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Multigram Synthesis of Advanced 6,6-Difluorospiro[3.3]heptane-derived Building Blocks

Oleksandr S. Olifir[a,b], Anton V. Chernykh[a], Alexey V. Dobrydnev[a,b], Oleksandr O. Grygorenko[a,b], Yuriy S. Moroz[b,c], Zoia V. Voitenko[b], and Dmytro S. Radchenko*[a]

Dedicated to 63th anniversary of Prof. Andrey A. Tolmachev

[a] O. S. Olifir, Dr. A. V. Chernykh, Dr. A. V. Dobrydnev, Dr. O. O. Grygorenko, Dr.D. S. Radchenko
Enamine Ltd. (www.enamine.net),
Chervonotkatska Street 78, Kyiv 02094, Ukraine
E-mail: dmitry.radchenko@gmail.com
[b] O. S. Olifir, Dr. A. V. Dobrydnev, Dr. O. O. Grygorenko, Prof. Dr. Z. V. Voitenko,
Taras Shevchenko National University of Kyiv
Volodymyrska Street 60, Kyiv 01601, Ukraine
[c] Dr. Y. S. Moroz
Chemspace
Ilukstes iela 38-5, Riga, LV-1082, Latvia

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Abstract: A convenient methodology for constructing 6,6-difluorospiro[3.3]heptane scaffold – a conformationally restricted isostere of *gem*-difluorocycloalkanes – is developed. A large array of novel 2-mono- and 2,2-bifunctionalized difluorospiro[3.3]heptane building blocks was obtained through the convergent synthesis strategy using a common synthetic precursor – 1,1-bis(bromomethyl)-3,3-difluorocyclobutane. The target compounds and intermediates were prepared by short reaction sequences (6–10 steps) on multigram scale (up to 0.47 kg).

Introduction

Creating new chemical entities (NCE) for drug discovery drives organic and medicinal chemists to develop structural motifs with unique characteristics that improve physico-chemical properties of drug-like molecules.[1] In this regard, the *gem*-difluoromethylene unit is of special interest[2] since it can be considered as a lipophilic bioisostere of carbonyl and many other groups.[3] Introducing the CF_2 unit into sp^3-enriched carbo- and heterocycles makes them useful scaffolds for medicinal chemistry,[4] which is confirmed by structures of FDA-approved marketed drugs Maraviroc (**1**),[5] a selective inhibitor of chemokine receptor CCR5 with anti-HIV-1 activity, and Ivosidenib (**2**)[6] used to treat acute myeloid leukemia (Figure 1).

Another trend driven by drug discovery is exploiting spiro scaffolds for fine-tuning pharmacodynamic and pharmacokinetic parameters of the parent molecule during optimization.[7] In this view, 2,5- and 2,6-functionalized spiro[3.3]heptane derivatives have been considered as structural isosteres and conformationally restricted surrogates of 1,3- or 1,4-substituted cyclohexanes, respectively (Figure 2a).[8] Moreover, a series of heteroatom-substituted azaspiro[3.3]heptanes were designed as restricted surrogates of piperidine, piperazine, morpholine, or thiomorpholine derivatives (Figure 2).[9] Further biological evaluation have revealed that replacement of six-membered monocyclic unit in a lead molecule with the corresponding spiro[3.3]heptane analog significantly improves its pharmacological profile.[9b] Specifically, the modified molecule retains its biological activity amid increased aqueous solubility and metabolic stability, while lipophilicity is reduced.

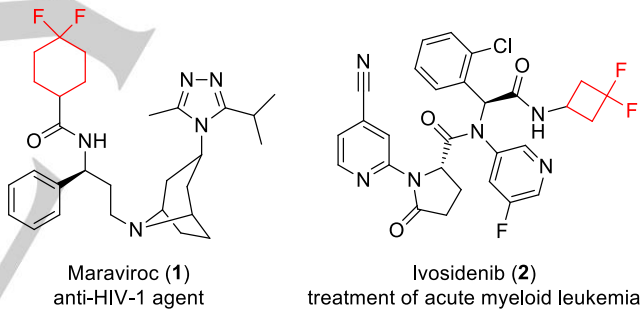


Figure 1. *gem*-Difluocycloalkanes – marketed drugs.

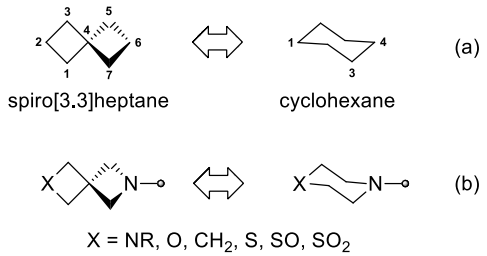
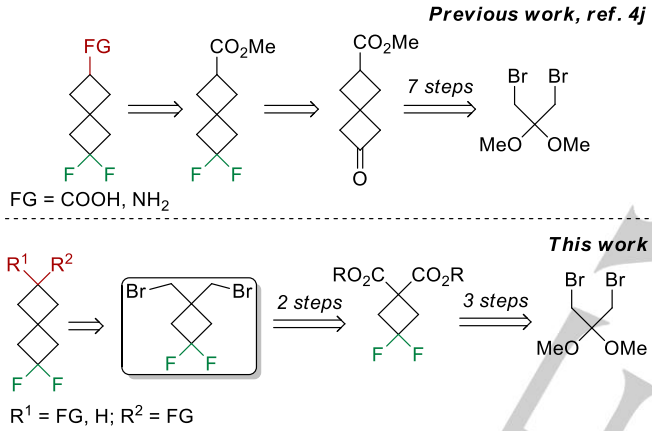


Figure 2. Spirocyclic analogues of saturated carbo- and heterocyclic six-membered rings.

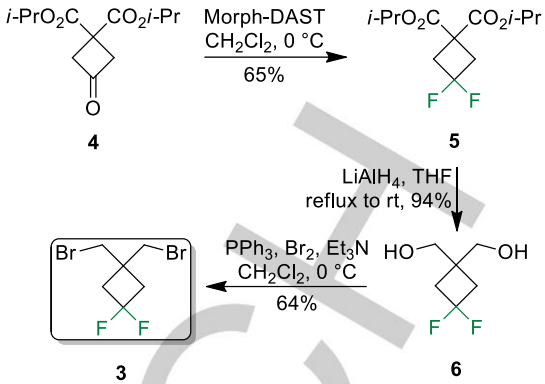
In line with the above discussion, we have turned our attention to 6,6-difluorospiro[3.3]heptane building blocks, that might be used as surrogates of *gem*-difluorocycloalkanes (including 4,4-difluorocyclohexane and 3,3-difluorocyclobutane derivatives like those shown in Figure 1). Previously we have disclosed synthesis of 6,6-difluorospiro[3.3]heptan-2-amine and 6,6-difluorospiro[3.3]heptane-2-carboxylic acid trough the conse-

cutive synthesis strategy.[10] Both compounds were obtained from the corresponding ester, in turn prepared by deoxofluorination of methyl 6-oxospiro[3.3]heptane-2-carboxylate – a product of a seven-step reaction sequence (Scheme 1). The major drawback of this method was its poor scalability and limited diversity of the functionalized derivatives that could be prepared.

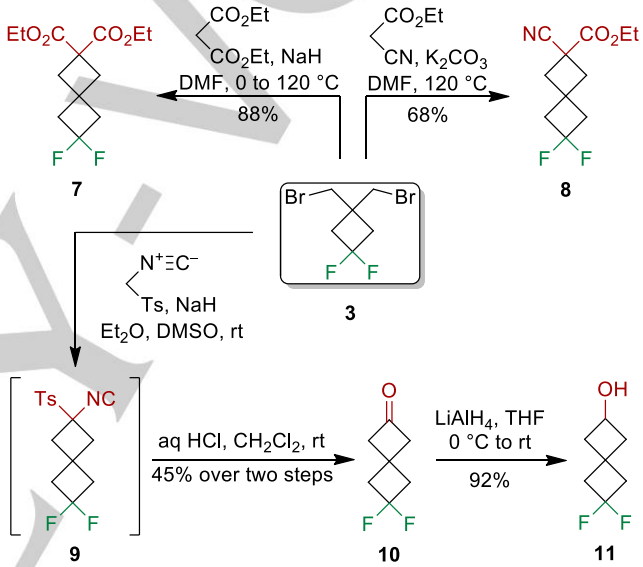
The present work is aimed at developing an alternative approach for the preparation of numerous 6,6-difluorospiro[3.3]heptane-containing building blocks, based on more efficient convergent synthetic strategy. In this regard, 1,1-bis-(bromomethyl)-3,3-difluorocyclobutane (**3**) was envisaged as the key synthetic precursor to obtain all the target derivatives. Compound **3** can be synthesized from dialkyl 3,3-difluorocyclobutane-1,1-dicarboxylate, which should be accessible by deoxofluorination of the corresponding cyclobutanone derivative **4**. Preparation of compound **4** is well-documented in the literature and commences from alkylation of diisopropylmalonate with 1,3-dibromo-2,2-dimethoxypropane.[11]



Scheme 1. Retrosynthetic disconnection of 6,6-difluorospiro[3.3]heptane-containing building blocks.



Scheme 2. The synthesis of the key precursor **3**.



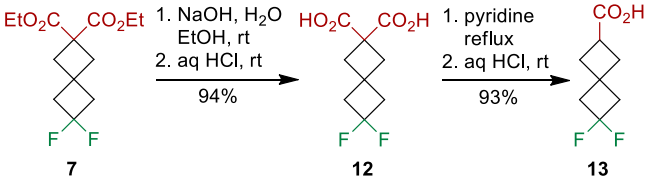
Scheme 3. The synthesis of common synthetic intermediates.

Results and Discussion

We initiated our study with synthesis of the key precursor **3**. In this way, diisopropyl 3-oxocyclobutane-1,1-dicarboxylate (**4**), was deoxofluorinated with Morph-DAST to give 3,3-difluorocyclobutane-containing diester **5** (65% yield). This product smoothly reacted with $LiAlH_4$ affording dialcohol **6** (94% yield). Further modified Appel reaction[12] afforded the target dibromide **3** in 64% yield (Scheme 2). Notably, nearly 600 g of this key precursor could be obtained from a single run of the latter step.

With large quantities of compound **3** in hands, we could prepare several common synthetic intermediates bearing the 6,6-difluorospiro[3.3]heptane scaffold by double alkylation of the corresponding active methylene compounds (Scheme 3). Particularly, the NaH-mediated alkylation of diethyl malonate afforded diester **7** (88% yield, 472 g), while reaction with ethyl cyanoacetate in the presence of K_2CO_3 as a base gave cyano ester **8** (68% yield, 221 g). Finally, NaH-mediated alkylation of tosylmethyl isocyanide (TosMIC) followed by hydrolysis of the intermediate isonitrile **9** led to ketone **10** (45% yield over two steps). The subsequent reduction of ketone **10** with $LiAlH_4$ led to the corresponding alcohol **11** (92% yield, 18.6 g).

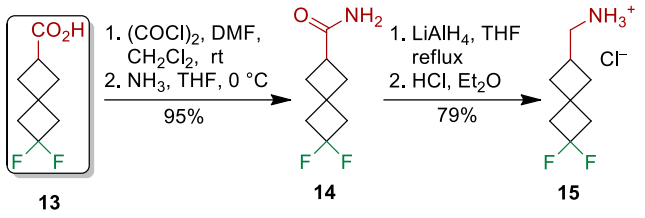
Saponification of diester **7** under mild conditions (NaOH, aq. EtOH, rt, 12 h), followed by thermal pyridine-mediated decarboxylation of product **12** allowed for the preparation of carboxylic acid **13** in 87% overall yield (Scheme 4). The latter appeared to be another supremely versatile synthetic intermediate for preparation of the target building blocks.



Scheme 4. Synthesis of carboxylic acid **13**.

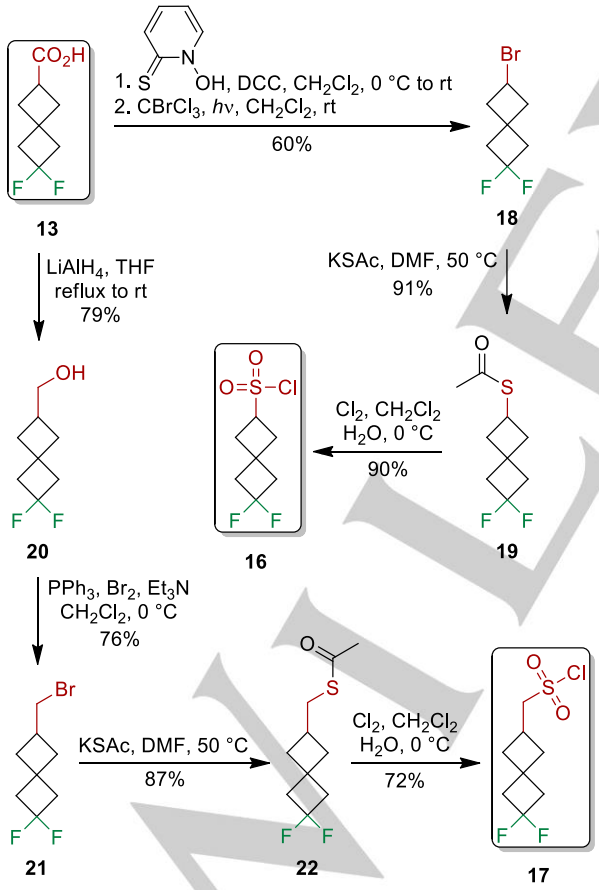
First of all, carboxylic acid **13** was converted to amide **14** (95% yield) under typical conditions (oxalyl chloride in CH_2Cl_2, followed by NH_3 in THF at 0 °C). In turn, $LiAlH_4$-mediated

reduction of **14** yielded primary amine **15** (79% yield, 36 g, isolated as hydrochloride).



Scheme 5. The synthesis of amine **15**.

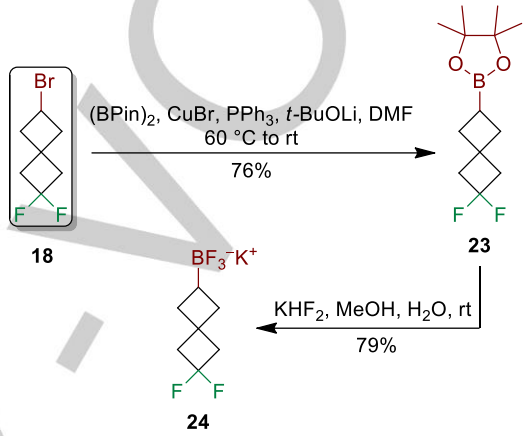
Acid **13** was also the entry point for the route to homologous sulfonyl chlorides **16** and **17** (Scheme 6). Particularly, Barton decarboxylative bromination[13] of **13** produced bromide **18** (60% yield, 90 g), which was involved into the nucleophilic substitution with AcS^- anion resulting in thioacetate **19** (91% yield). Ultimately, oxidative chlorination of **19** proceeded in a straightforward manner under typical conditions (Cl_2, CH_2Cl_2, water, 0 °C), and target sulfonyl chloride **16** was obtained in 90% yield, 16 g (Scheme 6).



Scheme 6. Synthesis of homologous sulfonyl cholrides **16** and **17**.

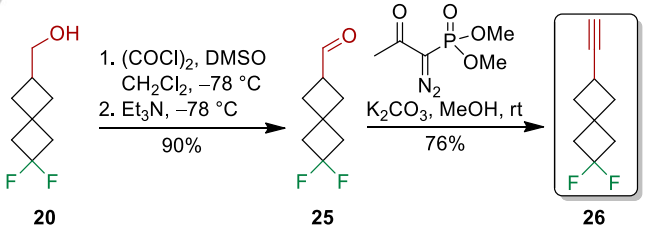
Approach to another sulfonyl chloride **17** involved reduction of acid **13** with $LiAlH_4$ giving alcohol **20** (79% yield), which was transformed into bromide **21** (76% yield) upon the modified Appel reaction conditions. The latter steps were similar to those described above and allowed for the preparation of thioacetate **22** (87% yield) and sulfonyl cholride **17** (72% yield, 53 g).

The synthetic utility of bromide **18** was also demonstrated by preparation of two novel organoboron reagents for the cross–couplingreactions.[14] Thus, treatment of **18** with bis(pinacolato)-diboron in the presence of $Cu(PPh_3)Br$ and *t*-BuOLi afforded pinacolate **23** (76% yield, 50 g). In turn, compound **23** reacted with KHF_2 in aq. MeOH to give the corresponding trifluoroborate **24** in 79% yield, 36.6 g (Scheme 7).



Scheme 7. Synthesis of organoboron derivatives **23** and **24**.

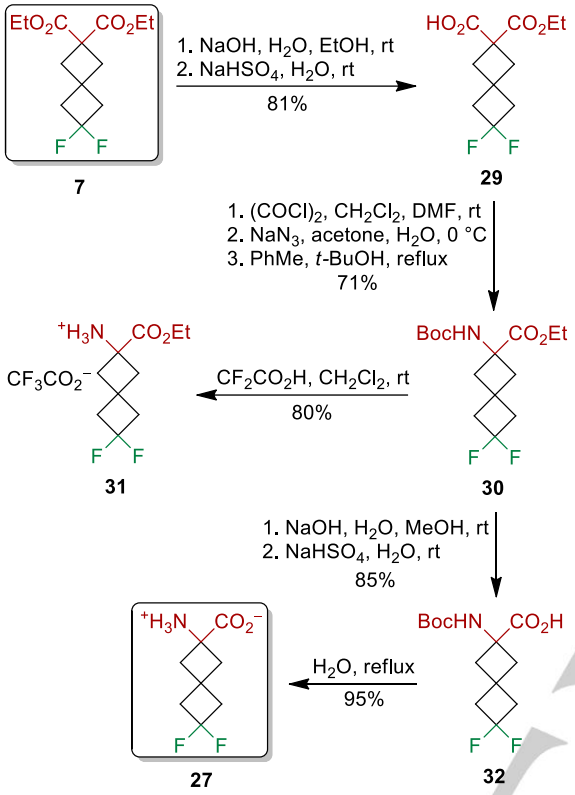
In addition, alcohol **20** was subjected to the Swern oxidation[15] to give aldehyde **25** (90% yield, 36 g). The subsequent Seyferth – Gilbert homologation[16] of **25** with the Ohira – Bestmann reagent[17] provided corresponding alkyne **26**, which was isolated in 76% yield, 30 g (Scheme 8).



Scheme 8. Synthesis of aldehyde **25** and alkyne **26**.

Finally, valorizing the importance of α,α-disubstituted amino acids that are useful not only as building blocks for drug discovery but also for the design of peptidomimetics inducing defined architectures when inserted in short sequences,[18] we envisioned the synthesis of two homologous representatives **27** and **28** (as well as their derivatives) bearing the 6,6-difluorospiro[3.3]heptane moiety (Schemes 9 and 10). In this way, diester **7** was saponified with an equimolar amount of NaOH to afford semiester **29** (81% yield). Furthermodified Curtius rearrangement of the corresponding acyl azide allowed for the preparation of Boc-protected α-amino ester **30** (71% yield). The latter was converted into amino ester **31** (80% yield,

isolated as trifluoroacetate) and Boc-protected amino acid **32** (85% yield) through the cleavage of the corresponding protective groups. Derivative **32** was processed into the target α-amino acid **27** (95% yield, 18.6 g) upon reflux in aqueous media (Scheme 9).



Scheme 9. The synthesis of α-amino acid **27** and its derivatives.

The structure of Boc-protected amino acid **32** was confirmed by X-ray diffraction studies (Figure 3).

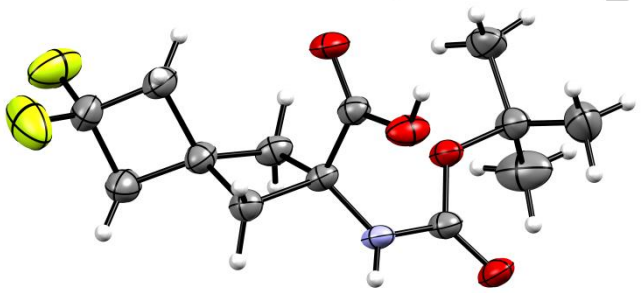
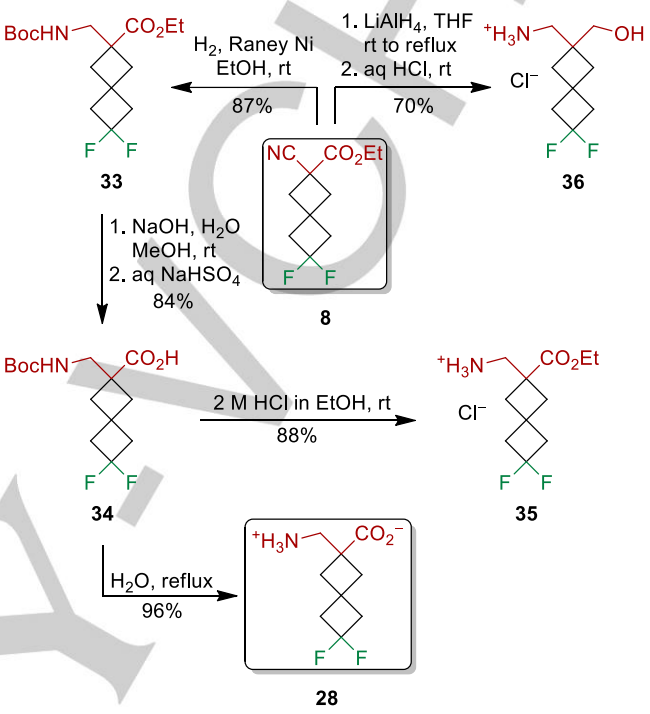


Figure 3. Molecular structure of compound **32** according to X-ray diffraction study.

Synthesis of β-amino acid **28** included the Raney Ni-catalyzed hydrogenation of cyano ester **8** in the presence of Boc_2O, that gave Boc-protected β-amino acid ester **33** in 87% yield. The further steps were similar to those described above for **27**. Thus, saponification of **33** yielded the *N*-Boc derivative **34** (84% yield) while further heating in aqueous media led to desired β-amino acid **28** (96% yield). Meanwhile, compound **34** was converted into the corresponding amino acid ester **35** (88% yield, 19.4 g, isolated as hydrochloride) when treated with 2 M ethanolic HCl (Scheme 10). Finally, amino alcohol **36** was obtained by reduction of cyano ester **8** with $LiAlH_4$ in THF media (70% yield, 27.8 g isolated as hydrochloride).



Scheme 10. The synthesis of β-amino acid **28** and its derivatives.

Conclusions

A convenient methodology to construct 6,6-difluorospiro[3.3]heptane scaffold was developed. The strategy was convergent and relied on double alkylation of the corresponding 1,1-binucleophiles with 1,1-bis(bromomethyl)-3,3-difluorocyclobutane. This allowed preparation of a diverse set of hereto unknown mono- and bifunctional 6,6-difluorospiro[3.3]heptane derivatives – conformationally restricted surrogates of appropriately functionalized *gem*-difluorocycloalkanes (first of all, 4,4-difluorocyclohexanes and 3,3-difluorocyclobutanes with confirmed medicinal relevance) All the intermediates as well as the target compounds were prepared using relatively short reaction sequences on multigram scale (at least 10 g; up to 0.47 kg). Results of this study enable wide applications of 6,6-difluorospiro[3.3]heptanes as promising lead-oriented building blocks for drug discovery[1d,19] and organic synthesis.

Experimental Section

The solvents were purified according to the standard procedures.[20] All the starting materials were obtained from Enamine Ltd. and UORSY. Melting points were measured on MPA100 OptiMelt automated melting point system. Analytical TLC was performed using Polychrom SI F254

plates. ^{1}H, $^{13}C\{^{1}H\}$, $^{19}F\{^{1}H\}$, and ^{11}B NMR spectra were recorded on a Agilent ProPulse 600 spectrometer (at 600 MHz for ^{1}H NMR and 151 MHz for ^{13}C NMR), a Bruker 170 Avance 500 spectrometer (at 500 MHz for ^{1}H, 126 MHz for ^{13}C, 470 MHz for ^{19}F, and 160.4 MHz for ^{11}B), or a Varian Unity Plus 400 spectrometer (at 400 MHz for ^{1}H, 101 MHz for ^{13}C, and 376 MHz for ^{19}F). Chemical shifts are reported in ppm downfield from TMS as an internal standard. Elemental analyses were performed on a CHNOS elementary Vario MICRO Cube analyzer. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization (APCI)) and Agilent 5890 Series II 5972 GCMS instrument (electron impact ionization (EI)). CCDC deposition number for the structure of **32** is 1993871. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

Diisopropyl 3,3-difluorocyclobutane-1,1-dicarboxylate (5): Diisopropyl 3-oxocyclobutane-1,1-dicarboxylate (**4**) (1.24 kg, 5.11 mol) was dissolved in CH_2Cl_2 (2 L) and the obtained solution was cooled to 0 °C. Then Morph-DAST (2.15kg, 12.3 mol) was added portionwise at the same temperature.The reaction mixture was allowed to warm to rt and left to react with stirring for 48 h. Then it was slowly added to the stirred cold (0 °C) solution of Na_2CO_3 (5.25kg, 49.5 mol) in water (20 L) over 0.5 h. The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (2×1.5 L). The combined organic layerswere dried (Na_2SO_4) and evaporated at reduced pressure. The residue was distilled *in vacuo* to give the title compound **5** as colorless liquid. Yield 872 g, 65%; b.p. 96 °C (1 mBar); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.09 (sept, *J* = 6.4 Hz, 2H), 3.11 (t, *J* = 11.9 Hz, 4H), 1.26 (d, *J* = 6.4 Hz, 12H) ppm; $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ = 169.2, 117.4 (t, *J* = 276.5 Hz), 69.9, 42.7 (t, *J* = 25.6 Hz), 42.6, 21.6 ppm; $^{19}F\{^{1}H\}$ NMR (470 MHz, $CDCl_3$): δ = –90.4 ppm; MS (APCI): *m*/z = 223 $[M+H–C_3H_6]^+$; elemental analysis calcd. (%) for $C_{12}H_{18}F_2O_4$: C 54.54, H 6.87; found: C 54.23, H 6.72.

(3,3-Difluorocyclobutane-1,1-diyl)dimethanol (6): Compound **5** (872 g, 3.30mol) was added dropwise to a stirred boiling suspension of $LiAlH_4$ (188 g, 4.95 mol) in THF (6.1 L), and the resulting mixture was allowed to stir at rt for 12 h. Then it was quenched by sequential dropwise addition of water (190 mL), 50% aq. NaOH (125 mL), and water (570 mL). Theprecipitate formedwas filtered off, and the filtrate was evaporated at reduced pressure to give the title compound **6** as colorless needles. Yield 500 g,99.6%; m.p. 66–67 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.76 (s, 4H), 2.37 (t, *J* = 12.6 Hz, 4H), 2.35 (s, 2H) ppm; $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): δ = 119.2 (t, *J* = 279.4 Hz), 68.3 (t, *J* = 3.6 Hz), 39.9 (t, *J* = 22.8 Hz), 32.9 (t, *J* = 9.6 Hz) ppm; $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$): δ = –86.5 ppm;MS (EI): *m/z* = 114 $[M–HF–H_2O]^+$; elemental analysis calcd. (%) for $C_6H_{10}F_2O_2$: C 47.37, H 6.63; found: C 47.30, H 6.30.

1,1-Bis(bromomethyl)-3,3-difluorocyclobutane (3): PPh_3 (2.50kg, 9.53 mol) was dissolved in CH_2Cl_2 (5 L), and the obtained solution was cooled to 0 °C. Br_2 (490 mL, 1.52kg, 9.49 mol) was added dropwise at the same temperature. The resulting mixture was additionally stirred at 0 °C for 1 h, then Et_3N (1.34 L, 973 g, 9.61 mol) was added dropwise maintaining the above temperature followed by additional stirring for 15 min. Next, a solution of **6** (500g, 3.286 mol) in CH_2Cl_2 (1 L) was added dropwise at 0 °C, and the reaction mixture was allowed to warm to rt and left to react with stirring overnight. Then it was extracted with water (1 L) and 15% aq.Na_2CO_3 (1L). The organic layer was dried (Na_2SO_4) and evaporated at reduced pressure. The remainder was triturated with hexane (5 L) and filtered. The filtrate was evaporated at reduced pressure, and the residue was distilled *in vacuo* to give the title compound **3** as colorless liquid. Yield 590 g, 64%; b.p. 45 °C (1 mBar); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.68 (s, 4H), 2.55 (t, *J* = 12.2 Hz, 4H) ppm; $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): δ = 116.70 (t, *J* = 278.1 Hz), 43.52 (t, *J* = 23.6 Hz), 39.30 (t, *J* = 4.3 Hz), 34.08 (t, *J* = 10.8 Hz) ppm; $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$): δ = –88.8 ppm;MS (EI): *m/z* = 214 $[M–CF_2=CH_2]^+$; elemental analysis calcd. (%) for $C_6H_8Br_2F_2$: C 25.93, H 2.90; found: C 26.03, H 3.01.

Diethyl 6,6-difluorospiro[3.3]heptane-2,2-dicarboxylate (7): Diethyl malonate (650 g, 4.06 mol) was added dropwise to a cold (0 °C) stirred suspension of NaH (60% dispersion in mineral oil, 154.6 g, 3.87 mol) in DMF (2.7 L) while the above temperature was maintained. The obtained mixture was slowly heated to 60 °C,and compound **3** (538 g, 1.94mol) was addeddropwise. The reaction mixture was slowly heated to 120 °C and stirred at this temperature for 12h. Then it was cooled to rt, diluted with water (4L) and extracted with EtOAc (3×1.5L). The combined extracts were washed with water (3×3L), dried (Na_2SO_4) and evaporated at reduced pressure. The residue was distilled *in vacuo* affording the title compound **7** as colorless liquid. Yield 472 g, 88%; b.p. 95 °C (1 mBar); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.21–4.16 (m, 4H), 2.65 (t, *J* = 2.6 Hz, 4H), 2.58 (tt, *J* = 12.2, 2.6 Hz, 4H), 1.28–1.16 (m, 6H) ppm; $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): δ = 171.3, 119.0 (t, *J* = 279.0 Hz), 61.6, 48.5, 47.6 (t, *J* = 22.3 Hz), 40.3, 27.3 (t, *J* = 9.6 Hz), 14.0 ppm; $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$): δ = –92.0 ppm; MS (EI): *m/z* = 276 $[M]^+$; elemental analysis calcd. (%) for $C_{13}H_{18}F_2O_4$: C 56.52, H 6.57; found: C 56.88, H 6.41.

Ethyl 2-cyano-6,6-difluorospiro[3.3]heptane-2-carboxylate (8): Compound **3** (391 g, 1.42 mol) was dissolved in DMF (1.95 L) followed by addition of ethyl 2-cyanoacetate (240 g, 2.12 mol) and K_2CO_3 (582 g, 4.22 mol). The resulting mixture was heated to 80 °C and stirred at this temperature for 12 h. Then it was cooled to rt, diluted with water (3L) and extracted with EtOAc (3×1000 mL). The combined organic layer was washed with water (3×200 mL), dried (Na_2SO_4) and evaporated at reduced pressure. The residue was distilled *in vacuo* to give the title compound **8** as colorless liquid. Yield 221 g, 68%; b.p. 90 °C (1 mBar); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.24 (q, *J* = 7.1 Hz, 2H), 2.86–2.79 (m, 2H), 2.79–2.68 (m, 4H), 2.63 (td, *J* = 12.1, 2.9 Hz, 2H), 1.30 (t, *J* = 7.1 Hz, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$): δ = 168.2, 119.6, 118.5 (t, *J* = 278.5 Hz), 63.1, 47.7 (t, *J* = 22.8 Hz), 47.4 (t, *J* = 22.8 Hz), 42.4 (t, *J* = 2.3 Hz), 35.5, 28.6 (t, *J* = 9.8 Hz), 13.9 ppm; $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$): δ = –92.2 ppm; MS (EI): *m/z* = 229 $[M]^+$; elemental analysis calcd. (%) for $C_{11}H_{13}F_2NO_2$: C 57.64, H 5.72, N 6.11; found: C 57.66, H, 5.93, N, 6.03.

6,6-Difluorospiro[3.3]heptan-2-one (10): Compound **3** (105 g, 378 mmol) was dissolved in Et_2O (1 L) followed by addition of NaH (60% dispersion in mineral oil, 52.8 g, 1.32 mol). Then the solution of TosMIC (200 g, 1.02 mol) in DMSO (1 L) was added dropwise upon stirring at rt. The resulting suspension was stirred at the same temperature for 2 h, poured into water (2.4 L), and extracted with EtOAc (3×900 mL). The combined organic layer was dried ($MgSO_4$) and evaporated at reduced pressure affording the crude compound **9**, which was dissolved in Et_2O (750 mL) followed by addition of 12 M aq. HCl (300 mL). The resulting mixture was stirred at rt for 16 h, diluted with water (900mL) and extracted with Et_2O (3×400 mL). The combined organic layer was dried (Na_2SO_4) and evaporated at reduced pressure. The residue was distilled *in vacuo* to give the title compound **10** as colorless liquid. Yield 25.0 g, 45%; b.p. 66 °C (7 mBar); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.24 (s, 4H), 2.82 (t, *J* = 11.9 Hz, 4H) ppm; $^{13}C\{^{1}H\}$ NMR (126 MHz, Cl_3): δ = 204.7, 118.6 (t, *J* = 278.5 Hz), 58.5 (t, *J* = 2.7 Hz), 46.7 (t, *J* = 22.9 Hz), 22.7 ppm; $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$): δ = –93.2 ppm; MS (EI): *m/z* = 146 $[M]^+$; elemental analysis calcd. (%) for $C_7H_8F_2O$: C 57.53, H 5.52; found: C 57.80, H, 5.18.

6,6-Difluorospiro[3.3]heptan-2-ol (11): Compound **10** (20.0g, 0.14mol) was added dropwise to the stirred cold (0 °C) suspension of $LiAlH_4$ (3.64 g, 0.10mol) in THF (150 mL) and the resulting mixture was allowed to equilibrate to rt and stirred for 3 h. Then it was quenched by sequential dropwise addition of water (4 mL), 50% aq. NaOH (2.7 mL), and water (10 mL) again, while the above temperature was maintained. The formed precipitate was filtered off and the filtrate was evaporated at reduced pressure to give the title compound **11** as yellowish liquid. Yield 18.6 g, 92%; ^{1}HNMR (400 MHz, $CDCl_3$): δ = 4.25 (p, *J* = 7.3 Hz, 1H), 2.54 (t, *J* = 12.3 Hz, 4H), 2.46 (ddd, *J* = 9.8, 7.3, 3.1 Hz, 2H), 2.06 (ddd, *J* = 9.8, 7.3, 3.1 Hz, 2H), 1.78 (s, 1H) ppm; $^{13}C\{^{1}H\}$NMR (126 MHz, $CDCl_3$): δ = 119.7 (t, *J* = 279.6 Hz), 62.8, 47.2 (t, *J* = 21.9 Hz), 46.5 (t, *J* = 21.9 Hz), 44.7 (t, *J* = 2.0 Hz), 23.9 (t, *J* = 9.5 Hz) ppm; $^{19}F\{^{1}H\}$NMR (376 MHz, $CDCl_3$): δ =

–91.6 ppm; MS (EI): *m/z* = 84 $[M–CF_2CH_2]^+$; elemental analysis calcd. (%) for $C_7H_{10}F_2O$: C 56.75, H 6.80; found: C 57.04, H 7.04.

6,6-Difluorospiro[3.3]heptane-2,2-dicarboxylic acid (12): Compound **7** (472 g, 1.71 mol) was dissolved in MeOH (1 L), and the resulting solution was added to the stirred solution of NaOH (272 g, 6.80 mol) in water (1 L). The reaction mixture was left to react with stirring at rt for 12 h. Then MeOH was evaporated at reduced pressure, the aqueous layer was extracted with *t*-BuOMe (500mL), acidified with 10 M aq. HCl to pH = 3 and extracted with EtOAc (3×800mL). The organic layer was dried (Na_2SO_4) and evaporated at reduced pressure to give the title compound **12** as colorless crystals. Yield 350 g, 94%; m.p. 190–191 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.78 (s, 2H), 2.55 (t, *J* = 12.4 Hz, 6H), 2.46 (t, *J* = 1.9 Hz, 2H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ = 173.11, 120.37 (t, *J* = 278.6 Hz), 48.33, 47.27 (t, *J* = 21.3 Hz), 40.07, 27.09 (t, *J* = 9.5 Hz) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6): δ = –89.9 ppm; MS (APCI): *m*/z = 219 $[M–H]^–$; elemental analysis calcd. (%) for $C_9H_{10}F_2O_4$: C 49.10, H 4.58; found: C 49.25, H 4.25.

6,6-Difluorospiro[3.3]heptane-2-carboxylic acid (13): Compound **12** (350 g, 1.59 mol) was dissolved in pyridine (2 L) and the resulting solution was refluxed for 12 h. Then it was evaporated at reduced pressure, the residue was diluted with water (1.5L), acidified with 10 M aq. HCl to pH = 3 and extracted with EtOAc (3×600mL). The combined organic layer was dried (Na_2SO_4) and evaporated at reduced pressure to give the title compound **13** as yellowish crystals. Yield 350 g, 93%; m.p. 46–47 °C. For spectral data, see ref.[4i]

6,6-Difluorospiro[3.3]heptane-2-carboxamide (14): Compound **13** (42.0 g, 0.24 mol) was dissolved in CH_2Cl_2 (500 mL) followed by addition of DMF (1mL) and oxalyl chloride (46.0 g, 0.36 mol).The resulting mixture was stirred until gas evolution ceased (ca. 2 h),then it was evaporated at reduced pressure, the residue was dissolved in THF (500mL), and the resulting solution was cooled to 0 °C. After, gaseous NH_3 was bubbled through the stirred reaction mixture until pH reached 8–9. The precipitate formed was filtered off and the filtrate was evaporated at reduced pressure to give the title compound **14** as white crystals. Yield 40.1 g, 95%; m.p. 139–141 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.13 (s, 1H), 6.68 (s, 1H), 2.84 (p, *J* = 8.4 Hz, 1H), 2.58 (t, *J* = 12.6 Hz, 2H), 2.45–2.38 (m, 2H), 2.22–2.14 (m, 2H), 2.10 (t, *J* = 10.2 Hz, 2H) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ = 175.9, 120.7 (t, *J* = 279.3 Hz), 47.3 (t, *J* = 21.2 Hz), 46.6 (t, *J* = 21.0 Hz), 36.5, 33.6, 28.7 (t, *J* = 9.3 Hz) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6): δ = –89.6 ppm; MS (EI): *m/z* = 175 $[M]^+$; elemental analysis calcd. (%) for $C_8H_{11}F_2NO$: C 54.85, H 6.33, N, 8.00; found: C 54.79, H 6.27, N, 8.13.

(6,6-Difluorospiro[3.3]heptan-2-yl)methanamine hydrochloride (15): Compound **14** (40.0g, 0.23mol) was added portionwise to the stirred boiling suspension of $LiAlH_4$ (13.0 g, 0.34mol) in THF (500 mL), and the resulting mixture was refluxed with stirring for 2 h. Then it was cooled to rt and quenched by sequential dropwise addition of water (13 mL), 50% aq. NaOH (8.7 mL), and water (40 mL). The precipitate was filtered off and the filtrate was evaporated at reduced pressure. The residue was dissolved in Et_2O (200mL) followed by addition of 4M HCl in Et_2O (40mL). The precipitate formed was filtered to give the title compound **15** as white powder. Yield 36.0 g, 79%; m.p. 186–188 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.01 (s, 3H), 2.79 (d, *J* = 7.5 Hz, 2H), 2.61 (t, *J* = 12.5 Hz, 2H), 2.54 (d, *J* = 12.5 Hz, 2H), 2.47–2.39 (m, 1H), 2.17 (ddd, *J* = 10.4, 8.1, 2.1 Hz, 2H), 1.93 (ddd, *J* = 10.4, 8.1, 2.1 Hz, 2H) ppm; $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6): δ = 120.7 (t, *J* = 279.5 Hz), 47.4 (t, *J* = 21.1 Hz), 46.8 (t, *J* = 21.1 Hz), 43.9, 37.2, 28.6 (t, *J* = 9.0 Hz), 27.8 ppm; $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6): δ = –89.5 ppm; MS (APCI): *m*/z = 162 $[M+H]^+$; elemental analysis calcd. (%) for $C_8H_{14}ClF_2N$: C 48.62, H 7.14, N 7.09; found: C 48.98, H 7.39, N 7.24.

6-Bromo-2,2-difluorospiro[3.3]heptane (18): Compound **13** (125 g, 0.71 mol) and 1-hydroxypyridine-2(1*H*)-thione (90.2 g, 0.71 mol) were dissolved in CH_2Cl_2 (1L) and the resulting solution was cooled to 0 °C. DCC (153.6 g, 0.74 mol) was added portionwise at the same temperature and the reaction mixture was allowed to equilibrate to rt and stirred for 12 h. Then it was filtered and evaporated to ca. 10%of initial volume at reduced pressure. The solution thus obtained was added to the stirred solution of $CBrCl_3$ (704 g, 350 mL, 3.55 mol) in CH_2Cl_2 (200mL) and the stirred reaction mixture was irradiated with 100 W tungsten bulb for 2 h and left to stir for additional 12 h. Then it was evaporated at reduced pressure, the residue was distilled *in vacuo* to give the title compound **18** as colorless liquid. Yield 90.3 g, 60%; b.p. 60 °C (7 mBar); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.35 (p, *J* = 7.5 Hz, 1H), 2.77 (ddd, *J* = 10.5, 7.5, 3.1 Hz, 2H), 2.67–2.54 (m, 6H) ppm; $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ = 119.2 (t, *J* = 279.5 Hz), 47.1 (t, *J* = 22.7 Hz), 47.0 (t, *J* = 22.7 Hz), 46.5, 36.6, 29.8 (t, *J* = 9.6 Hz) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ = –91.8 ppm; MS (EI): *m/z* = 131 $[M–Br]^+$; elemental analysis calcd. (%) for $C_7H_9BrF_2$: C 39.84, H 4.30; found: C 39.61, H 4.24.

(6,6-Difluorospiro[3.3]heptan-2-yl)methanol (20): Compound **13** (90g, 0.51mol) was added portionwise to the stirred boiling suspension of $LiAlH_4$ (31 g, 0.82mol) in THF (1.2 L) and the resulting mixture was allowed to stir at rt for 12 h. Then it was quenched by sequential dropwise addition of water (30 mL), 50% aq. NaOH (20 mL), and water (90 mL) again. The formed precipitate was filtered off and the filtrate was evaporated at reduced pressure. The residue was distilled *in vacuo* to give the title compound **20** as colorless liquid. Yield 65 g, 79%; b.p. 59 °C (1 mBar); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.57 (t, *J* = 5.3 Hz, 2H), 2.57 (t, *J* = 12.3 Hz, 2H), 2.47 (t, *J* = 12.3 Hz, 2H), 2.45–2.35 (m, 1H), 2.16 (dd, *J* = 12.3, 8.0 Hz, 2H), 1.90 (dd, *J* = 12.3, 8.0 Hz, 2H), 1.30 (t, *J* = 5.3 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ = 119.7 (t, *J* = 279.7 Hz), 66.7, 47.9 (t, *J* = 21.6 Hz), 47.3 (t, *J* = 21.6 Hz), 36.3, 31.7, 28.7 (t, *J* = 8.8 Hz) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ = –91.5 ppm; MS (EI): *m/z* = 162 $[M]^+$; elemental analysis calcd. (%) for $C_8H_{12}F_2O$: C 59.25, H 7.46; found: C 59.36, H 7.43.

6-(Bromomethyl)-2,2-difluorospiro[3.3]heptane (21): PPh_3 (81.0 g, 0.31 mol) was dissolved in CH_2Cl_2 (400 mL) and the obtained solution was cooled to 0 °C followed by dropwise addition of Br_2 (15.8 mL, 49.0 g, 0.31 mol) at the same temperature. The resulting mixture was additionally stirred at 0 °C for 1 h, then Et_3N (43 mL, 31.2 g, 0.31 mol) was added dropwise maintaining the above temperature followed by additional stirring for 15 min. After, the solution of **20** (40g,0.25 mol) in CH_2Cl_2 (100 mL) was added dropwise at 0 °C.The reaction mixture was allowed to equilibrate to rt and left to react with stirring overnight. Then it was subsequently extracted with water (1×100 mL) and 15% aq. Na_2CO_3 (1×100 mL). The organic layer was dried (Na_2SO_4) and evaporated at reduced pressure. The remainder was dispersed in hexane (1L) and filtered. The filtrate was evaporated at reduced pressure and the residue was distilled *in vacuo* to give the title compound **21** as colorless liquid. Yield 43 g, 76%; b.p. 47 °C (1 mBar); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.38 (d, *J* = 7.3 Hz, 2H), 2.69–2.61 (m, 1H), 2.58 (t, *J* = 11.5 Hz, 2H), 2.49 (t, *J* = 12.3 Hz, 2H), 2.24 (dd, *J* = 12.3, 8.2 Hz, 2H), 1.89 (dd, *J* = 12.3, 8.2 Hz, 2H) ppm; $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ = 119.5 (t, *J* = 279.7 Hz), 47.8 (t, *J* = 21.8 Hz), 47.0 (t, *J* = 21.8 Hz), 39.0, 38.5, 32.1, 27.5 (t, *J* = 8.7 Hz) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ = –91.6 ppm; MS (EI): *m/z* = 125 $[M–HF–Br]^+$; elemental analysis calcd. (%) for $C_8H_{11}BrF_2$: C 42.69, H 4.93; found: C 43.09, H 5.09.

General Procedure for the Preparation of Ethanethioates 19 and 22: The corresponding bromide **18**, **21** (0.17 mol) was dissolved in DMF (175 mL), then KSAc (28.3 g, 0.25 mol) was added and the resulting mixture was stirred at 50 °C for 12 h. Then it was diluted with water (400mL) and extracted with *t*-BuOMe (2×300 mL). The organic layer was washed with water (3×100 mL), dried (Na_2SO_4), and evaporated at reduced pressure to give title compound **19**, **22**.

***S*-(6,6-Difluorospiro[3.3]heptan-2-yl) ethanethioate (19):** from **18** (35.0 g, 0.17 mol), brown liquid (31.2 g, 91%; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.98 (p, *J* = 8.2 Hz, 1H), 2.65 (t, *J* = 12.6 Hz, 2H), 2.61–2.57 (m, 2H), 2.57–2.51 (m, 2H), 2.28 (s, 3H), 2.18 (ddd, *J* = 12.6, 6.3, 2.2 Hz, 2H)

ppm; $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ = 195.6, 119.6 (t, *J* = 279.8 Hz), 47.3 (t, *J* = 22.1 Hz), 47.0 (t, *J* = 22.1 Hz), 41.6 (t, *J* = 2.1 Hz), 31.7, 30.4, 29.8 (t, *J* = 9.2 Hz) ppm; $^{19}F\{^1H\}$ NMR (470 MHz, $CDCl_3$): δ = –91.3 ppm; MS (EI): *m/z* = 206 $[M]^+$; elemental analysis calcd. (%) for $C_9H_{12}F_2OS$: C 52.41, H 5.86, S 15.54; found: C 52.29, H 6.08, S 15.32.

***S*-((6,6-Difluorospiro[3.3]heptan-2-yl)methyl) ethanethioate (22):** from **21** (76.7 g, 0.34 mo) and KSAc (55.6 g, 0.49 mol), brown liquid (65.0 g, 87%; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.91 (d, *J* = 7.4 Hz, 2H), 2.54 (t, *J* = 12.4 Hz, 2H), 2.47 (t, *J* = 12.5 Hz, 2H), 2.42 – 2.33 (m, 1H), 2.31 (s, 3H), 2.22 – 2.13 (m, 2H), 1.86–1.75 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ = 195.7, 119.6 (t, *J* = 279.8 Hz), 47.7 (t, *J* = 21.7 Hz), 46.9 (t, *J*= 21.7 Hz), 39.2 (t, *J* = 1.7 Hz), 34.7, 30.6, 29.7, 28.2 (t, *J* = 8.9 Hz) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ = –91.5 ppm; MS (EI): *m/z* = 177 $[M–CH_3CO]^+$; elemental analysis calcd. (%) for $C_{10}H_{14}F_2OS$: C 54.53, H 6.41, S 14.55; found: C 54.65, H 6.39, S 14.59.

General Procedure for the Preparation of sulfonyl chlorides 16 and 17: The corresponding ethanethioate **19**, **22** (0.15 mol) was dissolved in CH_2Cl_2 (300 mL), then water (300 mL) was added, and the resulting mixture was cooled to 0 °C. After, Cl_2 was bubbled through the stirred reaction mixture until it became yellow green. The layers were separated, the organic phase was washed with water (2×100 mL), dried (Na_2SO_4) and evaporated at reduced pressure to give the title compound **16**, **17**.

6,6-Difluorospiro[3.3]heptane-2-sulfonyl chloride (16): from **19** (31.0 g, 0.15 mol), yellowish crystals (31.1 g, 90%), m.p. 42–44 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 4.33 (p, *J* = 7.9 Hz, 1H), 2.84 (dd, *J* = 14.0, 7.9 Hz, 2H), 2.73–2.61 (m, 6H) ppm; $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ = 118.3 (t, *J* = 278.8 Hz), 62.7, 47.4 (t, *J* = 22.7 Hz), 47.3 (t, *J* = 22.7 Hz), 36.5, 27.8 (t, *J* = 9.8 Hz) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ = –92.2 ppm; MS (APCI): *m*/z = 211 $[M–H]^–$ (for the corresponding sulfonic acid); elemental analysis calcd. (%) for $C_7H_9ClF_2O_2S$: C 36.45, H 3.93, S 13.90; found: C 36.69, H 4.00, S 13.93.

(6,6-Difluorospiro[3.3]heptan-2-yl)methanesulfonyl chloride (17): from **22** (65.0 g, 0.30 mol), yellowish oil (53.0 g, 72%; ^1H NMR (400 MHz, $CDCl_3$): δ = 3.74 (d, *J* = 7.3 Hz, 2H), 2.96 (p, *J* = 8.3 Hz, 1H), 2.66 (t, *J* = 11.9 Hz, 2H), 2.51 (t, *J* = 12.9 Hz, 2H), 2.43 (t, *J* = 9.5 Hz, 2H), 2.09 (dd, *J* = 12.9, 9.5 Hz, 2H) ppm; $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ = 119.1 (t, *J* = 279.5 Hz), 70.3, 47.5 (t, *J* = 22.1 Hz), 46.5 (t, *J* = 22.1 Hz), 39.3, 29.5 (t, *J* = 9.1 Hz), 25.6 ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ = –91.7 ppm; MS (APCI): *m*/z = 225 $[M–H]^–$ (for the corresponding sulfonic acid); elemental analysis calcd. (%) for $C_8H_{11}ClF_2O_2S$: C 39.27, H 4.53, S 13.10; found: C 39.02, H 4.72, S 12.88.

2-(6,6-Difluorospiro[3.3]heptan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (23): The solution of compound **18** (53.5 g, 0.25 mol) in DMF (540 mL) was added dropwise to the stirred solid mixture of CuBr (3.64 g, 25.3 mmol), PPh_3 (8.65 g, 33.0 mmol), *t*-BuOLi (40.6 g, 0.51 mol), and $(BPin)_2$ (96.6 g, 0.38 mol) under Ar atmosphere, while maintaining internal temperature below 60 °C (*Caution:* Exothermic reaction!). The resulting mixture was stirred at rt for 12 h. Then it was diluted with EtOAc (1.2L) and filtered through silica gel. The filtrate was washed with water (1×500 mL and 2×300 mL), dried (Na_2SO_4) and evaporated at reduced pressure. The residue was dissolved in hexane (100mL) and subjected to silica gel flash chromatography, using hexane (1 L) as eluent. The eluate was evaporated at reduced pressure to give the title compound **23** as colorless liquid. Yield 50.0g, 76%; ^1HNMR (500 MHz, $CDCl_3$): δ = 2.52 (q, *J* = 12.9 Hz, 4H), 2.20 (t, *J* = 9.5 Hz, 2H), 2.16–2.08 (m, 2H), 1.79 (p, *J* = 9.5 Hz, 1H), 1.24 (s, 12H) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ = 119.9 (t, *J* = 280.0 Hz), 83.2, 47.5 (t, *J* = 21.4 Hz), 47.4 (t, *J* = 21.4 Hz), 35.5, 32.0 (t, *J* = 8.5 Hz), 29.7, 24.7 ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ = –91.4 ppm; ^{11}BNMR (160 MHz, $CDCl_3$): δ = 33.9 ppm; MS (EI): *m/z* = 258 $[M]^+$; elemental analysis calcd. (%) for $C_{13}H_{21}BF_2O_2$: C 60.49, H 8.20; found: C 60.55, H 8.35.

Potassium (6,6-difluorospiro[3.3]heptan-2-yl)trifluoroborate (24): Compound **23** (50.0 g, 0.19 mol) was dissolved in MeOH (400 mL), then the solution of KHF_2 (91.0 g, 1.17 mol) in water (200 mL) was added in one portion and the resulting mixture was stirred at rt for 12 h. Then it was evaporated to dryness at reduced pressure, the remainder was triturated with MeCN (1 L) and filtered. The filtrate was evaporated to dryness at reduced pressure and the residue was dispersed in *t*-BuOMe (300 mL). The filtration afforded the title compound **24** as white crystals. Yield 36.6 g, 79%; m.p. 248–250 °C; ^1H NMR (400 MHz, DMSO-d_6): δ = 2.44 (t, *J* = 12.9 Hz, 2H), 2.33 (t, *J* = 12.9 Hz, 2H), 1.79 (p, *J* = 10.3 Hz, 4H), 1.11–0.97 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6): δ = 121.5 (t, *J* = 280.6 Hz), 48.4 (t, *J* = 20.0 Hz), 47.6 (t, *J* = 20.0 Hz), 36.1, 30.8 (t, *J* = 7.8 Hz), 25.4 ppm; $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6): δ = –88.79 (2F), –144.48 (3F) ppm; ^{11}B NMR (160 MHz, DMSO-d_6): δ = 4.31 ppm; elemental analysis calcd. (%) for $C_7H_9BF_5K$: C 35.32, H, 3.81; found: C 35.06, H 4.14.

6,6-Difluorospiro[3.3]heptane-2-carbaldehyde (25): DMSO (46.2 g, 0.59 mol) was dissolved in CH_2Cl_2 (800 mL) and the resulting solution was cooled to –78 °C. Then oxalyl chloride (37.6, 0.30 mol) was added dropwise, and the resulting mixture was stirred at above temperature until gas evolution ceased (ca. 30min). After, compound **20** (40.0 g, 0.25 mol) was added dropwise and the reaction mixture was stirred at –78 °C for 30 min followed by dropwise addition of Et_3N (100 g, 138 mL, 0.99 mol) at –50 °C. The resulting mixture was allowed to warm to 0 °C and extracted with water (3×150 mL). The organic layer was dried (Na_2SO_4), and evaporated at reduced pressure to give the title compound **25** as yellowish liquid. Yield 36.3 g, 90%; ^1H NMR (400 MHz, $CDCl_3$): δ = 9.69 (s, 1H), 3.11 (p, *J* = 7.3 Hz, 1H), 2.59 (t, *J* = 10.7 Hz, 2H), 2.47 (t, *J* = 12.2 Hz, 2H), 2.42–2.33 (m, 2H), 2.26 (t, *J* = 10.7 Hz, 2H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 201.5, 119.1 (t, *J* = 279.4 Hz), 47.6 (t, *J* = 22.0 Hz), 47.1 (t, *J* = 22.0 Hz), 40.3, 33.8 (t, *J* = 2.2 Hz), 29.3 (t, *J* = 9.2 Hz) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ = –91.8 ppm; MS (EI): *m/z* = 160 $[M]^+$; elemental analysis calcd. (%) for $C_8H_{10}F_2O$: C 59.99, H 6.29; found: C 60.34, H 6.39.

6-Ethynyl-2,2-difluorospiro[3.3]heptane (26): Compound **25** (40.0 g, 0.25 mol) and the Ohira – Bestmann reagent (57.6 g, 0.30 mol) were dissolved in MeOH (300 mL), then K_2CO_3 (103.4 g, 0.75 mol) was added portionwise. The reaction mixture was stirred at rt for 1.5 h, diluted with water (1.5 L) and extracted with hexane (4×250 mL). The organic layer was separated, dried (Na_2SO_4), and evaporated at reduced pressure. The residue was distilled *in vacuo* to give the title compound **26** as colorless liquid. Yield 29.8 g, 76%; b.p. 57 °C (37 mBar); ^1H NMR (400 MHz, $CDCl_3$): δ = 2.96 (pd, *J* = 8.3, 2.3 Hz, 1H), 2.59 (t, *J* = 12.2 Hz, 4H), 2.44 (td, *J* = 9.2, 8.3, 2.1 Hz, 2H), 2.28 (td, *J* = 9.2, 8.3, 2.3 Hz, 2H), 2.17 (d, *J* = 2.3 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ = 119.4 (t, *J* = 279.6 Hz), 87.3, 69.2, 47.3 (t, *J* = 22.0 Hz), 47.0 (t, *J* = 22.0 Hz), 40.9 (t, *J* = 2.0 Hz), 29.8 (t, *J* = 9.2 Hz), 19.7 (t, *J* = 1.5 Hz) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ = –91.7 ppm; MS (EI): *m/z* = 156 $[M]^+$; elemental analysis calcd. (%) for $C_9H_{10}F_2$: C 69.22, H 6.45; found: C 69.12, H, 6.49.

2-(Ethoxycarbonyl)-6,6-difluorospiro[3.3]heptane-2-carboxylic acid (29): Compound **7** (287 g, 1.01 mol) was dissolved in EtOH (2 L) and brought to boil. Then a solution of NaOH (40.0 g, 1.0 mol) in water (800 mL) was added dropwise and the resulting solution was stirred and refluxed for 1 h. The reaction mixture was cooled to rt, EtOH was evaporated at reduced pressure, the remaining aqueous layer was extracted with *t*-BuOMe (1×200 mL) and acidified with 20% aq. $NaHSO_4$ to pH 2. Then it was extracted with EtOAc (3×300 mL), the combined organic layerswere dried (Na_2SO_4) and evaporated at reduced pressure to give the title compound **29** as colorless liquid. Yield 200 g, 81%; ^1H NMR (400 MHz, $CDCl_3$): δ = 10.10 (s, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 2.71 (s, 4H), 2.60 (td, *J* = 12.1, 2.7 Hz, 4H), 1.26 (t, *J* = 7.1 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ = 177.0, 171.0, 118.9 (t, *J* = 278.8 Hz), 62.1, 48.4, 47.7 (t, *J* = 22.3 Hz), 47.6 (t, *J* = 22.3 Hz), 40.4, 27.3 (t, *J* = 9.6 Hz), 13.9 ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ = –92.1 ppm; MS

(APCI): *m*/z = 249 $[M+H]^+$; elemental analysis calcd. (%) for $C_{11}H_{14}F_2O_4$: C 53.23, H 5.69; found: C 52.89, H 5.47.

Ethyl 2-((*tert*-butoxycarbonyl)amino)-6,6-difluorospiro[3.3]heptane-2-carboxylate (30): Compound **29** (135 g, 0.54 mol) was dissolved in CH_2Cl_2 (1 L),and DMF (2.5mL) and oxalyl chloride (90.0 g, 0.71 mol) were added dropwise. The resulting mixture was stirred until gas evolution ceased (ca. 2 h). Then it was evaporated at reduced pressure, the residue was dissolved in acetone (210 mL) and the obtained solution was added dropwise to cold (0 °C) stirred solution of NaN_3 (106 g, 1.63 mol) in water (320 mL). The reaction mixture was stirred at 0 °C for 1 h and extracted with EtOAc (2×300 mL). The combined organic layer was dried (Na_2SO_4) and evaporated to ½ of initial volumeatreducedpressure. Thus obtained solution was added dropwise to the stirred hot (80 °C) mixture of PhMe (800 mL) and *t*-BuOH (400 mL). The resulting solution was refluxed with stirring for 12 h, cooled to rt, and evaporated at reduced pressure to give the title compound **29** as colorless needles. Yield 123 g, 71%; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.16 (s, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 2.69 (t, *J* = 12.6 Hz, 2H), 2.63 (t, *J* = 12.6 Hz, 2H), 2.64–2.43 (m, 4H),1.41 (s, 9H), 1.27 (t, *J* = 7.2 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ = 173.6, 154.7, 119.4 (t, *J* = 279.1 Hz), 61.6, 58.6, 54.3, 48.1 (t, *J* = 22.1 Hz), 48.0 (t, *J* = 22.1 Hz), 43.0, 28.3, 26.1 (t, *J* = 9.8 Hz), 14.1 ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ = –92.0 ppm; MS (APCI): *m*/z = 220 $[M–C_4H_8–CO_2+H]^+$; elemental analysis calcd. (%) for $C_{15}H_{23}F_2NO_4$: C 56.42, H 7.26, N 4.39; found: C 56.48, H 7.48, N 4.68.

Ethyl 2-amino-6,6-difluorospiro[3.3]heptane-2-carboxylate 2,2,2-trifluoroacetate (31): Compound **30** (30.0 g, 93.9 mmol) was dissolved in CH_2Cl_2 (200 mL), then TFA (50 mL) was added and the resulting mixture was stirred at rt overnight. Then it was evaporated to dryness at reduced pressure, the residue was triturated with Et_2O (200 mL), and filtered to give the title compound **31** as white powder. Yield 25.0 g, 80%; m.p. 170 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.61 (s, 3H), 4.23 (q, *J* = 7.1 Hz, 2H), 2.77 (t, *J* = 12.6 Hz, 2H), 2.70–2.54 (m, 6H), 1.27 (t, *J* = 7.1 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ = 171.1, 158.7 (q, *J* = 31.2 Hz), 120.4 (t, *J* = 277.8 Hz), 117.6 (q, *J* = 299.7 Hz), 62.6, 52.9, 47.9 (t, *J* = 21.8 Hz), 47.1 (t, *J* = 21.7 Hz), 41.3, 25.8 (t, *J* = 10.2 Hz), 14.19 ppm; $^{19}F\{^1H\}$NMR (376 MHz, DMSO-d_6): δ = –74.1 (s, 3F), –90.3 (s, 2F) ppm; MS (APCI): *m*/z = 220 $[M+H]^+$; elemental analysis calcd. (%) for $C_{12}H_{16}F_5NO_4$: C 43.25, H 4.84, N 4.20; found: C 43.28, H 4.98, N 4.52.

General Procedure for the Preparation of Boc-protected Amino Acids 32 and 34: The solution of the correspondingBoc-protected ester **30**, **33** (0.34 mol) in MeOH (800 mL) was added dropwise to the stirred solution of NaOH (54.0 g, 1.35 mol) in water (1 L) and the resulting mixture was stirred at rt for 12 h. MeOH was evaporated at reduced pressure, the remaining aqueous layer was extracted with *t*-BuOMe (1×300 mL) and acidified with 20% aq. $NaHSO_4$ to pH 3. Then it was extracted with EtOAc (3×400 mL), the combined organic layer was dried (Na_2SO_4), and evaporated at reduced pressure. The residue was recrystallized from *t*-BuOMe – hexane (1:1) affording the title compound **32**, **34**.

2-((*tert*-Butoxycarbonyl)amino)-6,6-difluorospiro[3.3]heptane-2-carboxylic acid (32): from **30** (107 g, 0.34 mol),colorless crystals (83.2 g, 85%; m.p. 213–215 °C;the title compound was obtained as a ca. 1:2.5 mixture of rotamers; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.35 (s, 1H), 7.50 and 7.22 (s, 1H), 2.67–2.53 (m, 6H), 2.28 (d, *J* = 12.3 Hz, 2H), 1.36 and 1.31 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ = 175.8 and 175.3, 155.2 and 154.7, 120.7 (t, *J* = 278.7 Hz), 78.6 and 78.5, 54.1 and 53.8, 47.7 (t, *J* = 20.8 Hz), 47.6 (t, *J* = 20.8 Hz), 47.4, 43.2 and 42.5, 28.7 and 28.4, 26.7 (t, *J* = 9.0 Hz) and 26.31 (t, *J* = 9.0 Hz) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, DMSO): δ = –89.8 ppm; MS (APCI): *m*/z = 290 $[M–H]^–$; elemental analysis calcd. (%) for $C_{13}H_{19}F_2NO_4$: C 53.60, H 6.57, N 4.81; found: C 53.70, H 6.53, N 4.90.

General Procedure for the Preparation of Amino Acids 27 and 28: The corresponding Boc-protected amino acid **32**, **34** (0.10 mol) was suspended in water (600 mL) and the resulting mixture was stirred and refluxed for 14 h. Then it was cooled and evaporated to dryness at reduced pressure. The residue was triturated with MeCN (200 mL) and filtered to give the title compound **27**, **28**.

2-Amino-6,6-difluorospiro[3.3]heptane-2-carboxylic acid (27): from **32** (30.0 g, 0.10 mol), white powder (18.6 g, 95%; m.p. 229–232 °C; ^{1}H NMR (400 MHz, D_2O): δ = 2.60 (dq, *J* = 26.7, 13.4 Hz, 6H), 2.40 (d, *J* = 13.4 Hz, 2H) ppm; $^{13}C\{^1H\}$ NMR (151 MHz, D_2O): δ = 176.4, 120.2 (t, *J* = 277.9 Hz), 54.3, 47.1 (t, *J* = 22.2 Hz), 46.8 (d, *J* = 22.2 Hz), 41.0, 25.1 (t, *J* = 9.3 Hz) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, D_2O): δ = – 92.1 ppm; MS (APCI): *m*/z = 192 $[M+H]^+$; elemental analysis calcd. (%) for $C_8H_{11}F_2NO_2$: C 50.26, H 5.80, N 7.33; found: C 50.56 H 5.71, N 7.43.

2-(Aminomethyl)-6,6-difluorospiro[3.3]heptane-2-carboxylic acid (28): from **34** (30.0 g, 0.10 mol), white powder (19.4 g, 96%; m.p. 234–237 °C; ^{1}H NMR (400 MHz, D_2O): δ = 3.10 (s, 2H), 2.55 (td, *J* = 14.5, 12.7, 5.0 Hz, 4H), 2.44 (d, *J* = 12.7 Hz, 2H), 2.06 (d, *J* = 12.7 Hz, 2H) ppm; $^{13}C\{^1H\}$ NMR (151 MHz, D_2O): δ = 181.8, 120.4 (t, *J* = 278.0 Hz), 47.1 (t, *J* = 22.4 Hz), 47.0 (t, *J* = 21.9 Hz), 45.5, 41.5, 39.6, 25.9 (t, *J* = 8.2 Hz) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, D_2O): δ = –91.3 ppm; MS (APCI): *m*/z = 206 $[M+H]^+$; elemental analysis calcd. (%) for $C_9H_{13}F_2NO_2$: C 52.68, H 6.39, N 6.83; found: C 52.75 H 6.30, N 6.52.

Ethyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-6,6-difluorospiro[3.3]-heptane-2-carboxylate (33): Compound **8** (90.0 g, 0.39 mol) was dissolved in EtOH (400 mL) followed by addition of Boc_2O (119 g, 0.55 mol) and Raney-Ni (prepared from 22.5 g of Raney Ni–Al alloy). The resulting mixture was loaded in an autoclave and hydrogenated at 10 MPa and rt for 48 h. Then it was filtered and evaporated at reduced pressure to give the title compound **33** as colorless oil. Yield 113 g, 87%; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.91 (s, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.42 (d, *J* = 6.2 Hz, 2H), 2.67 (t, *J* = 12.3 Hz, 2H), 2.60 (t, 12.3 Hz, 2H),2.49 (d, *J* = 12.3 Hz, 2H), 2.15 (d, *J* = 12.3 Hz, 2H), 1.42 (s, 9H), 1.27 (t, *J* = 7.1 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ = 175.5, 156.3, 119.3 (t, *J* = 279.3 Hz), 79.4, 61.1, 48. 3 (t, *J* = 22.2 Hz), 48.1 (t, *J* = 22.2 Hz), 45.7, 43.3, 39.8, 28.3, 26.8 (t, *J* = 9.4 Hz), 14.2 ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ = –91.6 ppm; MS (APCI): *m*/z = 234 $[M–C_4H_8–CO_2+H]^+$; elemental analysis calcd. (%) for $C_{16}H_{25}F_2NO_4$: C 57.65, H 7.56, N 4.20; found: C 57.81, H 7.32, N 4.14.

2-(((*tert*-Butoxycarbonyl)amino)methyl)-6,6-difluorospiro[3.3]hep-tane-2-carboxylic acid (34): from **33** (113 g, 0.34 mol), colorless crystals (87.2 g, 84%; m.p. 139–140 °C; the title compound was obtained as a ca. 1:2.3 mixture of rotamers; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.34 and 4.97 (s, 1H), 3.49–3.38 (m, 2H), 2.73–2.51 (m, 6H), 2.20 (d, *J* = 12.8 Hz) and 2.13 (d, *J* = 10.7 Hz, 1H), 1.48 and 1.42 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6): δ = 177.0, 156.6, 120.5 (t, *J* = 278.9 Hz), 78.2, 47.7 (t, *J* = 20.5 Hz), 47.6 (d, *J* = 20.5 Hz), 45.3, 43.8, 39.1, 28.6, 26.2 (t, *J* = 9.2 Hz) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ = –91.7 ppm; MS (APCI): *m*/z = 304 $[M–H]^–$; elemental analysis calcd. (%) for $C_{14}H_{21}F_2NO_4$: C 55.07, H 6.93, N 4.59; found: C 54.69, H 6.95, N 4.19.

Ethyl 2-(aminomethyl)-6,6-difluorospiro[3.3]heptane-2-carboxylate hydrochloride (35): Compound **34** (50.0 g, 0.16 mol) was dissolved in 2 M ethanolic HCl (400 mL) and the resulting solution was stirred at rt overnight. Then it was evaporated to dryness at reduced pressure, the residue was triturated with Et_2O (200 mL), and filtered to give the title compound **35** as white powder. Yield 38.5 g, 88%; m.p. 111–131 °C;^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.19 (s, 3H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.33 (s, 2H), 2.67 (dt, *J* = 18.7, 12.7 Hz, 4H), 2.47 (d, *J* = 12.7 Hz, 2H), 2.37 (d, *J* = 12.7 Hz, 2H), 1.22 (t, *J* = 7.1 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6): δ = 173.9, 120.5 (t, *J* = 278.6 Hz), 61.5, 47.8 (t, *J* = 21.4 Hz), 47.4 (t, *J* = 21.5 Hz), 43.6, 41.3, 39.4, 26.7 (t, *J* = 9.6 Hz), 14.3 ppm; $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6): δ = –89.6 ppm; MS (APCI): *m*/z = 234 $[M+H]^+$; elemental analysis calcd. (%) for $C_{11}H_{18}ClF_2NO_2$: C 48.98, H 6.73, N 5.19; found: C 49.05, H 6.33, N 5.44.

(2-(Aminomethyl)-6,6-difluorospiro[3.3]heptan-2-yl)methanol hydrochloride (36): Compound **8** (40.0 g, 0.17 mol) was added portionwise to the stirred suspension of $LiAlH_4$ (13.3 g, 0.35mol) in THF (500 mL) at rt and the resulting mixture was refluxed with stirring for 1 h. Then it was cooled to 0 °C and quenched by sequential dropwise addition of water (13 mL), 50% aq. NaOH (8.7 mL), and water (40 mL) while maintaining the above temperature. The precipitate was filtered off and the filtrate was evaporated at reduced pressure. The residue was dissolved in Et_2O (300 mL) followed by addition of 4M HCl in Et_2O (40mL) and the resulting mixture was evaporated to dryness at reduced pressure. The residue was recrystallized from EtOAc – hexanes (1:5) to give the title compound **36** as yellowish crystals. Yield 27.8 g, 70%; m.p. 135–137 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.92 (s, 3H), 5.10 (s, 1H), 3.41 (s, 2H), 2.85 (s, 2H), 2.60 (td, *J* = 12.6, 7.0 Hz, 4H), 2.07 (d, *J* = 12.6 Hz, 2H), 1.96 (d, *J* = 12.6 Hz, 2H) ppm; ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ = 120.7 (t, *J* = 279.2 Hz), 65.4, 48.2 (t, *J* = 21.0 Hz), 47.8 (t, *J* = 21.0 Hz), 44.5, 38. 6, 37.3, 26.1 (t, *J* = 9.0 Hz) ppm; ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6): δ = –89.3 ppm; MS (APCI): *m*/z = 192 $[M+H]^+$; elemental analysis calcd. (%) for $C_9H_{16}ClF_2NO$: C 47.48, H 7.08, N 6.15; found: C 47.58, H 6.93, N 6.15.

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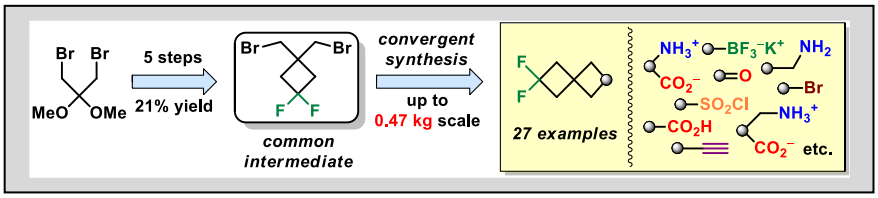

Spiro compounds

An approach to 6,6-difluorospiro[3.3]heptane scaffold – a conformationally restricted isostere of *gem*-difluorocycloalkanes – is developed. A large array of novel 2-mono- and 2,2-difunctionalized 6,6-difluorospiro[3.3]heptane building blocks was obtained in multigram scale through the convergent synthesis strategy using a common synthetic intermediate – 1,1-bis(bromomethyl)-3,3-difluorocyclobutane.

Institute and/or researcher Twitter usernames: @EnamineLtd @KyivUniversity