS (EI): *m*/z = 178 (M^+), 158 (M^+–HF). Anal. Calcd for $C_8H_{12}F_2O_2$: C, 53.93; H, 6.79. Found: C, 53.89; H, 6.39.

*4.5. Ethyl 3,3-difluorocyclohexane carboxylate (**26**)*

To a suspension of XtalFluor-E (**24**) (33.8 g, 0.147 mol) in 1,2-dichloroethane (200 mL), $Et_3N{\cdot}3HF$ (14.2 g, 88.4 mmol) was added. To the resulting mixture, a solution of ketoester **23** (10.0 g, 58.8 mmol) in 1,2-dichloroethane (20 mL) was added at 15 °C. The reaction mixture was stirred at rt for 30 min and then refluxed until the starting material disappeared (*ca.* 8 h, monitored by ^{1}H NMR), then cooled to rt, quenched with saturated aq $NaHCO_3$ solution and extracted with 1,2-dichloroethane (3×100 mL). The combined organic extracts were washed with 10% aq citric acid (2×100 mL), brine (100 mL), dried over Na_2SO_4 and evaporated. The residue was distilled under reduced pressure to give **26**. Yield 7.74 g, 68%. Colorless oil. Bp 39–41 °C / 1.8 mbar. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.15 (q, *J* = 7.1 Hz, 2H), 2.61 (tdd, *J* = 12.2, 3.8, 2.2 Hz, 1H), 2.38 – 2.26 (m, 1H), 2.14 – 1.97 (m, 2H), 1.96 – 1.77 (m, 2H), 1.75 – 1.52 (m, 2H), 1.47 – 1.34 (m, 1H), 1.26 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 173.3 (d, *J* = 1.6 Hz), 122.6 (dd, *J* = 242, 239 Hz), 60.4, 40.0 (d, *J* = 9.6 Hz), 35.7 (t, *J* = 25.0 Hz), 33.1 (dd, *J* = 25.1, 22.0 Hz), 27.1 (d, *J* = 1.6 Hz), 21.4 (d, *J* = 9.6 Hz), 14.0. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = –91.1 (d, *J* = 239 Hz), –101.5 (dt, *J* = 239, 32.1 Hz). MS (EI): *m*/z = 192 (M^+), 172 (M^+–HF). Anal. Calcd for $C_9H_{14}F_2O_2$: C, 56.24; H, 7.34. Found: C, 56.60; H, 7.19.

*4.6. 3,3-Difluorocyclopentanecarboxylic acid (**14**)*

Carboxylic acid **14** was prepared from the compound **25** using the procedure described below for the compound **15**. Yield 5.57 g, 99%. Yellowish oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 12.01 (br s, 1H), 3.14 – 2.98 (m, 1H), 2.48 – 2.33 (m, 2H), 2.29 – 2.01 (m, 4H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 180.2, 131.0 (dd, *J* = 250, 247 Hz), 40.4 (dd, *J* = 5.2, 3.2 Hz), 37.9 (t, *J* = 26.9 Hz), 34.8 (t, *J* = 25.2 Hz), 26.1 (dd, *J* = 4.2, 3.6 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz): δ = –92.4 (d, *J* = 225 Hz), –95.2 (d, *J* = 225 Hz). MS (EI): *m*/z = 130 (M^+–HF), 85 (M^+ – HF – COOH). Anal. Calcd for $C_6H_8F_2O_2$: C, 48.00; H, 5.37. Found: C, 47.71; H, 5.14.

*4.7. 3,3-Difluorocyclohexanecarboxylic acid (**15**)*

To a solution of ester **26** (2.00 g, 10.4 mmol) in ethanol (20 mL), a cold solution of NaOH (0.50 g, 12.5 mmol) in H_2O (1 mL) was added. The reaction mixture was stirred at rt overnight. Ethanol was evaporated in vacuo, the residue was dissolved in H_2O (10 mL) and washed with Et_2O (10 mL). The aqueous layer was acidified with 10% aq HCl to pH=3 and extracted with $CHCl_3$ (3×10 mL). The combined organic extracts were dried over Na_2SO_4 and evaporated in vacuo to give **15**. The analytical sample was obtained by recrystallization from cyclohexane. Yield 1.57 g, 92%. White solid. Mp = 71–73 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.69 (ttd, *J* = 12.2, 3.7, 1.5 Hz, 1H), 2.43 – 2.30 (m, 1H), 2.16 – 2.01 (m, 2H), 1.99 – 1.79 (m, 2H), 1.77 – 1.54 (m, 2H), 1.51 – 1.37 (m, 1H); COO*H* is exchanged with HDO. ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 179.8, 122.4 (t, *J* = 240 Hz), 39.8 (d, *J* = 9.3 Hz), 35.4 (t, *J* = 25.4 Hz), 33.1 (t, *J* = 23.5 Hz), 26.9, 21.4 (d, *J* = 9.4 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ –91.3 (d, *J* = 238 Hz), –101.5 (dt, *J* = 238 31.5 Hz). MS (EI): *m*/z = 164 (M^+), 144 (M^+–HF), 126 (M^+–HF–H_2O), 99 (M^+ - HF – COOH). Anal. Calcd for $C_7H_{10}F_2O_2$: C, 51.22; H, 6.14. Found: C, 51.03; H, 6.25.

*4.8. 3,3-Difluorocyclopentanamine hydrochloride (**16**·HCl)*

Hydrochloride **16**·HCl was prepared from the compound **14** using the procedure described below for the compound **17**·HCl. Yield 0.215 g, 52%. White solid. Mp 194–197 °C (dec). ^{1}H NMR (D_2O), 400 MHz): δ = 3.94 – 3.82 (m, 1H), 2.73 – 2.58 (m, 1H), 2.43 – 2.09

(m, 4H), 1.97 – 1.82 (m, 1H). ^{13}C NMR (D_2O, 101 MHz): δ = 127.9 (t, *J* = 247 Hz), 45.3, 36.5 (t, *J* = 26.7 Hz), 30.6 (t, *J* = 24.7 Hz), 24.6. ^{19}F NMR (DMSO-d_6, 376 MHz): δ = –88.9 (dquint, *J* = 228, 15.0 Hz), –90.5 (br d, *J* = 228 Hz). MS (EI): *m*/z = 121 (M^+), 92 (NH_2^+=CH–CH=CF_2). Anal. Calcd for $C_5H_{10}ClF_2N$: C, 38.11; H, 6.40; Cl, 22.50; N 8.89. Found: C, 38.00; H, 6.77; Cl, 22.37; N 9.07.

*4.9. 3,3-Difluorocyclohexanamine hydrochloride (**17**·HCl)*

Carboxylic acid **15** (1.00 g, 6.10 mmol) was dissolved in $CHCl_3$ (30 mL), and 98% H_2SO_4 (2 mL) was added. The mixture was heated to 50 °C, and NaN_3 (0.80 g, 12.2 mmol) was added in portions at this temperature over 3 h. Then the reaction mixture was stirred at 45–50 °C for additional 3 h, cooled to rt and stirred for 48 h. Then the mixture was poured into ice (10 g), and the organic layer was separated. The aqueous phase was adjusted to pH = 12–13 with 15% aq NaOH and extracted with CH_2Cl_2 (4×10 mL). The organic phase was acidified with HCl in Et_2O (20 mL) until the precipitate started to form, and then evaporated to dryness to give the target product **17**·HCl. Yield 0.653 g, 62%. White solid. Mp 285–288 °C (dec). ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 8.46 (br s, 3H), 3.20 – 3.06 (m, 1H), 2.48 – 2.36 (m, 1H), 2.08 – 1.86 (m, 3H), 1.86 – 1.60 (m, 2H), 1.51 – 1.31 (m, 2H). ^{13}C NMR (DMSO-d_6, 101 MHz): δ = 123.2 (dd, *J* = 242, 239 Hz), 46.7 (d, *J* = 11.4 Hz), 37.2 (t, *J* = 24.8 Hz), 32.2 (dd, *J* = 24.2, 21.6 Hz), 27.8, 19.2 (d, *J* = 10.0 Hz). ^{19}F NMR (DMSO-d_6, 376 MHz): δ = –87.5 (d, *J* = 240 Hz), –97.8 (dtt, *J* = 240, 34.4, 9.3 Hz). MS (EI): *m*/z = 135 (M^+), 92 (NH_2^+=CH–CH=CF_2). Anal. Calcd for $C_6H_{12}ClF_2N$: C, 41.99; H, 7.05; Cl, 20.66; N, 8.16. Found: C, 42.21; H, 7.26; Cl, 20.46; N, 8.48.

*4.10. Ethyl 2,2-dimethoxycyclopentanecarboxylate (**35**)*

Ethyl 2-oxocyclopentane-1-carboxylate (50.0 g, 0.320 mol), trimethyl orthoformate (84.9 g, 0.800 mol) and *p*-toluenesulfonic acid monohydrate (550 mg, 2.89 mmol) in dry MeOH (300 mL) were heated under reflux under argon atmosphere overnight. The crude mixture was cooled to room temperature, quenched with solid Na_2CO_3 (1 g), filtered and concentrated in vacuo. The residue was distilled in vacuo. Yield 62.0 g, 96%. Colorless liquid. Bp 53–55 °C / 1 mbar. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.22 – 4.08 (m, 2H), 3.26 (s, 3H), 3.22 (s, 3H), 2.97 (dd, *J* = 8.4, 5.6 Hz, 1H), 2.09 – 1.98 (m, 1H), 1.94 – 1.78 (m, 4H), 1.68 – 1.55 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 172.6, 111.9, 60.0, 50.2, 50.0, 48.5, 34.1, 27.3, 21.8, 14.0. MS (EI): *m*/z = 202 (M^+), 171 (M^+–OMe), 101 (MeO^+=C(OMe)–CH=CH_2). Anal. Calcd. for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97. Found: C, 59.52; H, 8.80.

*4.11. Ethyl 2,2-dimethoxycyclohexanecarboxylate (**36**)*

Compound **36** was prepared from ethyl 2-oxocyclohexane-1-carboxylate using the procedure described above for the compound **35**. Yield 50.2 g, 98%. Colorless liquid. Bp 75–76 °C / 1 mbar. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.19 – 4.10 (m, 2H), 3.21 (s, 3H), 3.17 (s, 3H), 2.95 (app. dt, *J* = 4.8, 2.5 Hz, 1H), 2.02 (app. td, *J* = 13.4, 4.1 Hz, 1H), 1.88 – 1.76 (m, 2H), 1.76 – 1.60 (m, 3H), 1.49 – 1.33 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ =^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0, 99.6, 59.8, 47.5, 47.0, 45.5, 28.2, 25.9, 22.0, 20.5, 14.0. MS (EI): *m*/z = 216 (M^+), 185 (M^+–OMe), 101 (MeO^+=C(OMe)–CH=CH_2). Anal. Calcd. for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 61.15; H, 9.27.

*4.12. (2,2-Dimethoxycyclopentyl)methanol (**37**)*

To a suspension of $LiAlH_4$ (24.3 g, 0.640 mol) in dry THF (900 mL), ketal **35** (62.0 g, 0.306 mmol) in dry THF (200 mL) was added dropwise at 0 °C. The reaction mixture was warmed to rt, stirred for 1 h, then quenched by dropwise addition of H_2O (25 mL), 10 % aq NaOH (50 mL) and H_2O (75 mL). The reaction mixture was filtered, and evaporated in vacuo. The residue was dissolved in CH_2Cl_2 (500 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give the target product. Yield 46.7 g, 95%. Amber oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.64 – 3.49 (m, 2H), 3.28 (s, 3H), 3.23 (s, 3H), 2.67 (br s, 1H), 2.36 – 2.27 (m, 1H), 1.96 – 1.80 (m, 2H), 1.79 – 1.68 (m, 1H), 1.68 – 1.52 (m, 2H), 1.44 – 1.33 (m, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 112.8, 64.0, 49.8, 48.0, 44.4, 35.1, 26.8, 21.6. MS (EI): *m*/z = 160 (M^+), 143 (M^+–OH), 129 (M^+–OMe), 101 (MeO^+=C(OMe)–CH=CH_2). Anal. Calcd. for $C_8H_{16}O_3$: C, 59.97; H, 10.07. Found: C, 59.72; H, 10.27.

*4.13. (2,2-Dimethoxycyclohexyl)methanol (**38**)*

Compound **38** was prepared from compound **36** using the procedure described above for the compound **37**. Yield 35.4 g, 88%. Yellowish oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.90 (dd, *J* = 11.2, 8.6 Hz, 1H), 3.60 – 3.49 (m, 1H), 3.23 (s, 3H), 3.20 (s, 3H), 2.99 (d, *J* = 8.7 Hz, 1H), 2.20 – 2.11 (m, 1H), 1.90 – 1.77 (m, 1H), 1.64 – 1.55 (m, 4H), 1.55 – 1.36 (m, 2H), 1.32 – 1.18 (m, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 102.5, 63.4, 47.3, 47.2, 40.5, 28.7, 25.7, 22.5, 20.9. MS (EI): *m*/z = 174 (M^+), 157 (M^+–OH), 143 (M^+–OMe), 101 (MeO^+=C(OMe)–CH=CH_2). Anal. Calcd. for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 61.85; H, 10.59.

*4.14. (2-Oxocyclopentyl)methyl acetate (**29**)*

Alcohol **37** (46.7 g, 0.292 mol) and DMAP (370 mg, 3.03 mmol) were dissolved in dry pyridine (105 mL) under argon atmosphere. Ac_2O (40.0 mL, 0.419 mol) was added dropwise (CAUTION! Exothermic reaction), and the resulting mixture was stirred overnight. The reaction mixture was quenched with 2 M HCl (600 mL) and Et_2O (500 mL) upon vigorous stirring over 5 min. The organic phase was separated, and the aqueous phase extracted with Et_2O (3×400 mL). The combined organic extracts were neutralized with saturated aq $NaHCO_3$, dried over $MgSO_4$ and concentrated in vacuo. Yield 38.1 g, 84%. Yellowish oil ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.25 (dd, *J* = 11.2, 4.1 Hz, 1H), 4.13 (dd, *J* = 11.2, 5.8 Hz, 1H), 2.41 – 2.22 (m, 2H), 2.17 (ddt, *J* = 11.4, 4.0, 2.6 Hz, 1H), 2.12 – 2.04 (m, 1H), 2.04 – 1.93 (m, 1H), 1.98 (s, 3H), 1.84 – 1.65 (m, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 217.1, 170.3, 62.5, 47.8, 38.0, 26.6, 20.6, 20.4. MS (EI): *m*/z = 156 (M^+), 114 (M^+–CH_2=C=O), 96 (M^+–AcOH), 43(CH_3CO^+). Anal. Calcd. for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.24; H, 7.79.

*4.15. (2-Oxocyclohexyl)methyl acetate (**30**)*

Compound **30** was prepared from compound **38** using the procedure described above for the compound **29**. Yield 29.6 g, 86%. Yellowish oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.35 (dd, *J* = 11.3, 5.9 Hz, 1H), 4.02 (dd, *J* = 11.3, 6.3 Hz, 1H), 2.70 – 2.60 (m, 1H), 2.44 – 2.36 (m, 1H), 2.36 – 2.25 (m, 1H), 2.20 – 2.11 (m, 1H), 2.11 – 2.04 (m, 1H), 2.01 (s, 3H), 1.94 – 1.83 (m, 1H), 1.74 – 1.57 (m, 2H), 1.51 – 1.35 (m, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 209.7, 170.4, 63.0, 49.2, 41.8, 30.7, 27.4, 24.5, 20.7. MS (EI): *m*/z = 170 (M^+), 127 (M^+–Ac), 110 (M^+–AcOH), 43(CH_3CO^+). Anal. Calcd. for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.74; H, 7.98.

*4.16. (2,2-Difluorocyclopentyl)methyl acetate (**31**)*

To a solution of DAST (156 g, 128 mL, 0.968 mol) in CH_2Cl_2 (650 mL), a solution of **29** (37.8 g, 0.242 mol) in CH_2Cl_2 (400 mL) was added at rt. The reaction mixture was refluxed for 72 h (monitored by ^{1}H NMR), then cooled. Saturated aq $NaHCO_3$ was added to pH = 7. Aqueous layer was extracted with CH_2Cl_2 (2×100 mL). The combined organic extracts were dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by column chromathography (hexanes –EtOAc (14 : 1) as eluent). Yield 20.5 g, 48%. Colourless oil. R_f = 0.42 (hexanes –EtOAc (14 : 1)). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.21 (dd, *J* = 11.3, 7.1 Hz, 1H), 4.12 (dd, *J* = 11.3, 6.7 Hz, 1H), 2.56 – 2.39 (m, 1H), 2.24 – 1.93 (m, 3H), 2.06 (s, 3H), 1.88 – 1.66 (m, 2H), 1.59 – 1.48 (m, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 170.3, 131.1 (t, *J* = 251 Hz), 61.8 (d, *J* = 7.4 Hz), 44.7 (dd, *J* = 23.8, 21.4 Hz), 35.2 (t, *J* = 24.7 Hz), 26.5 (d, *J* = 5.8 Hz), 20.6, 20.1 (t, *J* = 4.5 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz): δ = –96.0 (ddd, *J* = 231, 25.7, 13.4 Hz), –107.0 (ddd, *J* = 231, 32.9, 16.0 Hz). MS (EI): *m*/z = 178 (M^+), 98 (M^+ – AcOH – HF), 86, 43 (CH_3CO^+). Anal. Calcd. for $C_8H_{12}F_2O_2$: C, 53.93; H, 6.79. Found: C, 53.72; H, 6.66.

*4.17. (2,2-Difluorocyclohexyl)methyl acetate (**32**)*

Compound **32** was prepared from compound **30** using the procedure described above for the compound **29**. Yield 15.0 g, 45%. Colorless oil. R_f = 0.38 (hexanes –EtOAc (14 : 1)). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.38 (dd, *J* = 11.2, 5.1 Hz, 1H), 4.03 (dd, *J* = 11.2, 7.9 Hz, 1H), 2.17 – 2.02 (m, 2H), 2.06 (s, 3H), 1.94 – 1.82 (m, 1H), 1.82 – 1.44 (m, 4H), 1.42 – 1.20 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.4, 123.0 (t, *J* = 244 Hz), 62.2 (t, *J* = 4.0 Hz), 42.7 (dd, *J* = 22.0, 19.7 Hz), 34.0 (dd, *J* = 24.7, 22.0 Hz), 26.3 (d, *J* = 6.5 Hz), 23.5, 22.4 (d, *J* = 9.1 Hz), 20.7. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = –96.9 (d, *J* = 237 Hz), -114.1 (br d, *J* = 237 Hz). MS (EI): *m*/z = 172 (M^+–HF), 112 (M^+–AcOH–HF), 43 (CH_3CO^+). Anal. Calcd. for $C_9H_{14}F_2O_2$: C, 56.24; H, 7.34. Found: C, 56.25; H, 7.10.

*4.18. (2,2-Difluorocyclopentyl)methanol (**33**)*

Ester **31** (19.4 g, 0.109 mol) was dissolved in MeOH (200 mL), and NaOH (8.70 g, 0.218 mol) in H_2O (20 mL) was added. The reaction mixture was stirred at room temperature overnight. The solvent was evaporated, water (100 mL) was added, and the mixture was extracted with CH_2Cl_2 (3×100 mL). The organic layer was dried over Na_2SO_4 and evaporated in vacuo. Yield 12.1 g, 82%. Yellowish oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.80 (dd, *J* = 11.5, 7.1 Hz, 1H), 3.69 (dd, *J* = 11.5, 5.5 Hz, 1H), 2.45 – 2.27 (m, 1H), 2.22 – 1.91 (m, 3H), 1.83 (br s, 1H), 1.82 – 1.64 (m, 2H), 1.63 – 1.50 (m, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 132.5 (t, *J* = 251 Hz), 60.8 (d, *J* = 7.9 Hz), 47.7 (t, *J* = 21.7 Hz), 35.5 (t, *J* = 24.5 Hz), 25.9 (d, *J* = 5.0 Hz), 20.4. ^{19}F NMR ($CDCl_3$, 376 MHz): δ –93.4 (dq, *J* = 230, 14.0 Hz), –107.2 (dq, *J* = 230, 15.2 Hz). MS (EI): *m*/z = 136 (M^+), 86 (M^+–HF–CH_2O). Anal. Calcd. for $C_6H_{10}F_2O$: C, 52.93; H, 7.40. Found: C, 52.98; H, 7.12.

*4.19. (2,2-Difluorocyclohexyl)methanol (**34**)*

Compound **34** was prepared from compound **32** using the procedure described above for the compound **33**. Used in the next step without further purification. Yield 10.5 g, 90%. Yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.96 (dd, *J* = 11.4, 5.7 Hz, 1H), 3.62 (dd, *J* = 11.4, 5.6 Hz, 1H), 2.16 – 2.02 (m, 1H), 2.02 – 1.82 (m, 2H), 1.82 – 1.45 (m, 5H), 1.34 (tt, *J* = 24.1, 12.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 124.5 (t, *J* = 243 Hz), 61.2 (t, *J* = 3.7 Hz), 45.7 (dd, *J* = 21.6, 18.7 Hz), 34.1 (dd, *J* = 24.9, 22.0 Hz), 25.9 (d, *J* = 7.0 Hz),

23.7 (d, *J* = 1.4 Hz), 22.6 (d, *J* = 9.3 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz): δ = –95.93 (d, *J* = 235 Hz), –113.71 (br d, *J* = 235 Hz). MS (EI): *m*/z = 150 (M^+), 130 (M^+–HF), 100 (M^+–HF–CH_2O). Anal. Calcd. for $C_7H_{12}F_2O$: C, 55.99; H, 8.05. Found: C, 55.69; H, 7.99.

*4.20. 2,2-Difluorocyclopentanecarboxylic acid (**18**)*

Sulfuric acid (17.4 g, 9.5 mL, 0.178 mol) was added carefully to CrO_3 (13.3 g, 0.133 mol) and H_2O (40 mL). The mixture was cooled to 0 °C, and a solution of the substrate (12.1 g, 88.9 mmol) in acetone (200 mL) was added at this temperature. The reaction mixture was stirred overnight at rt, 10% aq NaOH to pH = 10 was added, and the mixture was washed with EtOAc (2×100 mL). Aqueous layer was acidified with 10% aq HCl to pH = 2–3 and extracted with EtOAc (4×100 mL). The organic layer was dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by flash chromatography (hexanes – EtOAc (1:1) as eluent), followed by recrystallization from heptane. Yield 6.45 g, 48%. White solid. Mp 68–69 °C. R_f = 0.78 (hexanes – EtOAc (1:1)). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.26 – 3.08 (m, 1H), 2.30 – 2.04 (m, 4H), 2.01 – 1.88 (m, 1H), 1.87 – 1.72 (m, 1H); COO*H* is exchanged with HDO. ^{13}C NMR ($CDCl_3$, 101 MHz): δ = δ 175.5, 130.1 (t, *J* = 254 Hz), 51.2 (t, *J* = 24.3 Hz), 35.1 (t, *J* = 24.0 Hz), 26.0 (d, *J* = 2.4 Hz), 20.4. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = –93.2 (dq, *J* = 231.3, 14.3 Hz), –101.3 (dq, *J* = 231.4, 13.7 Hz). MS (EI): *m*/z = 150 (M^+), 130 (M^+–HF), 85 (M^+–HF–COOH). Anal. Calcd. for $C_6H_8F_2O_2$: C, 48.00; H, 5.37. Found: C, 48.29; H, 5.22.

*4.21. 2,2-Difluorocyclohexanecarboxylic acid (**19**)*

Compound **19** was prepared from compound **34** using the procedure described above for the compound **18**. Yield 6.18 g, 54%. White solid. Mp 74–75 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.00 – 2.83 (m, 1H), 2.33 – 2.17 (m, 1H), 2.05 – 1.89 (m, 2H), 1.89 – 1.61 (m, 4H), 1.48 – 1.34 (m, 1H); COO*H* is exchanged with HDO. ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 176.0 (d, *J* = 5.2 Hz), 121.0 (t, *J* = 245 Hz), 48.5 (t, *J* = 22.9 Hz), 33.0 (t, *J* = 22.7 Hz), 26.2 (dd, *J* = 3.2, 2.5 Hz), 22.1, 22.0. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = -95.0 (d, *J* = 238 Hz), -105.7 (br s). MS (EI): *m*/z = 144 (M^+–HF), 99 (M^+–HF–COOH). Anal. Calcd. for $C_7H_{10}F_2O_2$: C, 51.22; H, 6.14. Found: C, 51.61; H, 6.12.

*4.22. 2,2,2-Trifluoro-N-(trans-2-hydroxycyclopentyl)acetamide (**45**)*

Amino alcohol **41** (11.4 g, 0.113 mol) and triethylamine (14.8 g, 0.146 mol) were dissolved in dry CH_2Cl_2 (900 mL). The resulting solution was cooled to –30 °C, and trifluoracetic anhydride (23.7 g; 0.113 mol) was added dropwise. The reaction mixture was stirred at rt overnight, and then evaporated. The residue was purified by column chromatography ($CHCl_3$ – MeOH (25:1) as eluent). Yield 17.3 g, 78%. Mp 116–117 °C. R_f = 0.23 ($CHCl_3$ – MeOH (25:1)). ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 9.27 (br s, 1H), 4.91 (br s, 1H), 3.93 (dd, *J* = 11.2, 6.3 Hz, 1H), 3.83 (dd, *J* = 13.4, 7.5 Hz, 1H), 2.00 – 1.89 (m, 1H), 1.87 – 1.76 (m, 1H), 1.69 – 1.56 (m, 2H), 1.51 – 1.39 (m, 2H). ^{13}C NMR (DMSO-d_6, 101 MHz): δ = 155.8 (q, *J* = 35.8 Hz), 115.8 (q, *J* = 288 Hz), 75.2, 58.1, 32.1, 28.6, 20.1. ^{19}F NMR (DMSO-d_6, 376 MHz): δ = –74.4. MS (EI): *m*/z = 197 (M^+), 179 (M^+–H_2O), 84 (M^+–$CF_3C(O)NH_2$). Anal. Calcd. for $C_7H_{10}F_3NO_2$: C, 42.64; H, 5.11; N, 7.10. Found: C, 42.78; H, 5.25; N, 7.11.

*4.23. 2,2,2-Trifluoro-N-(trans-2-hydroxycyclohexyl)acetamide (**46**)*

Compound **46** was prepared from compound **42** using the procedure described above for the compound **45**. Yield 27.1 g, 74%. White solid. Mp 129–130 °C. R_f = 0.26 ($CHCl_3$ – MeOH (25:1)). ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 9.12 (br s, 1H), 4.76 (br s, 1H), 3.49 – 3.41 (m, 1H), 3.37 – 3.30 (m, 1H), 1.92 – 1.81 (m, 1H), 1.76 – 1.67 (m, 1H), 1.67 – 1.55 (m, 2H), 1.35 – 1.11 (m, 4H). ^{13}C NMR (DMSO-d_6, 101 MHz): δ = 155.7 (q, *J* = 35.6 Hz), 116.0 (q, *J* = 288 Hz), 70.3, 55.5, 34.4, 30.4, 24.3, 24.0. ^{19}F NMR (DMSO-d_6, 376 MHz): δ = –74.5. MS (EI): *m*/z = 206 (M^+), 193 (M^+–H_2O), 98 (M^+–$CF_3C(O)NH_2$). Anal. Calcd. for $C_8H_{12}F_3NO_2$: C, 45.50; H, 5.73; N, 6.63. Found: C, 45.33; H, 5.84; N, 6.52

*4.24. 2,2,2-Trifluoro-N-(2-oxocyclopentyl)acetamide (**39**)*

Freshly prepared pyridinium chlorochromate (34.9 g, 0.162 mol) was suspended in CH_2Cl_2 (1000 mL), and alcohol **45** (21.0 g, 0.106 mol) was added. The reaction mixture was stirred at rt overnight, decanted from the solid, filtered through SiO_2 pad (100 g), washed with CH_2Cl_2 (350 mL) and evaporated in vacuo. Yield 13.9 g, 67%. White solid. Mp 63–64 °C. R_f = 0.21 (Hexanes – EtOAc (4:1)). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.04 (br s, 1H), 4.24 – 4.10 (m, 1H), 2.73 – 2.59 (m, 1H), 2.46 (dd, *J* = 19.2, 8.8 Hz, 1H), 2.24 (dd, *J* = 19.5, 9.5 Hz, 1H), 2.19 – 2.07 (m, 1H), 2.00 – 1.83 (m, 1H), 1.70 (app qd, *J* = 12.3, 6.7 Hz, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 212.4, 157.0 (q, *J* = 37.4 Hz), 115.2 (q, *J* = 287 Hz), 57.6, 34.4, 28.8, 17.9. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = –77.5. MS (EI): *m*/z = 195 (M^+). Anal. Calcd. for $C_7H_8F_3NO_2$: C, 43.08; H, 4.13; N, 7.18. Found: C, 43.39; H, 4.39; N, 7.10.

*4.25. 2,2,2-Trifluoro-N-(2-oxocyclohexyl)acetamide (**40**)*

Compound **40** was prepared from compound **46** using the procedure described above for the compound **39**. Yield 20.3 g, 72%. White solid. Mp 69–70 °C. R_f = 0.37 (hexanes – EtOAc (4:1)). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.42 (br s, 1H), 4.44 (dt, *J* = 12.3, 6.0 Hz, 1H), 2.71 (dtd, *J* = 12.3, 6.0, 3.0 Hz, 1H), 2.58 (ddt, *J* = 13.5, 4.2, 2.1 Hz, 1H), 2.42 (app. td, *J* = 13.6, 6.3 Hz, 1H), 2.24 – 2.12 (m, 1H), 1.97 – 1.88 (m, 1H), 1.88 – 1.73 (m, 1H), 1.73 – 1.59 (m, 1H), 1.43 (app. qd, *J* = 12.7, 3.9 Hz, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ = ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.0, 156.0 (q, *J* = 37.3 Hz), 115.2 (q, *J* = 287 Hz). 57.8, 40.5, 34.0, 27.5, 23.5. ^{19}F NMR (DMSO-d_6, 376 MHz): δ –78.8. MS (EI): *m*/z = 209 (M^+). Anal. Calcd. for $C_8H_{10}F_3NO_2$: C, 45.94; H, 4.82; N, 6.70. Found: C, 46.18; H, 4.50; N, 6.52.

*4.26. N-(2,2-Difluorocyclopentyl)-2,2,2-trifluoroacetamide (**43**)*

Ketone **39** (5.00 g, 25.6 mmol) was dissolved in CH_2Cl_2 (150 mL) under argon atmosphere, and the solution was cooled to –70 °C. DAST (10.3 g, 64.0 mmol) was added dropwise at this temperature. The reaction mixture was slowly warmed to rt and stirred for 24 h. DAST (4.12 g, 25.6 mmol) was added, and the resulting mixture was stirred overnight (monitored by NMR). Saturated aq $NaHCO_3$ was added dropwise to pH = 8, and the phases were separated. The organic layer was dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by column chromatography (hexanes – EtOAc (4:1) as eluent); ^{19}F NMR was used for the product detection). Yield 2.59 g, 46%. White solid. Mp 72–74 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ =6.51 (br s, 1H), 4.55 – 4.34 (m, 1H), 2.39 – 2.11 (m, 3H), 1.99 – 1.76 (m, 2H), 1.74 – 1.57 (m, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 156.6 (q, *J* = 37.4 Hz), 127.8 (dd, *J* = 258, 248 Hz), 115.2 (q, *J* = 287 Hz), 54.4 (dd, *J* = 26.1, 19.8 Hz), 32.5 (t, *J* = 23.5 Hz), 28.8 (d, *J* = 6.1 Hz), 17.8 (dd, *J* = 5.6, 3.1 Hz). ^{19}F NMR ($CDCl_3$,

376 MHz): δ = –79.0, –107.4 (d, *J* = 230 Hz), –108.9 (ddd, *J* = 229, 36.3, 20.0 Hz). MS (EI): *m*/z = 217 (M^+), 197 (M^+–HF), 152 ($CF_3C(O)NHCH{=}CHCH_2^+$). Anal. Calcd. for $C_7H_8F_5NO$: C, 38.72; H, 3.71; N, 6.45. Found: C, 38.45; H, 3.79; N, 6.08.

*4.27. N-(2,2-Difluorocyclohexyl)-2,2,2-trifluoroacetamide (**44**)*

Compound **44** was prepared from compound **40** using the procedure described above for the compound **43**. Yield 2.63 g, 48%. White solid. Mp 106–107 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.52 (br s, 1H), 4.35 – 4.10 (m, 1H), 2.31 – 2.16 (m, 1H), 2.10 – 1.99 (m, 1H), 1.89 – .77 (m, 2H), 1.80 – 1.65 (m, 1H), 1.61 – 1.34 (m, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 156.7 (q, *J* = 37.5 Hz), 120.8 (dd, *J* = 249, 241 Hz), 115.2 (q, *J* = 287 Hz), 52.0 (t, *J* = 20.7 Hz), 33.2 (dd, *J* = 24.1, 20.4 Hz), 29.4 (d, *J* = 5.4 Hz), 23.1, 21.8 (d, *J* = 9.3 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz): δ = –79.0, –103.6 (d, *J* = 244 Hz), –120.5 (br d, *J* = 244 Hz). MS (EI): *m*/z = 231 (M^+), 211 (M^+–HF), 152 ($CF_3C(O)NHCH{=}CHCH_2^+$). Anal. Calcd. for $C_8H_{10}F_5NO$: C, 41.57; H, 4.36; N, 6.06. Found: C, 41.82; H, 4.41; N, 6.24.

*4.28. 2,2-Difluorocyclopentanamine hydrochloride (**20**·HCl)*

Amide **43** (1.28 g, 5.90 mmol) was dissolved in MeOH (5 mL), and aq HCl (30%, 5 mL) was added. The reaction mixture was stirred at 35 °C overnight, and then evaporated to dryness. The residue was triturated with Et_2O (5 mL), filtered and dried in vacuo. Yield 0.746 g, 80%. Brownish solid. Mp 178–181 °C (dec.). ^{1}H NMR (D_2O, 400 MHz): δ = 3.98 – 3.82 (m, 1H), 2.44 – 2.17 (m, 3H), 2.04 – 1.79 (m, 3H). ^{13}C NMR (DMSO-d_6, 101 MHz): δ = 129.0 (dd, *J* = 254, 253 Hz), 53.7 (dd, *J* = 30.5, 20.1 Hz), 32.9 (t, *J* = 23.1 Hz), 27.3 (d, *J* = 4.7 Hz), 18.4 (t, *J* = 4.4 Hz). ^{19}F NMR (DMSO-d_6, 376 MHz): –98.1 (dq, *J* = 231, 13.3 Hz), –105.2 (dq, *J* = 231, 14.3 Hz). MS (EI): *m*/z = 121 (M^+), 56 ($CH_2{=}CH{-}CH{=}NH_2^+$). Anal. Calcd. for $C_5H_{10}ClF_2N$: C, 38.11; H, 6.4; N, 8.89; Cl, 22.50. Found: C, 38.06; H, 6.62; N, 9.26; Cl, 22.67

*4.29. 2,2-Difluorocyclohexanamine hydrochloride (**21**·HCl)*

Compound **21**·HCl was prepared from compound **44** using the procedure described above for the compound **20**·HCl. Yield 0.627 g, 72%. Brownish solid. Mp 239–242 °C (dec.). ^{1}H NMR (D_2O, 400 MHz): δ = 3.69 – 3.53 (m, 1H), 2.33 – 2.17 (m, 1H), 2.08 (dd, *J* = 8.4, 3.9 Hz, 1H), 1.92 – 1.71 (m, 3H), 1.68 – 1.55 (m, 1H), 1.55 – 1.32 (m, 2H). ^{13}C NMR (D_2O, 101 MHz): δ = 118.6 (t, *J* = 244 Hz), 50.4 (t, *J* = 21.5 Hz), 29.5 (t, *J* = 21.3 Hz), 24.6 (d, *J* = 3.9 Hz), 19.5, 18.7 (dd, *J* = 9.4, 3.2 Hz). ^{19}F NMR (DMSO-d_6, 376 MHz): δ = –98.8 (d, *J* = 239 Hz), –114.7 (br d, *J* = 239 Hz). MS (EI): *m*/z = 135 (M^+), 56 ($CH_2{=}CH{-}CH{=}NH_2^+$). Anal. Calcd. for $C_6H_{12}ClF_2N$: C, 41.99; H, 7.05; N, 8.16; Cl, 20.66. Found: C, 41.94; H, 7.27; N, 7.79; Cl, 20.57.

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