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Last of the *gem*-Difluorocycloalkanes 2: Synthesis of Fluorinated Cycloheptane Building Blocks

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The *gem*-difluorocycloalkane family was extended to all possible regioisomers of the *gem*-difluorocycloheptane, monofunctionalized by carboxilic-, amino- or keto- group, that were synthesized on a multigram scale. The preparation of the corresponding building blocks was achieved from readily accessible starting materials either via six-membered ring homologation or deoxofluorination of the appropriate seven-membered cyclic ketones.

Introduction

Fluorinated substituents have found a broad application in medicinal chemistry[1–5] and chemical biology,[6,7] and have become outstanding isosteric replacements for diverse functional groups.[8,9] Introduction of fluorine atoms is commonly used for the modulation of physicochemical and pharmacokinetic properties, potency, and selectivity. A prominent feature of such optimization is the possibility to control the degree of various properties alteration by rational selection of the fluorinated fragment along with position the most suitable to introduce it.[10–13] Therefore, the design and synthesis of new fine-tuned fluorinated motifs have become a promising topic with a great potential for application in other research fields.[14]

Mono-, di- and polyfluoro-substituted cycloalkanes are among the most attractive types of fluorinated compounds which have gained increased attention recently. The decreased conformational flexibility of cycloalkane scaffolds can be used to fix the spatial orientation of the dipole moments of both fluorinated fragments and additional functional groups. For example, O'Hagan and colleagues implemented this approach into the design of facially-polarized 'Janus face' all-*cis* trifluorocyclopropanes **1**,[15] tetrafluorocyclohexanes **2** (and their penta- and hexa-fluorinated analogs),[16–19] as well as tetrafluorocyclohexane derivatives **3**[20] containing two *gem*-difluoromethylene moieties (Figure 1A).

Gem-difluorocyclohexane and *gem*-difluorocyclobutane motifs present in marketed drugs maraviroc[21] and ivosidenib[22] (approved in 2007 and 2018, respectively, Figure 1B) are the representative compounds with the fluorinated cycloalkane substituents that have already found successful application in medicinal chemistry.

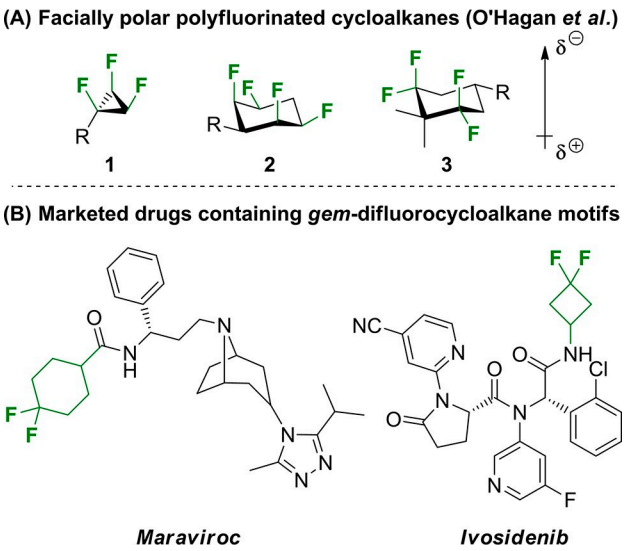

Figure 1. Face-polarized trifluorocyclopropanes and tetrafluorocyclohexanes reported by O'Hagan *et al.* (**A**); marketed drugs containing *gem*-difluorocyclohexane and *gem*-difluorocyclobutane motifs (**B**)

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All the aforementioned works motivated us to develop convenient synthetic routes to all isomeric *gem*-difluorocycloalkanes which can be used to access multigram quantities of the corresponding building blocks. To date, we have reported the preparation of three-to-six-membered fluorinated alicyclic compounds.[23–28] Yet, a Reaxys database search[29] has revealed that the synthesis and application of higher homologs – *gem*-difluorinated cycloheptane derivatives – remain to be scarcely explored both in papers[30–32] and patents (Figure 2A). Meanwhile, it should be stressed that the aforementioned cycloheptane building blocks are not just other representatives of the *gem*-difluorocycloalkane homologous series. Recently, we have shown that seven-membered rings provide a unique three-dimensional disposition of the functional groups attached that cannot easily be achieved by lower homologs.[33] Therefore, *gem*-difluorinated cycloheptanes can be considered as promising building blocks for drug discovery that substantially extend possible relative orientations of the corresponding functional moieties present in their molecules.

In this work, we describe the straightforward and efficient synthesis of *gem*-difluorocycloheptanes monofunctionalized by carboxilic-, amino- or keto- group in α-, β- or γ- position on a multigram scale (Figure 2B). In particular, we have focused on the preparation of the corresponding carboxylic acids **4**, **7**, **10**, amine derivatives **5**, **8**, **11**, and ketones **6**, **9**, **12** due to the versatile utility of these functional groups in medicinal chemistry. Noteworthy (and somewhat unexpectedly), the previous methodologies for the synthesis of the corresponding five- and six-membered counterparts appeared not to be applicable for the preparation of building blocks **4**–**12**; therefore, the development of different synthetic pathways was required for these compounds.

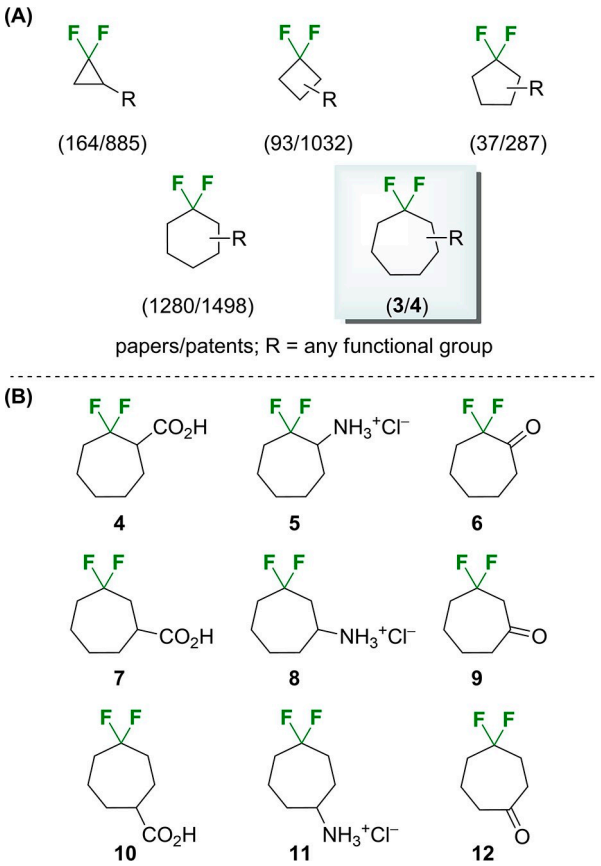
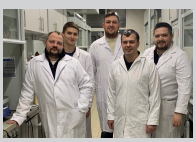


Figure 2. (**A**) *Reaxys*® database search of papers/patents referencing monosubstituted *gem*-difluorocycloalkanes; (**B**) structures of *gem*-difluorocycloheptane building blocks obtained in this work.

Prof. Dr. Sergey V. Ryabukhin is a Professor at the Institute of High Technologies, Kyiv National Taras Shevchenko University. He was awarded his Ph.D. by Kyiv National University in 2008 and obtained Dr. Sci. in 2018. He has 10+ years' experience in managing combinatorial chemistry departments as well as chemical outsourcing projects having previously worked in contract research organizations (2005–2010: Director of Combinatorial Chemistry department at Enamine Ltd., 2010–2014: Vice-President at Curplyx–Macrochem, 2014–2017: CRO Curpys Chemicals). Now he is also working at Enamine Ltd. as a senior scientific advisor. Dr. Ryabukhin is an expert in combinatorial and medicinal chemistry, organometallics, heterocyclic chemistry, new methodologies in organic synthesis. He has a strong collaboration with numerous synthetic scientific groups at both Enamine Ltd and Kyiv National Taras Shevchenko University.



This paper is a result of such collaboration with his perennial friend, colleague, and co-author Prof. Dr. Dmitriy M. Volochnyuk, the scientific group of Dr. Kostiantyn P. Melnykov, who was obtained his Ph.D. degree in 2019 under his supervision, and the team of young perspective postgraduate Dmytro V. Yarmoliuk. All these researchers focus their interests in particular on fluorine chemistry and fluorine contained building blocks.

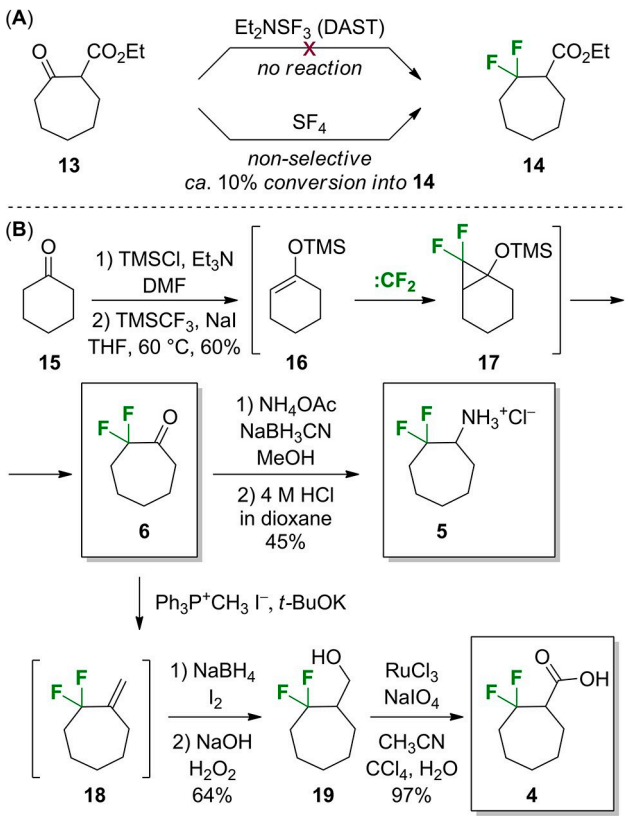
On the photo (from left to right): Prof. Dr. Dmitriy M. Volochnyuk, Maksym Herasymchuk, Dmytro V. Yarmoliuk, Dr. Kostiantyn P. Melnykov, and Prof. Dr. Sergey V. Ryabukhin.

Results and Discussion

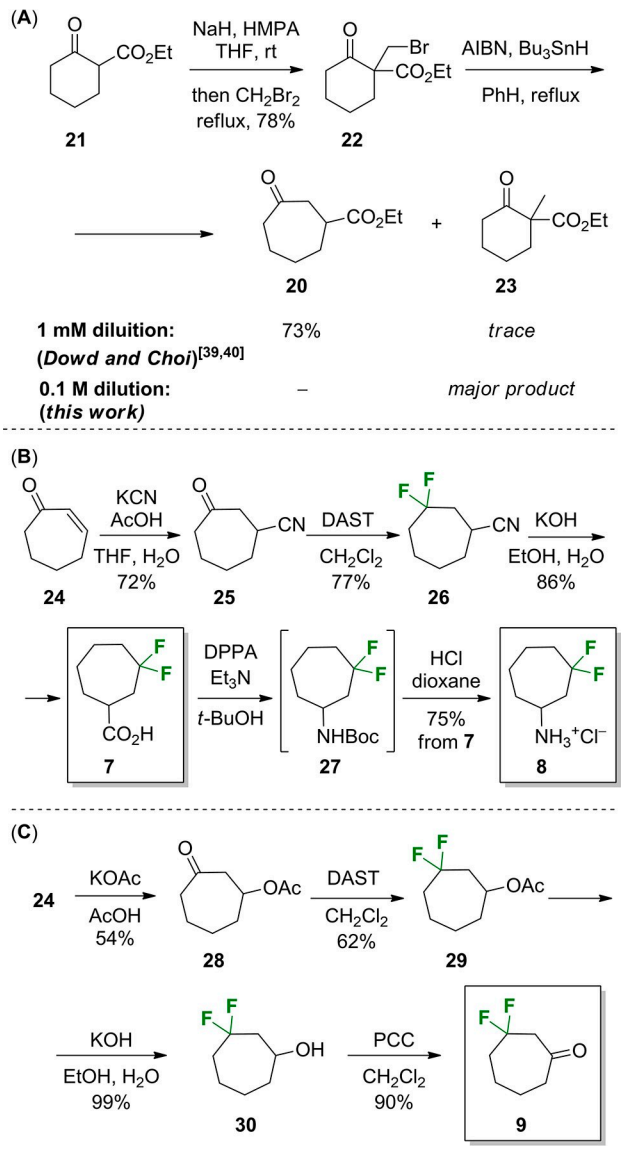
Our initial attempts to access 2,2-difluorocycloheptanecarboxylic acid **4** were based on deoxofluorination of the cycloheptanone moiety of ketoester **13** (Scheme 1A). However, no reaction took place when **13** was treated with Et_2NSF_3 (DAST). In our previous report on the deoxofluorination of β-keto esters, it was also shown that **13** reacted unselectively upon treatment with SF_4 and gave target derivative **14** with low conversion.[34] These results motivated us to examine an alternative approach – homologation of the corresponding six-membered ring derivatives.

A facile transformation of cyclohexanone (**15**) into 2,2-difluoro-substituted cycloheptanone **6** (Scheme 1B) was previously described by Amii and colleagues.[35] In their work, $BrCF_2CO_2Na$ was used as the difluorocarbene source that was added to silyl enol ether **16** at 150 °C to give siloxydifluorocyclopropane intermediate **17**. In contrast to Amii's report, herein we suggested the application of the $TMSCF_3$–NaI system for the formation of difluorocarbene under milder conditions.[26,27,36–38] With this system, up to 150 g of **6** could be obtained in one load (60% yield from **15**). Next reductive amination of **6** followed by treatment with 4 M HCl in dioxane allowed access to the target amine derivative **5** in 45% yield. Furthermore, 2,2-difluorocycloheptanone (**6**) was also used as a synthetic intermediate for the preparation of carboxylic acid **4**. In this case, Wittig olefination of **6** followed by hydroboration–oxidation of **18** gave alcohol **19** (64% yield from **6**) that was further oxidized to carboxylic acid **4** with high (97%) yield using $RuCl_3$–$NaIO_4$ system.

Synthesis of 3,3-difluorocycloheptanecarboxylic acid **7** commenced from testing the possibility of scaling up the procedure that was previously reported by Dowd and Choi (Scheme 2A).[39,40] According to their work, a milligram amount of ester **20** was obtained by alkylation of β-keto ester **21** followed by AIBN-promoted radical rearrangement of **22**. It was shown that this transformation proceeded with the formation of **20** (73% yield) in a mixture with a trace amount of **23** under high dilution conditions (1 mM solution of *n*-Bu_3SnH) or upon prolonged addition of *n*-Bu_3SnH using a syringe pump (10 mM solution). However, all our attempts to decrease the dilution level and adjust the reported procedure for the synthesis of **20** on the multigram scale were



Scheme 1. (**A**) Unsuccessful attempts of deoxofluorination of β-keto ester **13**; (**B**) synthesis of *gem*-difluorocycloheptane derivatives **4**–**6**.



Scheme 2. (**A**) Unsuccessful attempts of preparation of **20** by AIBN-promoted radical rearrangement of **22**; (**B**) synthesis of *gem*-difluorocycloheptane derivatives **7**, **8**, (**C**), and **9**.

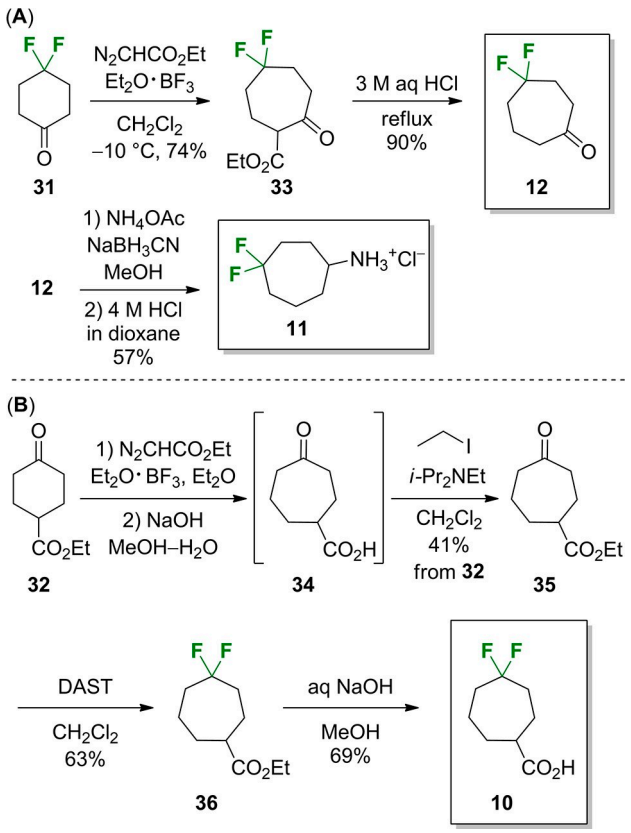
unsuccessful and led to the predominant formation of **23**. Therefore, the six-membered ring homologation strategy was abandoned in the case of fluorinated cycloheptane derivative **7**.

Meanwhile, the application of cyclohept-2-enone (**24**) as a starting material for the synthesis of fluorinated cycloheptanes **7**–**9** appeared to be a convenient alternative and allowed us to obtain carboxylic acid **7** in just three steps (Scheme 2B). Hydrocyanation of **24** followed by deoxofluorination of **25** with DAST was used to form *gem*-difluorocycloheptane-derived nitrile **26** (55% yield over two steps). Next alkaline hydrolysis of **26** gave the target compound **7** in 86% yield. Derivative **7** was further converted into amine hydrochloride **8** by Curtius rearrangement – Boc-deprotection of **27** in 75% overall yield.

Analogously, 3,3-difluorocycloheptanone (**9**) was prepared in just four synthetic steps starting from **24** (Scheme 2C). Sequential addition of HOAc to **24** (54% yield) and deoxofluorination of **28** with DAST (62% yield) provided fluorinated intermediate **29**. After alkaline hydrolysis of **29**, the resulting alcohol **30** was subjected to an oxidation reaction using PCC to give target ketone **9** in 89% yield over two steps.

Finally, the remaining *gem*-difluorocycloheptane derivatives **10**–**12** were obtained from either cyclohexanone substrate **31** or **32** by ring homologation using diazoalkane reagent (Scheme 3A). Treatment of 4,4-difluorocyclohexanone (**31**) with ethyl diazoacetate followed by acidic hydrolysis and decarboxylation of **33** was used for the preparation of 4,4-difluorocycloheptanone (**12**) (67% over two steps). The next reductive amination of **12** along with protonation in 4 M HCl solution in 1,4-dioxane provided target product **11** in 57% yield.

Alternatively, ring homologation of ethyl 4-oxocyclohexanecarboxylate (**32**) followed by diester hydrolysis and decarboxylation under basic conditions was carried out for the preparation of seven-membered δ-keto carboxylic acid **34** (Scheme 3B). Compound **34** was further converted into ester **35** (41% yield from **32**) and next subjected to deoxofluorination step using DAST (63% yield). Alkaline hydrolysis of the obtained intermediate **36** allowed to obtain carboxylic acid **10** in 69% yield.



Scheme 3. (**A**) Synthesis of *gem*-difluorocycloheptane derivatives **12**, **11**, (**B**) and **10**.

Conclusions

A previously synthesized library of three-to-six membered cycloalkanes bearing a *gem*-difluoromethylene moiety was complemented with nine functionalized *gem*-difluorocycloheptane derivatives. The target building blocks were obtained in two to six synthetic steps from commercially available starting materials. Three strategies were used to access the target compounds with the additional group in a variable position: cyclohexanone homologation with difluorocarbene for the preparation of 1-functionalized 2,2-difluoro-substituted cycloheptanes (27–60% overall yield), cyclohept-2-enone functionalization/deoxofluorination – for 3,3-difluoro-substituted cycloheptanes (30–48% yield), and homologation of either fluorinated or non-fluorinated cyclohexanones using diazoalkane reagent – for 4,4-difluoro-substituted cycloheptanes (18–67% yield). The described synthetic approaches allowed us to obtain target products on multigram scale (up to 133 g). The accessed fluorinated motifs present a great interest in medicinal chemistry and can be potentially used in drug optimization programs.

Experimental Section

General methods

The solvents were purified according to the standard procedures.[41] Melting points were measured on MPA100 OptiMelt automated melting point system. 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, ^{19}F, and ^{13}C NMR spectra were recorded at 500 MHz or 400 MHz, 470 or 376 MHz, and 126 MHz or 101 MHz, respectively. Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, Taras Shevchenko National University of Kyiv. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization (APCI), electrospray ionization (ESI)) and Agilent 5890 Series II 5972 GCMS instrument (electron impact ionization (EI)).

2,2-Difluorocycloheptanone (6)

Compound **15** (161 g, 1.64 mol) and triethylamine (180 mL, 2.46 mol) were dissolved in DMF (2.5 L), and Me_3SiCl (184 mL, 1.97 mol) was added in one portion. The mixture was stirred at 80 °C for 12 h. The mixture was cooled to rt, poured into ice-cold water (2.5 L), and then washed with hexane (5×800 mL). The combined organic phases were washed with ice-cold water (3× 500 mL) and brine (2×400 mL), dried over Na_2SO_4, filtered, and concentrated to obtain compound **16** (250 g) as an orange liquid.

Crude product **16** (250 g) and NaI (44.0 g, 0.294 mol) were dissolved in THF (3 L) in a conical flat-bottomed flask, and CF_3SiMe_3 (402 mL, 2.94 mol) was added (CAUTION! The reaction may proceed too vigorously at the higher scale, so that further scale-up should be avoided). The reaction mixture was heated carefully to 61 °C in an oil bath upon stirring. When the reaction started, the stirring was stopped; shortly after, a vigorous reaction occurred that caused boiling of the solution. After that, the external heating was continued for additional 18 h. Then the mixture was cooled to rt and evaporated. The residue was dissolved in *t*-BuOMe (1400 mL) and stirred for 15 min. The precipitate was filtered off, and the solution was concentrated to give **17** (283 g) that was used further without purification.

Crude product **17** (283 g) was dissolved in MeOH (4 L), and Na_2CO_3 (136 g, 1.28 mol) was added. The mixture was stirred at rt for 30 min, the inorganic sludge was filtered off, and the filtrate was concentrated under reduced pressure. The residue was dissolved in *t*-BuOMe (1.5 L) and washed with water (3×400 mL). The organic phase was dried over Na_2SO_4, filtered, and evaporated in vacuo. The crude product was subjected to column chromatography (gradient hexane to hexane – *t*-BuOMe (85:15) as eluent) to produce compound **6**. Yield 133 g (55% over 3 steps). Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.66 (t, J=6.7 Hz, 2H), 2.07 (tt, J=15.2, 6.1 Hz, 2H), 1.87–1.78 (m, 2H), 1.75–1.67 (m, 2H), 1.65–1.58 (m, 2H) ppm. ^{13}C NMR (126 MHz $CDCl_3$) δ 201.4 (t, J=27.3 Hz), 118.7 (t, J= 250.9 Hz), 39.0, 33.9 (t, J=23.9 Hz), 27.7, 23.7, 23.0 (t, J=5.8 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ −105.5 ppm. MS (EI): m/z=148 $[M]^+$. Anal. Calcd. for $C_7H_{10}F_2O$: C 56.75; H 6.80. Found: C 56.35; H 6.78.

2,2-Difluorocycloheptanaminium chloride (5)

Compound **6** (94.7 g, 0.640 mol) was dissolved in MeOH (3.5 L), and ammonium acetate (493 g, 6.40 mol) was added. The reaction mixture was stirred at rt for 1 h, then $NaBH_3CN$ (121 g, 1.93 mol) was added in five nearly equal portions, and the mixture was stirred for 18 h. The mixture was concentrated, diluted with water (1.2 L), and 10% aq NaOH was added to pH=12. The aqueous phase was extracted with CH_2Cl_2 (3×500 mL), the combined organic phases were dried over Na_2SO_4 and filtered. 4 M HCl in dioxane (750 mL) was added to the CH_2Cl_2 solution, and the precipitate formed was filtered to give **5**. Yield 53.6 g (45%). White solid, mp 144–146 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (s, 3H), 3.66 (dt, J=19.5, 8.6 Hz, 1H), 2.26–2.04 (m, 2H), 1.99–1.87 (m, 1H), 1.82–1.72 (m, 1H), 1.71–1.36 (m, 6H) ppm. ^{13}C NMR (151 MHz, DMSO-d_6) δ 124.0 (dd, J= 247.1, 242.8 Hz), 55.3 (dd, J=25.8, 21.9 Hz), 33.9 (t, J=23.7 Hz), 26.1, 26.0, 23.0, 18.9 (t, J=6.4 Hz) ppm. ^{19}F NMR (376 MHz, DMSO-d_6) δ −88.8 (d, J=240.6 Hz), −106.2 (d, J=240.6 Hz) ppm. MS (APCI): m/z=150 $[M–Cl]^+$. Anal. Calcd. for $C_7H_{14}ClF_2N$: C 45.29; H 7.60; N 7.55; Cl 19.10. Found: C 45.34; H 7.93; N 7.37; Cl 19.44.

(2,2-Difluorocycloheptyl)methanol (19)

To a suspension of triphenylphosphonium iodide (15.0 g, 37.1 mmol) in THF (100 mL), *t*-BuOK (4.00 g, 35.6 mmol) was added at 0–5 °C, and the mixture was stirred for 30 min. A solution of ketone **6** (5.00 g, 33.8 mmol) in THF (50 mL) was added dropwise at the same temperature. The reaction mixture was stirred at 0–5 °C for 15 min and at rt for 4 h (monitored by ^{19}F NMR spectra). After the starting material disappeared, the reaction mixture was filtered, and the filtrate containing **18** was used in the next step. A solution of I_2 (10.3 g, 40.5 mmol) in THF (100 mL) was added to a suspension of powdered $NaBH_4$ (3.20 g, 84.4 mmol) in THF (70 mL) dropwise at rt. The reaction mixture was stirred for 30 min, which was accompanied by discoloring. Then, the solution of alkene **18** in THF was added dropwise over 10 min, and the resulting mixture was stirred for 90 min (monitored by ^{19}F NMR spectra). 3 M aq NaOH (45 mL) was added dropwise over 30 min (CAUTION! Exothermic reaction). Then, 30% aq H_2O_2 (16 mL) was added dropwise over the next 30 min. The resulting mixture was stirred at rt for 1 h, diluted with brine (200 mL), and extracted with EtOAc (3×100 mL). The combined organic layers were evaporated in vacuo, and the residue was redissolved in CH_2Cl_2 (150 mL). The traces of water were separated; the organic layer was dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by column chromatography to give **19**. Yield 3.55 g (64%). Yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.87 (dd, J=11.3, 5.3 Hz, 1H), 3.63 (t, J= 11.3, 6.2 Hz, 1H), 2.18–1.96 (m, 3H), 1.95–1.83 (m, 2H), 1.78–1.71 (m, 2H), 1.70–1.63 (m, 1H), 1.54–1.48 (m, 1H), 1.47–1.39 (m, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 128.2 (dd, J=243.3, 241.7 Hz), 62.4 (dd, J=8.7, 3.2 Hz), 49.6 (t, J=22.2 Hz), 37.8 (t, J=26.0 Hz), 28.7, 27.6, 25.1 (d, J=8.9 Hz), 20.9 (dd, J=8.3, 4.9 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ −86.5 (d, J=242.6 Hz), −102.1 (d, J=242.6 Hz) ppm. MS (EI): m/z=144 $[M–HF]^+$, 114 $[M–HF–CH_2O]^+$. Anal. Calcd. for $C_8H_{14}F_2O$: C 58.52; H 8.59. Found: C 58.36; H 8.36.

2,2-Difluorocycloheptanecarboxylic Acid (4)

To a mixture of alcohol **19** (3.80 g, 23.1 mmol) and $NaIO_4$ (19.8 g, 92.6 mmol) in CCl_4 (40 mL), CH_3CN (40 mL), H_2O (60 mL), and $RuCl_3{\cdot}xH_2O$ (0.260 g, 1.16 mmol) were added, the mixture was stirred at rt for 2 h and neutralized with saturated aq. $NaHCO_3$ (30 mL). The precipitate was filtered and washed with H_2O (20 mL). The combined filtrates were extracted with $CHCl_3$ (2×25 mL), the aqueous phase was separated, acidified with 10% aq $NaHSO_4$ to pH=3, and extracted with EtOAc (3×40 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give **4**. Yield 4.00 g (97%). Colorless solid, mp 51–53 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.60 (s, 1H), 3.09 (dtd, J=17.2, 9.6, 3.6 Hz, 1H), 2.36–2.07 (m, 2H), 2.04–1.78 (m, 3H), 1.77–1.64 (m, 2H), 1.61–1.45 (m, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.0 (d, J=6.8 Hz), 124.5 (dd, J=246.6, 243.0 Hz), 52.8 (dd, J= 26.8, 23.9 Hz), 36.8 (t, J=25.1 Hz), 27.4, 25.8, 25.2 (t, J=4.5 Hz), 20.7 (dd, J=8.2, 4.8 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ −85.8 (d, J= 249.0 Hz), −93.1 (d, J=249.0 Hz) ppm. MS (APCI): m/z=177 $[M–H]^-$. Anal. Calcd. for $C_8H_{12}F_2O_2$: C 53.93; H 6.79. Found: C 53.76; H 6.85.

3-Oxocycloheptanecarbonitrile (25)[42]

A mixture of cyclohept-2-enone (100 g, 91% purity, 0.908 mol) and AcOH (55 mL, 0.960 mol) in THF (1.8 L) was added to a solution of KCN (117 g, 1.80 mol) in H_2O (300 mL). The reaction mixture was stirred at 80 °C overnight, cooled to rt, and diluted with H_2O (1.8 L). The resulting solution was extracted with CH_2Cl_2 (3×1 L). The combined organic layers were dried over anhydrous Na_2SO_4 and then concentrated under vacuo. The obtained residue was dissolved in *t*-BuOMe (1 L) and filtered through a plug of silica gel

(800 g) that was washed with additional *t*-BuOMe (1 L). The resulting solution was concentrated *in vacuo* to give the crude product with 90% purity (110 g). Purification of the title compound was performed by vacuo distillation (120 °C/0.5 mbar). Yield 90.8 g (72%). Yellow oil, bp = 120 °C/0.5 mbar. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.05–2.93 (m, 1H), 2.86–2.71 (m, 2H), 2.68–2.57 (m, 1H), 2.55–2.46 (m, 1H), 2.03–1.89 (m, 3H), 1.81–1.67 (m, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.1, 120.8, 45.5, 43.7, 33.4, 27.4, 26.7, 23.5 ppm. MS (EI): *m/z* = 137 $[M]^+$. Anal. Calcd. for $C_8H_{11}NO$: C 70.04; H 8.08; N 10.21. Found: C 69.78; H 7.74; N 10.07.

3,3-Difluorocycloheptanecarbonitrile (26)

To a solution of ketone **25** (25.0 g, 182 mmol) in CH_2Cl_2 (1 L), Et_2NSF_3 (DAST, 146.8 g, 911 mmol) was added dropwise at rt. The reaction mixture was stirred at 40 °C for 48 h and then poured into sat aq $NaHCO_3$ (1 L). After stirring for 30 min, the layers were separated and aqueous phase was extracted with CH_2Cl_2 (2× 400 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and then concentrated under vacuo to give 27.5 g of the crude product. Purification of the title compound was performed by column chromatography (hexanes – EtOAc (40:1) as eluent, R_f = 0.30).Yield 22.3 g (77%). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.89 (t, *J* = 9.2 Hz, 1H), 2.57–2.27 (m, 2H), 2.19–2.03 (m, 3H), 1.98–1.78 (m, 2H), 1.72–1.58 (m, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 124.4 (t, *J* = 241.0 Hz), 121.4, 40.2 (t, *J* = 29.3 Hz), 37.3 (t, *J* = 26.0 Hz), 32.3, 26.1, 24.7 (dd, *J* = 10.2, 5.4 Hz), 20.7 (dd, *J* = 7.8, 4.8 Hz) ppm. ^{19}F NMR (470 MHz, $CDCl_3$) δ −85.0 (ddq, *J* = 249.5, 22.1, 11.0 Hz), −90.3 (dtt, *J* = 249.5, 23.5, 13.0 Hz) ppm. MS (EI): *m/z* = 159 $[M]^+$. Anal. Calcd. for $C_8H_{11}F_2N$: C 60.36; H 6.97; N 8.80. Found: C 60.52; H 7.34; N 8.88.

3,3-Difluorocycloheptanecarboxylic acid (7)

A solution of KOH (35.2 g, 628 mmol) in H_2O (200 mL) was added to a solution of nitrile **26** (20.0 g, 126 mmol) in EtOH (200 mL), and the solution was heated at 70 °C for 72 h. The resulting solution was allowed to cool to rt and concentrated under reduced pressure. The residue was diluted with H_2O (200 mL) and washed with CH_2Cl_2 (150 mL). The aqueous layer was then separated, acidified with $NaHSO_4$ and extracted with CH_2Cl_2 (3×200 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and then concentrated under vacuo to give pure product. Yield 19.2 g (86%). Yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.54 (br s, 1H), 2.65 (t, *J* = 10.8 Hz, 1H), 2.49 (q, *J* = 12.9 Hz, 1H), 2.25–1.99 (m, 4H), 1.85–1.74 (m, 1H), 1.73–1.51 (m, 4H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 181.7, 125.4 (dd, *J* = 239.3, 239.2 Hz), 39.1 (dd, *J* = 29.3, 27.5 Hz), 38.7 (d, *J* = 10.9 Hz), 37.8 (t, *J* = 26.2 Hz), 31.6, 26.8, 21.1 (t, *J* = 6.3 Hz) ppm. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ −84.3 (d, *J* = 244.7 Hz), −91.8 (d, *J* = 244.7 Hz) ppm. MS (APCI): *m/z* = 177 $[M–H]^-$. Anal. Calcd. for $C_8H_{12}F_2O_2$: C 53.93; H 6.79. Found: C 54.22; H 6.92.

tert-Butyl (3,3-difluorocycloheptyl)carbamate (27)

To a solution of carboxylic acid **7** (9.50 g, 53.3 mmol) in *t*-BuOH (100 mL), Et_3N (6.40 g, 63.9 mmol) was added and was followed by the addition of $(PhO)_2P(O)N_3$ (DPPA, 17.6 g, 63.9 mmol). After heating the reaction mixture at 80 °C for 18 h, it was allowed to cool to rt and was concentrated under reduced pressure. The residue was dissolved in *t*-BuOMe (200 mL), washed with sat aq Na_2CO_3 (2×100 mL) and with aq $NaHSO_4$ (100 mL), dried over anhydrous Na_2SO_4 and then concentrated under vacuo. The crude product (12.1 g) was used in the next step without additional purification. An analytical sample was obtained after purification by column chromatography (hexanes – EtOAc (4:1) as eluent, R_f = 0.39). Beige solid, mp 77–79 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.59 (s, 1H), 3.81 (s, 1H), 2.40 (q, *J* = 13.1 Hz, 1H), 2.21–1.92 (m, 4H), 1.80–1.65 (m, 2H), 1.63–1.49 (m, 3H), 1.44 (s, 9H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.9, 125.1 (dd, *J* = 241.6, 238.3 Hz), 79.6, 46.0, 44.2 (t, *J* = 25.2 Hz), 37.6 (t, *J* = 25.9 Hz), 35.7, 28.5, 25.1, 21.5 ppm. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ −86.1 (d, *J* = 247.0 Hz), −87.6 (d, *J* = 247.0 Hz) ppm. MS (EI): *m/z* = 249 $[M^+]$, 193 $[M–C(CH_3)_2CH_2]^+$, 149 $[M–CO_2–C(CH_3)_2CH_2]^+$. Anal. Calcd. for $C_{12}H_{21}F_2NO_2$: C 57.81; H 8.49; N 5.62. Found: C 57.92; H 8.56; N 5.49.

3,3-Difluorocycloheptanaminium chloride (8)

Crude compound **27** (12.1 g) was dissolved in 4 M HCl in dioxane (100 mL) and stirred at rt for 18 h. The resulting solution was concentrated under reduced pressure, and the residue was triturated with *t*-BuOMe. The solid product was filtered and dried under vacuo. Yield 7.50 g (75%) over 2 steps from **7** (9.50 g, 53.3 mmol). White solid, mp 187–189 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.31 (s, 3H), 3.36–3.31 (m, 1H), 2.48–2.42 (m, 1H), 2.39–2.23 (m, 1H), 2.20–2.08 (m, 1H), 2.07–1.93 (m, 2H), 1.83–1.69 (m, 1H), 1.69–1.55 (m, 2H), 1.55–1.39 (m, 2H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6) δ 124.8 (dd, *J* = 239.4, 239.0 Hz), 45.6 (dd, *J* = 12.7, 2.4 Hz), 41.2 (t, *J* = 28.0 Hz), 36.6 (t, *J* = 25.4 Hz), 32.7, 24.2, 20.2 (t, *J* = 6.4 Hz) ppm. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ −82.0 (d, *J* = 243.8 Hz), −87.0 (d, *J* = 243.8 Hz) ppm. MS (APCI): *m/z* = 150 $[M–Cl]^+$. Anal. Calcd. for $C_7H_{14}ClF_2N$: C 45.29; H 7.60; N 7.55; Cl 19.10. Found: C 45.58; H 7.24; N 7.88; Cl 19.30.

3-Oxocycloheptyl acetate (28)

To a solution of cyclohept-2-enone (30.0 g, 91% purity, 273 mmol) in glacial AcOH (75 mL), KOAc (30.0 g, 306 mol) was added. After the maximum conversion of 60% was achieved (7 days), the reaction mixture was neutralized carefully with saturated aq $NaHCO_3$ and extracted with CH_2Cl_2 (3×300 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and then concentrated under vacuo. The product was purified by column chromatography (hexanes – EtOAc (4:1) as eluent, R_f = 0.48). Cyclohept-2-enone (12.2 g) was also recovered from the reaction mixture (R_f = 0.81). Yield 25.3 g (54%). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.14–5.07 (m, 1H), 2.80–2.74 (m, 2H), 2.51–2.45 (m, 2H), 2.01 (s, 3H), 1.95 (q, *J* = 7.1 Hz, 1H), 1.88–1.76 (m, 2H), 1.7xt5–1.66 (m, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.4, 170.0, 69.3, 48.3, 44.4, 35.2, 24.9, 23.9, 21.2 ppm. MS (EI): *m/z* = 170 $[M]^+$, 110 $[M–CH_3CO_2H]^+$. Anal. Calcd. for $C_9H_{14}O_3$: C 63.51; H 8.29. Found: C 63.23; H 8.06.

3,3-Difluorocycloheptyl acetate (29)

Compound **28** (5.00 g, 29.4 mmol) was dissolved in CH_2Cl_2 (500 mL), and DAST (23.8 g, 148 mmol) was added dropwise at rt. The reaction mixture was stirred at 40 °C for 48 h, then DAST (4.75 g, 29.5 mmol) was added, and the mixture was stirred at the same temperature for additional 18 h. The reaction mixture was poured into saturated aq $NaHCO_3$ (1500 mL). After stirring for 30 min, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2×200 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and the solvents were removed in vacuo. The compound was purified by column chromatography (hexanes – EtOAc (20:1) as eluent, R_f = 0.45). Yield 3.51 g (62%). Yellowish oil, bp 33 °C/0.5 mbar. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.06–4.93 (m, 1H), 2.47–2.27 (m, 2H), 2.23–2.05 (m, 2H), 2.04 (s, 3H), 1.98–1.90 (m, 1H), 1.80–1.69 (m, 2H), 1.68–1.56 (m, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 124.5 (t, *J* = 239.9 Hz), 68.9 (dd, *J* = 10.1, 5.4 Hz), 43.1 (t, *J* = 27.8 Hz), 37.8 (t, *J* = 26.0 Hz), 34.2, 24.3, 21.5 (t, *J* = 6.4 Hz), 21.3 ppm.

$^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −84.4 (d, J = 245.2 Hz), −87.7 (d, J = 245.2 Hz) ppm. MS (EI): m/z = 112 $[M–CH_3CO_2H–HF]^+$. Anal. Calcd. for $C_9H_{14}F_2O_2$: C 56.24; H 7.34. Found: C 56.41; H 7.21.

3,3-Difluorocycloheptanol (30)

Compound **29** (0.300 g, 1.56 mmol) was dissolved in MeOH (5 mL), and a solution of KOH (0.360 g, 6.42 mmol) in water (2 mL) was added. The reaction mixture was stirred at rt for 1 h (monitored by TLC). MeOH was removed in vacuo, the residue was diluted with water (5 mL) and extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated in vacuo. Yield 0.231 g (99%). Yellowish oil. ^1H NMR (500 MHz, $CDCl_3$) δ 3.98 (s, 1H), 2.43 (q, J = 13.9 Hz, 1H), 2.31–2.08 (m, 2H), 2.04–1.89 (m, 2H), 1.83–1.73 (m, 1H), 1.72–1.61 (m, 2H), 1.60–1.46 (m, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 124.8 (t, J = 239.5 Hz), 66.9 (dd, J = 10.8, 4.1 Hz), 46.4 (t, J = 26.0 Hz), 38.2, 37.9 (t, J = 26.1 Hz), 24.3, 21.5 (t, J = 6.3 Hz) ppm. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −84.1 (d, J = 246.6 Hz), −87.5 (d, J = 246.6 Hz) ppm. MS (EI): m/z = 130 $[M–HF]^+$, 112 $[M–HF–H_2O]^+$. Anal. Calcd. for $C_7H_{12}F_2O$: C 55.99; H 8.05. Found: C 56.38; H 7.98.

3,3-Difluorocycloheptanone (9)

Compound **30** (100 mg, 0.667 mmol) was dissolved in CH_2Cl_2 (5 mL), and pyridinium chlorochromate (0.334 g, 1.55 mmol) was added in one portion. The reaction mixture was stirred at rt for 5 h (monitored by TLC), then filtered through a silica gel pad (1 g) that was then washed with CH_2Cl_2 (50 mL). The solvent was removed in vacuo to obtain **9**. Yield 89.8 mg (91%). Yellowish oil. ^1H NMR (400 MHz, $CDCl_3$) δ 3.10 (t, J = 14.5 Hz, 2H), 2.58–2.53 (m, 2H), 2.19 (t, J = 13.4 Hz, 2H), 1.86–1.78 (m, 4H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.5 (t, J = 7.4 Hz), 121.6 (t, J = 241.5 Hz), 52.2 (t, J = 28.0 Hz), 44.0, 38.5 (t, J = 25.5 Hz), 23.4, 23.2 (t, J = 6.4 Hz) ppm. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −91.7 ppm. MS (EI): m/z = 148 $[M]^+$, 128 $[M–HF]^+$. Anal. Calcd. for $C_7H_{10}F_2O$: C 56.75; H 6.80. Found: C 56.48; H 6.69.

Ethyl 5,5-Difluoro-2-oxocycloheptanecarboxylate (33)

A three-necked flask was charged with **31** (70.0 g, 522 mmol) and dry CH_2Cl_2 (1.4 L) under nitrogen atmosphere. The mixture was cooled to −10 °C and stirred for 15 min. Then a solution of $Et_2O{\cdot}BF_3$ (85.2 mL, 678 mmol) in CH_2Cl_2 (350 mL) was added dropwise at −10 °C. The resulting mixture was stirred at the same temperature for 10 min, and a solution of ethyl diazoacetate (72.2 mL, 678 mmol) in CH_2Cl_2 (350 mL) was added dropwise. The mixture was stirred for an additional 1 h at the same temperature, then allowed to warm to rt and quenched with 30% aq K_2CO_3 (700 mL). The organic phase was separated and washed with brine (2×500 mL), then dried over Na_2SO_4, filtered, and evaporated in vacuo. Yield 88.6 g (73%). Orangeish amorphous solid. The compound existed as *ca.* 1:2 mixture of ketone and enol tautomers. ^1H NMR (500 MHz, $CDCl_3$) δ 12.68 (s, 0.7H), 4.22 (q, J = 6.0 Hz, 2H), 3.58–3.49 (m, 0.3H), 2.81–2.71 (m, 0.3H), 2.64–2.54 (m, 0.3H), 2.51–2.41 (m, 2.7H), 2.38–2.25 (m, 0.7H), 2.23–2.12 (m, 1H), 2.09–1.99 (m, 1.7H), 1.98–1.85 (m, 1.3H), 1.37–1.24 (m, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.1 (ketone *C*O), 177.0 (enol *C*OH), 172.4 and 169.6 (*C*O_2Et), 124.4 (m, *C*F_2), 100.8 (enol *C*(COH)CO_2Et), 61.7 (*C*(CO)CO_2Et), 61.0 and 58.6 (O*C*H_2), 36.1 (t, J = 24.2 Hz) and 35.4 (t, J = 26.9 Hz, *C*H_2CF_2), 35.4 (*C*H_2CO), 33.2 (t, J = 26.3 Hz) and 32.5 (t, J = 28.0 Hz, *C*H_2CF_2), 28.0 (t, J = 6.8 Hz) and 17.8 (t, J = 6.6 Hz, *C*$H_2CH_2CF_2$), 14.4 and 14.2 (CH_3) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ −91.7 (d, J = 246.0 Hz), −96.1 (d, J = 246.0 Hz) ppm. Anal. Calcd. for $C_{10}H_{14}F_2O_3$: C 54.54; H 6.41. Found: C 54.31; H 6.81.

4,4-Difluorocycloheptanone (12)

A mixture of **33** (250 g, 1.13 mol) and 3 M aq HCl (600 mL) was heated at reflux overnight, then cooled to rt and evaporated under reduced pressure. The residue was purified by flash chromatography (gradient hexanes to hexanes – *t*-BuOMe (85:15) as eluent). Yield 150 g (90%). Yellowish liquid. ^1H NMR (400 MHz, $CDCl_3$) δ 2.62–2.51 (m, 4H), 2.23–2.03 (m, 4H), 1.92–1.81 (m, 2H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.7, 124.0 (t, J = 240.3 Hz), 43.3, 38.1 (t, J = 26.2 Hz), 35.8 (t, J = 6.6 Hz), 32.3 (t, J = 27.8 Hz), 17.7 (t, J = 6.4 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ −93.6 ppm. MS (EI): m/z = 148 $[M]^+$, 128 $[M–HF]^+$. Anal. Calcd. for $C_7H_{10}F_2O$: C 56.75; H 6.80. Found: C 56.80; H 6.84.

4,4-Difluorocycloheptanaminium chloride (11)

Compound **12** (12.0 g, 81.0 mmol) was dissolved in MeOH (350 mL). Ammonium acetate (62.4 g, 0.810 mol) was added, and the reaction mixture was stirred at rt for 30 min. Then $NaBH_3CN$ (15.3 g, 244 mmol) was added, and the resulting mixture was stirred at rt overnight, and then diluted with water (180 mL). 10% aq Na_2CO_3 was added to pH = 12, and the mixture was extracted with CH_2Cl_2 (3×100 mL). The organic phase was washed with brine (90 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. 4 M HCl in dioxane (100 mL) was added to the residue, and the resulting mixture was stirred at rt for 3 h. The precipitate was filtered, washed with diethyl ether (100 mL), and dried in vacuo. Yield 8.27 g (55%). Beige solid, mp 186–188 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 8.26 (s, 3H), 3.31–3.17 (m, 1H), 2.31–1.87 (m, 6H), 1.82–1.36 (m, 4H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6) δ 126.6 (t, J = 238.7 Hz), 50.4, 37.3 (t, J = 26.2 Hz), 32.1, 32.0 (t, J = 27.2 Hz), 24.5 (dd, J = 9.1, 4.0 Hz), 17.2 (dd, J = 6.9, 4.9 Hz) ppm. ^{19}F NMR (376 MHz, DMSO-d_6) δ −83.8 (d, J = 238.4 Hz), −85.3 (d, J = 238.4 Hz) ppm. Anal. Calcd. for $C_7H_{14}ClF_2N$: C 45.29; H 7.60; N 7.55; Cl 19.10. Found: C 44.91; H 7.45; N 7.79; Cl 19.04.

Ethyl 4-Oxocycloheptanecarboxylate (35)[43]

Ethyl 4-oxocyclohexanecarboxylate (**32**) (50.0 g, 294 mmol) was dissolved in Et_2O (750 mL) and cooled to 0 °C. A solution of BF_3-Et_2O (55 mL) in Et_2O (150 mL) was added dropwise and then a solution of ethyldiazoacetate (55 mL, 90% solution in CH_2Cl_2) in Et_2O (150 mL) was added slowly to the reaction mixture. The resulting solution was stirred at 0 °C for 2 h and then at rt for additional 2 h (monitored by ^1H NMR). After the full conversion of starting material was achieved, aq $NaHCO_3$ (1 L) was added and the mixture was stirred for 10 min. After the complete neutralization of the solution, the organic layer was separated and concentrated in vacuo. The residue was dissolved in MeOH (500 mL), a solution of NaOH (50.0 g, 1.25 mol) in H_2O (450 mL) was added and the reaction mixture was stirred for 24 h. MeOH was evaporated under vacuum. The remaining aqueous phase was washed with CH_2Cl_2 (2×200 mL), acidified with aq $NaHSO_4$ to pH = 3, and then extracted with *t*-BuOMe (3×300 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo to give crude 4-oxocycloheptanecarboxylic acid (**34**) (35.2 g, *ca.* 80% purity according to ^1H NMR) which was used in the next step without additional purification. ^1H NMR (400 MHz, $CDCl_3$) δ 10.33 (s, 1H), 2.81–2.30 (m, 5H), 2.23–2.07 (m, 2H), 2.05–1.83 (m, 2H), 1.82–1.61 (m, 2H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 214.1, 180.9, 46.2, 43.5, 41.5, 32.4, 26.1, 22.3 ppm.

i-Pr_2NEt (38.0 g, 294 mmol) was added to a solution of crude compound **34** (35.2 g, *ca.* 80% purity) in CH_2Cl_2 (500 mL). Ethyl iodide (68.8 g, 441 mmol) was added dropwise and the solution

was stirred at rt for 48 h. The resulting mixture was washed with aq $NaHSO_4$ (500 mL). The organic phase was dried over anhydrous Na_2SO_4 and solvent was removed in vacuo. The residue was purified by column chromatography using hexane:*t*-BuOMe (2:1) as eluent (R_f = 0.4) to give pure compound **35**. Yield 22.1 g (41% from compound **32**). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.13 (q, *J* = 7.1 Hz, 2H), 2.60 (ddd, *J* = 15.9, 7.3, 2.9 Hz, 1H), 2.56–2.43 (m, 4H), 2.16–2.04 (m, 2H), 2.00–1.81 (m, 2H), 1.78–1.69 (m, 1H), 1.69–1.61 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 213.7, 175.1, 60.6, 46.6, 43.6, 41.7, 32.7, 26.4, 22.5, 14.3 ppm. MS (EI): *m/z* = 184 $[M]^+$, 139 $[M–OC_2H_5]^+$. Anal. Calcd. for $C_{10}H_{16}O3$: C 65.19; H 8.75. Found: C 65.33; H 8.63.

Ethyl 4,4-Difluorocycloheptanecarboxylate (36)

Compound **35** (22.0 g, 119 mmol) was dissolved in CH_2Cl_2 (440 mL) and DAST (95.9 g, 595 mmol) was added dropwise at rt. The reaction mixture was stirred for at rt for 72 h and the 85% conversion of the starting material (according to GCMS) was achieved (the further addition of DAST (19.2 g, 119 mmol) did not influence the conversion). The resulting mixture was neutralized with aq $NaHCO_3$ (1000 mL). The organic layer was separated, filtered through a thin layer of silica and concentrated in vacuo. The residue was purified by vacuum distillation (bp 49 °C/1 mbar) to give compound **4**. Yield 15.5 g (63%). Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.17–4.09 (m, 2H), 2.58–2.50 (m, 1H), 2.27–2.08 (m, 2H), 2.06–1.89 (m, 4H), 1.85–1.70 (m, 3H), 1.60–1.51 (m, 1H), 1.30–1.22 (m, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.7, 126.4 (t, *J* = 239.5 Hz), 44.6, 38.0 (t, *J* = 26.6 Hz), 35.3 (t, *J* = 27.2 Hz), 30.8, 23.1 (t, *J* = 6.8 Hz), 19.7 (t, *J* = 6.2 Hz), 14.3 ppm. ^{19}F NMR (470 MHz, $CDCl_3$) δ −86.0 (dq, *J* = 20.1, 13.9 Hz, 1F),−86.5 (dq, *J* = 20.1, 13.9 Hz, 1F) ppm. MS (EI): *m/z* = 206 $[M]^+$, 186 $[M–HF]^+$, 161 $[M–OC_2H_5]^+$. Anal. Calcd. for $C_{10}H_{16}F_2O_2$: C 58.24; H 7.82. Found: C 58.60; H 7.84.

4,4-Difluorocycloheptanecarboxylic Acid (10)

A solution of NaOH (2.33 g, 58.2 mmol) in H_2O (4 mL) was added to the solution of ester **4** (10.0 g, 48.5 mmol) in MeOH (200 mL). The reaction mixture was stirred at rt overnight. The solution was concentrated in vacuo, the residue was diluted with water (100 mL) and then acidified with 20% aq HCl to pH = 2. The product was extracted with CH_2Cl_2 (3x75 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum to give pure product **5**. Yield 5.96 g (69%). Beige solid, mp 74–76 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.78 (br s, 1H), 2.61 (tt, *J* = 9.4, 4.9 Hz, 1H), 2.33–2.17 (m, 1H), 2.16–1.90 (m, 5H), 1.90–1.72 (m, 3H), 1.66–1.48 (m, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 182.2, 126.2 (t, *J* = 239.7 Hz), 44.2, 38.1 (t, *J* = 26.6 Hz), 35.1 (t, *J* = 27.2 Hz), 30.5, 22.8 (t, *J* = 6.8 Hz), 19.6 (t, *J* = 6.3 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ −86.9, −87.0 ppm. MS (EI): *m/z* = 158 $[M–HF]^+$. Anal. Calcd. for $C_8H_{12}F_2O_2$: C 53.93; H 6.79. Found: C 53.83; H 6.62.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Fluorine · Cycloalkane · Cycloheptane · Deoxofluorination · Building blocks

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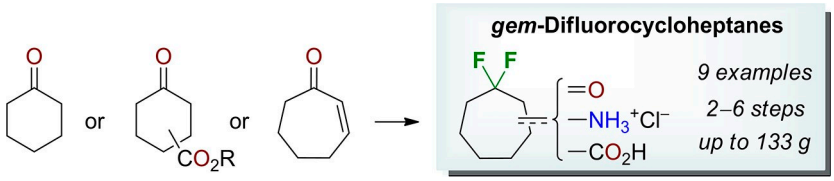

A series of isomeric *gem*-difluorocycloheptane derivatives were obtained in two to six synthetic steps from readily available starting materials. The developed synthetic approaches were shown to be efficient for a multigram-scale synthesis of target compounds and involved six-membered ring homologation and/or deoxofluorination reactions as the key steps.

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Last of the *gem*-Difluorocycloalkanes 2: Synthesis of Fluorinated Cycloheptane Building Blocks